

Development of Nano-Scale DNA Computing Devices

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Abstract: DNA computing employs DNA molecule as a main resource to fulfill computing tasks. However, the concept of primary DNA computing unit keeps obscure. It is recently realized that there are multiple forms of basic DNA computing units, all with the fundamental property of nano-scale DNA fragments of Watson-Crick pairing. In this review five non-exclusive types of the main DNA computing units were summarized one by one, and they are Adleman unit, Tiling unit, Rothemund-Shapiro unit, Ribozyme unit and Paun unit. Adleman unit is actually just basic Watson-Crick pairing/ligation, or a simplified version of DNA assembly; Tiling unit is from various DNA tiles, with assembly as computing process; Rothemund-Shapiro unit is Turing machine-like autonomous DNA automaton. Ribozyme unit is an endeavor that may first lead to protein enzyme-free DNA automaton. There is another special DNA computing unit called here as "Paun unit", which is the membrane computing unit. It is not easy to comment which unit is most promising in the future, but studies on all these units will certainly promote DNA manipulation technologies and thus development of novel nano-scale DNA computing devices.

Keywords: Nano-scale DNA Computing Unit.

DNA COMPUTING STUDY TODAY

Since Adleman's pioneering work [1] in 1994, DNA computing study has enjoyed her 10th birth-year. Scientists around the world witnessed the whole process DNA computing study experienced. Right in the beginning, DNA computing attracted a lot of attentions from scientists in related fields, governmental organizations and mass media. After that people started to use direct or indirect grants for DNA computer study. Every year there is an international meeting (DNA10 in 2004) on DNA-based computers. From 1994 to 2001, there are a dozen of papers published on Science, Nature or other top journals, demonstrating how DNA molecules can tackle NP problems that are believed to be difficult to solve in conventional electronic computers. In 2001, Shapiro's group published a paper [2] showing that DNA molecules can work as Turing-like computing machines. The machine's size could be as small as 10 nm long and 3 nm wide, absolutely the smallest molecular computing device in the world so far.

In the past three to five years, people began to realize that DNA computing is unable to quickly fulfill its tasks as originally expected. At current DNA manipulation technology levels, DNA computing provides no advantage over electronic computers, for example, when encoding the computing task with DNA molecule in Adleman's HPP problem, if the n is equal to 100, the amount of DNA required would be larger than the weight of the earth. There is not enough room for improvement on algorithm to make

the number of DNA molecules practically small. At this stage, some people began to worry about the directions of DNA computing study. However, in other sub-fields of DNA computing, great progress has been made [3-6, 13-18]. As stated in DNA9 (The Ninth International Meeting on DNA-based Computing) by the meeting organizers, "There are currently several research disciplines driving towards the creation and use of DNA nanostructures for both biological and non-biological applications. These converging areas are: the miniaturization of biosensors and biochips into the nanometer scale regime; the fabrication of nano-scale objects that can be placed in intracellular locations for monitoring and modifying cell function; the replacement of silicon devices with nano-scale molecular-based computational systems, and the application of biopolymers in the formation of novel nano-structured materials with unique optical and selective transport properties."

Two Types of Basic Molecular Manipulations for DNA Computing

Computing can be processed in unlimited ways. For DNA-based or DNA-related computing, there are certainly a number of ways to perform computation. But in the context of molecular manipulation on DNA molecule, there are two main types: simple hybridization and enzymatic treatment. Hybridization is the basic form of DNA activity, while enzymatic treatment provides ways for transaction among different DNA forms. If we investigate the DNA states in all DNA computing approaches, like assembly-based DNA computing and different DNA automata, it is clear that hybridization/dehybridization is everywhere, no matter whether DNA fragments stay in single-stranded (ssDNA) or double-stranded (dsDNA) forms. Enzymatic treatment may touch any sort of enzymes, including polymerase, highly

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diverse restriction enzymes, ligases, exonucleases, even ribozymes. But in the future, many other molecular manipulations will likely come around DNA molecules, for example, DNA may be modified/de-modified with some kind of small molecules or metal atoms, proteins may bind specific DNA motifs in assembled DNA matrix, etc.

Primary DNA Computing Units

DNA computing research has passed ten years, but apparently it is still in its preliminary stage. Lots of fundamental questions need answers. For example, what is the general feasibility for DNA molecule to perform complicated computing tasks? What is the primary role for DNA computing to potentially play in the orchestra composed of electronic computing, quantum computing, optical computing and biological computing? What is the best role for DNA to play in nano-technology development? In order to answer many such questions, first we have to get clear what the primary DNA computing units are. These basic units may highlight the near future of DNA computing at different angles. In a not strictly exclusive way, there are five primary DNA computing units: Adleman unit, Rothemund-Shapiro unit, Tiling unit, Ribozyme unit, and Paun unit. Maybe other equally or more important units will emerge quickly. From the function and modular organization of a molecular computer [47], a primary computing unit should provide any forms of the following components: input, computation module, and output; most DNA computing units have not shown clear attempts to develop memory and other functional modules.

