A systems perspective to digital structures in molecular analysis

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Within the last decade, the advance of miniaturization has opened the window to new systems that permit digital and molecular science to intersect, suggesting a new role for organic chemistry. Currently, fusion of molecules and electronic digits, as well as molecular-based digital structures, have expanded the conventional interpretation of the digit. This emergence has already generated new technological platforms with unique applications for molecular analysis and computation. We provide a brief overview of the conventional understanding of digital devices, examine the concept of molecular-based digits, and suggest new architectures by examining studies conducted on the compact discs. This analysis presents a perspective for the unique interaction of molecules and digits and the development of digital-based platforms for molecular analysis.

Introduction

Today organic chemistry lies at a crossroads between basic discovery and applied science. This unique position enables the organic chemist to participate in the development of new fields through selective leverage of skills and technologies. Here we discuss an emerging scientific area, the integration of molecules into computational frameworks, which relies upon creative organic chemistry for successful development of the field. To date, organic chemists have only participated tangentially in the digital revolution of computer and internet development. However, we see this

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trend changing as molecular information becomes increasingly fused with digital information. Molecular analysis, a scientific arena both necessary for and dependent upon the practice of organic chemistry, provides an exciting arena where digits and molecules are now being integrated.

Molecular analysis involves the recognition of disparate molecules and screening the interactions between them. Several analytical methods are commonly used in a variety of scientific and medical fields, including nuclear magnetic resonance (NMR) spectrometry, electrochemistry, spectrophotometry, and mass spectrometry (MS). All of these techniques are analog devices developed with digital platforms. As a result, discrete logic is playing a significant role in their performance. Here, access to advanced algorithms and accompanying software applications, such as in multi-dimensional methods (*e.g.*, 2D NMR spectroscopy), provide a superior means to interpret molecular events. Comparable advances have been observed in the development of familiar consumer electronic components such as audio/visual devices, cameras, computers, and television.

Fundamentally, a digital signal can contain more information and be processed, transmitted or stored more efficiently with less noise compared to an analog signal.[1–4] It is within this capacity that digital processing has become the primary choice in the development of electronic systems. A simple example can be derived from digital television. For instance, each digital television channel has ~19.2 Mbs (megabits per second) capacity to transfer audio and visual data.[5,6] This has provided the capability to transfer video with a resolution of 1920 × 1080 pixels (207 3600 total pixels) at >60 frames second.[7] This conduit far surpasses the 427–465 by 242–290 pixels delivered at a rate of 25–30 frames/s by conventional analog television signals.

For molecular science, digital structures have evolved significantly. Currently, digital architectures are not limited to electronic machines that operate and process analytical devices, rather through molecular design, organic chemistry has developed a means to depict digits within molecular systems. It is the intention of this discussion to provide an overview of existing digital structures with respect to molecular analytics and computational applications, including our own program to integrate molecules with digital information for molecular analytical applications. For this purpose, we have classified digital structures in molecular systems into three major groups consisting of: (a) silicon-based digits; (b) molecular-based digits; and (c) hybrid systems. Specifications as well as advantages of each composite will be examined, and the perspective for integration of digits and molecules is investigated. The discussion begins historically with silicon-based digits.

Silicon-based digits

In the context of electronics, there are two major architectures for processing, transmitting, and storage of signals: digital and analog. A digital signal is a non-continuous signal that changes between a unique set of states. It consists of pulses or digits with discrete levels of intensity. An analog signal is one with continuous diversity that varies in time. Schematic representations of digital and analog signals have been demonstrated in the source boxes of Fig. 1 and 2, respectively. Basically, information can be conveyed through either analog or digital architectures; however, there are

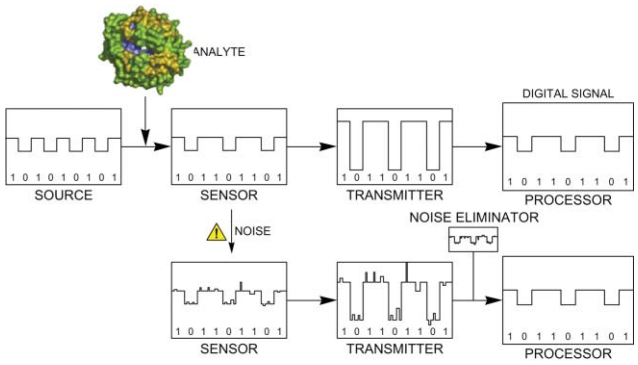

Fig. 1 Generating, transmitting and processing of a digital signal and the effect of noise on the quality of the signal. Triangle denotes the appearance of noise.

