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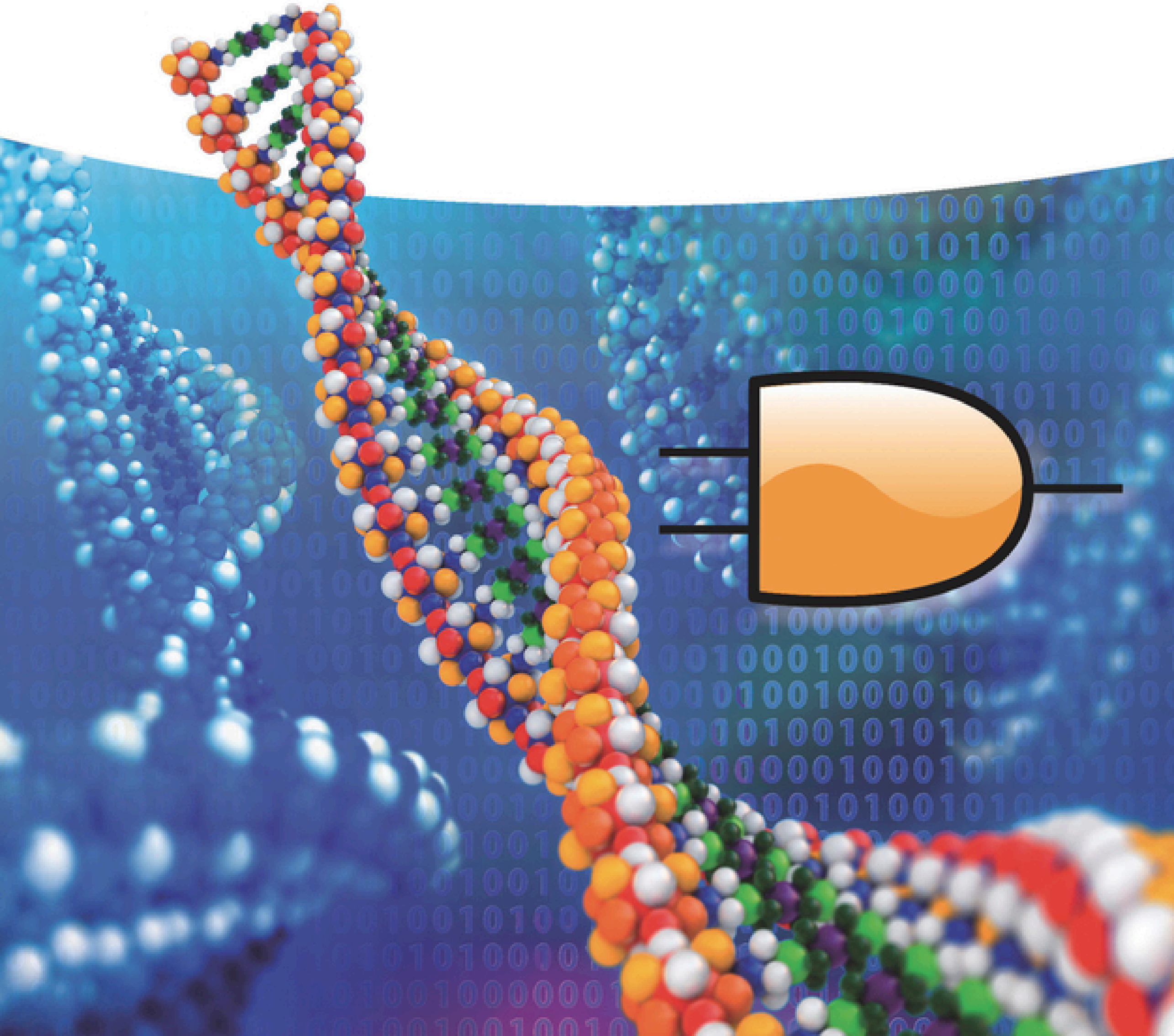

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Contents

Preface

The use of biomolecular systems for processing information, performing logic operations, computational operations, and even automata performance is a rapidly developing research area. The entire field was named with the general buzzwords, "biomolecular computing" or "biocomputing." Exciting advances in the area include the use of various biomolecular systems including proteins/enzymes, DNA, RNA, DNAzymes, antigens/antibodies, and even whole biological (usually microbial) cells operating as "hardware" for unconventional computing. The present book concentrates on DNA and RNA molecules utilized for information processing (biocomputing). Extensive ongoing research in the DNA- and RNA-based biocomputing has been motivated by speeding up computation, at least for solving some special problems, due to massive parallel operation of numerous biomolecules. The advantages of the DNA and RNA computing systems are also in their ability to operate in a biological environment for solving biomedical problems in terms of diagnostics and possibly therapeutic action, operating as nanorobots in living organisms. DNA molecules are also applicable as memory material with extremely high data density storage.

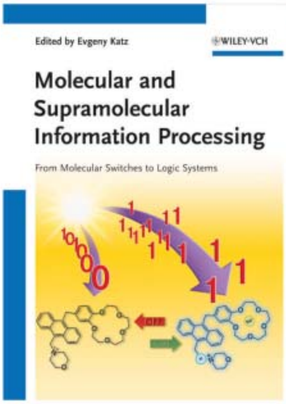
The present book summarizes research efforts of many groups in different universities and countries. The book reviews and exemplifies these developments, as well as offering an outlook for possible future research foci. The various topics covered highlight key aspects and the future perspectives of the DNA- and RNA-based computing. The different topics addressed in this book will be of high interest to the interdisciplinary community active in the area of unconventional biocomputing. The readers can find additional complementary material on molecular [1], biomolecular [2], and enzyme-based [3] computing published recently by Wiley-VCH (see book cover pages below). It is hoped that the present book will be important and beneficial for researchers and students working in various areas related to biochemical computing, including biochemistry, materials science, computer science, and so on. Furthermore, the book is aimed to attract young scientists and introduce them to the field while providing newcomers with an enormous collection of literature references. I, indeed, hope that the book will spark the imagination of scientists to further develop the topic.

