Coupling 2-Aminopurine with DNA Copper Nanoparticles as a Rapid and Enzyme-Free System for Operating DNA Contrary Logic Pairs

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Abstract: Exploring affordable and efficient platform for innovative DNA computing is of great significance. Herein, by coupling 2-aminopurine (2AP) with DNA copper nanoparticles (CuNPs) as two universal opposite outputs, we, for the first time, fabricated a rapid and enzyme-free system for operating DNA contrary logic pairs (D-CLPs). Notably, derived from the rapid and concomitant response of both fluorescent probes, different D-CLPs can be achieved via a “double-results-half-efforts” manner in less than 20 min with low-cost. Moreover, based on the same system, the smart ratiometric analysis of target DNA was realized by employing the high reliability and accuracy of D-CLPs, providing a robust and typical paradigm for the exploration of smart nucleic acid sensors.

Keywords: 2AP; CuNPs; ratiometric fluorescent; D-CLPs

1. Introduction

In recent decades, we have witnessed the significant impacts generated by silicon-templated semiconductor computers on various aspects of our lives. Meanwhile, when it comes to the word “Molecular Computation”, this can be traced back to the groundbreaking work of Prof. de Silva in 1993 [1]. Through mimicking the Boolean operation (0/1) at the molecular level, different output signals can be obtained after inputting specific binary stimuli to the appropriate platforms. Since the first molecular AND gate was designed [1], this area has flourished by utilizing multifarious components (proteins, enzymes, antibodies, nanomaterials, etc.) as building blocks [2–7], and recent efforts have been largely directed to the fields “where silicon counterparts cannot go”. Among the various molecular logic systems, DNA-based ones have aroused substantial interest from molecular engineers. Because of the affordability, controllable design, and accuracy of Watson–Crick pairs, this kind of genetic material has been recognized as the most outstanding and interesting candidate [8–13]. With the surprising progress of DNA nanotechnology over the past several decades [14–19], DNA-based computing systems have been extensively explored and widely applied to logic-controlled biosensing, cancer diagnosis, drug release, subcellular imaging, and other smart bio-applications [20–26]. In particular, Dong’s group proposed a novel concept of DNA “contrary logic pair” (CLP) not long ago, and designed an intelligent platform for operating CLPs and combinatorial circuits based on the peroxidase-like property of G-quadruplex DNAzyme [27,28], in which logic gates with opposite functions (e.g., YES + NOT) were executed via the same DNA reaction simultaneously. After that, electrochemical [29] and electro-chemiluminescent [30] CLP systems were successively reported by using toehold-mediated strand displacement (TMSD) reactions and exonuclease III (Exo III). Despite the above achievements, there
are still great restrictions in current CLP platforms. For example, the expensive tool enzymes (such as Exo III) that require critical conditions and nanomaterials (upconversion nanoparticles (UNCPs) and C3N4 nanosheets) that need tedious synthesis steps [28,31] were frequently used, resulting in almost unchanged long operation times (2-6 h) and high costs. Taking the above drawbacks into account, there is an urgent need to develop a rapid and enzyme-free system for executing CLP functions.

Functional nucleic acids (FNAs) are DNA/RNA molecules with specific structures or functions, such as G-quadruplex (G4), i-motif, DNA-templated nanomaterials, etc. [32–38]. Similar to FNAs, some nucleoside bases with specific properties are also promising building blocks for DNA computing. Among these, 2-aminopurine (2AP), a fluorescent analogue of adenine [39,40], has been confirmed to act as excellent quencher-free fluorescent probe and the fluorescence of 2AP greatly relies on its surrounding microenvironment. In particular, Li’s group demonstrated that the fluorescence intensity at 370 nm of single-base looped-out 2AP in duplex can be greatly improved, when compared with that of 2AP in single-stranded DNA and fully complemented duplexes [41]. This phenomenon can be attributed to the destruction of electron transfer quenching of π-π aromatic stacking between two neighboring bases. Based on the instant and sensitive fluorescence properties of 2AP, many versatile biosensors have been constructed [42–44]. Apart from 2AP, DNA-templated copper nanoparticles (CuNPs) are also excellent fluorophores via reducing Cu²⁺ on DNA strands using ascorbic acid. Specifically, Wang’s group found that poly-thymine strands could work as satisfactory templates for the formation of CuNPs at minute levels, which can exhibit high fluorescence intensity at 625 nm [45,46]. Moreover, subsequent works also reported that poly-adenine strands could work as excellent blocking elements for poly-T CuNPs [45]. Due to the easy synthesis, instant response, and flexible design, DNA CuNPs have been widely employed in biosensing, biocomputing, and even cellular imaging. The characteristic fluorescence emissions and fast responses of these two probes inspired us to explore the possibility of integrating them together as a universal dual-output to design CLPs.