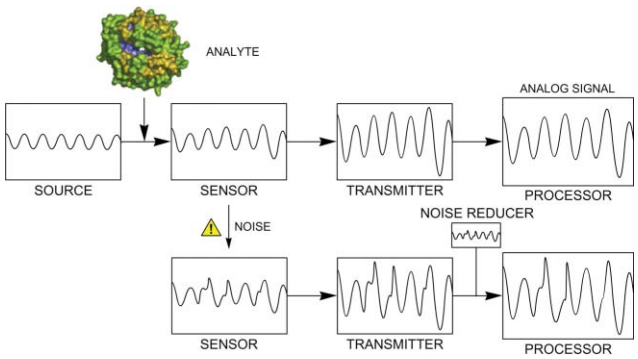

Fig. 2 Sensing, transmitting and processing of an analog signal and the effect of noise on the quality of the signal. Triangle denotes the appearance of noise.

significant advantages in the use of digits (discrete numbers) over continuous signals.

Discrete numbers in digital systems are mostly binary systems (base 2), where numeric values are represented by two symbols, typically 0 and 1, referred to as bits. In contrast, an analog signal could be any variable signal continuous in both time and amplitude. The value of any analog signal can be represented in binary format by the combination of 0s and 1s. This combination can be used to convert an analog to a digital signal.

Noise, or random variations in a signal, can appear during reading, copying, processing, or transmitting data. If the signal is continuous, as in analog systems, noise can directly distort the original signal.[2,8] The effect of noise on the quality of an analog signal originating from measurement or recognition of an analyte is shown in Fig. 2. As shown in this figure, noise changes the amplitude of an analog signal that cannot be eliminated completely. This is the primary disadvantage of analog systems. Electrically, these distortions can be reduced to some extent through electronic techniques, such as the use of cut-off frequency filters (*i.e.*, low pass filters) in analog audio systems. However, it is almost impossible to recover the complete original signal. On the other hand, noise in digital signals cannot distort the quality of the information, as any signal close to a particular value (0 or 1 in binary systems) will be interpreted as that value[8,9] (Fig. 1). Moreover, error correction algorithms can be implemented by computer processing in digital format to correct a distorted signal through comparison with known or predicted data.[10] Additionally, binary systems can be

easily implemented on large-scale electronic circuitry through well-established integrated circuit (IC) fabrication technology.[11,12] This technology has dramatically boosted the development of digital computing devices.

The Atanasoff-Berry Computer (ABC) launched the development of digital computing in 1937.[13,14] In this computer, binary digits were used to represent all numbers, electronics were implemented to perform calculations rather than mechanical wheels and switches that had been used in analog computing systems, and separate memory and computing modules were incorporated into the hardware architecture. This development was advanced in 1941 by the invention of Konrad Zuse's programmable digital Z3 computer,[15] and further improvement came in 1944 with IBM's programmable large-scale automatic digital computer, ASCC (Automatic Sequence Controlled Calculator).[16] These early versions of digital computing consisted of thousands of relays, switches, rotating shafts, and hundreds of miles of wire. Within a ten year period of their conception, significant improvements were made, such as substitution of all electromechanical devices with electronic components (transistors, diodes, capacitors) and the use of magnetic memory.

A major improvement in computational devices arose through the advancement in fabrication of ICs. Integrated systems were miniaturized in electronic circuits consisting of millions of semiconductor devices that were manufactured on a thin substrate (*e.g.*, 0.75 mm think) of a semiconductor material, principally silicon.[11,17] Interestingly, the semiconductor devices that are extensively used in electronic circuitry (analog and digital) to perform required operations such as logic functions, amplification, switching, and signal modulation exploit electronic properties of semiconductor materials that depend on the atomic and molecular structure of these materials. The conductivity behaviour of a semiconductor (*e.g.*, silicon and germanium) can be altered by doping with impurity atoms (*e.g.*, phosphorous or boron).[18] This principle has been employed for production of numerous semiconductor devices, such as diodes and transistors.[17,18] These examples indicate that even advanced electronic circuitry with primarily computational or electronic applications are fundamentally influenced by molecular and atomic structures of their constituent materials, which indicates an early level of convergence between molecules and electronic digits.

Photolithography and other related methods also facilitated the mass fabrication of millions of semiconductor devices on a silicon wafer constituting the IC, which has steadily reduced the size of computing devices and allowed faster and less expensive assembly.[17,19] Within this domain, a trend (Moore's law) has been observed stating that the complexity of ICs (*i.e.*, the number of components on an IC or computing processing power) doubles every 24 months.[20] Currently, high performance digital processing chips, such as central processing units (CPUs) or in general CMOS microcontroller chips, are the central components of computing devices.