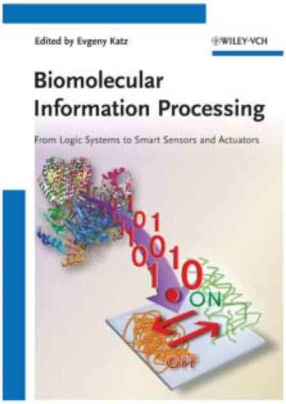
I would like to conclude this preface by thanking my wife Nina for her support in every respect in the past 49 years. Without her help it would not have been possible to complete this work. Also, cooperation and hard work of all authors working together with me on this edited volume are highly appreciated.

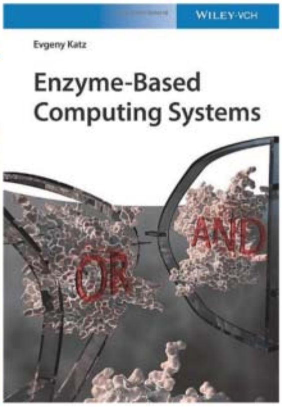
Potsdam, NY, USA *Evgeny Katz*
January 2020

References

1 Katz, E. (ed.) (2012). *Molecular and Supramolecular Information Processing: From Molecular Switches to Logic Systems*. Weinheim: Wiley-VCH.
2 Katz, E. (ed.) (2012). *Biomolecular Information Processing – From Logic Systems to Smart Sensors and Actuators*. Weinheim: Wiley-VCH.
3 Katz, E. (2019). *Enzyme-Based Computing Systems*. Weinheim: Wiley-VCH.







1

DNA Computing: Origination, Motivation, and Goals – Illustrated Introduction

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1.1 Motivation and Applications

Exponential development of computing systems based on silicon materials and binary algorithms formulated as "Moore's law" [1] (Figure 1.1) is coming to the end being limited by further component miniaturization and by the speed of operation. Conceptually novel ideas are needed to break through these limitations. The quest for novel ideas in the information processing has resulted in several exciting directions in the general area of unconventional computing [2–4], including research in quantum computing [5] and biologically inspired molecular computing [6–9]. Molecular computing systems, generally motivated by mimicking natural biological information processing [10, 11], are not necessarily based on biomolecules and could be represented by synthetic molecules with signal-controlled switchable properties. Synthetic molecular systems and nano-species have been designed to mimic operation of Boolean logic gates and demonstrate basic arithmetic functions and memory units. However, despite progress achieved in assembling synthetic molecular systems performing basic Boolean operations and simple computations [6–9], these systems have limited complexity, and further increase of their complexity is very challenging. A new advance in the development of molecular information systems has been achieved with use of biomolecular species [12] (Figure 1.2) such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) [13–16], oligopeptides [17], proteins [18], enzymes [2, 19, 20], antigens/antibodies [21], and even whole biological cells/organisms [22–24] capable of operating in a biological environment [25], borrowing some ideas from systems biology [26]. The advantage of the biomolecular computing systems is their ability to be integrated in artificially designed complex reacting processes mimicking multistep information processing networks. These systems are still far away from the natural information processing in cells but are already much more complex than pure synthetic molecular systems. In fact, biochemical reactions are at the core of the mechanism of life itself, and therefore one could set rather ambitious expectations for how far can (bio)chemical reaction systems be scaled up in complexity, if not speed, for information processing. While in a long perspective

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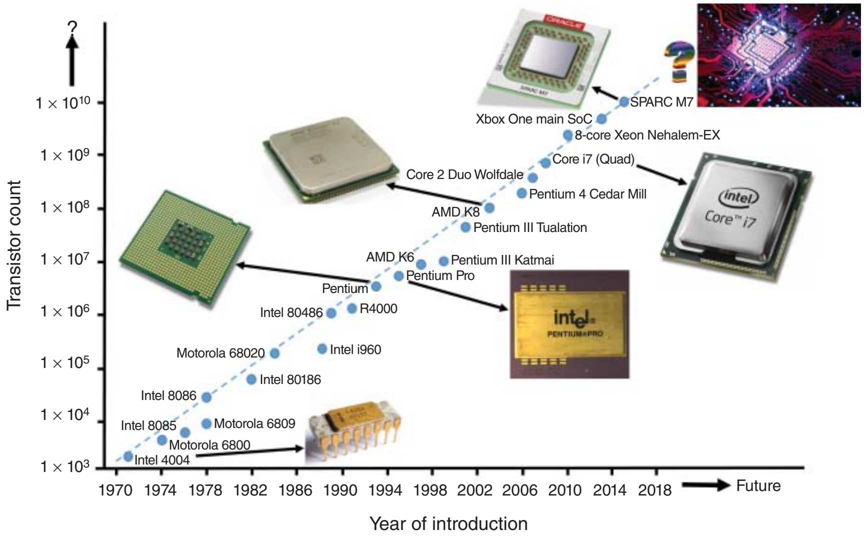


Figure 1.1 Moore's law – exponential increase of transistors on integrated circuit chips. (The plot shown in the figure is based on the data provided by Wikipedia: https://en.wikipedia.org/wiki/Moore%27s_law.) Source: From Katz [2]. Reprinted with the permission of John Wiley and Sons.

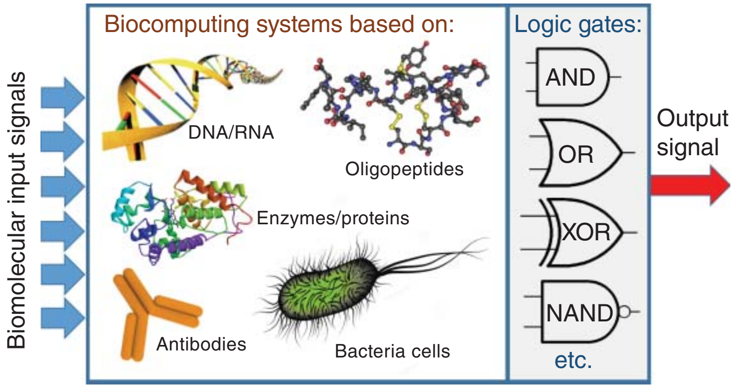


Figure 1.2 Biomolecular computing systems mimicking operation of different Boolean logic gates and circuitries can be based on various species including oligopeptides, enzymes/proteins, DNA/RNA, antibodies, and even whole biological (e.g., microbial) cells. Source: From Katz 2019 [2], Boolean Logic Gates Realized with Enzyme-Catalyzed Reactions – Unusual Look at Usual Chemical Reactions. ChemPhysChem © 2018. Reproduced with the permission of John Wiley & Sons.

