Comparator Logic Circuits Based on DNA Strand Displacement by DNA Hairpin

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Abstract. DNA computing is a hot research topic in recent years, molecular logic gate is an important foundation of DNA computer architecture and implementation. Local hairpin DNA chain substitution reaction can increase the reliability of molecular logic gates, Make the reaction more efficient and more thoroughly. In this paper, using local hairpin DNA strand displacement, the comparator circuit is coded and simulated base on the double logic circuit. The simulation results further confirmed the feasibility and effectiveness of the DNA strand displacement reaction in the study of biochemical logic circuits, The comparator circuit can be used for biological computer and building large-scale molecular logic circuits in the future.

Keywords: DNA strand displacement · Comparator · Visual DSD · DNA hairpin

1 Introduction

Demand for high-performance scientific computing keep rising, while the traditional electronic computer components production is near limit, the scientific community is looking for a new computing model to break through the limit of traditional computer systems [1–4]. DNA computing has been got attention for its high parallelism, low energy consumption and large information storage capacity [5–7]. Since the end of the 20th century, DNA computing has made great progress in theory and technology. In 2006, Seelig based on chain substitution reaction principle, design and gate, or gate, not gate logic module, and use of these modules into logic circuit [8]. In 2011, Winfree and Lulu Qian design improved the DNA of a single gate - seesaw gate, join a new concept called "fuel", for the groundwork of large-scale circuits [9–11]. Paving the way for the composition of large-scale circuits in the future [12–15].

As a new type of calculation method, DNA strand displacement technology has prominent advantages and powerful functions [16–19]. In this paper, based on the structure of DNA strand displacement by DNA hairpin, the comparator logic circuit is coded and simulated on the basis of the double logic circuit. As the overall DNA molecular strand displacement reaction has slow diffusion speed

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and wrong molecular collision problems, to solve this problem, Muscat proposed the basic module construction mechanism based on locality DNA hairpin strand displacement reaction [20–22], and combined with the dual logic thought, we successfully constructed the local half-adder logic circuit and the local full adder logic circuit on the DNA origami substrate. The experimental data demonstrate that there is excellent transmission performance among the three bound DNA cards. So we use the locality replacement of the molecular chain to increase its stability in this article. The simulation results show that the model has the advantages of fast reaction speed, high reliability and more thoroughly, it is more easy to combine the current biochip technology for large-scale integrated circuits on account of DNA.

2 DNA Hairpin Strand Displacement

DNA molecules are an ideal material for molecular computing, provide a great potential for construction of molecular logic circuits [23,24]. Because of the relatively slow molecular diffusion and the wrong molecular collision in the DNA molecular strand displacement, more and more researchers have preferred to application of locality DNA strand displacement. Based on the principle of nonlinear system [25–27], in the locality DNA molecular circuit, part of the DNA molecules are bounded to one DNA substrate, then the DNA molecules only be react to DNA molecules that get close enough, which effectively avoid the problems of slow diffusion speed and wrong molecular collision in overall DNA molecular strand displacement reaction [28–30].

DNA hairpin is a DNA structure that form by self complementary and joined by single-stranded loop. Locality DNA strand displacement reaction is shown in Fig. 1. We fix DNA hairpin on the origami, and each card defines a coordinate, to facilitate our experiments and simulation. In the DSD simulation [31], only one chain with the same coordinates can react. In Fig. 1, we add an input single chain $<a_0, s>$, a_0 in this single strand is paired with the small point a_0* of the hairpin, Then, the s chain in $<a_0, s>$ is paired with the card's s^*, single chain $<a_0, s>$ and $<a_0^*, s^*>$ pair into double chain at this time. While y and s in the card are opened, y and s are in single stranded forms at the other end of the complementary chain s^* and a_0^*. At this point, the single ring of the hairpin is opened, the y which was not involved in the reaction is activated, and then it can conduct pairing reaction with other DNA chain. The DNA card is fixed (A_0, Y) and can't move. This will avoid the collision problem between wrong molecular.