Adleman Unit

Adleman uses short oligonucleotides to encode mathematical problems. The computing process is mainly performed in the form of hybridization. Ligation and other molecular manipulation steps are used for output abstraction. The correct answer is hidden in a vast amount of different hybridization results. Theoretically, the lengths of DNA oligonucleotides are not strictly fixed, for example, 20~30nt (in the range of 15 nanometer) should all be fine, except that each oligonucleotide should not self-hybridize or form duplex in a high tendency. Specific mathematical problems will pose specific requirements on DNA sequences. Most DNA sequences can be designed quantitatively using some softwares. It is not easy to use Adleman unit in encoding specific computational problems. Normally the algorithms, or recombinant DNA manipulations, could be quite complex, although each step of such manipulations is relatively simple. When encoding simple problems, the calculation could be single-step hybridization, like a simplified self-assembly process; but when encoding in a relatively complex way, many enzymatic DNA treatment steps will be involved. Though Adleman's DNA computing scheme may be still difficult to solve NP problems in a practical way, his experiment is the first demonstration that bio-computing is possible, highlighting a molecular computing path for so many people to follow. Some similar or better algorithms were devised later on. Today the DNA computing domain has visibly shifted towards nano-technology, but many researchers are still working hard on how to get such kinds

of molecular computing into real life applications. Hopefully some new technology may help to provide a solution.

Rothemund-Shapiro Unit

Benenson and co-workers published another pioneering study [2] in which an autonomous programmable DNA automaton is created. They use a double-stranded DNA as input, endonuclease and DNA ligase as main hardware, transition molecules as software, thus creating a two-state molecular finite automaton with a two-symbol input, eight transition rules and 765 syntactically distinct programs. Before Benenson's work, Rothemund proposed similar ideas [46]. This is a Turing machine-like DNA computing unit, and we call it "Rothemund-Shapiro unit". In their computing system, the volume of a drop of water has billions of molecular computers; each such molecular computer could be treated as one "Rothemund-Shapiro unit". It seems they have not cared much on whether this unit could have power to develop universal DNA computing devices, but this is really a very special automaton. As stated by Shapiro, their DNA computing system would be directly applied in analyzing gene expression patterns that are disease-specific, and is likely to develop other biomedical applications. In the beginning, Rothemund-Shapiro unit consists of input DNA, enzymes (restriction enzymes and ligases), transition molecules, reporter molecules and buffer system, but now the unit has evolved into a ligase-free system. An enzyme-free Rothemund-Shapiro unit may be developed in the near future [31].

Tiling Unit

Seeman's group has been doing self-assembly study on DNA for about twenty years [19], but DNA assembly's computing capability emerged only several years ago. Some scientists made their contributions to DNA assembly as a computing regime. Together with Reif and Winfree's work [20-25, 48], DNA assembly has become one of the most important directions for DNA computing. Because of its universal computing capability, DNA assembly provides another avenue for universal DNA computer development. DNA computing by self-assembly is basically a tiling process, and the tile types can vary a lot. The tiles can be formed with several (e.g., two, three, four, or five) single-stranded oligos, and each tile can have different sticky DNA ends for a number of combinations with other same or different tiles. The tiling can be designed in a two-dimensional or three-dimensional way, and the scale for tiling should also be able to control. In the near future, much effort will be put on nano-scale DNA computing devices fabricated by DNA assembly. DNA assembly can be completely programmed, though molecular biology experiments are still a bottle-neck for large scale assembly. Using Wolfram's cellular automaton approach, Winfree and Reif *et al.* [48, 49] brought a new landscape for this avenue. We are also trying to use combinatorial cellular automata in designing any tiling shapes. Besides, the natural affinity of DNA to bind with proteins, some types of small molecules, even metal atoms, makes it possible that assembled DNA can work as an inherent or transient matrix for novel computing devices.

