

# DNA computing: the arrival of biological mathematics

Lila Kari<sup>1</sup>

*“Come forth into the light of things  
Let nature be your teacher.” [47]*

## 1 Biological mathematics: the tables turned

The field usually referred to as *mathematical biology* is a highly interdisciplinary area that lies at the intersection of mathematics and biology. Classical illustrations include the development of stochastic processes and statistical methods to solve problems in genetics and epidemiology. As the name used to describe work in this field indicates, with “biology” the noun, and “mathematical” the modifying adjective, the relationship between mathematics and biology has so far been one-way. Typically, mathematical results have emerged from or have been used to solve biological problems (see [24] for a comprehensive survey). In contrast, Leonard Adleman, [1], succeeded in solving an instance of the directed Hamiltonian path problem solely by manipulating DNA strings. This marks the first instance of the connection being reversed: a mathematical problem is the end toward which the tools of biology are used. To be semantically correct, instead of categorizing the research in DNA computing as belonging to mathematical biology, we should be employing the mirror-image term *biological mathematics* for the field born in November 1994.

Despite the complexity of the technology involved, the idea behind biological mathematics is the simple observation that the following two processes, one biological and one mathematical, are analogous:

(a) the very complex structure of a living being is the result of applying simple operations (copying, splicing, etc.) to initial information encoded in a DNA sequence,

(b) the result  $f(w)$  of applying a computable function to an argument  $w$  can be obtained by applying a combination of basic simple functions to  $w$  (see Section ?? or [42] for details).

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<sup>1</sup>Department of Mathematics, University of Western Ontario, London, Ontario, N6A 5B7 Canada, email:lkari@julian.uwo.ca

If noticing this analogy were the only ingredient necessary to cook a computing DNA soup, we would have been playing computer games on our DNA laptops a long time ago! It took in fact the ripening of several factors and a renaissance mind like Adleman's, a mathematician knowledgeable in biology, to bring together these apparently independent phenomena. Adleman realized that not only are the two processes similar but, thanks to the advances in molecular biology technology, one can use the biological to simulate the mathematical. More precisely, DNA strings can be used to encode information while enzymes can be employed to simulate simple computations, in a way described below.

DNA (deoxyribonucleic acid) is found in every living creature as the storage medium for genetic information. It is composed of units called nucleotides, distinguished by the chemical group, or base, attached to them. The four bases are *adenine*, *guanine*, *cytosine* and *thymine*, abbreviated as *A*, *G*, *C*, and *T*. Single nucleotides are linked together end-to-end to form DNA strands. The DNA sequence has a *polarity*: a sequence of DNA is distinct from its reverse. Taken as pairs, the nucleotides *A* and *T* and the nucleotides *C* and *G* are said to be *complementary*. Two complementary single-stranded DNA sequences with opposite polarity will join together to form a double helix in a process called *annealing*. The reverse process – a double helix coming apart to yield its two constituent single strands – is called *melting*.

A single strand of DNA can be likened to a string consisting of a combination of four different symbols, *A*, *G*, *C*, *T*. Mathematically, this means we have at our disposal a 4 letter alphabet  $\Sigma = \{A, G, C, T\}$  to encode information, which is more than enough, considering that an electronic computer needs only two digits, 0 and 1, for the same purpose.

The simple operations that can be performed on DNA sequences are accomplished by a number of commercially available enzymes that execute some basic tasks. One class of enzymes, called *restriction endonucleases*, will recognize a specific short sequence in a strand and then “cut” the strand at that location. Another enzyme, called the *DNA ligase*, will hook together, or “ligate”, the sticky end of a freshly cut DNA strand to another strand. There are many other enzymes that could potentially be useful, but for our models of computation these are sufficient.

The practical possibilities of encoding information in a DNA sequence and of performing simple bio-operations were used in [1] to solve a 7 node instance of the Directed Hamiltonian Path Problem. A directed graph  $G$  with designated vertices  $v_{in}$  and  $v_{out}$  is said to have a Hamiltonian path if and only if there exists a sequence of compatible “one-way” edges  $e_1, e_2, \dots, e_z$  (that is, a path) that begins at  $v_{in}$ , ends at  $v_{out}$  and enters every other vertex exactly once.

