A Brief Survey of Results from the DNA Computing Field

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Abstract

In this paper we give an overview of the biological foundations, problems, and possible applications associated with the emerging field of DNA computing. We begin by pointing out that the end is in sight for Moore's Law unless classical computers are supplemented or replaced by other types of computing technology. We then summarize the biochemical oddities of DNA that allow for computation using it to be a possibility, and a couple of known methods for using it to simulate Turing Machines. We discuss some problems with this technology that have been found by attempting to put it into practice, such as the chemical errors that are responsible for the mutation and evolution of life. Finally, we conclude that baring any monumental field-changing insights, DNA will not replace classical computers for general purpose computation, but it may prove useful for specific applications in biomedicine or nano-technology.

1 Introduction

For the last several decades the speed and compactness of computing technology has increased exponentially in rough accord with Moore's Law. However, exponential growth cannot continue indefinitely, and in particular the speed of a classical computer with integrated circuitry is bounded by certain physical constants. For example, since the propagation time of electrical signals is fixed at the speed of light, decreasing the cycle time of a processor requires transistors to become smaller and more tightly crammed together. The problem of course is that we cannot imagine transistors that are smaller than a molecule, and molecules are only so small. The width of an atom, which would be the absolute lowest bound on the size of a transistor, is on the order of 0.1 nm, and in the last decade we have developed CPUs with transistors on the order of only 10nm [13].

Since huge improvements in the performance of classical computing systems seems to be close to an end, many researchers are looking into a variety of radically different physical models for computation, such as quantum computing and optical computing. The possibility we investigate here is the still emerging field of DNA computing.

2 Biological Background

The current model of DNA computing was first put forth by Leonard Adleman in an article he published in "Science" in 1994. While researchers such as Charles Bennett and Rolf Landauer had been considering the physical limitations of transistor-based computers and possible alternatives (including DNA) much earlier [3], Adleman was the first to bring more recent biological discoveries together into a working model [2].

Adleman's model was fundamentally based on the properties of DNA polymerase, an enzyme critical in the process of DNA replication. When put in contact with a strand of DNA in solution, DNA polymerase will produce a second strand with a different structure in which each of the bases is replaced by its Watson-Crick complement [15]. When two complementary strands come into contact, they anneal, forming hydrogen bonds at each of the matching pairs [17]. Adleman compared this process to the function of a Turing machine, reading bases from a tape and writing their respective complements into the output [2].

Adleman also saw a computational use for DNA nucleases and ligases, enzymes which cut a strand at a predetermined sequence and covalently bond two strands into a single, longer strand respectively [1].

DNA molecules in a gel solution can be forced to undergo a type of sorting operation, in which longer strands are separated from shorter ones. This is done through gel electrophoresis, a technique in which current is applied to the solution and the negatively charged DNA molecules move toward the electrode. Shorter strands move more quickly than longer strands, and thus sort themselves by size [9].

Adleman then demonstrated the ability to solve combinatorial problems with these principles and techniques, using the Hamiltonian path problem as an example. He first carefully designed the problem, assigning a DNA sequence comprised of two parts to each node in the graph, as well as a sequence for each existing edge made up of the second part of the origin node sequence and the first part of the destination node sequence concatenated together [1].

The next step was simply to synthesize DNA molecules from the edge sequences and the complements of the node sequences. This allowed the edge molecules to join with their assigned connected nodes at the complementary section, and eventually construct longer, more complex strands through repeated bonding. This generated DNA molecules representing all the possible paths through the graph [1].

Using the two short DNA primer strands representing the start and end nodes, Adleman was able to create a controlled polymerase chain reaction which produced copies of strands with correct start and end points exponentially fast, while ignoring the incorrect strands [2].

Through a series of separation procedures, Adleman was able to extract only those strands which passed through each node on the graph, and was able to determine both if a Hamiltonian path existed (if any DNA molecules are remaining) and which is the shortest through the use of gel electrophoresis [1].

This or a similar process can theoretically represent any Turing machine, and solve any Turing-computable problem given enough of the restriction enzymes [16].