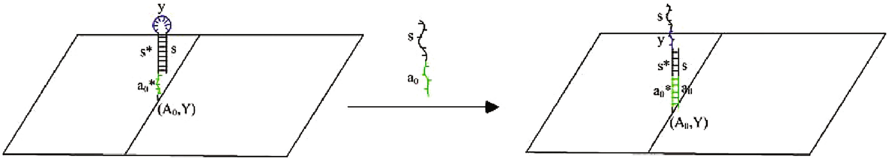


Fig. 1. Locality DNA hairpin strand displacement reaction

3 Construct Comparator Circuits by Locality DNA Hairpin

3.1 Construct Basic Gates by Locality DNA Hairpin

The molecular circuit is composed of different logic gates, basic logic gates include AND gates, OR gates, and NOT gates. But for Biochemical circuit, there are many difficult in constructing NOT gate. So we adopt the thought of double logic circuit, it is all made of AND gate and OR gate, has dynamic binding between AND gate and OR gate, then comparator's logic circuit is finished. Before this, we should design AND gate and NOT gate's locality DNA hairpin logic circuit.

Locality DNA hairpin strand displacement AND gate reaction has shown in Fig. 2, We fix four DNA hairpin on the origami, define coordinates as (A_0, Y), $(B_0, Y), (A_0, B_0), (X, Y)$. At same time, we define the distance between (A_0, Y), (B_0, Y) to (A_0, B_0) less than the distance to (X, Y), $<a_0, s>$ and $<b_0, s>$ as input, $<z, s>$ as output what we need.

1. When we add a single chain a_0, the fulcrum a_0 will complementary pair the DNA hairpin a_0* in (A_0, Y) firstly, then open (A_0, Y) fulcrum y, y will complementary pair fuel $y*$, open fulcrum x, it will react with nearest DNA

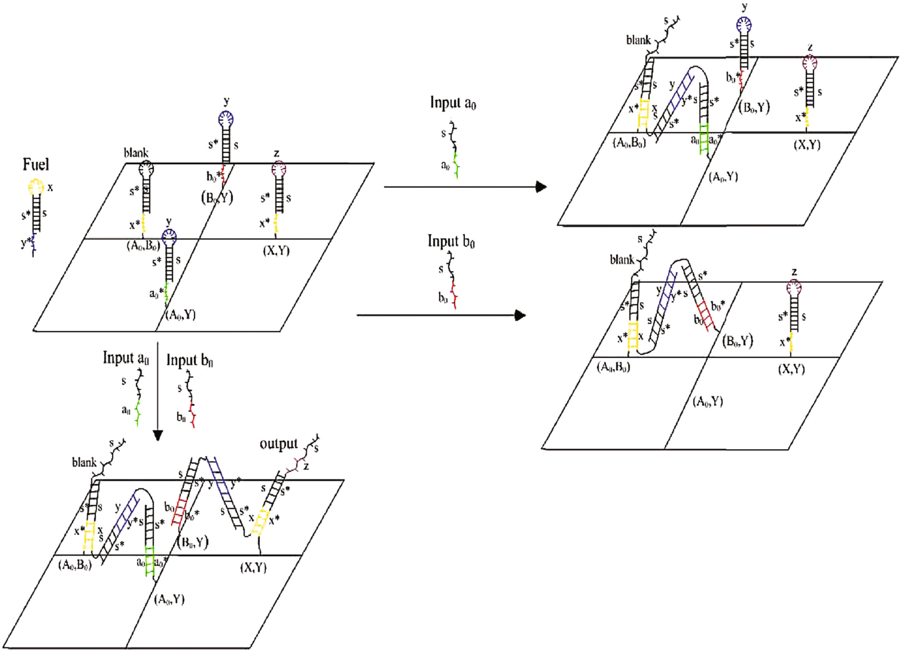


Fig. 2. AND gate construction of locality DNA hairpin strand displacement reaction

because of the feature of locality DNA hairpin strand displacement. So fulcrum x will complementary pair $x*$ in (A_0, B_0), open blank, the reaction finish. No output.

2. When we add a single chain b_0, the fulcrum b_0 will complementary pair the DNA hairpin b_0* in (B_0, Y) firstly, then open (B_0, Y) fulcrum y, y will complementary pair fuel $y*$, open fulcrum x, x will firstly complementary pair $x*$ in (A_0, B_0) at this time, open blank, the reaction finish. As we can see, we couldn't get output we need when add chain $<a_0, s>$ or $<b_0, s>$ singly.
3. We add input chain $<a_0, s>$ and $<b_0, s>$, $<a_0, s>$ will complementary pair the DNA hairpin a_0^* in (A_0, Y), it conduct the reaction progress that only has chain $<a_0, s>$, open blank. But meanwhile $<b_0, s>$ will complementary pair the DNA hairpin b_0^* in (B_0, Y), open fulcrum y in (B_0, Y), y will complementary pair fuel y^*, open fulcrum x, so x will react with DNA hairpin in (X, Y), and will complementary pair x^*, then open hairpin structure, get output $<z, s>$ that we need.