Computers are not the only systems that have benefited from a digital architecture. Another tangible recent example is television. For instance, a digital television signal with 6 Mhz bandwidth can carry five times more information than an analog one at the same bandwidth.[4,5] This is because of the capability to compact digital signals through data compression algorithms. Additionally, in digital format, television is not merely used to deliver video but also offers an interactive environment for programming. This is derived from the ability for a digital stream of bits (0s and 1s) to contain other data in addition to video/audio information. In other words, a convergence between computation and television media in digital format can occur.

The conventional definition for digits as elaborated above is referred in this paper as silicon-based digits, as silicon is the predominant material used in IC manufacturing. With respect to molecular analysis, the performance (reliability, precision, and speed) of most analytical technologies has been improved through the use of digital systems in conjunction with existing analytical devices. This improvement is derived from the integration of digital computing devices and software to process the data arising from analytical measurements.

Most contemporary molecular analytical devices (*e.g.* microarrays, mass spectrometers, and NMR) are fundamentally analog in nature, yet the readout from these machines is digitally controlled. Digital processing and computing techniques have been used to measure, process, and transfer data pertaining to the existence of specific molecules or the occurrence of chemical reactions. A molecular analytical system is conceptually an integration of three separate modules (Fig. 3). The modules are: (a) a digital component for controlling the instrument and processing of extracted data (right, Fig. 3); (b) an analytical device (left, Fig. 3); and (c) adaptor modules used to convert between analog and digital components (A/D and D/A modules, Fig. 3). Normally, molecules or reactions are identified through an intermediary physical phenomenon (*i.e.*, absorption of light, fluorescent emission, or the behavior of particles in an electric or magnetic field). It is noteworthy that although these physical phenomena are measured in an analog manner and processed on digital computing systems, there is no direct interaction between molecules and their corresponding digital data.

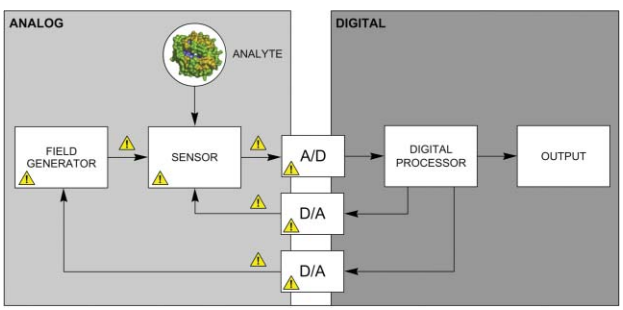

Fig. 3 System level architecture of conventional molecular analytical systems (A/D: analog to digital adaptor; D/A: digital to analog adaptor). Triangles denote regions in which noise can appear.

Molecule-based digits

In direct contrast with the electronic devices described in the prior section, computation can be also performed with molecules. While the role of the organic chemist has only been modest in the development of IC devices, molecular-based computation replaces electronic signals with complex chemical reactions. Here the role of the chemist is critical to the establishment of chemical functions that delivers discreet logic and also permits complex levels of entry and calculation.

There are two major formats of molecular computation. The first develops its signals over an assembly of molecules (intramolecular systems) and the later arises through events that can be conducted within a molecule (intermolecular systems).

Intramolecular systems predominantly develop computation based on reaction-diffusion using a physical phenomenon called the Belousov–Zhabotinskii (BZ) reaction (Fig. 4a).[21,22] Data are represented by varying the concentration of molecules in a BZ medium, and computations are performed by the diffusion process. These studies developed a binary system through monitoring the cycling of a chemical reaction between yellow and colorless solutions. Here a colorimetric response was used to denote this binary system.

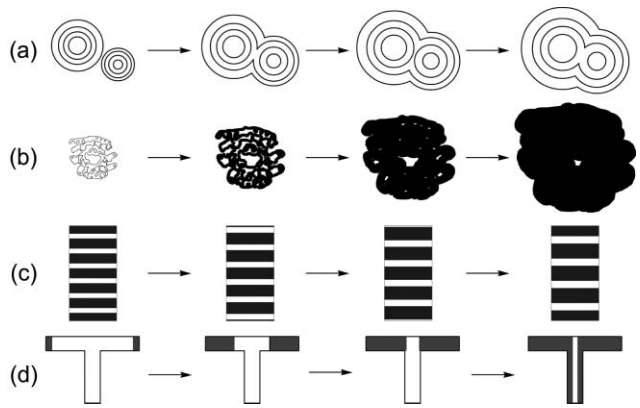

Fig. 4 Schematic representation of some examples of intramolecular systems, (a) fusion of chemical waves in a BZ medium; (b) progression of chemical reactions in a light-sensitive BZ medium; (c) calculation of Voronoi diagram using BZ reaction, as one moves from left to right the bars grow in size and diffuse from the center of the object; (d) implementation of logic gates using BZ media, the reactants diffuse along the chamber and interact with each other.

