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Review

DNA Computing Revolutionizes Medical World

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Abstract

When we speak about DNA computers, most of us are thinking of our desktop personal computers or our handy laptop. DNA computers are an entirely different concept, although they still have applications that could support our daily computing needs. DNA computers can be tiny enough to work in the human body, where they may perform tasks such as identifying diseased cells. Biomolecular (DNA) computing is a novel computation paradigm which offers a completely new way of looking at and performing computations. The main idea is that data can be encoded in DNA strands, while molecular biology laboratory techniques (called bio-operations) that involve manipulation of DNA strands in test tubes can be used to simulate arithmetical and logical operations. These practical incentives and the fascination of being able to perform computations with biological means have inspired many researchers to pursue the challenging topic of DNA computing. Indeed DNA computing sheds new light onto the very nature of computation, and opens vistas for computability models totally different from the classical ones. The objectives of this paper are firstly to introduce DNA computing, and secondly to demonstrate how DNA computing can be applied to solve large, complex combinatorial problems, in various fields of study especially, Medicine.

Keywords: Applications, DNA computing, Interactions to Medicine

INTRODUCTION

”It is not the world that attracts attention now and that a usual physical law sways in the minute (nano) world but the world of a quantum-mechanics-law.” This is described in famous ‘uncertainty principle’ which Heisenberg in Germany discovered in 1927. Today it is hard to imagine a world without implanted computers to monitor our health and diagnose our illnesses. Union of DNA and informatics, involves the technology that uses computers for storage, retrieval, manipulation and distribution of information related to biological macromolecules, such as DNA, RNA and proteins. DNA consists of four bases of molecule structure, named adenine (A), guanine (G), cytosine (C) and thymine (T). Moreover, constraints apply to connections between these bases: more specifically, A can connect only with T, and G only with C – this connecting rule is referred to as ‘Watson-Crick complementarily’. This property is essential to realize the separate operation (discussed later). In other words, it is possible to separate a partial string of characters ‘ad’ so that a DNA sequence complementary to the DNA denoting ‘ad’ is marked, input into a test tube, hybridized to form a double strand helix of DNA, then abstracted. Further, this property enables us to randomly create a set of character strings according to some rule (Adleman, 1994).

Definition

DNA computing is a form of computing which uses DNA, biochemistry and molecular biology, instead of the traditional silicon-based computer technologies. DNA computing, or, more generally, biomolecular computing, is a fast developing interdisciplinary area. Research and development in this area concerns theory, ex-periments, and applications of DNA computing. The term

"molectronics" has sometimes been used, but this term had already been used for an earlier technology, an unsuccessful rival of the first integrated circuits(Lipton, 1995); this term has also been used more generally, for molecular-scale technology (Lin et al., 2004). But what about these fascinating computers have made this all possible?