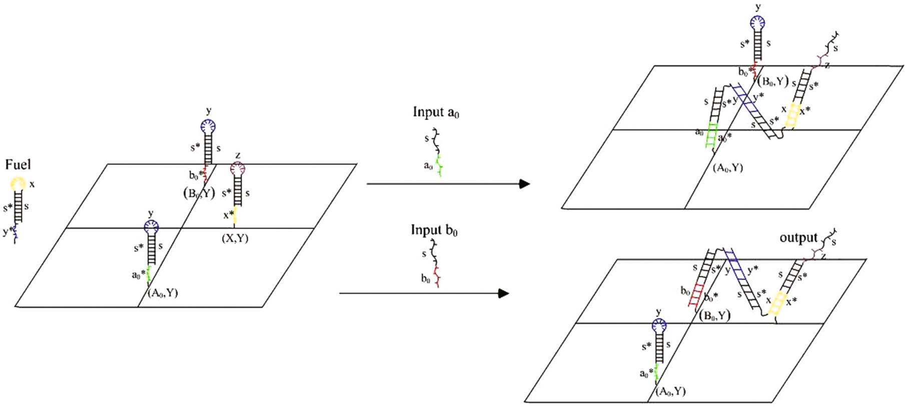


Fig. 3. OR gate construction of locality DNA hairpin strand displacement reaction

Then we conduct locality DNA hairpin strand displacement OR gate reaction. As shown in Fig. 3, OR gate only fixes three DNA hairpin on the origami, $(A_0, Y), (B_0, Y), (X, Y)$. We define chain $<a_0, s>$ and $<b_0, s>$ as input, $<z, s>$ as output what we need.

1. When we add a single chain a_0, the fulcrum a_0 will complementary pair the DNA hairpin a_0^* in (A_0, Y) firstly, then open (A_0, Y) is fulcrum y, y will complementary pair fuel y^*, open fulcrum x, it will react with DNA hairpin in (X, Y) and will complementary pair x^*, open hairpin structure, we can get output $<z, s>$ that we need.
2. When we add single chain b_0, the reaction progress is same as when add a_0, we can get output $<z, s>$ which we need.

3.2 Construct Comparator Circuits by Locality DNA Hairpin

A digital comparator compares binary that has same figure, judge numeric value of logic circuit. Compare two n-bit binary, need judge from high to low, if the altitude is same, we can be re-judged next, result are greater, equal or smaller respectively. The two outputs of the comparator circuit represent a state respectively. The input of circuit are two binary numbers x_1 and x_2, output are y_1, y_2, Respectively indicate $x_1 > x_2$ and $x_1 < x_2$.

In this article, we use the idea of dual logic circuits, dual logic circuits uses two different DNA chain for logic 0 and 1. When $x^0x^1 = 01$, x^0 and x^1 are stand for logic 1, logic 0 is $x^0x^1 = 10$. The truth table is shown in Table 1. In dual logic circuit, circuit initial state only happen when x^0 and x^1 are 0 at same time. When x^0 and x^1 are 1 at same time, which stand for circuit error. Considering these above, we design comparator logical circuits in Fig. 4.

Table 1. Digital comparator true table

X_1^0	X_1^1	X_2^0	X_2^1	Y_1^0	Y_1^1	Y_2^0	Y_2^1	Result
1	0	1	0	1	0	1	0	Equal
0	1	0	1	1	0	1	0	Equal
1	0	0	1	1	0	0	1	Smaller
0	1	1	0	0	1	1	0	Greater