The first computational application of the BZ reaction was published in 1989 by Kuhnert,[23] in which light-sensitive chemical reactions (waves) in a BZ medium were used for the purpose of image processing (Fig. 4b). Before this investigation, image-processing functions were performed using computer analysis to process a digital image. However, Kuhnert showed that various functions, such as segmenting a picture or smoothing a degraded picture, can be performed through the BZ reaction. This work was a breakthrough in the field of chemical computing. The simplicity of the method in comparison with conventional techniques, based on the use of complicated digital microprocessors, exists as the main argument for molecular systems presenting competition to silicon-based digits.

Kuhnert's concept has progressed significantly since 1989. It has been shown that BZ media are capable of solving complex image processes, calculating Voronoi diagrams (Fig. 4c),[24–27] conducting pattern recognition,[28,29] and planning paths.[30,31] Furthermore, production of logical gates with BZ media has also been studied. Logical gates are basic operations required for all computational purposes. Traditionally, a logical gate has a two bit input (0 or 1) and one output subjective to the type of the logical operation (*e.g.*, AND, OR, NAND). For example, Blittersdorf built Boolean logic gates from a network of three chemical reactors in which the binary state was represented by the level of acidity.[32] In 2002, Adamatzky demonstrated that simple logic gates can be implemented using concentration waves as they constructively or destructively interfere within a given T-shape structure cut from a BZ media gel (Fig. 4d).[33]

It should be noted that the concept of reaction-diffusion computation is actually a type of analog computation, as the element of analysis arises through a dynamic physical phenomenon rather than a single logic gate. Furthermore, detection requires peripheral instrumentation, primarily optical capture systems that involve analog to digital conversions. Nevertheless, the manipulation of chemical diffusion within a BZ computer is equivalent to the data processing structure used by digital processors. In comparison with modern microprocessors, a chemical can be simple, stable, small, and inexpensive to produce. The concept of chemical computation is still in its infancy; however, it can become a more effective device for some specific processes. In conventional microprocessors, processing of bits of data is performed sequentially, and data transfer/interaction should be performed through specific communication channels. Chemical waves representing bits of information can move in all dimensions and simultaneously interact with each other, thereby permitting a multitude of simultaneous operations. This property provides the capability of handling significantly higher levels of data flux than silicon-based systems.

Currently, there are two primary types of intermolecular computation (Fig. 5). The first type develops a logic gate based on the manipulation of a small molecule. In the first example (Fig. 5a), the fluorescence of a solvatochromic dye is manipulated by its atmosphere. Here switching between Ar and CO_2 atmospheres can be used to regulate the fluorescence derived from a dye, thereby delivering a two stage process.[34] These events can be examined at the single molecule level, wherein fluorescent molecules are observed in one state (with Ar) and not in another (with CO_2). A panel of more sophisticated events has been developed with switches that can be regulated by light, current, ion strength, temperature or chemical reactivity.[35–51] In a second example, the absorbance properties of a chromaphore can be used for switching. Conversion between an *N*,*O*-acetal and its corresponding ring-opened tautomer (breakage about the line in Fig. 5b) provides a distinct colorimetric change. This change can be regulated by the wavelength of light or by pH.[50,52,53] Alternatively, polychromic materials can deliver a multi-state device through photoisomerization. An example of this process is provided in Fig. 5c. Here, a two staged device is developed by the conversion of a dihydroindolizine to its corresponding betaine with UV light and return by exposure to visible light or heat.[54]

A second type of intermolecular device is based on examining the reactivity of a molecule. The first example of this class arises through the regulation of multiple states in supramolecular complexes. As shown in Fig. 5d, this regulatory behaviour can be used to generate a distinct colorimetric or electrochemical response (Fig. 5d).[55–57] Enzyme reactions also provide a further medium to display logic functions (Fig. 5e).[58–61] In this type of experiment, multiple inputs are given by the addition of substrates (or inhibitors), and logic is developed over the progression of an enzymatic process. Again, these methods are typically monitored by examining reactivity within a bulk medium rather than examined one molecule at a time.[34,62,63]