a "biocomputer" might become a reality [27], particularly for some special applications, e.g., for solving complex combinatorial problems [28], potentially promising to have an advantage over silicon-based electronic computers due to parallel computing performed by numerous biomolecular units, the present level of technology does not allow any practical use of biomolecular systems for real computational applications. For achieving any practical result soon, some other applications, different from making a biocomputer, should be considered using the (bio)molecular systems with a limited complexity. One of the immediate possible applications for molecular logic systems is a special kind of biosensing [29–31] where the multiple input signals are logically processed through chemical reactions resulting in YES/NO decisions in the binary (**0**,**1**) format. In this subarea of biomolecular logic systems, practical results are already possible at the present level of the system complexity, particularly for biomedical applications [32–35]. Overall, the research in molecular/biomolecular information processing, which has been motivated originally to progress unconventional computing applications, is broadly developing to areas not directly related to computing in its narrow definition. This research is bringing us to novel areas in sensing/biosensing [29–31], switchable "smart" materials controlled by logically processed signals [32–36], bioelectronic devices (e.g., biofuel cells) controlled by external signals [37, 38], signal-controlled release processes [39–43], etc.

1.2 DNA- and RNA-Based Biocomputing Systems in Progress

While the general topics of the biomolecular computing [12] and specifically the enzyme-based computing [44] have been covered with recently published books, the present book is concentrated on the use of DNA and RNA molecules in computing systems, broadly defined as information processing systems. From the time (1953) when James D. Watson and Francis H.C. Crick (Figure 1.3) discovered chemical structure of DNA (Figure 1.4) [45], the progress in the DNA study resulted in many novel fundamental scientific concepts [46–48] and highly important practical applications [49]. Among many other, mostly biomedical applications, DNA molecules have been extensively studied over last two decades for unconventional biomolecular computing [13, 15, 50–55], following the pioneer work (1994) by Leonard M. Adleman [28, 56] (Figure 1.5). In his seminal work Adleman demonstrated for the first time computational use of DNA molecules for solving a "traveling salesman problem," Hamiltonian path problem. Actually, this work initiated (bio)molecular computing research not necessary using DNA molecules.

The "traveling salesman problem" asks the following question [57–59]: "Given a list of cities and the distances between each pair of cities, what is the shortest possible route that visits each city and returns to the origin city?" It is a problem in combinatorial optimization, important in theoretical computer science. It is frequently used to test computational algorithms and computer hardware. In general, the traveling salesman problem is hard to solve, particularly when the number of the visited cities is increasing. Adleman solved the problem for seven cities only (Figure 1.6), which was rather a trivial task, but importantly it was solved using computational power of DNA reactions [28, 56]. The DNA molecules hybridized in a special way to solve the problem, and the computation was performed by numerous DNA sequences (actually rather short oligonucleotides) operating in parallel. This was important conceptual difference from

Figure 1.3 The discoverers of the structure of DNA. James Watson (b.1928) at left and Francis Crick (1916–2004), with their model of part of a DNA molecule in 1953. Photographed in the Cavendish Laboratory, University of Cambridge, UK, in May 1953. Source: From Watson and Crick [45]. https://cnx.org/contents/8M7b3dzJ@2/DNA-Structure. Licensed Under CC BY 4.0.

Si-based electronic computers that perform all operations in a sequence. The computation in Adleman's experiment was performed at the speed of 1014 operations per second, a rate of 100 teraflops or 100 trillion floating point operations per second (comparable to the fastest presently available quantum computer) – all because of massively parallel processing capabilities of the DNA computing operation [54, 60]. The promise for extremely fast computation ignited the interest to the DNA computing concept, then being extended to a broader area of molecular [8] and biomolecular [12] computing. Despite the fact that the practical results have not been obtained after almost 25 years of the active research, optimistic expectations for building DNA computers are still present [27, 55, 61, 62]. The advantages of the DNA and RNA computing systems are not only in their potentially high speed of operation due to the parallel information processing but also in their ability to operate in a biological environment for solving biomedical problems in terms of diagnostics and possibly therapeutic action (theranostics) [16, 63], for example, for logic control of gene expression [64]. RNA-based computing systems are particularly promising for *in vivo* operation, thus being excellent candidates for nanomedicine with implemented Boolean logic [65]. DNA computers can operate as a Turing machine [51] and can be sophisticated enough to mimic neural network computations similar

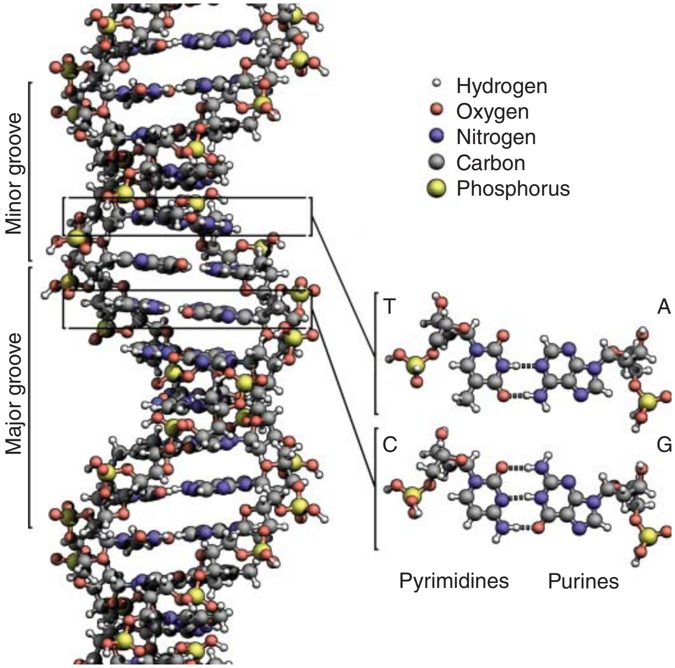


Figure 1.4 The structure of the DNA double helix. The atoms in the structure are color-coded by element, and the detailed structures of two base pairs are shown in the bottom right. Source: From Watson and Crick [45]. Also adapted from Zephyris, DNA Structure, Wikimedia commons, 2011. Public Domain.