The following (nondeterministic) algorithm solves the problem:

- Step 1. Generate random paths through the graph.
- Step 2. Keep only those paths that begin with  $v_{in}$  and end with  $v_{end}$ .
- Step 3. If the graph has  $n$  vertices, then keep only those paths that enter exactly  $n$  vertices.

Step 4. Keep only those paths that enter all of the vertices of the graph at least once.

Step 5. If any paths remain, say “YES”; otherwise say “NO”.

To implement Step 1, each vertex of the graph was encoded into a random 20–nucleotide strand (20–letter sequence) of DNA. Then, for each (oriented) edge of the graph, a DNA sequence was created consisting of the second half of the sequence encoding the source vertex and the first half of the sequence encoding the target vertex. By using complements of the vertices as splints, DNA sequences corresponding to compatible edges were ligated, that is, linked together. Hence, the ligation reaction resulted in the formation of DNA molecules encoding random paths through the graph.

To implement Step 2, the product of Step 1 was amplified by polymerase chain reaction (PCR). Thus, only those molecules encoding paths that begin with  $v_{in}$  and end with  $v_{end}$  were amplified.

For implementing Step 3, a technique called gel–electrophoresis was used, that makes possible the separation of DNA strands by length. (The molecules are placed at the top of a wet gel, to which an electric field is applied, drawing them to the bottom. Larger molecules travel more slowly through the gel. After a period, the molecules spread out into distinct bands according to size.)

Step 4 was accomplished by iteratively using a process called affinity purification. This process permits single strands containing a given subsequence  $v$  (encoding a vertex of the graph) to be filtered out from a heterogeneous pool of other strands. (After synthesizing strands complementary to  $v$  and attaching them to magnetic beads, the heterogeneous solution is passed over the beads. Those strands containing  $v$  anneal to the complementary sequence and are retained. Strands not containing  $v$  pass through without being retained.)

To implement Step 5, the presence of a molecule encoding a Hamiltonian path was checked. (This was done by amplifying the result of Step 4 by polymerase chain reaction and then determining the DNA sequence of the amplified molecules).

A remarkable fact about Adleman’s result is that not only does it give a solution to a mathematical problem, but that the problem solved is a hard computational problem in the sense explained below (see [20], [17]).

Problems can be ranked in difficulty according to how long the best algorithm to solve the problem will take to execute on a single computer. Algorithms whose running time is bounded by a polynomial (respectively exponential) function, in terms of the size of the input describing the problem, are in the “polynomial time” class P (respectively the “exponential time” class EXP). A problem is called *intractable* if it is so hard that no polynomial time algorithm can possibly solve it.

A special class of problems, apparently intractable, including P and included in EXP is the “non–deterministic polynomial time” class, or NP. The following

inclusions between classes of problems hold:

$$P \subseteq NP \subseteq EXP \subseteq \text{Universal}.$$

NP contains the problems for which no polynomial time algorithm solving them is known, but that can be solved in polynomial time by using a non-deterministic computer (a computer that has the ability to pursue an unbounded number of independent computational searches in parallel). The directed Hamiltonian path problem is a special kind of problem in NP known as “NP-complete”. An NP-complete problem has the property that every other problem in NP can be reduced to it in polynomial time. Thus, in a sense, NP-complete problems are the “hardest” problems in NP.

The question of whether or not the NP-complete problems are intractable, mathematically formulated as “Does  $P$  equal  $NP$ ?”, is now considered to be one of the foremost open problems of contemporary mathematics and computer science. Because the directed Hamiltonian path problem has been shown to be NP-complete, it seems likely that no efficient (that is, polynomial time) algorithm exists for solving it with an electronic computer.

Following [1], in [25] a potential DNA experiment was described for finding a solution to another NP-complete problem, the Satisfiability Problem. The Satisfiability Problem consists of a Boolean expression, the question being whether or not there is an assignment of truth values – true or false – to its variables, that makes the value of the whole expression true. Later on, the method from [25] was used in [28], [27] and [26], to show how other NP-complete problems can be solved.