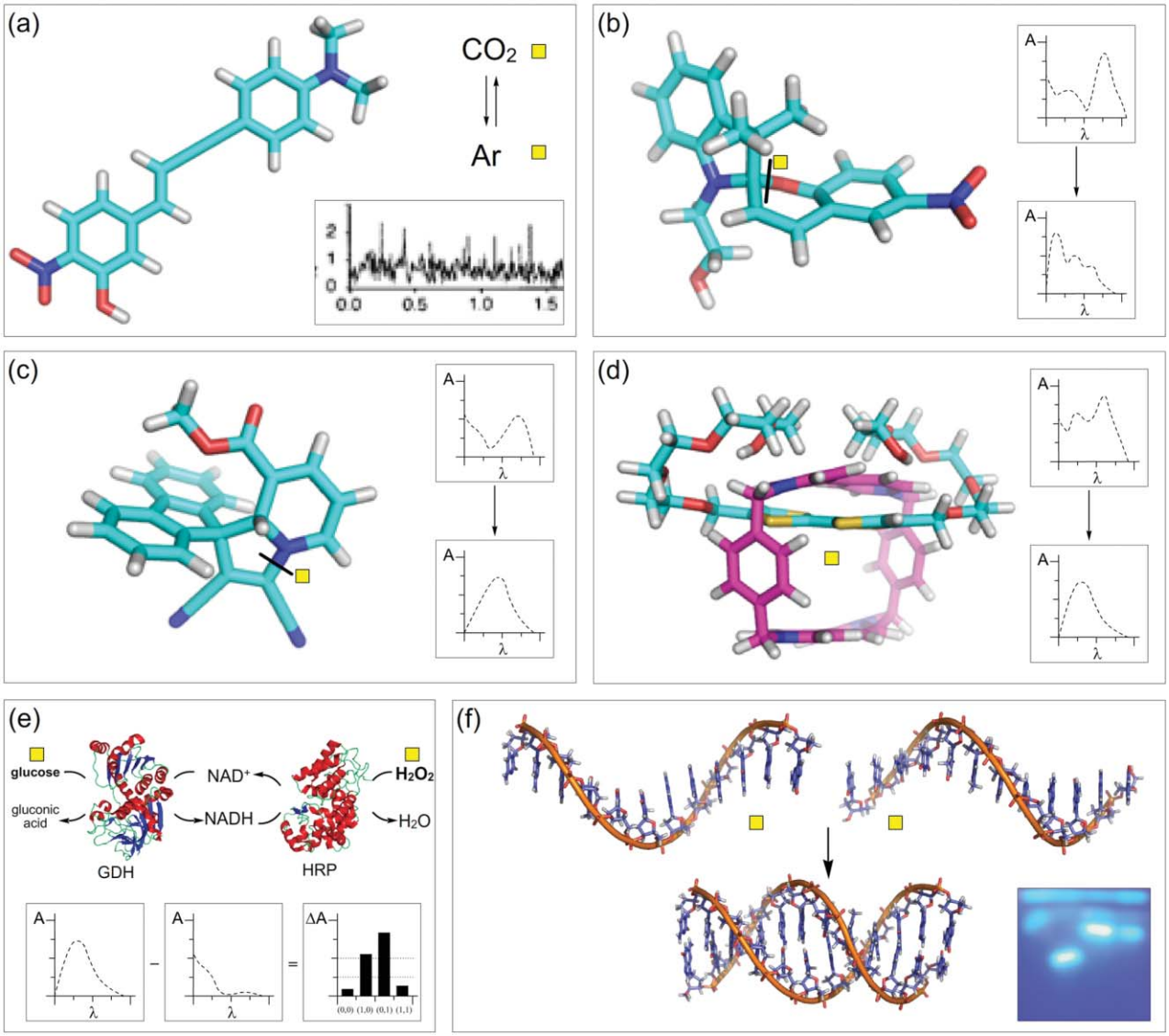

Fig. 5 Examples of intermolecular systems for logic gates development. Based on small molecule manipulation: (a) regulating the fluorescence of solvatochromic dye by changing the atmosphere between Ar and CO_2; (b) switching using absorbance property of a chromaphore; (c) a multi-state bilateral phenomenon by exposing dihydroindolizine to UV light. Based on the reactivity of a molecule: (d) regulation of multiple states in supramolecular complexes; (e) logical gate development using enzyme reactions; (f) oligonucleotides hybridization for performing logical operations. Dark lines in (b) and (c) denote bonds broken during the two-state process. Yellow boxes denote regions of input or output.

