SemiSynBio is an emerging topic toward the construction of platforms for next-generation information processing. Recent research has indicated its promising prospect toward information processing including algorithm design and pattern manipulation with the DNA TMSD reaction, which is one of the cores of the SemiSynBio technology route. The DNA TMSD reaction is the process in which an invader strand displaces the incumbent strand from the gate strand through initiation at the exposed toehold domain. Also, the DNA TMSD reaction generally involves three processes: toehold association, branch migration and strand disassociation. Herein, we review the recent progress on information processing with the DNA TMSD reaction. We highlight the diverse developments on information processing with the logic circuit, analog circuit, combinational circuit and information relay with the DNA origami structure. Additionally, we explore the current challenges and various trends toward the design and application of the DNA TMSD reaction in future information processing.

1. Introduction

According to Moore’s law, the number of subunits on the integrated circuit will double per eighteen to twenty-four months, while maintaining the cost. Also, this trend has been maintained for over half century. Inevitably, the physical limitation is on the nanometer scale due to the quantum effect, but the size of the subunit has reached several nanometers recently, which has prompted researchers to search for smaller sized subunits to maintain the computing function.

SemiSynBio is an emerging topic toward the application of synthetic biology in semiconductor technology, as indicated by several recent breakthrough studies. The topic of SemiSynBio generally deals with the fundamental problem of biology and semiconductor technology to fabricate novel biomaterials for...
devices and systems, including novel storage and computing models, basic algorithm designs, novel architecture designs for biomaterials and nanodevices, fabrication of electronic systems for biomaterial communication, and extension of novel characterization systems. As a cross-disciplinary topic, SemiSynBio may totally redefine the design and construction routes of semiconductor structures due to its totally different properties such as programable, low cost, and low energy nature, which is based on the cooperation of multi-regions such as DNA synthesis, DNA characterization, electronic design automation, nanofabrication technology, and high effect information process. Among the general nanomaterials investigated such as DNA, RNA, proteins and micro-molecules, DNA emerges as the most promising material in information storage.2,3 Thus, DNA exhibits promising prospect toward next-generation digital information storage and processing.

Nature is an open system, which keeps away from the equilibrium state through material and energy exchange processes. From the origin, DNA functions as the chief medium to store heredity information and manipulates sophisticated reaction processes.4 DNA is composed of four types of nucleotides with four bases (adenine (A), thymine (T), guanine (G), and cytosine (C)). According to the simple base-pairing principle that A conjugates with T and C conjugates with G,5 DNA transforms into diverse complex structures with multifunctions.6–8

Among the sophisticated biochemical reactions of DNA strands, various research has revealed that the strand displacement reaction is a highly programable and practical path to anticipate information processing at the molecular level such as logic information processing,9 analog information processing,10–12 combinational information processing,13 and reconfigurable information relay.7,14 The logic information process deals with digital signals with a logic circuit.15 The analog information process deals with continuous signal transformation with an analog circuit.16 The combinational information process deals with both logic and analog information with both logic and analog circuits.11 The reconfigurable information relay focuses on the structure transformation with DNA origami.7 Simultaneously, both the circuit and transformation are mainly associated with the DNA TMSD reaction.

The DNA TMSD reaction is the transformation process in which an invader strand displaces the incumbent strand from the substrate strand, which is initiated from the toehold domain and is similar to homologus recombination.17 This transformation process generally turns the strand system from an active state to a stable state, which is driven by Gibbs free energy and thermal disruption.18–20 Since the pioneer work of the construction of DNA “tweezers” by Yurke et al.,21 diverse DNA nanomachines have been designed to carry out different functions for information processing. The early works focused on the investigation of the fundamental properties of the DNA TMSD reaction such as controlling the kinetic property of the DNA TMSD reaction with the toehold domain,18 together with the construction of basic logic information operations of AND, OR and NOT gates,9 finite state machines for DNA transducer design,22 and biological biped walking motors,23 which were even designed with synchronized walking fashion.24 Then, several complex reaction networks or patterns were devised to perform more sophisticated functions ranging from structure manipulation,25–28 algorithm investigation such as half/full adder,29 square-rooting function,30–32 network communication,33–37 DNA algorithmic logic unit,38 and oscillator,39,40 to diagnostic therapy including drug delivery systems41–45 and sensing.