3 Example Turing Machine Implementation

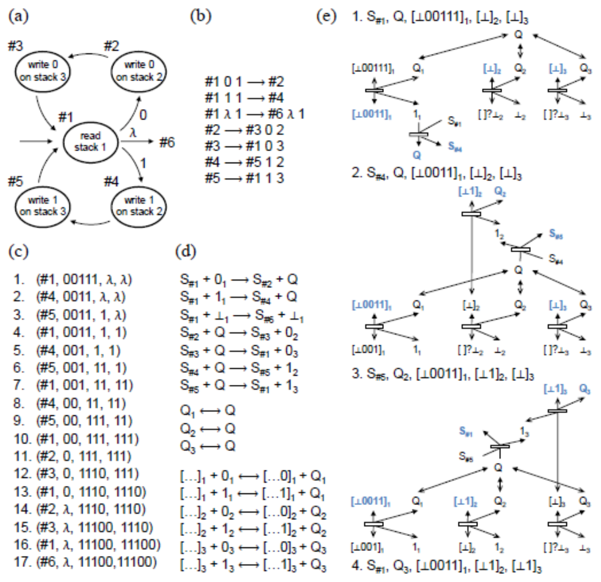
Qian, Soloveichik, and Winfree proposed one way of using DNA to create a Turing-complete computation system [12]. Instead of directly implementing a Turing machine, their proposal involves a multiple stack system that is Turing complete and as efficient as multi-tape Turing machines [10]. This decision relates to DNA polymers lending themselves more readily to creating stacks than traditional Turing tapes.

The basic structure consists of one or more stack polymers where each molecule represents a particular letter $x \in \Sigma$. Chemical reaction networks are used as state transitions, adding and removing molecules from the stack. Importantly, this is done in a way that is reversible, which allows a particular addition or removal to be undone without adding to the energy cost [12].

Reactions rely on a DNA fuel species that is specific to a particular DNA molecule. For example, fuel species F_{1X} applies only to attaching molecule X to the stack 1 polymer. Additionally, each time a molecule is added to the stack, it releases a confirmations molecule (Q) that is used later when querying the stack. This Q molecule is also easily changed from a stack specific molecule (Q_1) to a generic form.

The stack consists of a polymer with a fixed end and a growing end. The fixed end is denoted with a special molecule that indicates an empty stack. Molecules are added to the stack when both the correct fuel and molecule are present. It is worth noting that several fuels may be attempted unsuccessfully before the correct match is made. If a fuel (specific to a particular stack) attempts to bond with that stack polymer, it will only succeed if the correct input molecule is present as well. For instance, any fuel F_{1Y} may attempt to bond with stack 1, but will fail if molecule X instead of Y is present. This can result in many fuel attempts before F_{1X} successfully bonds X to the growing end of stack 1.

For an example computation, consider an input polymer (S_1) that is to be copied to two output polymers (S_2 and S_3) using an alphabet of $\{0, 1\}$. The state transitions consist generally of popping S_1 and copying that molecule to S_2 then S_3. Using the Q molecule, the top element of S_1 is removed. This leads to the states where molecules representing that same element are added to S_2 and S_3, creating their own Q confirmation molecules. This process is repeated until S_1 reaches the empty stack molecule. There is an illustration of this process in Fig. 1.