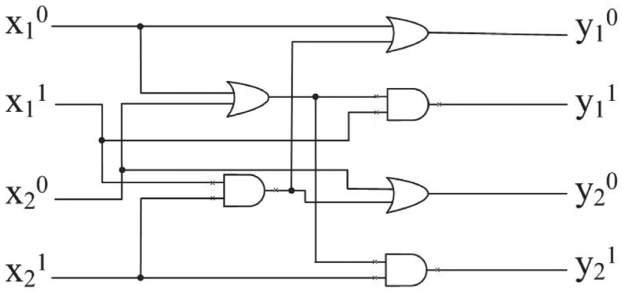


Fig. 4. The logic circuit of the digital comparator

Through the digital comparator logic circuit and true table, we can make dynamic binding between DNA hairpin strand displacement AND gate and OR gate, design locality DNA hairpin strand displacement reaction circuit Figure on DNA origami, as shown in Fig. 5. We also design biochemical experimental logic circuit Figure accordingly, as shown in Fig. 6.

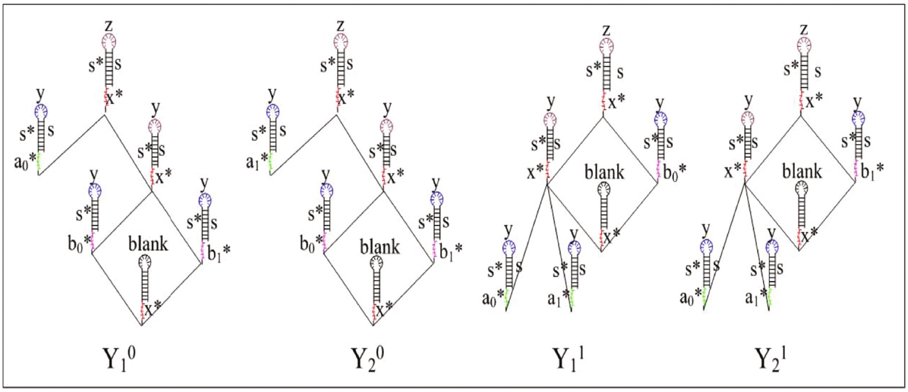


Fig. 5. The design of digital comparator for locality DNA hairpin strand displacement

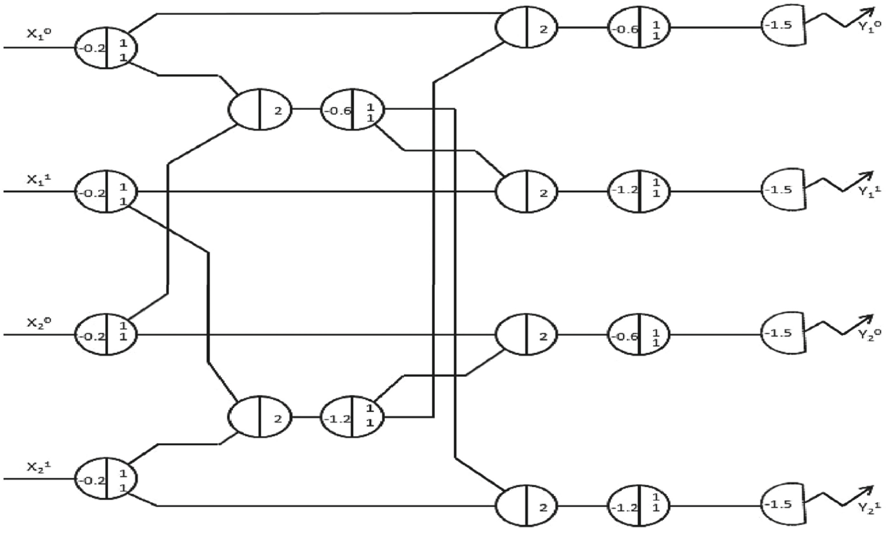


Fig. 6. Experimental logic circuit Figure of digital comparator

3.3 Simulation in Visual DSD

Visual DSD is a kind of simulation test based on DNA strand displacement reaction of biochemical circuit software. This software is designed by Matthew Lakin et al. In this paper, Visual DSD software platform is used to simulate the operation process of molecular logic circuits, The feasibility and accuracy of the data selector logic circuit are verified.

In order to fully and completely biochemical reaction, set the reaction time is 50000 s. Define 2 kinds of fluorescence signals in Fig. 7(a)–(d), said Y_1^0 and Y_2^0 respectively. Define 2 kinds of fluorescence signals in Fig. 7(e)–(h), said Y_1^1 and

Y_2^1 respectively. The definition of standard concentration is 1, when the concentration value of 0.85 nM−1 nM represents logic 1, simulation mode selection "Deterministic", can get a smooth simulation curve.