2. Principle of DNA TMSD reaction

The three general steps of the DNA TMSD reaction are toehold association, branch migration and strand dissociation.36 Driven by the Gibbs free energy, all the strands reach steady equilibrium states through the TMSD reaction.57 The common TMSD reaction is composed of two strands, one invader strand and one substrate strand, which contains an incumbent strand and a bottom gate strand. The invader strand first binds to the bottom gate strand through the toehold domain, then starts the branch migration process through random walk and dissociates the incumbent strand from the bottom gate strand.19 Generally, the TMSD reaction provides a direct path for the reconfiguration of the invader strand and the substrate strand, which has been widely investigated and applied in various areas including algorithm computation, molecular machines, and pattern formation.

Since the application of the TMSD reaction in DNA tweezers by Yurke et al. in 2000,21 the TMSD reaction has been designed into various reaction patterns with distinctly different functions.38 Herein, we class the TMSD reaction into the toehold displacement (TD) reaction and toehold exchange (TE) reaction for the design of the TMSD reaction based on whether the reaction is irreversible.

2.1 TD reaction

The TD reaction is defined as the TMSD reaction in which the invader strand fully occupies the incumbent strand domain and the toehold domain, causing the reaction to be irreversible. As shown in Fig. 1A, the invader strand first binds to the substrate strand on the a* domain. After the branch migration process, the incumbent strand is released from the bottom gate strand, and the invader strand forms an inert double strand structure with the bottom gate strand. As the substrate strand and invader strand are both added to the solution, the TD reaction proceeds irreversibly and is thoroughly consumed until one reactant is exhausted. The TD reaction is a second order reaction, which reacts at an exponential speed that largely depends on the kinetic constant of the reaction. According to the research work by Zhang et al.18 the kinetic constant of the TD reaction can vary by several magnitudes, ranging from 1 M⁻¹ s⁻¹ to 6 × 10⁶ M⁻¹ s⁻¹ by modifying the length and the sequence of toehold domain.

To quantitatively understand the process of the TD reaction A + S → O + W, according to the law of mass action, we can obtain differential eqn (1).

\[
\frac{d[O]}{dt} = k_f \times [A] \times [S]
\] (1)

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will react with strand S2 to re-generate strand A and S1, causing the exchange of the toehold region from a* to c*. Also, strand O reversibly displaces the incumbent strand O from substrate strand S1, the inert double strand structure W. (B) TE reaction: invader strand A reversibly displaces the incumbent strand O from substrate strand S1, causing the exchange of the toehold region from a* to c*. Also, strand O will react with strand S2 to re-generate strand A and S1.

where [\xi] is the extent of reaction to quantify the amount of each product during the reaction process. [A] and [S] are the concentration of reactants A and S, respectively, and \( k_f \) is the forward reaction kinetic constant.

Then the extent of reaction \([\xi]\) is given by

\[
[\xi] = \frac{[S]_0 - ([S]_0 - [A]_0) e^{-(k_f/k_b) t} - [S]_0}{[A]_0 e^{-(k_f/k_b) t} - [S]_0} + [S]_0
\]  

where \([A]_0\) and \([S]_0\) are the initial concentration of A and S in eqn (2). Thus, it can be concluded that the concentrations of the reactants in the TD reaction generally change at an exponential speed. Once one of the reactants is exhausted, the reaction stops.

2.2 TE reaction

The TE reaction is defined as the TMSD reaction in which an invader strand partially occupies the incumbent strand domain, indicating that the double strand structure always keeps a free toehold domain overhanging and the reaction is reversible. Different from the full displacement of the incumbent strand in the TD reaction, the released incumbent strand in the TE reaction can bind to the new substrate strand and re-release the invader strand due to the exposed toehold domain, which can be regarded as a toehold exchange reaction. As shown in Fig. 1B, strand A can invade substrate strand S1 through domain a*, causing the release of the incumbent strand O and the new substrate strand S2. Additionally, the released incumbent strand O can also hybridize with S2 through domain c*, and re-release invader strand A. Overall, the exposed toehold domain is exchanged from a* to c* in the TE reaction, keeping the substrate strand active. Similarly, the TE reaction is also a second-order reaction but is reversible, which indicates that the final balance state depends on the forward and backward kinetic constants. Similarly, to quantify the reaction process of the TE reaction \( A + S \leftrightarrow O + W \), we can obtain differential eqn (3),

\[
\frac{d[\xi]}{dt} = k_f [A]_0 [S]_0 - k_b [O]_0 [S]_0
\]  