Figure 1.5 Leonard Adleman – a pioneer of the biomolecular computing; the photo of 1993 when the first experiments on DNA computing were running. Source: Courtesy of Prof. Leonard Adleman.

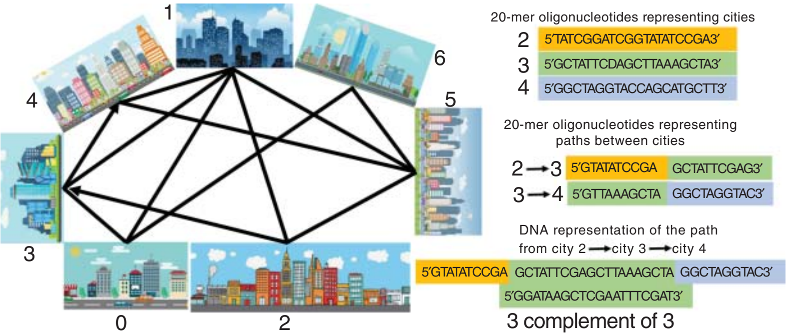


Figure 1.6 The principle of Leonard Adleman's DNA computer to solve the "traveling salesman problem" (see detailed explanation in Ref. [54]). Source: Based on Parker [54].

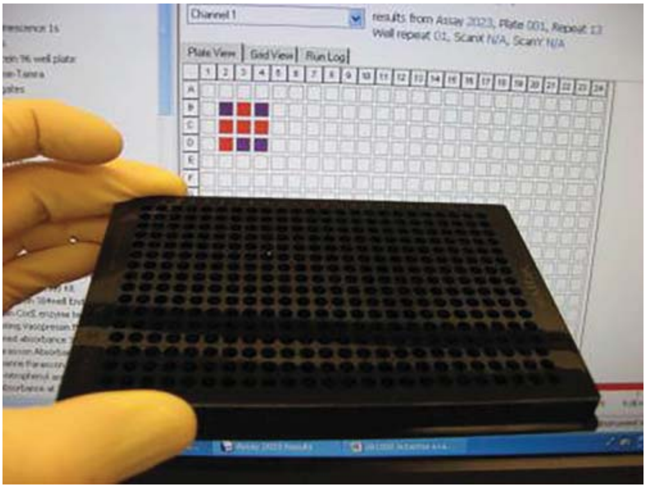


Figure 1.7 The DNA computer playing the tic-tac-toe game. Shown in the foreground is a cell culture plate containing pieces of DNA that code for possible "moves." A display screen (background) shows that the computer (red squares) has won the game against a human opponent (blue). Source: Courtesy of Prof. Milan Stojanovic, Columbia University.

to human brain, obviously in a very simplified way [66]. The DNA computing systems playing a tic-tac-toe game against human have been "smart" enough to win [13, 67–69] (Figure 1.7).

The progress in the DNA computing has been based on three major developments: (i) the use of sophisticated DNA structures (e.g., origami), (ii) the use of more powerful instrumentation for automatic operation of DNA computing steps (DNA chips), and (iii) specialized programming languages specifically developed for the DNA computing. The invention of the DNA origami structures [70, 71] – nanoscale folding of DNA resulting in nonarbitrary two- and three-dimensional shapes [72, 73] (Figure 1.8) – resulted in further sophistication of the DNA computing systems [74], capable of operating as nanorobots in living organisms [75–77]. The use of DNA microarrays (DNA chips [78]) allowed

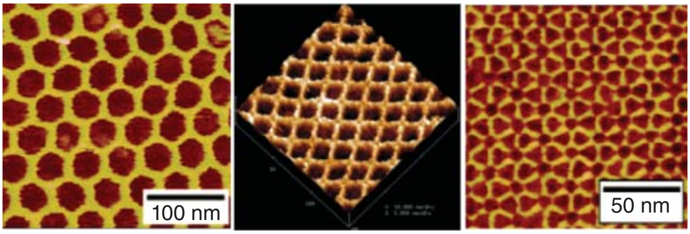


Figure 1.8 Atomic force microscopy (AFM) images of DNA origami with different shapes. Source: From Hong et al. [73]. Reprinted with the permission of American Chemical Society.

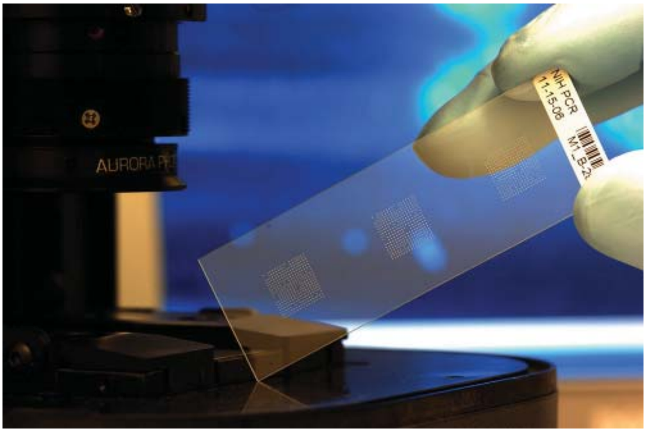
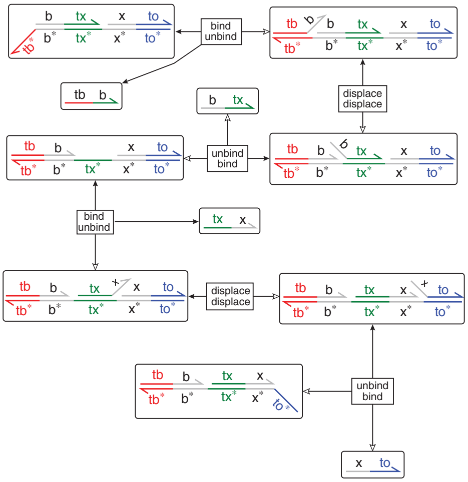