As shown in Fig. 4, the binary state of the data selector input is $1010, 0101, 1001$ and 0110. The results of the simulation output as shown in Fig. 7 are obtained. The total signal concentration is 1, which is the total value of $N = 1$ nM, If the final concentration of the output signal is between 0 nM and 0.15 nM, the output signal is a logical "0" state; If the final concentration of the output signal is between 0.85 nM and 1 nM, the output signal is a logical "1" state.

According to the input, the simulation is divided into four parts, as shown in Fig. 7:

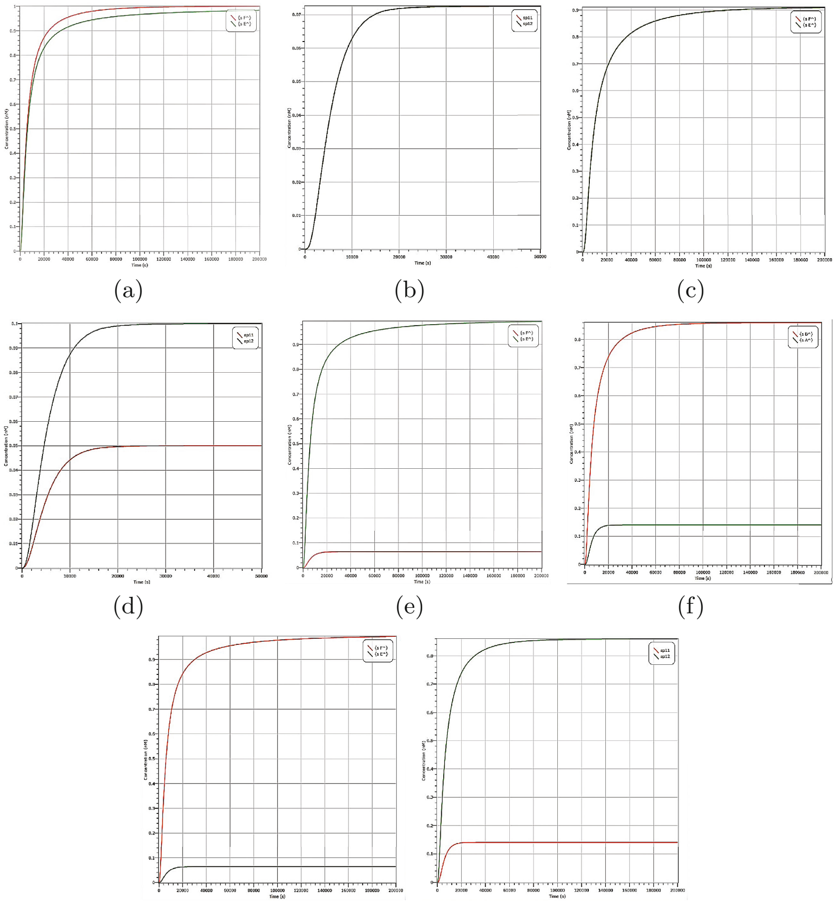
1. Figure (a) and (b) indicate that when the signal input is $X_1^0 X_1^1 X_2^0 X_2^1 = 1010$, output $Y_1^0 Y_1^1 = 10, Y_2^0 Y_2^1 = 10$, indicating that the $X_1^0 X_1^1 = X_2^0 X_2^1$.
2. Figure (c) and (d) indicate that when the signal input is $X_1^0 X_1^1 X_2^0 X_2^1 = 0101$, output $Y_1^0 Y_1^1 = 10, Y_2^0 Y_2^1 = 10$, indicating that the $X_1^0 X_1^1 = X_2^0 X_2^1$.
3. Figure (e) and (f) indicate that when the signal input is $X_1^0 X_1^1 X_2^0 X_2^1 = 1001$, output $Y_1^0 Y_1^1 = 10, Y_2^0 Y_2^1 = 01$, indicating that the $X_1^0 X_1^1 < X_2^0 X_2^1$.
4. Figure (g) and (h) indicate that when the signal input is $X_1^0 X_1^1 X_2^0 X_2^1 = 0110$, output $Y_1^0 Y_1^1 = 01, Y_2^0 Y_2^1 = 10$, indicating that the $X_1^0 X_1^1 > X_2^0 X_2^1$.