where \([\xi]\) is the extent of reaction to quantify the amount of each product during the reaction process. \([A]_0\), \([S]_1\), and \([S]_2\) are the concentration of reactants A, S1 and S2, respectively. \( k_f \) and \( k_b \) are the forward and backward reaction kinetic constants, respectively. As the reaction reaches the equilibrium state, \([\xi]\) becomes the maximum value and \( \frac{d[\xi]}{dt} \) becomes zero. Then, we obtain

\[
\frac{[O]_0 [S]_2}{[A]_0 [S]_1} = k_f/k_b = K_e
\]  

where \( K_e \) is the equilibrium constant of reaction eqn (4), which is determined by the energy distribution. Particularly, for the initial condition that \([A]_0 = [S]_1\), \([O]_0 = [S]_2\), \( [O]_0 = [S]_2\), \( K_e = 1 \), we can obtain the value of \([\xi]\) at the equilibrium state.

\[
[\xi] = \frac{[A]_0}{2}
\]  

Thus, the reaction process is the redistribution of the concentration of reactants.

3. Application in logic circuit

Logic circuit (also digital circuit) is a type of circuit to transform and manipulate digital signals, which is based on Boolean algebra 0 and 1, while 0 refers to a low signal and 1 refers to a high signal. Owing to their unique programmable properties, TMSD reactions are broadly utilized in logic circuits from basic gates including AND, OR, XOR, and NAND to special functions such as half/full adder, multiplexer, and square roots.

3.1 Basic gate design

The logic circuit is composed of three basic logic gates, including the AND gate, OR gate and NOT gate. The AND gate and OR gate generally require two input signals and generate one output signal. In addition, the AND gate exports a high-level output signal only when both inputs are high-level, otherwise the output signal will be low-level. However, the OR gate requires either one input signal to be high-level and generates one high-level output signal, otherwise the output signal will be low-level signal. However, the NOT gate only needs one input signal and generates one inverted output signal.

To adapt to various circumstances with multi-inputs and multi-functions, general composite logic circuits are introduced. The general composite logic circuits contain NAND, NOR, XOR, XNOR, etc. The truth table of these gates are listed in Table 1. The NAND gate generates a high-level signal once any low-level signal is input and vice versa. The NOR gate generates a high-level signal only if all the inputs are low-level
signals and vice versa. The XOR gate generates a high-level signal only if the two input signals are opposite levels and vice versa. The XNOR gate generates a high-level signal only if the two inputs are same level signals and vice versa, which is opposite to the XOR gate.

### 3.2 Logic computation

#### 3.2.1 Half/full adder

A half adder is the unit that adds two binary digits, generating a sum digit and a carry digit, as shown in Fig. 2A. A half adder circuit requires a XOR gate and an AND gate. The output of the XOR gate is the sum digit and the output of the AND gate is the carry digit. A full adder is the unit that adds three binary digits including two binary digits to be added and one carry digit from the upstream adder, as shown in Fig. 2B. The full adder also generates a sum digit and a carry digit. Consequently, the full adder obtains the function to add a multibit binary number and realizes the function of addition.

Li et al. proposed the half adder and full adder design based on the DNA TMSD reaction in 2016. Fig. 2C shows the strand reaction path for the XOR gate, where only the addition of strand X or Y will cause the release of the signal strand and generate a fluorescence signal. However, both the addition of strand X and Y would cause the hybridization of the strand X2+ and Y2+ through domain A and A*. Firstly, the input strand X replaces strand X1+ from the substrate strand X1+/X1− through the TE reaction, which is initiated at toehold domain T1. Then strand X1+ replaces strand X2+ from substrate strand X2+/X2− through the TE reaction via toehold domain T3*. Strand X2+ binds with toehold domain T5 on the hairpin structure H and opens the hairpin structure, causing the overhang of domain T6*. Finally, the fluorescence signal strand R+ is released from the quencher strand R− via the opened hairpin structure. Similarly, input strand Y undergoes a similar reaction path in solution. As shown in the reaction path of the AND gate in Fig. 2D, the addition of strand X or Y will release the intermediate strand P+. However, due to the longer toehold domain of substrate strand Q+/Q− than V+/V−, strand P+ will react with Q+/Q− first. As strand Q+/Q− has been exhausted, the residual strand P+ will react with strand V+/V− and release strand V− for downstream reaction and release the fluorescence signal, which becomes the concentration-determined gate. With the XOR gate and the AND gate, the half adder and full adder can be realized through the further cascade reactions.