To date, DNA computing is the most developed type of intermolecular computation, wherein the binary nature of oligonucleotides is adapted to represent digits.[64–70] This field was proposed by Adleman in 1994.[71] He showed the feasibility of using DNA molecules as a form of computation to solve the mathematically complicated problem of a seven-point Hamiltonian path.[71] In Adleman's approach (Fig. 5f), DNA fragments were produced and encoded corresponding to different variables of a problem, and DNA hybridization was used to reach to the solution. DNA computing is fundamentally very similar to parallel computing, whereby highly complex mixtures of DNA molecules simultaneously evaluate many different possibilities. For certain specialized problems, DNA computing could provide a faster and smaller computational element than that required by parallel networks of silicon-based processors. Assuming that hybridization of two DNA molecules is considered a single operation, the readily accessible operation in a DNA computer at *e.g.*, 10^{20} or more calculations/second[71] can easily exceed the speed of the fastest digital computer at ~280.6 TFlop/s ("teraflops" or trillions of calculations/second). In the case of the seven-point Hamiltonian problem attempted by Adleman, a random 20-mer oligonucleotide was generated representing each vertex and edge in the problem. Aliquots containing 50 pmol of these 20-mers were mixed together, allowing each combination of the nucleobases to hybridize, representing a comprehensive operation.[71]

The major challenge in molecular computation lies in its generality. For each problem, one must design a new set of experiments, each requiring a new, yet refined, set or class of molecules. This problem is further complicated by the need for a diverse set of analytical methods to collect the data

(*i.e.*, spectrophotometer or CCD camera) and convert it to the respective digital output. Moreover, the demand for molecular quantity grows exponentially with the size of the problem, and the amount of molecules required for complex computation is often too large to be practical at the single molecule level (*e.g.*, it would take 960 years to complete a calculation that evaluates 10^{20} molecules at 3.3 molecules/nanosecond). Additionally, molecular computation requires the specification of chemical reactions, which often requires complex transfer of liquids, solids, or gasses. Most of these transformations cannot be conducted within a time frame comparable to that of electrical circuits.

Major advances have been made in the field of DNA computation since its discovery. The research in this domain has focused on two major aspects: (a) application of biomolecular computers for computational problems;[71–75] and (b) molecular scale programmable computers for logical control of biological systems.[76–78] As an example of the latter in 2004, Benenson demonstrated a molecular-scale logical control of gene expression in a DNA computer with molecular input and output modules capable of diagnosing cancerous activity within a cell and releasing an anti-cancer drug upon diagnosis.

While complications exist, the advance of the small molecule, enzymatic, and DNA computation suggests a merge between molecular and computational sciences through which both aspects gain in function. In the next section, hybrid systems are introduced in which digital streams are directly affected by molecules.

Hybrid systems

Recently, the concept of molecular analysis through direct interaction between molecules and digits, or hybrid systems, has become an active research topic. In these systems, molecular analysis is conducted through the ability of molecules to alter the transmission of a digital stream. Hybrid systems include silicon-based digits, such as conventional analytical molecular systems, however molecular recognition is not based on detection of an intermediary physical phenomenon. Rather, a molecular event is detected by its ability to manipulate a digital sequence, thus a true interaction between digits and molecules is achieved in these analytical systems.

The compact disc (CD) has been greatly studied recently for molecular analysis in the context of hybrid systems.[79] In 2000, Hammock suggested that a CD format for the fabrication of microarrays could be implemented for molecular detection in a method analogous to data reading off a conventional compact disc.[80] The reading of a CD employs a process called destructive interference in order to deliver binary information.[81] Briefly, a CD laser beam focuses on a track of pits and land (the data track) below a layer of polycarbonate. The laser reflects off the aluminium data track and is read by an opto-electronic device that detects changes in light. The land regions reflect the light differently than the pits, and the optical sensor detects the change in reflectivity as a digital signal (such as on/off or 1/0). The depth of the pits is chosen as one quarter of the laser beam wavelength (780 nm). As a result, the reflected laser beam from a land region is out of phase as much as π with the light reflected from a land.[81]

Effectively, each pit acts as a micro-interfrometer through which data can be digitally perceived. Hammock suggested a similar approach for molecular detection, assuming that the distance between the top of a molecule on a reflective surface resulted from conducting an immunobead-based assay using reflective beads, with the surface being one quarter of the laser beam wavelength in distance. In this scenario, the same destructive interference can be observed using a system similar to conventional CD players. In other words, molecules generate a digital stream of data that can be used for molecular detection (Type IA, Fig. 6). Recently, a similar method for detection of molecules labeled with reflective particles has been reported in which molecules produce a digital stream of data resulting from the reflection of a laser beam from metallised labeled molecules (Type IA, Fig. 6).[82] This method has been used for the quantitative measurement of biomolecular binding.[82] For readability with conventional CD players, bioactive receptor sites (*e.g.*, CPR antibodies) were stamped according to a pit structure for conventional CDs (0.6 μm wide and 1.5–6 μm long), and the screening assay was performed on the surface of the CD.[82]