Herein, by coupling 2AP with DNA CuNPs as universal opposite dual output, we, for the first time, report a rapid and enzyme-free system for operating DNA CLPs (D-CLPs). It should be noted that, benefiting from the rapid and concomitant response of both fluorescent probes, different D-CLPs were achieved via a “double-results-half-efforts” way in just less than 20 min. Moreover, based on the above system and taking A25 strand as a model target, the smart ratiometric analysis of poly-A DNA was achieved by taking advantage of the high reliability and accuracy of D-CLPs.

2. Discussion and Results

2.1. Experimental Section

2.1.1. Materials and Reagents

All DNA samples were obtained from Shanghai Sangon Biotechnology Co. (Shanghai, China) and the sequences are shown in Table S1 (in the Supplementary Information). The oligonucleotides were dissolved in ultrapure water as stock solutions. All experiments were conducted using 3-(N-morpholino) propanesulfonic acid (MOPS) buffer (10 mM MOPS, 150 mM NaCl, pH 7.5). MOPS was purchased from Aldrich (USA); CuSO₄ and ascorbic acid (AA) were obtained from Sinopharm Chemical Regent Co. (Shanghai, China). All chemicals were of analytical grade and the water used in the experiments was purified by a Millipore system.

2.1.2. Synthesis of CuNPs and Characterization

In a typical process, the stock solutions of template DNA (2AP-T20) were diluted to the desired concentrations (250 nM) with 1 × MOPS buffer. After that, 2 mM AA was added, followed by shaking for 1 min. Then, 100 µM of CuSO₄ was added, followed by another 2 min of shaking. After incubation at room temperature for approximately 10 min, the fluorescence spectra of the CuNPs were collected. High-resolution transmission
electron microscopy (HRTEM) tests of CuNPs were performed using an FEI-TECNAI-G2-F20 microscope that operates at 200 KV.

2.1.3. Apparatus
The fluorescence spectra were collected using a F-4700 Fluorescence Spectrofluorometer (Hitachi High-Tech Science Corporation, Tokyo Japan). The emission spectra of 2AP were collected from 325 to 550 nm with an excitation wavelength of 300 nm. The slit widths for the excitation and emission were 5 nm and 10 nm, respectively. The fluorescence spectra of the CuNPs were obtained from 550 nm to 660 nm after excitation at 340 nm and the excitation and emission slit widths were both 10 nm.

2.1.4. Native Polyacrylamide Gel Electrophoresis (PAGE)
The DNA stock solutions were diluted to a suitable concentration by 1 × MOPS buffer and heated at 88 °C for 8 min, then slowly cooled down to room temperature. After that, the desired volume of the 2AP-T20 and A20-C2 solution was mixed and added into 1 × MOPS buffer to give a final concentration of 2 µM. After a 30 min incubation, the DNA solutions were analyzed using a 15% native polyacrylamide gel. Electrophoresis was conducted in 1 × TBE (17.80 mM Tris, 17.80 mM boric acid, 2 mM EDTA, pH 8.0) at a constant voltage of 60 V for 2.5 h. After staining with gel dye, the gels were scanned by a UV transilluminator.

2.1.5. Operation of YES/NOT Gate
Firstly, all the DNA solutions were heated at 88 °C for 8 min and slowly cooled down to room temperature. In addition, three important elements of 250 nM 2AP-T20, 2 mM AA, and 100 µM Cu²⁺ were used as the platform of the contrary logical pairs in this work.

For the construction of the YES/NOT gate, 300 nM A20-C1 was used as the input; 300 nM A20-C1 was incubated with 250 nM 2AP-T20 for 15 min in 1 × MOPS buffer. Then, the collected fluorescence signal of 2AP at 370 nm was the output of the YES gate. After that, 2 mM AA was added to the solution, followed by the addition of 100 µM Cu²⁺. After shaking, the mixture was reacted in a dark environment for another 10 min. The fluorescence intensity of the CuNPs at 625 nm (output of the NOT gate) was measured under excitation at 340 nm.

2.1.6. Operation of OR/NOR Gate
The annealing process of all DNAs and the platform were the same as the YES/NOT gate mentioned above. For the construction of the OR/NOR gate, 300 nM A20-C1 and 300 nM A22-C1 were used as two inputs. Different input combinations were added into the platform for 15 min. The subsequent steps were the same as those for the construction of the YES/NOT gate, after which, the fluorescence signals of 2AP and CuNPs were collected.