Figure 1.9 An example of a DNA chip used in the DNA sensing and computing. The chip represents a DNA microarray as a collection of microscopic DNA spots attached to a solid surface. Each DNA spot contains picomoles of a specific DNA sequence. The chip allows simultaneous analysis of many DNA probes. The analysis of the probes can be performed optically (as it is in the present example) or electrochemically (then the chip should be based on a microelectrode array). Source: Courtesy of Argonne National Laboratory and Mr. Calvin Chimes.

simultaneous analysis of large numbers of DNA probes [53], thus introducing a powerful hardware for the DNA computing (Figure 1.9). A special computational language, DNA strand displacement (DSD) tool, similar to programming languages used in electronic computers, has been developed by scientists at Microsoft Research for programing DNA computing [79, 80] (Figure 1.10). The language uses DSD as the main computational mechanism, which allows devices to be designed solely in terms of nucleic acids. DSD is a first step toward the development of design and analysis tools for DSD and complements the emergence of novel implementation strategies for DNA computing. The DNA computation can be performed in living cells by DNA-encoded circuits that process sensory information and control biological functions. A special computing language, “Cello,” has been developed for programing DNA logic operations *in vivo* [81]. Overall, the use of computing languages simplified the design of DNA computing systems of high complexity.

```
directive rules {
bind(P1,P2,Q,D!i) :-
  P1 = C1 [D], P2 = C2 [D′], compl(D, D′),
  Q = C1 [D!i} I C2 [D′!i}, freshBond(D!i, P1|P2).

displace(P,Q,E!j,D!i) :-
  P = C [E!j D] [D!i] [D′!i E′!j],
  Q = C [E!j D!i] [D] [D'!i E'!j].

displaceL(P,Q,E!j,D!i) :-
  P = C [D!i] [D E!j] [E'!j D'!i],
  Q = C [D] [D!i E!j] [E'!j D'!i].

unbind(P,Q,D!i) :-
  P = C [D!i] [D'!i], toehold(D),
  Q = C [D] [D′], not adjacent(D!i,_,P).

adjacent(D!i,E!j,P) :- P = C [D!i E!j} [E′!j D′!i].
adjacent(D!i,E!j,P) :- P = C [E!j D!i] [D′!i E′!j].

reaction([P1;P2], “bind”,Q) :- bind(P1,P2,Q,_).
reaction([P],”displace”,Q) :- displace(P,Q,_,_).
reaction([P],”displace”,Q) :- displaceL(P,Q,_,_).
reaction([P],”unbind”,Q) :- unbind(P,Q,_).
}
directive parameters [
  bind = 0.003; displace = 1; unbind = 0.1
]
( 10 [<tb^ b>]
| 10 [<tx^ x>]
| 100 [<to^*!1 x*!2 tx^*!3 b*!4 tb^*>
      | <x!2 to^!1> | <b!4 tx^!3>] )
```

(a)



(b)

Figure 1.10 Logic program (a) and automatically generated chemical reaction network (b) for a DNA strand displacement example. Source: Adapted from Spaccasassi et al. 2019 [80] with permission; open access paper.

1.3 DNA-Based Information Storage Systems

Human civilization generates huge amount of information increasing exponentially and required to be stored. The total digital information today amounts to 3.52×10^{22} bits globally and at its consistent exponential rate of growth is expected to reach 3×10^{24} bits by 2040 [82]. Data storage density of silicon chips is limited, and magnetic tapes used to maintain large-scale permanent archives begin to deteriorate within 20 years. Alternative methods/materials for storing high density/large amount of information with reliable preservation over long period of time are urgently needed. DNA has been recognized as a promising natural medium for information storage [83]. Indeed, the DNA molecules were created by nature to keep the genetic code, which can be easily “written” and “read” by biomolecular systems. With information retention times that range from thousands to millions of years, volumetric density 10^3 times greater than flash memory, and energy of operation 10^8 times less, DNA is a memory storage material viable and compelling alternative to electronic memory. Recent research in the area of information storage with DNA molecules resulted in the proof-of-the-concept systems [82, 84–87], while the practical use of the DNA memory systems is only limited by technological problems. Both processes in the information storage with DNA, “writing” and “reading” information, are available, but they are not as simple as needed to be implemented with the present computer technology. In other words, the DNA memory is technically possible, but it is not convenient enough to be integrated with standard Si-based computers operated by end users.

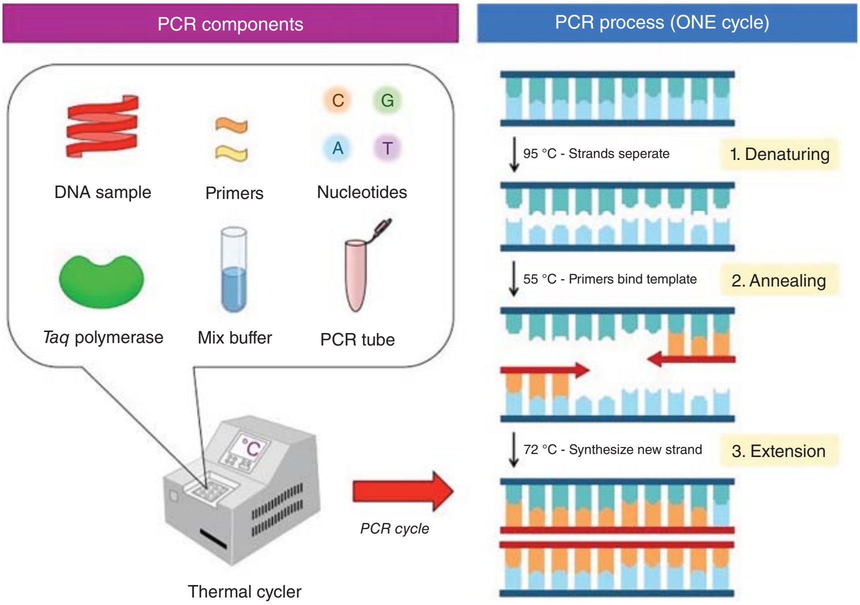


Figure 1.11 PCR method for copying DNA molecules: a thermal cycler, components of the reaction mixture, and reaction steps. For detailed description of the method and instrument see Refs. [89–92]. Source: From Keagile Bati, Polymerase Chain Reaction: Innovation that Revolutionized Molecular Biology, Nov 2018. Public Domain.