3.4 Result Analysis and Discussion

Through the observation and analysis of Fig. 7, Can find: When the input chain is added to the solution, the DNA chain begins to diffuse, The complementary DNA chains react with each other and displace the output chain by strand displacement, Because the strand displacement is a process of molecular motion, the motion releases heat energy, The temperature in the solution will rise slightly with the reaction. The temperature rise accelerates the diffusion motion between the DNA chains, Therefore, the curve of output at this time is in a state of rapid rise; As the reaction proceeds, the concentration of the input chain decreases. The curve gradually leveled off, The concentration of output will gradually stabilize between 0.85 nM and 1 nM.

Simulation show that: When the simulation time arrives at 50000 s, When the simulation time arrives at 50000 s, the curve representing logic 1 is stable within the reasonable range of 0.85 nM−1 nM, This curve represents the "ON". Curve that represents the logical "0", close to the X axis, Although some of the curves have slight shocks, they are still within the bounds of the "OFF" range of 0 nM−0.15 nM.

Through the simulation, we can see that the molecular circuit can achieve the function of the comparator better, and the speed is fast, the effect is accurate, and the implementation is simple, Moreover, the circuit has good expansibility, It creates the foundation for the realization of large-scale cascaded circuits in the future.



(a) (b) (c)

(d) (e) (f)

(g) (h)

Fig. 7. The simulation in Visual DSD

4 Conclusion

In this paper, based on the special information storage mode of DNA computing and its ability of parallel computing, we introduce the DNA replacement reaction into the molecular circuit model of comparator.

The model has the following characteristics: (1) the molecular components are simple in structure, stable in operation, and can plug and play. (2) the biochemical reaction is carried out at room temperature without external force and catalyst, the cost is low, the operation is simple, the experimental conditions are low, and the error is small. (3) the ability of information hiding and logical judgment. Finally, based on the DSD simulation platform, this paper has carried on the simulation to this molecular logic circuit model. The results show that the molecular logic circuit designed in this paper can realize the function of the comparator, the scheme is feasible and the result is reliable.

To sum up, DNA strand displacement technology has a broad application prospect in both theoretical research and practical application. With the development of science and technology, the strand displacement technology will promote the development of DNA computing, thus providing new ideas for the research of cryptography, computer science, medicine and so on.

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References

1. Adleman, L.M.: Molecular computation of solutions to combinatorial problems. Science **266**(5187), 1021–1024 (1994)
2. Seeman, C.: DNA nanotechnology: novel DNA constructions. Ann. Rev. Biophys. Biomol. **27**, 225–248 (1998)
3. Mao, C., Sun, W., Seeman, N.C.: Designed two dimensional DNA holliday junction arrays visualized by atomic force microscopy. J. Am. Chem. Soc. **121**(23), 5437–5443 (1999)
4. Thubagere, A.J., Thachuk, C., Berleant, J.: Compiler-aided systematic construction of large-scale DNA strand displacement circuits using unpurified components. Nat. Commun. **8**, 14373 (2017)
5. Mao, C., Labean, T.H., Reif, J.H.: Logical computation using algorithmic self-assembly of DNA triple-crossover molecules. Nature **407**(6803), 493–496 (2000)
6. Rothemund, P.W.K., Papadakis, N., Winfree, E.: Algorithmic self-assembly of DNA Sierpinski triangles. PLoS Biol. **2**(12), 2041–2053 (2004)
7. Song, T., Garg, S., Mokhtar, R.: Analog computation by DNA strand displacement circuits. ACS Synth. Biol. **5**(8), 898–912 (2016)
8. Georg, S., David, S.: Enzyme-free nucleic acid logic circuits. Science **314**(8), 1585–1588 (2006)
9. Qian, L., Winfree, E.: A simple DNA gate motif for synthesizing large-scale circuits. In: Goel, A., Simmel, F.C., Sosík, P. (eds.) DNA 2008. LNCS, vol. 5347, pp. 70–89. Springer, Heidelberg (2009). https://doi.org/10.1007/978-3-642-03076-5_7
10. Qian, L.L., Winfree, E.: Scaling up digital circuit computation with DNA strand displacement cascades. Science **332**(6034), 1196–1201 (2011)
11. Qian, L.L., Winfree, E., Bruck, J.: Neural network computation with DNA strand displacement cascades. Nature **475**(7356), 368–372 (2011)
12. Brun, Y.: Arithmetic computation in the tile assembly model: addition and multiplication. Theor. Comput. Sci. **378**(1), 17–31 (2006)
13. Bartlett, E.J., Brissett, N.C., Plocinski, P.: Molecular basis for DNA strand displacement by NHEJ repair polymerases. Nucleic Acids Res. **44**(5), 2173–2186 (2016)
14. Zhang, Z., Fan, T.W., Hsing, I.M.: Integrating DNA strand displacement circuitry to nonlinear hybridization chain reaction. Nanoscale **9**(8), 2748–2754 (2007)
15. David, Y., Erik, W.: Control of DNA strand displacement kinetics using toehold exchange. J. Am. Chem. Soc. **131**(47), 17303–17314 (2009)
16. Yuan, J., Nell, D.: Programmable chemical controllers made from DNA. Nat. Nanotechnol. **8**, 755–762 (2013)