2.1.7. Ratiometric Fluorescent Detection of A25
Firstly, 250 nM T30-2AP and different concentrations of A25 were annealed. Then, both were hybridized in 1 × MOPS buffer with a final volume of 460 µL for 15 min and the fluorescence spectra of 2AP were collected. Subsequently, the CuNPs could be synthesized and their fluorescence signals were also obtained after following the steps mentioned above.

2.2. Mechanism and Verification Experiments
Before the operation of DNA CLPs (D-CLPs), the definitions of platform, inputs, and outputs are illustrated and the corresponding verification experiments were performed. The mixture of AA, Cu²⁺, and 2AP-T20 was used as the universal platform (Scheme 1), in which 2AP-T20 is a single strand that integrates 20 consecutive T bases at the 3′ end (blue color) with 21 random sequences (X part, orange color) at the 5′ end, and 2AP was inserted as the 11th base of the X part. The fluorescence emission of 2AP at 370 nm and that of the CuNPs at 625 nm were employed as the positive Output 1 and negative Output 2 of the D-CLPs, respectively (Scheme 1). A normalized fluorescence intensity of 0.40 was set as the
universal threshold value to judge the high and low outputs. The high fluorescence signal was defined as “1”, and conversely, the low one was defined as “0”. To achieve different logic functions, distinct poly-A strands with subtle design were used as inputs.

![Scheme 1](image)

**Scheme 1.** Mechanism of DNA contrary logic pairs based on the integration of 2AP and CuNPs.

As for the verification experiments, strand A20-C1 was introduced into the system to interact with 2AP-T20. To make it clear, A20-C1 is another single strand that is fully complementary to the X and T20 sections of 2AP-T20 (green and purple parts, respectively). As shown in Figure 1A, only 2AP-T20 exhibited relatively low fluorescence at 370 nm, but could generate high fluorescence at 625 nm after the formation of CuNPs (HRTEM image in Figure 1B). However, after adding a certain concentration of A20-C1 to the platform, it will hybridize with 2AP-T20 and form duplex. Accordingly, the 2AP base will be looped out, yielding remarkably high fluorescence at 370 nm because of the disruption of $\pi-\pi$ stacking electron transfer quenching. Meanwhile, the generation of CuNPs will be blocked as a result of the absence of a poly-T template, yielding an ultra-low fluorescence signal at 625 nm. Moreover, the fluorescent kinetics of CuNPs in the absence and presence of a poly-T template were also tested (Figure S1 and Figure 1C). The fluorescence intensity at 625 nm increased gradually after reducing Cu$^{2+}$ using AA and reached a plateau in less than 20 min, indicating the surprising rapid response of both probes. It should be noted that the kinetics of 2AP demonstrated almost an instant response (Figure 1D). Moreover, the hybridization between 2AP-T20 and A20-C1 was vividly identified by the PAGE experiment (Figure 2). The disappearance of single-stranded bands and appearance of a new band in Lane 3 indicated the formation of a 2AP-T20/A20-C1 duplex. All the above phenomena prove the reliable looping out of the 2AP base, the successful preparation of CuNPs, and the possibility of integrating them together as dual output to construct D-CLPs.

2.2.1. Construction of YES/NOT Logic Pair

Among the various molecular logic devices, the YES and NOT logic gates are the simplest and the most essential ones [47–49]. Again, the mixture of AA, Cu$^{2+}$, and 2AP-T20 was used as the platform of the YES/NOT logic pair (Figure 3A,B), and strand A20-C1 was the input. The absence/presence of strand A20-C1 were assigned as the input state of “0” and “1”, respectively. The detailed operating principles of the YES/NOT D-CLP are illustrated in Figure 3A. In the absence of any strand, the negligibly low signal at 370 nm of free 2AP was obtained, and the high fluorescence intensity of the CuNPs (625 nm) could be clearly observed at the same time, generating the output state “0, 1”. However, after adding suitable concentrations of A20-C1 to the solution, 2AP will be looped out and the interaction between 2AP-T20 and A20-C1 will inhibit the formation of CuNPs, yielding an output state of “1, 0”. The fluorescence spectra of the YES/NOT logic gate and the essential
optimization experiments can be found in Figures S2 and S3, respectively. The CLPs were implemented under the optimal conditions. The corresponding fluorescent column bars are depicted in Figure 3D. The above operating principle featured the characteristics and truth table of YES/NOT CLPs (Figure 3C,D), proving its reasonable operation.

**Figure 1.** (A) Fluorescence spectra of 2AP and CuNPs in the absence and presence of A20-C1; (B) HRTEM image of CuNPs; (C) fluorescence kinetics of CuNPs in the presence of 250 nM 2AP-T20 strand; (D) fluorescence kinetics of 2AP after the addition of 300 nM A20-C1 strand.