Synthetic procedure for production of DNA molecules with specific nucleotide sequences is well known in organic chemistry [88] and can be used to "write" information in the DNA. Once the DNA molecules with the encoded information are prepared, they can be multiplied using a polymerase chain reaction (PCR) [89–92] (Figure 1.11), which is a technique to make many copies of a specific DNA *in vitro* (in a test tube rather than an organism). This technique is rather advanced in the instrumental realization but still requires special apparatus that cannot be connected easily to an electronic computer, at least at the end-user convenience. "Reading" the DNA-encoded information (DNA sequencing [93]) was advanced during the Human Genome Project [94] and presently is very technologically effective. Further improvements in sequencing throughput ($>10^4$) and parallelization ($>10^7$) are expected in the next five years [84]. Emerging technologies such as nanopore sequencing [95] will further reduce errors, cost, time, and energetics during reading the DNA-encoded information. While future advances can result in novel technological approaches, already available techniques based on the DNA memo-chips have been tested [96]. A simple chemical, rather than electronic, apparatus operating as the end-to-end automatic DNA data storage was designed and demonstrated the automatic "writing"–"reading" DNA processes [97] (Figure 1.12). The recent research efforts opened the way toward practical, high-capacity, low-maintenance information storage in synthesized DNA [98–100]. As an example, a 5.27-megabit book was stored using DNA microchips and then read the book by using the

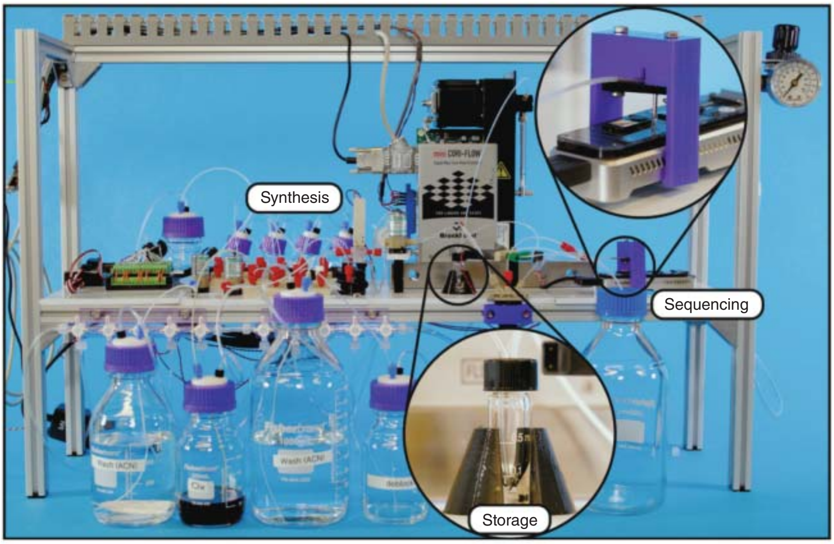


Figure 1.12 Apparatus operating as the end-to-end automatic DNA data storage allowing automatic “writing”–“reading” DNA processes. Source: From Takahashi et al. [97]. https://www.nature.com/articles/s41598-019-41228-8. Licensed Under CC BY 4.0.

DNA sequencing [101]. Other, even more impressive, examples demonstrated encoding the pixel values of black-and-white images and a short movie into the genomes of a population of living bacteria and then retrieving them back by the DNA sequencing [102].

1.4 Short Conclusions and Comments on the Book

Overall, the DNA computing is a multidisciplinary research area with major contributions from synthetic biology, nanotechnology, computer science, chemical engineering, biosensing and biotechnology, biology and medicine, etc. Some of the research areas are already reaching the mature states, while others are still in the infancy. It is still not easy to predict in what direction the research will go and what applications will be more benefiting from the DNA computing. In the most probability, practical applications will be in two major subareas: medicine with the DNA information processing nanorobotic systems operating *in vivo* [103, 104] and large data storage systems providing extremely high density of the information storage [84, 105]. Many other applications of the DNA computing are in the research and discussion [106, 107]. However, it is quite unexpected that the DNA computing will come to the end users instead of standard electronic computers, at least in the short perspective.

The present book, composed of the chapters written by the best experts in the field, covers all subtopics of the DNA computing, including the design of Boolean logic gates and circuitries, programming the DNA information processing systems, their biomedical applications and operation *in vivo*, DNA data storage and nanopore DNA decoding, and interfacing of the DNA computing with enzyme logic systems, and many more detailed explanations on the DNA and RNA computing with many references and illustrations.