History

The practical possibility of using molecules of DNA as a medium for computation was first demonstrated by Adleman in 1994 (Ding and Ren, 2000). Adleman's primary intention was to prove the feasibility of biomolecular computation but his work also gave an indication that the emergence of this new computational paradigm could provide an advantage over conventional electronic computing techniques. Specifically, DNA was shown to have massively parallel processing capabilities that might allow a DNA based computer to solve hard computational problems in a reasonable amount of time. His study performed in the field of DNA computing, was the solution of the problem of travelling salesmen composed of 7 cities by Adleman using real DNA molecules (Kim and Lee, 2008). The application was realized by creating solution environment in the biology laboratory and using biochemical reactions. The cities and distances that make up the problem of traveling salesmen were coded using DNA series and all ways that might be solution were created using polymer chain reaction. After Adleman successfully solved a directed Hamiltonian path problem using the tools of biomolecular engineering, others followed, applying similar algorithms to other hard computation problems, as well as devising more efficient computational schemes. In the continuation of this study Lipton solved satisfiability problem included in NP (nonpolynomial) problem class using DNA computing in a similar way (Wang et al., 2005). Lipton demonstrated the application an that DNA computing can be used for the solution of the problems containing logical equations as well. After this study (Zhang et al., 2011) performed the design and optimization of PI (proportional integral) parameters using DNA computing. Ding and Ren used similar DNA computing algorithm with the abovementioned study for setting turbid inspecting parameters (Sridhar and Balasubramaniam, 2011). Kim and Lee applied DNA computing algorithm with a different method for setting the PID parameters (Çigdem and Karaköse, 2011). In the study performed DNA molecules were used in coding and setting the PI parameters. The results of the application through computer simulation indicated that high success was acquired in this field. Wang et al. compared DNA computers and electronic computers and suggested that DNA computers were more advantageous (Li et al., 2011). As a result of the applications given above, DNA computing was developed rapidly and used in many scientific studies (Huang and He, 2011). It has been used frequently, particularly in NP problems, coloring problems of graphics in setting the inspecting parameters, arithmetic operations, signal processing problems, and ciphering the data (Xu et al., 2011). DNA computing algorithm performs computing using the natural characteristics of DNA molecules. Those characteristics include parallel operations, storing high amount of data, providing energy saving, and having significant role in computing. Those characteristics are listed quite effectively in the solution of complex and difficult problems. In order to use the DNA computing more effectively, scientists dealt with the design of total natural DNA computers composed of DNA molecules. DNA logic gates are extremely small and they pick up various fragments of a genome as input before creating a single output from the fragments. Try to imagine a gate joining two DNA inputs to allow their end bits to lock. To fill in any gaps, an enzyme called DNA ligase creates an effective seal, which then results in a new strand. When electrophoresis is used, a scientist can measure the length of this new strand, thus giving an answer to the input strands (Mitra and Das, 2011).

METHODS

There are multiple methods for building a computing device based on DNA, each with its own advantages and disadvantages. Most of these build the basic logic gates (AND, OR, NOT) associated with digital logic from a DNA basis. Some of the different bases include DNAzymes, deoxyoligonucleotides, enzymes, DNA tiling, and polymerase chain reaction.

DNAzymes

Catalytic DNA (deoxyribozyme or DNAzyme) catalyze a reaction when interacting with the appropriate input, such as a matching oligonucleotide. These DNAzymes are used to build logic gates analogous to digital logic in silicon; however, DNAzymes are limited to 1-, 2-, and 3-input gates with no current implementation for evaluating statements in series. The DNAzyme logic gate changes its structure when it binds to a matching oligonucleotide and the fluorogenic substrate it is bonded to is cleaved free. While other materials can be used, most models use a fluorescence-based substrate because it is very easy to detect, even at the single molecule limit (Jiao et al., 2011). The amount of fluorescence can then be measured to tell whether or not a reaction took place. The DNAzyme that changes is then “used,” and cannot initiate any more reactions. Because of this, these reactions take place in a device such as a continuous stirred-tank reactor, where old product is removed and

new molecules added. Two commonly used DNAzymes are named E6 and 8-17. These are popular because they allow cleaving of a substrate in any arbitrary location (Yin et al., 2010). Stojanovic and MacDonald have used the E6 DNAzymes to build the MAYA I (Xu et al., 2010) and MAYA II (Huang et al., 2010) machines, respectively; Stojanovic has also demonstrated logic gates using the 8-17 DNAzyme (Yin et al., 2010). While these DNAzymes have been demonstrated to be useful for constructing logic gates, they are limited by the need for a metal cofactor to function, such as Zn2+ or Mn2+, and thus are not useful in vivo (Lin et al., 2004). A design called a stem loop, consisting of a single strand of DNA which has a loop at an end, are a dynamic structure that opens and closes when a piece of DNA bonds to the loop part. This effect has been exploited to create several logic gates. These logic gates have been used to create the computers MAYA I and MAYA II which can play tic-tac-toe to some extent (Lin et al., 2004).