17. Matthew, R., Simon, Y., Luca, C., Andrew, P.: Abstractions for DNA circuit design. R. Soc. Interface 470–486 (2011)
18. Yurke, B., Mills, A.P.: Using DNA to power nanostructures. Genet. J. Program. Evolvable Mach. **4**, 111–122 (2003)
19. Phillips, A., Cardelli, L.: A programming language for composable DNA circuits. Interface **6**(4), 419–436 (2009)
20. Yang, X., Tang, Y., Traynor, S.M.: Regulation of DNA strand displacement using an allosteric DNA toehold. J. Am. Chem. Soc. **138**(42), 14076–14082 (2016)
21. Lakin, M.R., Youssef, S., Cardrlli, L.: Abstractions for DNA circuit design. J. R. Soc. Interface **9**(68), 470–486 (2012)
22. Matthew, R., David, P.: Design and analysis of DNA strand displacement devices using probabilistic model checking. J. R. Soc. Interface **7**(72), 1470–1485 (2012)
23. Thachuk, C., Winfree, E., Soloveichik, D.: Leakless DNA strand displacement systems. In: Phillips, A., Yin, P. (eds.) DNA 2015. LNCS, vol. 9211, pp. 133–153. Springer, Cham (2015). https://doi.org/10.1007/978-3-319-21999-8_9
24. Shi, X.L., Lu, W., Wang, Z.Y., Pan, L.Q., Cui, G.Z., Xu, J., Thomas, H.L.: Programmable DNA tile self-assembly using a hierarchical sub-tile strategy. Nanotechnology **25**(7), 075602 (2014)
25. Sun, J., Wu, Y., Cui, G.: Finite-time real combination synchronization of three complex-variable chaotic systems with unknown parameters via sliding mode control. Nonlinear Dynam. **88**(3), 1677–1690 (2014)
26. Sun, J., Wang, Y., Wang, Y.: Finite-time synchronization between two complex-variable chaotic systems with unknown parameters via nonsingular terminal sliding mode control. Nonlinear Dynam. **85**, 1105–1117 (2016)
27. Sun, J., Shen, Y.: Quasi-ideal memory system. IEEE Trans. Cybern. **45**(7), 1353–1362 (2015)
28. Yang, J., Jiang, S.X., Liu, X.R., Pan, L.Q., Zhang, Q.: Aptamer-binding directed DNA origami pattern for logic gates. ACS Appl. Mater. Inter. **8**, 34054–34060 (2016)
29. Yang, J., Dong, C., Dong, Y.F., Liu, S., Pan, L.Q., Zhang, C.: Logic nanoparticle beacon triggered by the binding-induced effect of multiple inputs. ACS Appl. Mater. Inter. **6**(16), 14486–14492 (2014)
30. Shi, X.L., Wang, Z.Y., Deng, C.Y., Song, T., Pan, L.Q., Chen, Z.H.: A novel biosensor based on DNA strand displacement. PLoS ONE **9**(10), e108856 (2014)
31. Matthew, L., Simon, Y.: Visual DSD: a design and analysis tool for DNA strand displacement systems. Bioinformatics **27**(22), 3211–3213 (2011)