References

1 Moore, G.E. (1998). *Proc. IEEE* 86: 82–85.
2 Katz, E. (2019). *ChemPhysChem* 20: 9–22.
3 Calude, C.S., Costa, J.F., Dershowitz, N. et al. (eds.) (2009). *Unconventional Computation*, Lecture Notes in Computer Science, vol. 5715. Berlin: Springer.
4 Adamatzky, A. (ed.) (2017). *Advances in Unconventional Computing*, Emergence, Complexity and Computation, 2 volumes. Switzerland: Springer.
5 Mermin, N.D. (2007). *Quantum Computer Science: An Introduction.* Cambridge: Cambridge University Press.
6 Szacilowski, K. (2012). *Infochemistry – Information Processing at the Nanoscale.* Chichester: Wiley.
7 de Silva, A.P. (2013). *Molecular Logic-Based Computation.* Cambridge: Royal Society of Chemistry.
8 Katz, E. (ed.) (2012). *Molecular and Supramolecular Information Processing – From Molecular Switches to Logic Systems.* Weinheim: Willey-VCH.
9 Sienko, T. (ed.) (2003). *Molecular Computing* (Series Eds.: Adamatzky, A., Conrad, M., and Rambidi, N.G.). Cambridge, MA: MIT Press.
10 Spitzer, N.C. and Sejnowski, T.J. (1997). *Science* 277: 1060–1061.
11 Kampfner, R.R. (1989). *BioSystems* 22: 223–230.
12 Katz, E. (ed.) (2012). *Biomolecular Computing – From Logic Systems to Smart Sensors and Actuators.* Weinheim: Wiley-VCH.
13 Stojanovic, M.N., Stefanovic, D., and Rudchenko, S. (2014). *Acc. Chem. Res.* 47: 1845–1852.
14 Stojanovic, M.N. and Stefanovic, D. (2011). *J. Comput. Theor. Nanosci.* 8: 434–440.
15 Ezziane, Z. (2006). *Nanotechnology* 17: R27–R39.
16 Xie, Z., Wroblewska, L., Prochazka, L. et al. (2011). *Science* 333: 1307–1311.
17 Ashkenasy, G., Dadon, Z., Alesebi, S. et al. (2011). *Isr. J. Chem.* 51: 106–117.
18 Unger, R. and Moult, J. (2006). *Proteins* 63: 53–64.
19 Katz, E. and Privman, V. (2010). *Chem. Soc. Rev.* 39: 1835–1857.
20 Katz, E. (2015). *Curr. Opin. Biotechnol.* 34: 202–208.
21 Halámek, J., Tam, T.K., Chinnapareddy, S. et al. (2010). *J. Phys. Chem. Lett.* 1: 973–977.
22 Rinaudo, K., Bleris, L., Maddamsetti, R. et al. (2007). *Nat. Biotechnol.* 25: 795–801.
23 Arugula, M.A., Shroff, N., Katz, E., and He, Z. (2012). *Chem. Commun.* 48: 10174–10176.
24 Adamatzky, A. (2010). *Physarum Machines – Computers from Slime Mould.* London: World Scientific.

25 Kahan, M., Gil, B., Adar, R., and Shapiro, E. (2008). *Physica D* 237: 1165–1172.

26 Alon, U. (2006). *An Introduction to Systems Biology: Design Principles of Biological Circuits*. Boca Raton, FL: Chapman & Hall/CRC.

27 Benenson, Y. (2009). *Mol. Biosyst.* 5: 675–685.

28 Adleman, L.M. (1994). *Science* 266: 1021–1024.

29 Katz, E., Wang, J., Privman, M., and Halámek, J. (2012). *Anal. Chem.* 84: 5463–5469.

30 Wang, J. and Katz, E. (2011). *Isr. J. Chem.* 51: 141–150.

31 Wang, J. and Katz, E. (2010). *Anal. Bioanal. Chem.* 398: 1591–1603.

32 Halámková, L., Halámek, J., Bocharova, V. et al. (2012). *Analyst* 137: 1768–1770.

33 Halámek, J., Windmiller, J.R., Zhou, J. et al. (2010). *Analyst* 135: 2249–2259.

34 Minko, S., Katz, E., Motornov, M. et al. (2011). *J. Comput. Theor. Nanosci.* 8: 356–364.

35 Tokarev, I., Gopishetty, V., Zhou, J. et al. (2009). *ACS Appl. Mater. Interfaces* 1: 532–536.

36 Pita, M., Minko, S., and Katz, E. (2009). *J. Mater. Sci. - Mater. Med.* 20: 457–462.

37 Katz, E. and Minko, S. (2015). *Chem. Commun.* 51: 3493–3500.

38 Katz, E. (2010). *Electroanalysis* 22: 744–756.

39 Okhokhonin, A.V., Domanskyi, S., Filipov, Y. et al. (2018). *Electroanalysis* 30: 426–435.

40 Filipov, Y., Gamella, M., and Katz, E. (2018). *Electroanalysis* 30: 1281–1286.

41 Gamella, M., Privman, M., Bakshi, S. et al. (2017). *ChemPhysChem* 18: 1811–1821.

42 Gamella, M., Zakharchenko, A., Guz, N. et al. (2017). *Electroanalysis* 29: 398–408.

43 Katz, E., Pingarrón, J.M., Mailloux, S. et al. (2015). *J. Phys. Chem. Lett.* 6: 1340–1347.

44 Katz, E. (2019). *Enzyme-Based Computing Systems*. Wiley-VCH.

45 Watson, J.D. and Crick, F.H.C. (1953). *Nature* 171: 737–738.

46 Micklos, D. and Freyer, G. (2003). *DNA Science: A First Course*, 2e. New York: Cold Spring Harbor Laboratory Press.

47 Calladine, C.R., Drew, H., Luisi, B., and Travers, A. (2004). *Understanding DNA: The Molecule and How It Works*, 3e. San Diego, CA: Elsevier Academic Press.

48 Douglas, K. (2017). *DNA Nanoscience*. Boca Raton, FL: CRC Press.

49 Fitzgerald-Hayes, M. and Reichsman, F. (2009). *DNA and Biotechnology*, 3e. Amsterdam, Imprint: Academic Press: Elsevier.

50 Boneh, D., Dunworth, C., Lipton, R.J., and Sgall, J. (1996). *Discrete Appl. Math.* 71: 79–94.

51 Rozen, D.E., McGrew, S., and Ellington, A.D. (1996). *Curr. Biol.* 6: 254–257.

52 Eghdami, H. and Darehmiraki, M. (2012). *Artif. Intell. Rev.* 38: 223–235.

53 Ogihara, M. and Ray, A. (2000). *Nature* 403: 143–144.

54 Parker, J. (2003). *EMBO Rep.* 4: 7–10.

55 Mehrotra, A. (2015). *Int. J. Latest Technol. Eng. Manage. Appl. Sci. (IJL-TEMAS)* 4 (12): 62–67.

56 Adleman, L.M. (1998). *Sci. Am.* 279 (2): 54–61.

57 Lawler, E.L., Lenstra, J.K., Rinnooy Kan, A.H.G., and Shmoys, D.B. (eds.) (1995). *The Traveling Salesman Problem: A Guided Tour of Combinatorial Optimization*. Chichester: Wiley-Interscience.

58 Laporte, G. (1992). *Eur. J. Oper. Res.* 59: 231–247.

59 Applegate, D.L., Bixby, R.E., Chvátal, V., and Cook, W.J. (2006). *The Traveling Salesman Problem – A Computational Study*. Princeton, NJ: Princeton University Press.