Enzymes

Enzyme based DNA computers are usually of the form of a simple Turing machine; there is analogous hardware, in the form of an enzyme, and software, in the form of DNA (Henkel, 2005). Benenson, Shapiro and colleagues have demonstrated a DNA computer using the FokI enzyme (Qiu, 2003) and expanded on their work by going on to show automata that diagnose and react to prostate cancer: under expression of the genes PPAP2B and GSTP1 and an over expression of PIM1 and HPN. Their automata evaluated the expression of each gene, one gene at a time, and on positive diagnosis then released a single strand DNA molecule (ssDNA) that is an antisense for MDM2. MDM2 is a repressor of protein 53, which itself is a tumor suppressor (Rahman et al., 2012). On negative diagnosis it was decided to release a suppressor of the positive diagnosis drug instead of doing nothing. A limitation of this implementation is that two separate automata are required, one to administer each drug. The entire process of evaluation until drug release took around an hour to complete. This method also requires transition molecules as well as the FokI enzyme to be present. The requirement for the FokI enzyme limits application in vivo, at least for use in “cells of higher organisms” (Chaves-González et al., 2012). It should also be pointed out that the 'software' molecules can be reused in this case.

Toehold exchange

DNA computers have also been constructed using the concept of toehold exchange. In this system, an input DNA strand binds to a sticky end, or toehold, on another DNA molecule, which allows it to displace another strand segment from the molecule. This allows the creation of modular logic components such as AND, OR, and NOT gates and signal amplifiers, which can be linked into arbitrarily large computers. This class of DNA computers does not require enzymes or any chemical capability of the DNA (Zhang and Liu, 2009).

Algorithmic self-assembly

DNA arrays that display a representation of the Sierpinski gasket on their surfaces. Click the image for further details. Image from Rothemund et al., 2004. DNA nanotechnology has been applied to the related field of DNA computing. DNA tiles can be designed to contain multiple sticky ends with sequences chosen so that they act as Wang tiles. A DX array has been demonstrated whose assembly encodes an XOR operation; this allows the DNA array to implement a cellular automaton which generates a fractal called the Sierpinski gasket. This shows that computation can be incorporated into the assembly of DNA arrays, increasing its scope beyond simple periodic arrays (Rothemund et al., 2004).

Procedures

The main steps in DNA computing are: 1. separate (T,s) this operation separates a given set T into the set +(T,s) of characters, including character string s and the set –(T,s) of character strings that do not contain character string s. This operation corresponds to abstract experimentation on DNA molecules in a test tube. 2. Mix this operation mixes sets T1 and T2 into the union set T1 ∪ T2. This operation corresponds to mixing test tubes T1 and T2. 3. Detect (T) this operation returns ‘YES’ if the test tube T is not empty, and ‘NO’ if it is empty. The operation corresponds to an experimental procedure that detects the existence of DNA molecules by the electrophoretical fluorescent method. 4. Amplify (T) this operation corresponds to creating multiple sets T1 and T2 with the same contents as the given set T. This corresponds to an experimental treatment that amplifies the amount of molecules using polymerase chain reaction (PCR).

Benefits, Drawbacks and Challenges

While the practical benefits of DNA based computational schemes are still questionable and the vast majority of work to date has been theoretical, there have been many allusions to potential uses of this emerging computational paradigm. One of the most important reasons DNA computers as the most successful internal computers are the advanced capabilities of DNA. DNA can replicate extremely quickly and efficiently, giving biocomputers