Ribozyme Unit

Stojanovic *et al.* [27-30] pioneered in the (deoxy)ribozyme unit research area. (Deoxy)ribozyme is a piece of nucleic acid fragment with unique three-dimensional structure that has an enzymatic ability to cut specific complementary oligos as substrate. If another oligo binds with the (deoxy)ribozyme and prevents it from forming enzymatic conformation, the (deoxy)ribozyme stays in an inactive form. They found ribozymes can be easily manipulated as logical gates, thus can mimic conventional electronic computing devices and theoretically develop universal DNA computing system. Ribozymes can work as automaton, though for the time being ribozyme or deoxyribozyme automaton is still in its infancy. Ribozyme-based DNA computing unit may be extremely useful in designing logical computing devices in the future, for example, single-molecule logical gate. Besides the above, Bio-X DNA Computer Consortium (BDCC) in China is also trying to employ ribozyme-based DNA computing as a potential vehicle for *in vivo* DNA computing [31, 32]. Instead of making (deoxy)ribozymes into logical gates or automata, we are also using them to build simple automata that may be easier for *in vivo* usage.

When Benenson and co-workers published their autonomous DNA automaton system, people started to think about different modification forms of that system, including ligase-free DNA automaton, even enzyme-free system for DNA computing. In Benenson's system, FokI and ligase work as hardware, and DNA ligase can be omitted without compromising any computing performance, even better [44]; since ribozyme has both digestion and ligation activity on DNA molecule under appropriate conditions, it is natural to postulate a DNA computing system that is enzyme-free (actually protein enzyme free).

Paun Unit

Membrane computing [33 and therein, 45] can be regarded as a unique biological computing system. A cell is the basic unit for membrane computing system (P systems), here we call it "Paun Unit". This unit is not a DNA computing unit; however, membrane system provides another sort of self-assembly tile, and each Paun unit can hold DNA in it and may be able to translocate DNA molecules between each unit in the future, so we would like to treat Paun unit as a special DNA computing unit. It might be also called cell computing, a natural distributed architecture of a computing unit where any other DNA computing unit processes might be embedded. Since no kind of artificial P systems computing has been tested in the form of biochemical or physical biochemical experiments, it is likely that the natural cells may be firstly tried by cell molecular biology manipulations. So some *in vivo* DNA computing technology may be needed to develop beforehand. We believe that membrane computing will eventually merge, at least partially, with assembly-based DNA computing. At this moment, Paun unit provides a specific approach for tackling biological computing, even for lots of bioinformatics studies. Besides, Paun unit may be a tool to study the biological assembly patterns through which cells interact with each other to form multi-cell organisms.

Refinement of DNA Computing Units

It may be too early to talk about refinement of any DNA computing unit. One of the reasons is that we are not sure which kind(s) of unit will eventually be the final form to perform useful computing. We can assume that each type of unit is equally important, and all need refinement in stability, fidelity, energy efficiency and durability. The general trend is likely to refine the units into single-molecule [35] or quasi single-molecule computing devices. When nano-technology is deeply employed in molecular computing, new algorithms may reshape the DNA computing completely.

Integration of DNA Computing Units

Integration of DNA computing units is essential to create computing modules. There are two types of integration, one is integration of homogeneous units, and another is integration of heterogeneous units. For example, Tiling units can interact with each other under cellular automaton rules to form specific graphs, ribozyme units can link each other to form combinatorial logical gates for solving Boolean problems, but integration of heterogeneous units is still on its way. We haven't integrated different DNA computing automata that can be designed with all above DNA computing units.

Integration can be undertaken in different ways. There are quite a few highly parallel DNA computing platforms in the context of molecular biology experiments, for example, Illuminus Company has a large-scale Single Nucleotide Polymorphism (SNP) detection platform that integrates microarray, optical-fiber transmission of fluorescent signals, 96-well microplate, and highly parallel multi-target polymerase chain reaction (PCR) technologies. Such kind of platform is a good start for DNA computer demonstration if DNA computing is performed on microarray chips. We are trying to utilize such a platform for experimental DNA arithmetic system [31], though such platform still needs to be improved for nano-scale DNA manipulations. There are some reports on surface computing to solve specific mathematical problems [34], and we are also developing DNA computing microarrays to form several low-profile computing modules [31]. Besides, electrochemical reaction platforms are also considered for DNA computing (see below).

More integration can be considered. DNA computing has two terms, one is "DNA", and the other is "computing", so it is a typical integration between life sciences and computing sciences, not merely "computing by DNA". The basic unit of life is a cell, and a cell is a natural factory driven by nano-technology where DNA, RNA, proteins and many other kinds of small molecules integrate together.