In addition, other different models were also utilized to build the half adder or full adder, including molecular beacon by Yang et al., strand displacement model by Li et al., DNA polymerase model by Su et al. and DNA switch model by Wang et al.

<table>
<thead>
<tr>
<th>INPUT</th>
<th>AND</th>
<th>OR</th>
<th>NAND</th>
<th>NOR</th>
<th>XOR</th>
<th>XNOR</th>
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</table>

Fig. 2 Architecture design of half adder and full adder. (A and B) Logic design for half adder and full adder, respectively. (C and D) DNA TMSD reaction for the implementation of XOR gate and AND gate, respectively. Adapted from ref. 29 with permission from The Royal Society of Chemistry.
3.2.2 Square roots. A four-bit square root circuit was proposed by Qian et al.\textsuperscript{29} in 2011, as shown in Fig. 3A and C. The basic logic gates included only AND and OR gates, which were based on the seesaw model.

As shown in Fig. 3B, the addition of either strand $W_{1,2}$ or $W_{3,2}$ causes the release of the top strand in gate strand $G_{2,3,5}$ through the TE reaction. Then, the released top strand will react with the threshold strand first due to the longer toehold domain and the residual strand will react with gate strand $G_{5,5,6}$. Finally the signal strand is released through the released top strand $G_{3,5,6}$. However, different concentrations of the threshold strand $Th_{2,5,5}$ lead to different functions of the seesaw gate model. When the concentration of the threshold strand is set to 0.6, the model will release a fluorescence signal as the addition of either strand $W_{1,2}$ or $W_{3,2}$. However, the model will release a fluorescence signal only when both strands $W_{1,2}$ and $W_{3,2}$ are added as the concentration of the threshold strand is set to 1.2. Thus, the adjustment of the concentration of the threshold strand will realize the function of the OR and AND gate. However, the NOT gate is difficult to be directly implemented simply through a single strand since the downstream circuit will directly be triggered if there is no input signal addition and exhaust the use-once circuit substrate strands irreversibly. Therefore, a dual rail design was introduced to represent the logic ON and OFF with two input signals, instead of only one input signal. The addition of each input strand represents the input signal ON and OFF, respectively, transforming the concentration difference-dependent logic gate into a strand difference-dependent logic gate. Additionally, the signal restoration module was introduced into the circuit after each logic module to ensure the concentration of the output signal is high enough to be propagated continuously. Consequently, the four-bit square root circuit was implemented with the whole possible inputs based on the seesaw gate model, indicating the feasibility of the seesaw gate model to construct a large-scale circuit. When the circuit ran, 130 different DNA strands existed in one test tube.

However, it took too much time for the seesaw gate model to finish the computation process of the square root circuit, which was as long as about 6 h (half completion time). Thus, to obtain a better performance of time response of the square root circuit, Song et al.\textsuperscript{31} adopted Bst DNA polymerase to implement the four-bit square root circuit and decreased the half completion time to as low as 25 min at most for all the input combinations. Simultaneously, the composition of the reaction was decreased to ~37 DNA strands, compared with that by Qian et al.\textsuperscript{30} Wang et al. proposed the switch circuit design based on the DNA TMSD reaction and further decreased the number of strands to at most 24 with a higher computation speed.\textsuperscript{32} In addition, Zhou et al.\textsuperscript{60} extended the bit square root circuit to 10 bits. Each site was defined by a single strand and each output bit was defined by a distinct fluorescence signal. However, only an integer answer could be implemented based on the computing platform.

3.2.3 Other functions. Following the pioneer work of Adleman in molecular computation,\textsuperscript{61} plenty of other investigations in modular computation have been performed with DNA logic circuits. Yang et al. built a half subtractor based on the molecular beacon.\textsuperscript{29} The half subtractor was constructed by an INHIBIT gate and a XOR gate, where the INHIBIT gate generates a borrow-bit and the XOR gate generates a difference-bit. As shown in Fig. 4A, input signal $IA'$ subtracts input signal $IB'$ and a borrow bit with a difference bit is generated. Su et al. developed a 4:1 multiplexer through strand displacement synthesis,\textsuperscript{38} which realized a four-bit encoder design, as shown in Fig. 4B. The multiplexer had two control bits to control which input signal could transmit the signal to the output, thus directing the sequence of the output signal. Additionally, a more sophisticated function was introduced (Fig. 4C). A 1-bit DNA ALU (arithmetic logic unit) was first indicated by collocating the pre-established logic modular of full adder and 4:1 multiplexer, which is a core unit of a CPU. Arbitrary bit control could be implemented via the addition of correlative opcodes and generated the answer of corresponding bit computation, thus facilitating the programmable selective output. Various approaches have been implemented towards constructing more sophisticated circuits with advanced functions, which offer us a more intrinsic understanding of the splendid DNA reaction.