great capacities for transferring large amounts of data and also an immense memory capacity, roughly 100 times larger than the computers of two decades ago. Moreover, these vast repositories of information can fit into a very small volume, where 1 spoonful can hold 15 thousand trillion computers. DNA computers have a great ability to process many calculations in parallel, nearly 10^9 calculations per mL of DNA per second, in a highly energy efficient way, more than a million times more efficient than the computers of yesteryear (Goho, 2006). Another exciting benefit of DNA computing involves DNA microchips. Scientists suspect that if the newer, developing DNA microchips are combined with logic gates, there will be even more beneficial applications. These chips could mean that DNA computing is more rapid because it would allow for a quicker analysis of the DNA strands that hold useful answers. Instead of using electrophoresis, scientists would be able to mix in labelled strands to the chip, which would meld to strands of DNA and allow for researchers to pick answers up via the labels (Ian, 2013). Some other usefulness of developing techniques of DNA computing and ultimately developing working DNA computers can be described as falling into one of the following three general categories:

1. Applications making use of "classic" DNA computing schemes where the use of massive parallelism holds an advantage over traditional computing schemes, including potential polynomial time solutions to hard computational problems;
2. Applications making use of the "natural" capabilities of DNA, including those that make use of informational storage abilities and those that interact with existing and emerging biotechnology;
3. Contributions to fundamental research within both computer science and the physical sciences, especially concerning exploring the limitations of computability and to understanding and manipulating biomolecular chemistry.

By viewing the field of DNA computation as a number of interrelated and exciting new paradigms, the overall qualities and potential for this area of research can be seen. The primary advantage offered by most proposed models of DNA based computation is the ability to handle millions of operations in parallel. There are also many problems with DNA computing including the following:

• 'Preparation' and 'extraction' take too much time, and errors occur in copying DNA.
• Each stage of parallel operations requires time measured in hours or days, with extensive human or mechanical intervention between steps;
• Generating solution sets, even for some relatively simple problems, may require impractically large amounts of memory; and
• Many empirical uncertainties, including those involving: actual error rates, the generation of optimal encoding techniques, and the ability to perform necessary bio-operations conveniently in vitro or in vivo.
• One problem related to the development and use of DNA computing is that researchers have struggled for many years with the challenge of making a DNA computer that is as effective as a silicon-based system. The challenge relates to the nano-sized particles in DNA. Scientists hope to use DNA for providing the same success at solving problems as the silicon-based systems (Adleman, 1996).

DISCUSSION

While the development of DNA computational methods may have many directly applicable applications, the biggest contribution of research in this area may be much more fundamental and will likely fuel many indirect benefits. A particular area within the natural and applied sciences that may benefit from advances in DNA computation is Medicine. In a study done by Maojo. V et.al (2010), on Nanoinformatics and DNA-based computing, the results showed that Nanoinformatics and DNA-based computing are together likely to completely change the way we model and process information in biomedicine and impact the emerging field of nanomedicine most strongly (Martin-Sanchez et al., 2010). The findings of W. Florian Fricke et. Al., (2009) on The Role of Genomics in the Identification, Prediction, and Prevention of Biological Threats (2009) indicated that a DNA computing is a keystone for developing better identification technologies, diagnostic tools, and vaccines and improving our understanding of pathogen virulence and evolution. Enabling technologies and bioinformatics tools have shifted genomics from a separate research discipline to a tool so powerful that it can provide novel insights that were not imaginable a few years ago, including for example redefining the notion of strains or cultures in the context of biopreparedness or microbial forensics (Florian et al., 2009). Atul Kumar Pandey et.al., (2013) studied on Computational Features Prediction Model for Heart Disease Diagnosis .They found that Using medical profiles such as age, sex, blood pressure and blood sugar can predict the likelihood of patients getting a heart disease. The new hybrid feature selection namely CFS and DT followed by Part rule was proposed. The proposed algorithm gives better accuracy for Random Tree and Random Forest classifier. They concluded that CFS, Decision Tree and part rule based feature selector are best suitable for heart disease data prediction (Atul and Jaiswal, 2013). In a study done by Yu Zhang, Hao Yu Jianhua Qin, and Bingcheng Lin, on A microfluidic DNA computing processor for gene expression analysis and gene drug synthesis, the results show that microfluidic DNA computing processor performing Boolean calculations was constructed for gene expression analysis and gene drug synthesis. Two breast cancer-related genes (oncogene C-erbB-2 and antioncogene nm23) were used as input molecules. Their