Nano-Scale Biosensors Via Electronic Detection Potentially for Connecting DNA Computer Units

DNA computers have undoubtedly received great interest in both academic society and mass media, however, we should bear in mind that current DNA computers are still far too preliminary. Since DNA computers are largely based on recognition of complementary DNA sequences, detection of DNA molecules at extremely low concentration will be

likely more and more important to the construction of practical DNA computers. We note that, parallel to the development of DNA computers, DNA biosensors (genosensors) have also become a hot spot and made major progress in recent years. At present most DNA computing reactions, no matter whether the test-tube type or the surface-based, employ fluorescent DNA detections. However, progress in electronic (electrochemical) DNA sensors has made it possible to bridge the barrier between hybridization based DNA computers and modern silicon based electronic computers. That is, electronic detection transduces DNA hybridization events to electronic signals, which might be directly used as an output for other electronic units. Equally important, electronic detection makes it possible that we may be able to detect DNA hybridization reactions at a very sensitive level. Potentially, modern electrochemical techniques, e.g. scanning electrochemical microscopy (SECM) have even been able to detect even a single DNA hybridization event. When such sensitive levels are approached, the DNA computing algorithms will be virtually reshaped, and it is very likely that many difficulties we are faced up with now in DNA computing studies will thus be alleviated, even eliminated. For example, solving mathematical problems (which are difficult to solve by conventional electronic computer) by DNA computing needs a lot of DNA at current technology levels. But when DNA computing reactions are made possible at single- or quasi-single molecule levels, situations may be totally changed. Apparently, the above purposes bring heavy requirements on many aspects of DNA detection technologies. In view of this, we hereby briefly review the state-of-the-art electronic DNA biosensing technologies in order to facilitate their use in designing new-generation nano-scale DNA computing devices.

Early efforts in designing electrochemical DNA sensors pursued the direct reduction or oxidation of DNA bases, among which guanine (G) proved to be most oxidizable species. Nevertheless, in most cases, direct oxidation of G does not provide enough sensitivity to probe DNA hybridization. In an attempt to overcome this problem, Thorp *et al.* introduced polypyridyl complex of Ru(II), Ru(bpy)₃²⁺, which acts as an electron shuttle between G and the electrode, thus leading to a signal amplification. With this method they have been able to detect as low as 550 attomoles PCR products [12]. However, we note that oxidation of G leads to the destruction of DNA strands, thus this method may not be suitable for DNA computers. A more generally employed approach is to couple DNA hybridization with the introduction of an electroactive species (e.g. ferrocene). In this case, hybridization of DNA target brings the electroactive label to the proximity of the electrode, and thus leads to electrochemical current signals. Electroactive species could be introduced through conjugation with either an DNA double helix intercalator [11] or a DNA signaling probe [10]. In the former case, the intercalator distinguishes between the hybridized dsDNA and unhybridized ssDNA, therefore the electroactive species is only present at the electrode surface when hybridization occurs. In the latter case, target DNA sequence acts as a linker between the probe DNA and signaling DNA *via* a two-step hybridization; non-cognate DNA cannot bring the

two together, thus effectively eliminates signals in the absence of DNA targets. Signal amplification processes could be introduced to increase the sensitivity. For example, Willner and coworkers employed enzymes as the label. A single enzyme may turn over thousands of electroactive substrate molecules that translate to a significant increase in electronic signal [9]. In an alternative approach, Wang *et al.* proposed that quantum dots might act as electrochemical labels. Note that a single quantum dot contains thousands of electroactive molecules, which also offers great signal amplification [8]. More recently, Fan *et al.* developed a sensitive DNA sensor by employing a labeled, surface-confined DNA stem-loop structure. Hybridization alters the structure and leads to the electron transfer distance change between the label and the electrode, thus producing electronic signal readout [7].

Given all these advances, sensitivity of electrochemical DNA detection remains to be improved in order to meet the ultimate goal of single-molecular detection in DNA computing (e.g., with the development of SECM). In spite of this, we expect that combination of DNA array and electronic DNA detection technologies will eventually lead to a real, "computer-like", DNA computer. At the first stage of such studies, electronic detection can be incorporated into DNA computing algorithms and the sensitivity should be able to be improved steadily.

SUMMARY

DNA computing is a promising molecular computing area, and lots of progresses are being made rapidly worldwide [36-43]. As one kind of molecular computing, most computing elements involved are from nano- to micrometer scales. We examined the main DNA computing units developed in the past ten years and arrived at a happy conclusion that all these units seem to have potential to reshape DNA computing in the near future. We also reviewed the progress in DNA biosensors (genosensors) that may link all these computing units. It is a little bit too early to discuss on refinement and integration of these units; however, fine units with smart integration are prerequisite for creating DNA computing power and novel computing functions. We believe that the mentioned DNA computing units in this paper provide a good start to develop nano-scale computing devices where part of our great expectation on DNA computing is put on.

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