4. Application in analog circuit

The analog circuit always focuses on analysing the concrete values and sticks to consecutive and detail changes of the value.\textsuperscript{16,62,63} In the electronic circuit, the analog circuit processes information based on the properties of a specific module, such as resistance, capacitance, diode, and triode. Through the stoichiometric relation of the concentration of different DNA strands, different combinations of the DNA TMSD reaction form different algorithm results, dynamic systems and self-assemble patterns.
4.1 Analogue computation

Analogue computation generally deals with the sequential value or curve of functions to solve different math functions such as sqrt(x), ln(x) and exp(x). The DNA TMSD reaction provides a direct algorithm design path for analogue computation due to its unique reaction function, as shown in section 2. Through controlling the initial concentration ratios of different reactants and the kinetic constants of different reactions, specific concentration curves can be obtained.

Song et al. proposed three basic algorithm calculation models with the DNA circuit, consisting of addition, subtraction, and multiplication, as shown in Fig. 5. Both the input and output signals are analog values, referring to the corresponding concentrations of input strand and output strand, respectively. Based on the basic algorithm models, the polynomial function was implemented via a cascading reaction. Derived from the Taylor series and Newton iteration methodology, even a nonpolynomial function could also be realized with the basic models, such as exponential function and reciprocal function. Afterwards, they built three basic autocatalytic amplifier models to calculate the functions such as sqrt(x), ln(x), and exp(x), which were derived from the stoichiometry variation of relevant DNA species in a tunable range. However, these designed architectures were all realized via simulation codes, which indicated the potential for exploration in more analog circuit designs and implementations.

![Fig. 4 Other functions of logic circuit design.](https://example.com/fig4.png)

![Fig. 4 Other functions of logic circuit design.](https://example.com/fig4.png)

**Fig. 4** Other functions of logic circuit design. (A) Half-subtractor based on molecular beacon. Adapted from ref. 59 with permission from The Royal Society of Chemistry. (B) 4 : 1 multiplexer based on strand displacement synthesis. Adapted from ref. 38 with permission from Springer Nature. (C) 1-bit DNA ALU constructed with a full adder and a 4 : 1 multiplexer. Adapted from ref. 38 with permission from Springer Nature.

![Fig. 5 Schematics of three algorithm calculations: addition, subtraction, and multiplication.](https://example.com/fig5.png)

**Fig. 5** Schematics of three algorithm calculations: addition, subtraction, and multiplication. Adapted from ref. 10 with permission from the American Chemical Society.
4.2 Dynamic system

Based on the general principle to transform a chemical reaction to corresponding DNA strand displacement reaction, Soloveichik et al.\textsuperscript{40} proposed a common dynamic system design to construct an Oregonator oscillator, Rössler chaotic system, 2-bit pulse counter, and Incrementer state machine. Later, Srinivas et al.\textsuperscript{39} proposed a novel dynamic oscillator system, as seen in Fig. 6. Different from the general oscillator design derived from the gene circuit or cell,\textsuperscript{64} this indicated a simple molecular mechanism from scratch without a sophisticated enzyme-mediate environment. They constructed a rock-paper-scissors oscillator system purely dependent on the DNA strands. From the simple molecular program of rock-paper-scissors, they derived the corresponding DNA strand displacement reaction to simulate the molecular program. Although the challenge of the reaction system is the strand crosstalk and signal leakage, they proposed a systematic design principle for strand design and leakage inhibition to minimize the strand crosstalk and signal leakage, such as sequence symmetry minimization, using ACT alphabet, helices ending with GC base pairs, 5’ toehold initiation, isoenergetic toehold, strong base pairs at junctions, and “clamps”. This systematic sequence design principle indicates a comprehensive design methodology for DNA strand design. Finally, based on the design optimization listed above, all the DNA strands were added to a test tube and the result exhibited a damped oscillator wave. Accounting for the experimental result implemented, this illustrated the feasibility of the general transform principle for arbitrary chemical reaction.