expressions were identified in two parallel microfluidic channels simultaneously by interacting with the computing related DNA strands. Test for over-expression of C-erbB-2, the multistep operations involved hybridization, displacement, and transfer. Test for under-expression of nm23, the multistep operations involved displacement, rinse, and transfer. When the expressions of both genes fit in with the criteria for breast cancer diagnosis, positive diagnosis would be confirmed and a complete suicide gene could be synthesized by DNA ligation as an output molecule. By combining the specific design of the computing related molecules and the integrated functions of the microfluidics, the microfluidic DNA computing processor is able to analyze the multiple gene expressions simultaneously and realize the corresponding gene drug synthesis with simplicity and fast speed, which demonstrates the potential of this platform for DNA computing in biomedical applications (Yu et al., 2009). Accurately, quickly, and cheaply sequencing an individual's DNA is one way that medicine can personalize care for each patient. Professor Jean-Pierre Leburton, along with several collaborators (2013) at the Beckman Institute, based on sophisticated computational modelling, ECE, believes that the use of semiconductor nanotechnology has the potential to revolutionize individual health care by providing DNA sequencing on a scale that has not been reached previously. After 10 years of research, Leburton has found a way to exploit the electrical properties of graphene—a mono-atomic layer material obtained from carbon graphite—to create a solid-state transistor with a nanopore that has the ability to sequence the human genome electronically, which opens the door to high performance sequencing. Current methods of sequencing DNA use various kinds of biochemical processes that are expensive and tedious. In Leburton's recently published paper in Proceedings of the National Academy of Sciences (PNAS), entitled "Graphene quantum point contact transistor for DNA sensing," he and collaborators Klaus Schulten, Anuj Girdhar, and Chaitanya Sathe describe a novel methodology that exploits the high electrical conductivity of graphene in a very tiny transistor that allows an electrically charged DNA strand to push through a nanopore within the solid-state device. As the molecule threads through the nanopore, each nucleotide passing in front of the graphene's mono-layer scatters the current in graphene differently, which identifies the base sequence? "There are two main reasons why this technology is revolutionary," Leburton said. "It is a new paradigm for sequencing DNA, which uses an electrical constriction around a nanopore in graphene to sense and detect passing DNA nucleotides with the highest possible resolution. "Secondly, the graphene layer is embedded into a transistor structure containing an electrical gate that modulates the electrical sensitivity of the graphene layer, and corrects it from the detrimental influences of the edge roughness of the graphene constriction as well as from neighbouring charges in the insulating layers of the solid-state membrane. This is a completely new way of approaching DNA sequencing, and one that can be done quickly, reliably, and cheaply, once the technology could be developed into mass production."Rapidly sequencing the human genome in a cost-effective manner will revolutionize modern medicine (By media Center August Novel DNA, 2013). Bonnet J1, Subsoontorn P, Endy D. (2012) researched on Rewritable digital data storage in live cells. They demonstrated a rewriteable recombinase addressable data (RAD) module that reliably stores digital information within a chromosome. RAD modules use serine integrase and excisionase functions adapted from bacteriophage to invert and restore specific DNA sequences. The core RAD memory element is capable of passive information storage in the absence of heterologous gene expression for over 100 cell divisions and can be switched repeatedly without performance degradation, as is required to support combinatorial data storage. They also showed how programmed stochasticity in RAD system performance arising from bidirectional recombination can be achieved and tuned by varying the synthesis and degradation rates of recombinase proteins. The serine recombinase functions used here do not require cell-specific cofactors and should be useful in extending computing and control methods to the study and engineering of many biological systems (Bonnet et al., 2012). Li Y, Xiao L, Ruan L (2014), studied on Parallel molecular computation of modular-multiplication with two same inputs over finite field GF(2n) using self-assembly of DNA tiles. Tile assembly model is a highly distributed parallel model of DNA computing. Finite field GF(2n) is one of the most commonly used mathematic sets for constructing public-key cryptosystem. It is still an open question that how to implement the basic operations over finite field GF(2n) using DNA tiles. The parallel tile assembly process could be used for computing the modular-square, modular-multiplication with two same inputs, over finite field GF(2n). This system could obtain the final result within less steps than another molecular computing system designed in our previous study, because square and reduction are executed simultaneously and the previous system computes reduction after calculating square (Li et al., 2014). Wang D.et.al(2014) used Molecular Logic Gates on DNA Origami Nanostructures for MicroRNA Diagnostics. They came to this conclusion that molecular computing holds great promise for diagnosis and treatment of diseases at the molecular level; nevertheless, designing molecular logic gates to operate programmably and autonomously for molecular diagnostics still remains challenging. They designed logic gates on DNA Origami for microRNA analysis. As a demonstration, two indicators of heart failure, microRNA-21 and microRNA-195, were selected as the logic inputs. The logic gates contain two main modules: computation module and output module,