(a)
#3
write 0 on stack 3
#2
write 0 on stack 2
#1
read stack 1
0
λ
#6
1
#5
write 1 on stack 3
#4
write 1 on stack 2
(b)
#1 0 1 → #2
#1 1 1 → #4
#1 λ 1 → #6 λ 1
#2 → #3 0 2
#3 → #1 0 3
#4 → #5 1 2
#5 → #1 1 3
(c)
1. (#1, 00111, λ, λ)
2. (#4, 0011, λ, λ)
3. (#5, 0011, 1, λ)
4. (#1, 0011, 1, 1)
5. (#4, 001, 1, 1)
6. (#5, 001, 11, 1)
7. (#1, 001, 11, 11)
8. (#4, 00, 11, 11)
9. (#5, 00, 111, 11)
10. (#1, 00, 111, 111)
11. (#2, 0, 111, 111)
12. (#3, 0, 1110, 111)
13. (#1, 0, 1110, 1110)
14. (#2, λ, 1110, 1110)
15. (#3, λ, 11100, 1110)
16. (#1, λ, 11100, 11100)
17. (#6, λ, 11100,11100)
(d)
$S_{\#1} + 0_1 \longrightarrow S_{\#2} + Q$
$S_{\#1} + 1_1 \longrightarrow S_{\#4} + Q$
$S_{\#1} + \perp_1 \longrightarrow S_{\#6} + \perp_1$
$S_{\#2} + Q \longrightarrow S_{\#3} + 0_2$
$S_{\#3} + Q \longrightarrow S_{\#1} + 0_3$
$S_{\#4} + Q \longrightarrow S_{\#5} + 1_2$
$S_{\#5} + Q \longrightarrow S_{\#1} + 1_3$
$Q_1 \longleftrightarrow Q$
$Q_2 \longleftrightarrow Q$
$Q_3 \longleftrightarrow Q$
$[\ldots]_1 + 0_1 \longleftrightarrow [\ldots 0]_1 + Q_1$
$[\ldots]_1 + 1_1 \longleftrightarrow [\ldots 1]_1 + Q_1$
$[\ldots]_2 + 0_2 \longleftrightarrow [\ldots 0]_2 + Q_2$
$[\ldots]_2 + 1_2 \longleftrightarrow [\ldots 1]_2 + Q_2$
$[\ldots]_3 + 0_3 \longleftrightarrow [\ldots 0]_3 + Q_3$
$[\ldots]_3 + 1_3 \longleftrightarrow [\ldots 1]_3 + Q_3$
(e)
1. $S_{\#1}$, Q, $[\perp 00111]_1$, $[\perp]_2$, $[\perp]_3$
2. $S_{\#4}$, Q, $[\perp 0011]_1$, $[\perp]_2$, $[\perp]_3$
3. $S_{\#5}$, Q_2, $[\perp 0011]_1$, $[\perp 1]_2$, $[\perp]_3$
4. $S_{\#1}$, Q_3, $[\perp 0011]_1$, $[\perp 1]_2$, $[\perp 1]_3$

Fig. 1 [12]

This is only one example from the overall field and there are drawbacks to this method as well as advantages. The reversible reactions are more efficient than having two irreversible forward/back reactions, which is a considerable advantage. However, the need to have unique free-floating polymers (stacks) in the same solution limits the scope and parallelization of this method. Additionally, some other methods are able to use complete material recycling outside of the computation output, while this approach consumes materials.

4 Errors and Tile Computing

In basic DNA computing there are two varieties of errors, Type I and Type II. Type I errors are false negative errors. At some stage in the filtration process, some matching string was misidentified as not matching and was removed from the sample. This is the worst kind of error because it is impossible to recover that strand again. The other type of error, Type II, occurs when some non-matching strand is mistakenly matched. This simply means that we have carried over some strand when we should not have. This is not as bad as the first because there is a chance the strand will be later filtered out [4].

Many forms of DNA computing require filtering of DNA strands based on their composition. Most operations in DNA computing involve extracting strands that match a particular pattern. However, it may be considered acceptable to miss 5% of the strands matching a pattern. This means that if a particular good strand goes through 100 extraction operations there is only 0.5% chance that it will still remain even though it was what was looked for. This is a significant problem facing DNA computing. One possible solution is to add additional steps to the screening process. Boneh et al. suggest a constant volume process where the strands are doubled every time half of the material is weeded out. This will help ensure that a good strand survives. However it adds significant time to the final detection step because one may need to test many strands to see if they are a solution to the problem [4].

Another solution to help with filtering is the double encoding of data. This essentially gives the filtering process two places to match to every string, increasing the chance that good strings will survive a filtering process. However, this also requires that strands be twice as long so there may only be half as many strands. Depending on the number of extractions and the increased probability of survival by having doubly encoded data, this can help reduce false negatives [4].

Another promising approach to DNA computing is tile self assembly. Winfree has shown that tile self assembly in DNA computing is Turing universal [18]. It may also be more practical than other means of DNA computing because the smallest blocks are self assembled instead of being manipulated in some fashion.

Different kinds of errors are associated with DNA self assembly. There are growth errors, facet errors and nucleation errors. Growth errors happen when a DNA tile sticks someplace where a different tile should be. A facet error occurs when a tile attaches where no tile is supposed to attach and a nucleation error occurs when two free floating tiles attach separate from the seed structure [5] [6].

One proposed solution is to make tiles more unique. So where a tile may have used only two glues previously, we replace those glues with a more unique combination.