4.3 Self-assemble material

Depending on the continuous signal strand release process, Song et al.\textsuperscript{65} introduced the catalyst strand displacement reaction for the controllable aggregation of AuNPs, as shown in Fig. 7A. This catalyst strand displacement reaction showed a similar structure with the seesaw model. As a higher concentration of catalyst strands was set, a faster reaction rate could be obtained, causing a faster aggregation rate of AuNPs.

Then, Zhou et al.\textsuperscript{66} applied the entropy-driven amplifier circuit for the construction of a colloid assembly known as “programmable atom equivalents” (PAE), as shown in Fig. 7B. Although the general method for colloid assembly is a thermal annealing process based on precise temperature control instruments, the entropy-driven amplifier circuit applied here released the trigger strand for the assembly of DNA strands modified with Au nanoparticles. By adding a small amount of catalyst input “catassembler” strand, the trigger strand could be released at a slow velocity and built different colloidal structures such as FCC, BCC, AlB\textsubscript{2}, and CsCl. Through the strand design, different strands modified with nanoparticles could be released via a programmable pathway and formed two different colloidal structures, while the common thermal annealing process could only construct one colloidal structure. This investigation indicates a new promising prospect for the DNA catalyst amplifier circuit towards self-assembled materials, including DNA origami, DNA tiles and colloidal structures.

Fig. 6 Desired dynamic oscillation process for the molecular program rock-paper-scissors and the experimental realization of the oscillator based on the DNA strand displacement reaction. Adapted from ref. 39 with permission from The American Association for the Advancement of Science.

Fig. 7 Design of self-assembled material. (A) Mechanism of DNA–AuNP assembly. Adapted from ref. 65 with permission from the American Chemical Society. (B) PAE assembly of the temperature-invariant time-dependent interaction and energy-invariant thermal annealing process. Adapted from ref. 66 with permission from the National Academy of Sciences.
5. Application in combinational circuit

Early researchers proposed that investigation on the solely logic circuit or analog circuit would not obtain the highest efficiency in information processing. However, the combination of logic circuit and analog circuit would access the most efficient path for information processing. The combinational circuit is a distributed reaction network that focuses on the communication among diverse distributed reaction cores and network construction. Based on the free diffusion of DNA strands in solution, the DNA TMSD reaction can be manipulated to a specific path for sensing and computation.

5.1 Distributed computation

The general computing model is a centralized computing model, which has been broadly applied in most computing devices ranging from personal computers to large servers. With the development of the economy and the increase in computing complexity, the centralized computing model exposes the problem of a single model and poor velocity for several large computation demands. In contrast to the centralized computing model, the distributed computing model divides the large problem into several small sections and distributes small sections to various centralized computers elsewhere, realizing parallel computing with evolutionary velocity. Joesaar et al. first presented a computing platform called “bio-molecular implementation of protocellular communication” (BIO-PC) based on the controllable populations of synthetic protocells67 (Fig. 8). The single-strand DNA works as the information molecular for information transmission. Different computations were accomplished within the semipermeable microcapsules. The gate strands were localized inside the microcapsules located in the microfluidic trap platform, but the single-strand DNA could go through different microcapsules freely. Due to the distributed gate strands, the single strand DNA could react with a specific gate strand and generate the corresponding output strand DNA, which carried relevant information that was transmitted to downstream microcapsules. With the distributed microcapsules, different tasks have been implemented including detection, transduction, cascading, amplification, logic, and even feedback. As shown in Fig. 8, the AND gate is constructed so that the output strand would be released only when both A and B are input. Although the distributed synthetic protocell system does not exhibit comparable properties to a real living cell, the mimic design indicates wide potential toward application in the molecular communication and nonlinear regulatory mechanism.

5.2 Neural network

Neural network is a range of algorithms that involve sensing, recognizing, and memorizing, which functions much more like a mammalian brain. After gathering different characteristic information, the neurons gather the information and generate the result. Qian et al. first implemented a four-neuron Hopfield associative memory based on the seesaw model68 (Fig. 9A). The Hopfield network is a network integrated by quantities of artificial neurons entangled with each other, which can remember specific patterns after being trained. Initiated with partial elements of certain patterns, the Hopfield network could recognize the pattern and recover the full state of the

Fig. 8 Design elements for BIO-PC and the AND gate based on BIO-PC. Adapted from ref. 67 with permission from Springer Nature.