In [7], a “molecular program” was given for breaking the U.S. government’s Data Encryption Standard (DES). DES encrypts 64 bit messages and uses a 56-bit key. Breaking DES means that given one (plain-text, cipher-text) pair, we can find a key which maps the plain-text to the cipher-text. A conventional attack on DES would need to perform an exhaustive search through all of the  $2^{56}$  DES keys, which, at a rate of 100,000 operations per second, would take 10,000 years. In contrast, it was estimated that DES could be broken by using molecular computation in about 4 months of laboratory work.

The problems mentioned above show that molecular computation has the potential to outperform existing computers. One of the reasons is that the operations molecular biology currently provides can be used to organize massively parallel searches. It is estimated that DNA computing could yield tremendous advantages from the point of view of *speed*, *energy efficiency* and *economic information storing*. For example, in Adleman’s model, [2], the number of operations per second could be up to approximately  $1.2 \times 10^{18}$ . This is approximately 1,200,000 times faster than the fastest supercomputer. While existing supercomputers execute  $10^9$  operations per Joule, the energy efficiency of a DNA computer could be  $2 \times 10^{19}$  operations per Joule, that is, a DNA computer could be about  $10^{10}$  times more energy efficient (see [1]). Finally, according

to [1], storing information in molecules of DNA could allow for an information density of approximately 1 bit per cubic nanometer, while existing storage media store information at a density of approximately 1 bit per  $10^{12}$  nm<sup>3</sup>. As estimated in [3], a single DNA memory could hold more words than all the computer memories ever made.

## 2 Can DNA compute everything?

The potential advantages of DNA computing versus electronic computing are clear in the case of problems like the Directed Hamiltonian Path Problem, the Satisfiability Problem, and breaking DES. On the other hand, these are only particular problems solved by means of molecular biology. They are one-time experiments to derive a combinatorial solution to a particular sort of problem. This immediately leads to two fundamental questions, posed in Adleman's article and in [20] and [28]:

- (1) What kind of problems can be solved by DNA computing?
- (2) Is it possible, at least in principle, to design a programmable DNA computer?

More precisely, one can reformulate the problems above as:

- (1) Is the DNA model of computation computationally complete in the sense that the action of any computable function (or, equivalently, the computation of any Turing machine) can be carried out by DNA manipulation?
- (2) Does there exist a universal DNA system, i.e., a system that, given the encoding of a computable function as an input, can simulate the action of that function for any argument? (Here, the notion of function corresponds to the notion of a program in which an argument  $w$  is the input of the program and the value  $f(w)$  is the output of the program. The existence of a universal DNA system amounts thus to the existence of a DNA computer capable of running programs.)

Opinions differ as to whether the answer to these questions has practical relevance. One can argue as in [8] that from a practical point of view it maybe not be that important to simulate a Turing machine by a DNA computing device. Indeed, one should not aim to fit the DNA model into the Procrustean bed of classical models of computation, but try to completely rethink the notion of computation. On the other hand, finding out whether the class of DNA algorithms is computationally complete has many important implications. If the answer to it were unknown, then the practical efforts for solving a particular problem might be proven futile at any time: a Gödel minded person could suddenly announce that it belongs to a class of problems that are impossible to solve by DNA manipulation. The same holds for the theoretical proof of the existence of a DNA computer. As long as it is not proved that such a thing theoretically exists, the danger that the practical efforts will be in vane is always lurking in the shadow.

One more indication of the relevance of the questions concerning computational completeness and universality of DNA-based devices is that they have been addressed for most models of DNA computation that have so far been proposed.

The existing models of DNA computation are based on various combinations of a few primitive *biological operations*:

- *Synthesis* of a desired polynomial-length strand ([1], [2], [6], [5]);
- *Separation* of the strands by length ([1], [2], [8], [5], [6]);
- *Merging*: pour two test tubes into one to do union ([1], [2], [28]);
- *Extraction*: extract those strands containing a given pattern as a substring ([1], [2], [28], [8], [6]);
- *Melting/Annealing*: break apart/bond together two single DNA strands with complementary sequences ([8], [40], [46]);
- *Amplifying*: make copies of DNA strands by using the Polymerase Chain Reaction ([1], [2], [28], [8], [5], [6], [40]);
- *Cutting*: cut DNA strands by using restriction enzymes ([8], [5], [6], [21], [37], [40]);
- *Ligation*: paste DNA strands with complementary sticky ends by using ligases ([5], [6], [46], [21], [37], [40]);
- *Detection*: given a tube, say “yes” if it contains at least one DNA strand, and “no” otherwise ([1], [2], [28], [8]).