60 Reif, J.H. (1999). *Algorithmica* 25: 142–175.

61 Kumar, S.N. (2015). *Am. J. Nanomater.* 3 (1): 1–14.

62 Moe-Behrens, G.H.-G. (2013). *Comput. Struct. Biotechnol. J.* 7 (Art. No.: e201304003).

63 Bonnet, J., Yin, P., Ortiz, M.E. et al. (2013). *Science* 340: 599–603.

64 Benenson, Y., Gil, B., Ben-Dor, U. et al. (2004). *Nature* 429: 423–429.

65 Green, A.A., Kim, J., Ma, D. et al. (2017). *Nature* 548: 117–121.

66 Qian, L., Winfree, E., and Bruck, J. (2011). *Nature* 475: 368–372.

67 Macdonald, J., Stefanovic, D., and Stojanovic, M.N. (2008). *Sci. Am.* 299 (5): 84–91.

68 Stojanovic, M.N. and Stefanovic, D. (2003). *Nat. Biotechnol.* 21: 1069–1074.

69 Elstner, M. and Schiller, A. (2015). *J. Chem. Inf. Model.* 55: 1547–1551.

70 Seeman, N.C. (1982). *J. Theor. Biol.* 99: 237–247.

71 Rothemund, P.W.K. (2006). *Nature* 440: 297–302.

72 Jun, H., Zhang, F., Shepherd, T. et al. (2019). *Sci. Adv.* 5 (Art. No.: eaav0655).

73 Hong, F., Zhang, F., Liu, Y., and Yan, H. (2017). *Chem. Rev.* 117: 12584–12640.

74 Wang, D.F., Fu, Y.M., Yan, J. et al. (2014). *Anal. Chem.* 86: 1932–1936.

75 Amir, Y., Ben-Ishay, E., Levner, D. et al. (2014). *Nat. Nanotechnol.* 9: 353–357.

76 Kogikoski, S. Jr., Paschoalino, W.J., and Kubota, L.T. (2018). *TrAC, Trends Anal. Chem.* 108 (Art. No.: 88e97).

77 Endo, M. and Sugiyama, H. (2018). *Molecules* 23 (Art. No.: 1766).

78 Ramsay, G. (1998). *Nat. Biotechnol.* 16: 40–44.

79 Phillips, A. and Cardelli, L. (2009). *J. R. Soc. Interface* 6: S419–S436.

80 Spaccasassi, C., Lakin, M.R., and Phillips, A. (2019). *ACS Synth. Biol.* 8: 1530–1547.

81 Nielsen, A.A.K., Der, B.S., Shin, J. et al. (2016). *Science* 352 (6281): 53.

82 Panda, D., Molla, K.A., Baig, M.J. et al. (2018). *3 Biotech* 8 (Art. No.: 239).

83 Baum, E.B. (1995). *Science* 268: 584–585.

84 Zhirnov, V., Zadegan, R.M., Sandhu, G.S. et al. (2016). *Nat. Mater.* 15: 366–370.

85 Ceze, L., Nivala, J., and Strauss, K. (2019). *Nat. Rev. Genet.* 20: 456–466.

86 Zhang, S.F., Huang, B.B., Song, X.M. et al. (2019). *3 Biotech* 9 (Art. No.: 342).

87 Tomek, K.J., Volkel, K., Simpson, A. et al. (2019). *ACS Synth. Biol.* 8: 1241–1248.

88 Ma, S., Tang, N., and Tian, J. (2012). *Curr. Opin. Chem. Biol.* 16: 260–267.

89 Behlke, M.A., Berghof-Jäger, K., Brown, T. et al. (2019). *Polymerase Chain Reaction: Theory and Technology*. Poole: Caister Academic Press.

90 Garibyan, L. and Avashia, N. (2013). *J. Invest. Dermatol.* 133 (3), art No. e6.

91 Alves Valones, M.A., Lima Guimarães, R., Cavalcanti Brandão, L.A. et al. (2009). *Braz. J. Microbiol.* 40 (1): 1–11.

92 Powledge, T.M. (2004). *Adv. Physiol. Educ.* 28: 44–50.

93 Shendure, J., Balasubramanian, S., Church, G.M. et al. (2017). *Nature* 550: 345–353.

94 Dolgin, E. (2009). *Nature* 462: 843–845.

95 Agah, S., Zheng, M., Pasquali, M., and Kolomeisky, A.B. (2016). *J. Phys. D: Appl. Phys.* 49 (Art. No.: 413001).

96 Stefano, G.B., Wang, F.Z., and Kream, R.M. (2018). *Med. Sci. Monit.* 24: 1185–1187.

97 Takahashi, C.N., Nguyen, B.H., Strauss, K., and Ceze, L. (2019). *Sci. Rep.* 9 (Art. No.: 4998).

98 Goldman, N., Bertone, P., Chen, S. et al. (2013). *Nature* 494: 77–80.

99 Anavy, L., Vaknin, I., Atar, O. et al. (2019). *Nat. Biotechnol.* 37: 1229–1236.

100 Organick, L., Ang, S.D., Chen, Y.-J. et al. (2018). *Nat. Biotechnol.* 36: 242–248.

101 Church, G.M., Gao, Y., and Kosuri, S. (2012). *Science* 337: 1628.

102 Shipman, S.L., Nivala, J., Macklis, J.D., and Church, G.M. (2017). *Nature* 547: 345–349.

103 Li, S., Jiang, Q., Liu, S. et al. (2018). *Nat. Biotechnol.* 36: 258–264.

104 Ma, W., Zhan, Y., Zhang, Y. et al. (2019). *Nano Lett.* 19: 4505–4517.

105 De Silva, P.Y. and Ganegoda, G.U. (2016). *BioMed Res. Int.* 2016 (Art. No.: 8072463).

106 Tagore, S., Bhattacharya, S., Islam, M.A., and Islam, M.L. (2010). *J. Proteomics Bioinform.* 3: 234–243.

107 Currin, A., Korovin, K., Ababi, M. et al. (2017). *J. R. Soc. Interface* 14 (Art. No.: 20160990).