Fig. 9 Network design based on DNA TMSD reaction. (A) Four-neuron Hopfield associative memory based on seesaw gate design. Adapted from ref. 61 with permission from Springer Nature. (B) Winner-take-all neural network and implementation of the chemical reaction network design. Adapted from ref. 63 with permission from Springer Nature.
pattern. Thus, the Hopfield network functions as an artificial associative memory module, which can remember pre-trained patterns. Each neuron used in the experiment was constructed by scaling up the seesaw gate model with a linear threshold circuit. Through training in silico, the configuration parameters were obtained, and the corresponding stoichiometric concentrations of DNA strands were added to the system. This work associated the DNA strand displacement logic circuit with the neural network and exhibited a new branch for both DNA and artificial intelligence systems. Although the DNA-based Hopfield network required about 8 h to determine the relevant patterns, it indeed exhibited the thinking process within a test tube.

In 2018, Cherry and Qian extended the DNA-based neural network to a winner-take-all model (Fig. 9B). The winner-take-all model is an electoral mechanism to elect the winner based on the voting results from proportional representations. Different from the normal electoral mechanism based on uniform votes, the votes in the winner-take-all model are unequal with different weights. A winner-take-all neural network is a network that selects the neuron with the largest weight sum among all the neurons, which is based on a specific input. A basic neuron is comprised of five components including weight multiplication, summation, pairwise annihilation, signal restoration and reporting module. Based on the seesaw model, the weight values of different inputs can be transformed into the relevant stoichiometric concentrations of different gate strands. Simultaneously, the selection step is implemented via cooperative hybridization principle to exhaust all the components in pairs and the winner species remaining are amplified to transmit to downstream reaction. To demonstrate the power of the winner-take-all neural network, the weight values were set according to the standard database. Ultimately, the model realized the recognition of handwritten digits from 1 to 9 in 10 × 10 pixels. Briefly, the DNA-based neural network provides a novel approach to construct artificial molecular machines with memory and perception.

6. Application in information relay

Information relay is the general phenomenon used to assist and maintain diverse activities of all the matter in nature. One key challenge is how to imitate the information relay process at the molecular level. Recent research has revealed the information relay pattern from static patterns such as self-assembly, seedling growth, and dynamic pattern including reconfigurable structure transformation. In the case of the static pattern, Barish et al. presented the seed design, which could nucleate three types of crystal structures, and carried out the logic design for variable-width tile, copy tile, and binary counter tile. Additionally, Woods et al. proposed the iterated Boolean circuit (IBC) design for molecular computation with the self-assembly method. The specific seeding site would generate a specific hybridization pattern of DNA tiles, which refers to the different logic gate design. In the case of dynamic pattern, Song et al. first proposed a design to realize the information relay behaviour with the DNA origami structure and manipulated the transmission path through structural design. The orientation of the DNA origami structure could be easily transformed from the horizontal direction to the vertical direction through the addition of one trigger strand, as shown in Fig. 10A. The addition of the trigger strand introduced extra energy to the origami structure, which drove the newly formed origami structure to reconfigure to a stable orientation. Combined with the DNA circuit, different information transitions can be manipulated on DNA origami such as spatial control, information coding and digit operation.

6.1 Spatial control

Accounting for the orientation transformation of the DNA origami structure, Liu et al. extended the structure transformation to spatial transformation through the addition of a specific strand to limit the spatial domain. As shown in Fig. 10B, the addition of the red trigger strand enabled the transformation of the long blue R conformation to the short red S conformation. The linker strand was added to hybridize with the extended strand conformation at the end of the S conformation, with which the adjacent S conformation would be linked. Subsequently, the blue trigger strand was added, and the short S conformation was transformed to the long R conformation. Owing to the limitation of the linker strand, the R conformation was bended into a curve shape in the transition process. Finally, the three S domains were all transformed to the R conformation, and the plane structure 2D R3 was transformed to 3D R3. Simultaneously, Wang et al. proposed a design to program the curvatures with the reconfigurable DNA domino origami structure (Fig. 10C). Different from the origami design with uniform tiles, the un-uniform tiles with unequal length at each side would bend the structure into different curvatures after the mechanical structure transformation and indicated different structure information.