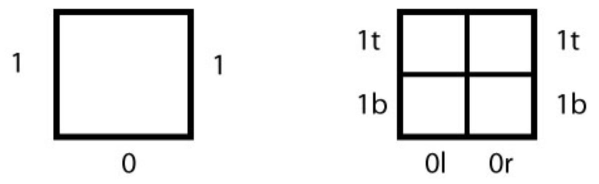


Fig. 2

For example, in Fig. 2, we replaced the 1 glue with a 1t and 1b glue and we replaced the 0 glue with a 0l and a 0r glue. Now, for a tile to incorrectly bind to this tile it will need to bind to two incorrect locations instead of just one [5]. The problem is that this has just doubled the complexity of our tiles and has also increased the space required to solve the problem.

Another solution proposed by Chen and Kao is to optimize the concentration of tiles based on the expected tile assembly. They suggest that the correct ratio of tiles to introduce into the system is the square root of the expected ratio of tiles [6]. So if we are using two tiles X and Y, and we expect to end with a ratio of 25:1 tiles, then the concentration of tiles we use when supplying tiles to assemble should be 5:1. They admit that these concentrations may vary greatly from the ideal concentration of tiles required to assemble the tiles quickly. So we have essentially traded time for errors in this situation. They also fail to address the problem that one needs to know the final ratio in order to determine the correct concentration.

5 Applicability

Although the field is still in its infancy, there have already been impressive breakthroughs demonstrating applications of DNA computers. Two obvious advantages of DNA computing are its massive parallelism and extremely dense storage capacity. While the potential is great, there are major hurdles that need to be overcome if DNA computing will ever become feasible.

Since Adleman's initial experiment, researchers have found new methods and uses for DNA computing. Shapiro and Beninson have produced a DNA automaton which detects cancerous cells and can release a drug when an infected cell is found [14]. Although this experiment was only performed in a test tube, the next goal is living cells. Eric Winfree has developed a method for building "molecular tiles" which could allow for complex self-assembling molecular structures [11]. This would be a major advancement for areas like nanotechnology.

The sheer computational advantage of DNA computing is easy to see; Adleman's TSP experiment ran at the equivalent of 100 Teraflops [11]. This processing speed comes from the parallelism inherent in DNA computing, the speed is proportional to the number of DNA molecules present. As a storage medium, DNA is very dense and capable of storing massive amounts of data. As an example, 1mol of DNA in 1L of water contains 10^{18} strands of DNA and each strand has a length of 40 which can encode 10 bytes [8]. This means 1L of solution has the potential to store around 8.7 exabytes.

Some problems are still not easily solvable even with seemingly boundless computing power and memory. If Adleman's experiment was scaled up to 200 cities, it is estimated the weight of the DNA required to represent all possible routes would be more than the earth [11]. Another problem is obtaining the output of the computations; it took Adleman a week to extract the solution to his TSP experiment [11].

As for the power efficiency of DNA computers, it is leaps ahead of current technology. IBM's recent Blue Gene supercomputer which is considered to be highly efficient runs at 1684 megaFLOPS/watt [7]. It was estimated by Adleman that a DNA based computer could achieve 20 petaFLOPS/watt [8].

6 Conclusion

Remarkable as it may seem, it has been shown that the same sort of processes that operate on the DNA within every living cell can be used to do Turing-complete computation by at least the two methods mentioned above: a stack-based method and a tiling-based method. Additionally, in theory DNA offers massively parallel computation, very efficient power consumption, and high-density memory storage.

Unfortunately, DNA computation is non-deterministic in the most undesirable sense, as the same sort of copying and bonding errors that cause cancer in life can randomly cause any DNA program to give garbage output. Furthermore, it is not known if and how the models of DNA computation that we have right now can scale effectively enough to solve the sort of complex and practical problems that we can currently solve using classical computers.

All in all, there are trade-offs for both DNA computers and current silicon-based systems. As a general computing platform, the consensus is that DNA computers will never directly replace silicon-based systems [11]. Amos suggests we shouldn't be looking at the two as competitors but we should be "looking outside the box for a niche for other application" [11]. Because DNA computers speak the language of living cells, they can accomplish tasks that silicon systems will never be able to, particularly for applications in molecular robotics, cancer diagnosis, and nano-technology. It is envisaged that DNA computers will act more as a complement, rather than a replacement, to classical computing [8].

If nothing else, even the fact that the properties of DNA can in theory be used to make something as powerful as a classical computer is interesting, and adds to the knowledge-base of theoretical computer science. Furthermore, we may eventually develop or discover other systems in nature that have properties similar to DNA, but happen to be more amenable to general purpose computation, for which we can put the theory into practice.

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