Another hybrid approach for molecular screening was suggested in 2004 by Nolte and Yu.[83] It is based on fabrication of microstructures that can act as microscopic interfrometers in a platform similar to a CD (Type IB, Fig. 6). Here a laser beam with a wavelength of 633 nm was used to detect the binding between target analytes with antibodies, antigens, or DNA molecules immobilized on a micro-interferometric element. This was performed with gold lines arranged as radial spokes on a disc-shaped platform. Binding interactions introduce an additional phase change in the reflected laser beam that can be detected in the far-field diffraction intensity. In other words, molecular detection is made by processing a string of created digits. In this approach, the thickness of gold spokes (79.1 nm) was chosen in such a way that they operate in quadrature with the laser read-out, resulting in maximum linear detection sensitivity.[83]

In 2003, we proposed a new CD-based molecular screening platform in which molecules were used to alter the digital stream of data as it is read from a conventional compact disc by a standard computer CD player.[84] In this approach, molecules do not create a digital signal but alter an existing digital stream. Positive molecular interaction events on the surface of the CD create interference within the digital steam as the CD is read by the player (Type II, Fig. 6). In this method, ligand molecules are deposited on a chemically modified CD surface, which creates an additional ligand layer on a conventional compact disc.[84,85] A specific data pattern is first written onto the internal digital layer of a CD, and ligands are subsequently deposited on the activated CD surface. Molecular screening is performed by reading the data off the CD before and after addition of a biomolecule and evaluating the error created by positive binding events.[84,85]

The unique characteristic of hybrid systems for molecular detection is the direct interactivity between a digital stream and a molecule. One of the major advantages that can be achieved through this interaction is the capability of providing a generic molecular analysis platform that is not subjective to the assay type and does not require expensive calibration procedures as with conventional molecular systems. In Type II hybrid molecular analytical systems, the analytical device and the computing device are not two separate entities as they are in conventional techniques. The analytical system is an integral part of the digital communication, and Type II hybrid systems can benefit from sophisticated logic and networking structures found in contemporary computing. However, it should be emphasized that