performing in a single DNA Origami nanostructure. The computation module recognizes disease indicators, while the output module display different nanoscale symbols, "+" (positive) or "-" (negative), depending on the computing results. They demonstrated that the molecular logic gates worked well with single and two input combinations (Wang et al., 2014). Huang WT.et.al., (2014) applied Fuzzy logic sensing of G-quadruplex DNA and its cleavage reagents based on reduced graphene oxide. By combining the merits of nanotechnology and fuzzy logic theory, they developed a simple, label-free, and general strategy based on an organic dye-graphene hybrid system for fluorescence intelligent sensing of G-quadruplexes (G4) formation, hydroxyl radical (HO·), and Fe2+ in vitro. By exploiting acridine orange (AO) dyes-graphene as a nanofilter and nanoswitch and the ability of graphene to interact with DNA with different structures, our approach can efficiently distinguish, quantitatively detect target analytes. In vitro assays with G4DNA demonstrated increases in fluorescence intensity of the AO-rGO system with a linear range of 16-338nM and a detection limit as low as 2.0nM. The requenched fluorescence of the G4TBA-AO-rGO system has a non-linear response to Fenton reagent. But this requenching reduces the fluorescence intensity in a manner proportional to the logarithm to the base 10 of the concentration of Fenton reagent in the range of 0.1-100μM and 100-2000μM, respectively (Huang et al., 2014). Sidoti F et. al., (2012). Studied on Development of a quantitative real-time nucleic acid sequence-based amplification assay with an internal control using molecular beacon probes for selective and sensitive detection of human rhinovirus serotypes. They developed the first quantitative real-time nucleic acid sequence-based amplification assay with an internal control using molecular beacon probes for selective and sensitive detection of human rhinovirus serotypes. They described a simple method to accurately quantify RNA target by computing the time to positivity (TTP) values for HRV RNA. Quantification capacity was assessed by plotting these TTP values against the starting number of target molecules. By using this simple method, They have significantly increased the diagnostic accuracy, precision, and trueness of real-time NASBA assay (Sidoti et al., 2012).

CONCLUSION

DNA computing that the key advantage is parallelism has the natural capabilities of DNA and large information storage abilities. Experimental results obtained with DNA computation show that proposed approach has effective optimization, high accuracy and high convergence speed .In addition, the proposed approach, is easier, simpler, and faster than conventional computing algorithm. With so many possible advantages over conventional techniques, DNA computing has great potential for practical use. Future work in this field should begin to incorporate cost-benefit analysis so that comparisons can be more appropriately made with existing techniques and so that increased funding can be obtained for this research that has the potential to benefit many circles of science and industry.

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