These operations are then used to write “programs” which receive a tube containing DNA strands as input and return as output either “yes” or “no” or a set of tubes. A computation consists of a sequence of tubes containing DNA strands.

There are pro’s and con’s for each model (combination of operations). The ones using operations similar to Adleman’s have the obvious advantage that they could already be successfully implemented in the lab. The obstacle preventing the large scale automatization of the process is that most bio-operations rely on mainly manual handling of tubes. In contrast, the model introduced by Tom Head in [21] aims to be an “one-pot” tube with all the operations carried out in principle by enzymes. Moreover, it has the theoretical advantage of being a mathematical model with all the claims backed up by mathematical proofs. Its disadvantage is that the current state of art in molecular biology has not allowed yet practical implementation. Overall, the existence of different models with complementing features shows the versatility of DNA computing and increases the likelihood of practically constructing a DNA-computing-based device.

It can be proved, [9], [16], that in the case of the *splicing system* model of DNA recombination, one can affirmatively answer both questions posed at the beginning of this section. Constructions showing how to simulate the work of a Turing machine by a DNA model of computation have also been proposed in [40], [37], [2], [8], [6], [46], [36]. In an optimistic way, one may think of an analogy between these results and the work on finding models of computation carried out in the 30’s, which has laid the foundation for the design of the electronic

computers. In a similar fashion, the results obtained about the models of DNA computation show that programmable DNA computers are not science fiction material, but the reality of the near future.

### 3 Meta-thoughts on biomathematics

We have seen in Section 2 that the bio-operations are quite different from the usual arithmetical operations. Indeed, even more striking than the quantitative differences between a virtual DNA computer and an electronic computer (the DNA computer winning the comparison on most fronts) are the qualitative differences between the two.

DNA computing is a new way of thinking about computation altogether. Maybe this is how nature does mathematics: not by adding and subtracting, but by cutting and pasting, by insertions and deletions. Perhaps the primitive functions we currently use for computation are just as dependent on the history of humankind, as the fact that we use base 10 for counting is dependent on our having ten fingers. In the same way humans moved on to counting in other bases, maybe it is time we realized that there are other ways to compute besides the ones we are familiar with.

The fact that phenomena happening inside living organisms (copying, cutting and pasting of DNA strands) could be computations in disguise suggests that life itself may consist of a series of complex computations. As life is one of the most complex natural phenomena, we could generalize by conjecturing the whole cosmos to consist of computations. The differences between the diverse forms of matter would then only reflect various degrees of computational complexity, with the qualitative differences pointing to huge computational speed-ups. From chaos to inorganic matter, from inorganic to organic, and from that to consciousness and mind, perhaps the entire evolution of the universe is a history of the ever-increasing complexity of computations.

Of course, the above is only a hypothesis, and the enigma whether modern man is “homo sapiens” or “homo computans” still awaits solving. But this is what makes DNA computing so captivating. Not only may it help compute faster and more efficiently, but it stirs the imagination and opens deeper philosophical issues. What can be more mesmerizing than something that makes you dream?

To a mathematician, DNA computing tells that perhaps mathematics is the foundation of all there is. Indeed, mathematics has already proven to be an intrinsic part of sciences like physics and chemistry, of music, visual arts (see [23]) and linguistics, to name just a few. The discovery of DNA computing, indicating that mathematics also lies at the root of biology, makes one wonder whether mathematics isn't in fact the core of all known and (with noneuclidean geometry in mind) possible reality.

Maybe indeed, Plato [35], was right: the material things are mere instances

of “ideas” that are everlasting, never being born nor perishing. By intimating that – besides everything else – mathematics lies at the very heart of life, DNA computing suggests we take Plato’s philosophy one step further: the eternal “ideas” reflected in the ephemeral material world could be mathematical ones.

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