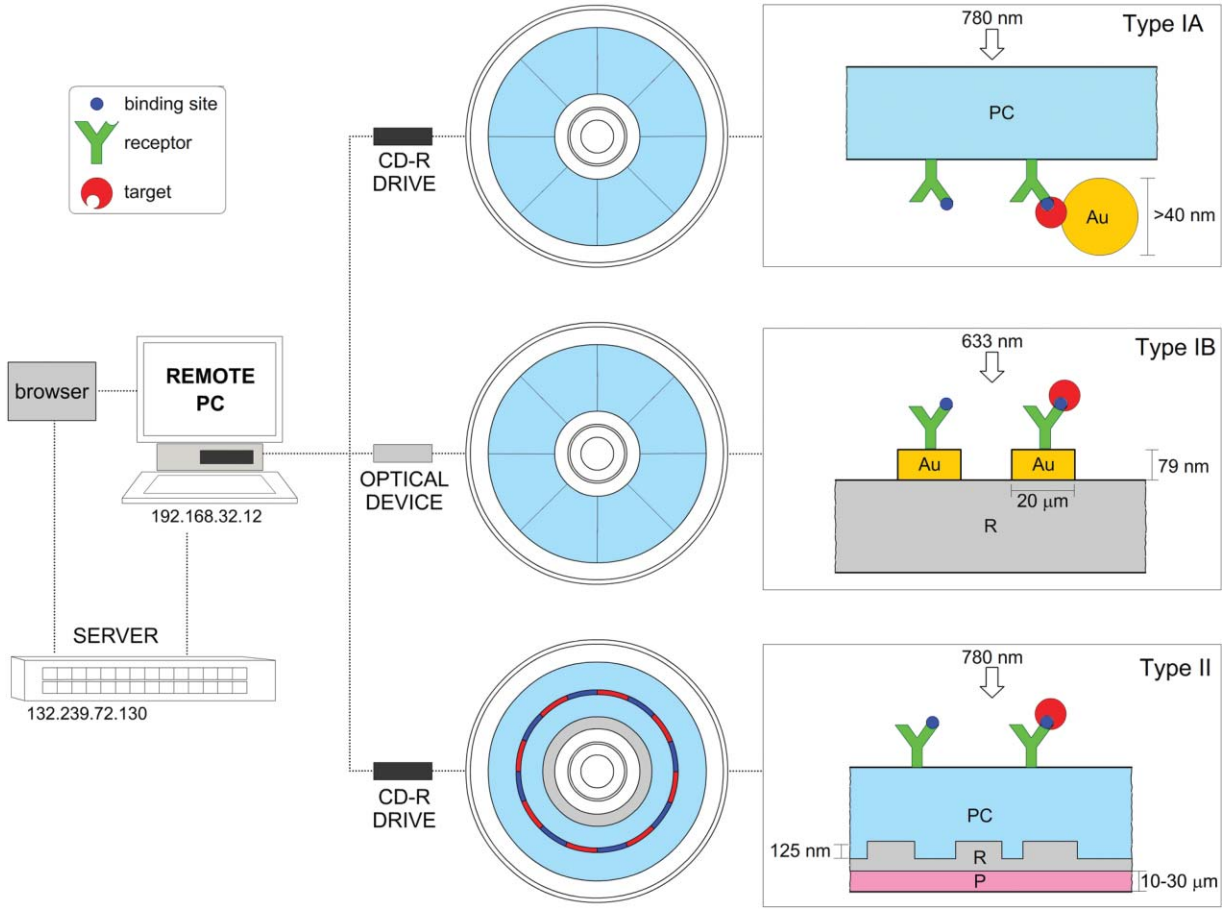

Fig. 6 Hybrid systems molecular detection architectures. Type IA: a digital signal is generated by the reflectivity of molecules labeled with reflective beads against a laser beam; Type IB: recognition of molecules based on processing of the phase of the reflected laser beam; Type II: molecular recognition based on their interferences with a pre-sorted digital signal. PC: polycarbonate layer, R: reflective layer, P: protective lacquer layer.

of the three hybrid computing systems, only Type II systems fit within this definition.

In Type IA and IB, a new set of digital information is generated for the creation of analytical data. In Type IA, the affinity event creates the digital signal, as given by its geometric positioning into byte structures. In Type IB, alteration of light reflection is employed to generate a digital signature. In other words, data are produced in an analog manner, but it is perceived and processed digitally. This is similar to conventional molecular analytical systems, but with platforms more suitable for digital architecture. Alternatively, the Type II creation of analytical information is based on the alteration of existing digital code (Fig. 7). This is an emergence between molecular analysis and contemporary digital machines in an advanced level. As a result, sophisticated molecular-based data manipulation and information flow is anticipated through this fusion.

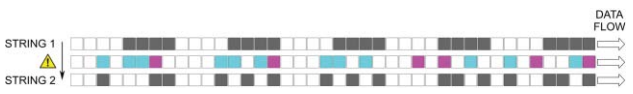

Fig. 7 Schematic representation of modulating a string of digits in Type II hybrid systems. The triangle denotes the appearance of data reading error.

Fig. 7 illustrates this concept in Type II systems. String 1 is the existing (pre-stored) digital data within a CD platform. White and grey boxes represent 0 and 1 bits, respectively. The middle data string is the statistical error signal that arises from the interference of molecules with the background digital stream (string 1). Statistically, this interference can produce two types of errors depicted as cyan and magenta boxes. Cyan represents a change in the value of the original bit (from 1 to 0 or 0 to 1) and magenta represents no change in the statistical data reading error creation. As a result, string 2 is an altered data set in comparison with string 1, and the difference between these two strings can be calculated. Thus, the alteration of data is directly responsible for molecular detection in Type II hybrid systems.

Conclusions and perspectives

The emergence of digital devices through computing has significantly impacted the human experience within a short period of time. With the advent of direct interaction between digital information and molecules, a parallel growth could be predicted for digital molecular analysis. In the short term, we believe that the true integration of digital streams with analytical instruments or direct interaction between molecules and digits (hybrid systems) could provide generic and inexpensive molecular analysis platforms (Fig. 8). The combination of new digital structures and their fusion with molecular systems provides an exciting area

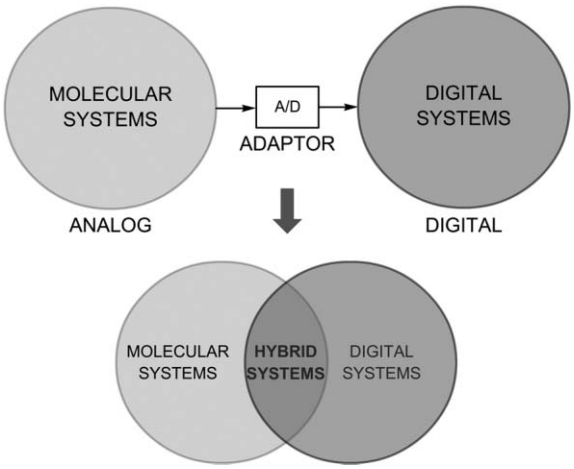

Fig. 8 System level structure of hybrid approach in the development of molecular detection platforms.

for discovery. Though it remains difficult to predict the optimal conduits between the molecule and the digit, competitive new technologies suggest new devices and media that can integrate with aspects of commercial electronics.

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