Furthermore, the spatial control could also be carried out through a self-assembled DNA-origami nanoactuator, as proposed by Marini et al. The input hybridizing target molecule binds to the probe strand and bends the internal disk structure from a plain structure to a curve structure. The third single strand can release the target from the probe, and thus the internal disk could be reset to the initial state. This design enables a DNA-origami nanoactuator with revertible function for on-off switch to be obtained.

6.2 Information coding

The reconfigurable structure of DNA origami indicates not only the shape transition, but also the position change at the molecular level. Fan et al. proposed a design to construct the molecular information coding (MIC) in a reconfigurable DNA origami domino array (DODA). As shown in Fig. 10D, the first trigger strand, which functions as decoding key 1, brings each immobilized strand on the origami closer. Then, decoding key II is added to remove the protect strand, activating...
strand T3 to react with adjoined strand T4 through the TD reaction. Thus, signal strand T5 can bind to free strand T2 and indicate the decoding answer. Without either decoding key I or II, the decoding answer will not be obtained. Before the addition of decoding keys I and II, the information on the DODA is encoded to an undistinguished state. After the decoding process, the information on the DODA can be obtained.

Furthermore, the MIC platform was further applied to decode the letters "SJTU". Before the decoding process, the dot matrix on the DODA was unable to recognize it. After the decoding process, the letters "SJTU" could be obtained on the DODA. Consequently, the MIC design on DODA exhibits potential application in molecular information encryption.

6.3 Digit operation

Digit operation is the fundamental procedure of digit information processing. Owing to the fact that information is coded and stored as a binary number style, digit operation, a bottom operation, indicates a convenient and fast information processing step such as bit shifting and logic operation. Similar to the operation in silico, DNA origami was also applied to realize the digit operation at the molecular scale. Fan et al. investigated the digit operation on the reconfigurable DNA origami domino array-based dynamic pattern operation (DODA DPO) system and realized digit writing, erasing and bit shifting operations. As shown in Fig. 10E, the writing operation consisted of four steps including activation, execution, toehold strand displacement and writing. The activation process is the transformation of the origami structure. The execution process is the displacement of protect strand W1 through the TD reaction. The toehold strand displacement process is the displacement of strand W3 to free the writing site. The writing process is the hybridization of signal strand W5 and writing site strand W2. After the writing operation, the information could be coded on the origami structure stably. Furthermore, the erasing and bit shifting operations were designed to proceed via similar reaction paths. However, accounting for three digits operations of writing, erasing and bit shifting, each structure could only be designed to one operation. Overall, the digit operation on the DODA DPO system still indicates promising prospect toward a unique information relay path on origami patterns.

7. Outlook

Owing to its unique biochemical properties, DNA indicates a totally different algorithm design and relay path for information processing compared with silicon materials. The TD reaction and TE reaction are two basic reaction patterns for the DNA TMSD reaction. Various reaction paths are designed via different flexible combinations of two reaction patterns. Following the function directions of the common logic circuit and analog circuit, DNA exhibits potential ability to attain the functions for computation or relay processes. However, there are still several challenges in information processing with the DNA TMSD reaction. Firstly, the signal leakage in the DNA TMSD reaction is the most common chal-
lenge. Even with a suitable design, signal leakage cannot be blocked. Based on several design principles to inhibit the initial leakage and asymptotic leakage, the signal leakage can be effectively weakened. However, the cascade reaction design can accumulate the signal leakage level by level, causing obvious leakage signals.

Secondly, the strand design complexity generally impedes the dimension expansion of the DNA strand displacement reaction. Although the coding principle enables sequence complexity as high as $4^n$ (where $n$ is the number of strands), large amounts of code results face the challenge of the formation of secondary structures, which disturb the pre-designed TMSD reaction paths.

Additionally, one trend of the DNA TMSD reaction in information processing is the molecular pattern formation that the concentration distributions of strands generate special reaction patterns. The difference in concentration distribution comes from the variation in the physical chemistry environment, which indicates the interaction toward detail transformation in nature. Another trend is the algorithm design that the transformation process of the concentrations of DNA strands in DNA circuits can serve as the unique reaction function according to the relevant input signals. The reaction function is the intrinsic property of the DNA circuit and can obtain specific complex results directly instead of plenty of computation steps in silicon.

Conflicts of interest
There are no conflicts to declare.

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