**Figure 2.** A 15% native polyacrylamide gel showing the interaction between A20-C1 and 2AP-T20. Lane 1: 2AP-T20, Lane 2: A20-C1, Lane 3: 2AP-T20+A20-C1.
Among the various molecular logic devices, the YES and NOT logic gates are the simplest and the most essential ones [47–49]. Again, the mixture of AA, Cu$^{2+}$, and 2AP was employed as the initial platform for the nucleic acid analysis and strand A25 was mostly consistent with the truth table (Figure 4C). The absence/presence of input strands were designated as the input state of “0” and “1”, respectively. The computing illustrations of the OR/NOR D-CLP are shown in Figure 4A,B. Different from the above logic system, the mixture of AA, Cu$^{2+}$, and T30-2AP strands was used as the model target (Figure 5A). It should be noted that T30-2AP is a single-stranded DNA with 30 consecutive T bases, in which 2AP is at the 16th position. Figure 5B displays the fluorescence emission spectra of 2AP and the CuNPs in the presence of different concentrations of A25. With the addition of strand A25, the FI$^{370}$ values were enhanced gradually, accompanied by the corresponding decrease in FI$^{625}$ values as the concentration of A25 increased from 12 nM to 250 nM. Accordingly, an excellent calibration curve of the

Figure 3. (A) Detailed operation of the “YES/NOT” logic pair; (B) equivalent logic symbol of “YES/NOT” logic pair; (C) truth table of “YES/NOT” logic pair; (D) normalized fluorescent column bars of the YES (blue, 2AP) and NOT (yellow, CuNPs) gates under different input variations.

2.2.2. Operation of OR/NOR Logic Pair

Apart from the YES/NOT pair, the OR/NOR pair was also constructed to testify the feasibility of this universal platform. Herein, the platform was the same as described above, while strands A20-C1 and A22-C1 were used as two inputs of the OR/NOR logic pair. Notably, A22-C1 is another single strand that is complementary to the X and T20 parts of 2AP-T20, but with two more A bases at the 5’ end (Figure 4A). Therefore, the function of A22-C1 during the construction of the CLPs is analogous to that of A20-C1. The absence/presence of input strands were designated as the input state of “0” and “1”, respectively. The computing illustrations of the OR/NOR D-CLP are shown in Figure 4A,B and the fluorescence spectra of the OR/NOR logic gate are presented in Figure S4. In the absence of any strand, the ultra-low signal at 370 nm from free 2AP and the high one at 625 nm from the CuNPs could be observed, producing the output state “0, 1”. Meanwhile, the presence of any one of the two inputs will induce the formation of the duplex, accompanied with the looping out of 2AP and no formation of CuNPs, which corresponds to an output state of “1, 0”. The fluorescent column bars under the different input states are given in Figure 4D, which was mostly consistent with the truth table (Figure 4C).

2.2.3. Ratiometric Fluorescent Detection of Poly-A Strand

A versatile logic platform could not only perform DNA computing, but also is capable of biosensing [50–53]. Inspired by the rapid and efficient response of both probes and based on the above platform, we further applied the contrary logic response to ratiometric fluorescent analysis of nucleic acids. It has been reported that poly-A tails can regulate the expression and stability of mRNA and is significant for the initiation of translation [54–56]. Therefore, the analysis of poly-A sequences could provide informative evidence for the early diagnosis of diseases.

Different from the above logic system, the mixture of AA, Cu$^{2+}$, and T30-2AP strands was employed as the initial platform for the nucleic acid analysis and strand A25 was used as the model target (Figure 5A). The fluorescence column bars of the YES (blue, 2AP) and NOT (yellow, CuNPs) gates under different input variations are given in Figure 4D, which was mostly consistent with the truth table (Figure 4C).
ratiometric values of FI\textsubscript{370}/FI\textsubscript{625} as a function of various concentrations of A25 is presented in Figure 5C. The linear regression equation was $F = -0.592 + 0.0068C$ ($F$ is the ratiometric value of $FI_{370}/FI_{625}$, and $C$ is the concentration of strand A25), and the limit of detection (LOD) was estimated to be as low as 17.2 nM according to $3\sigma/s$, which is comparable to most previously reported DNA sensors [57].

<table>
<thead>
<tr>
<th>Input 1</th>
<th>Input 2</th>
<th>Platform</th>
<th>Output 1</th>
<th>Output 2</th>
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<td>0</td>
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<tr>
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<tr>
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<td>1</td>
<td>CuNPs</td>
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<td>0</td>
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<tr>
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<td>0</td>
<td>A20-C1</td>
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![Figure 4](image_url)

**Figure 4.** (A) Detailed operation of the “OR/NOR” logic pair using strands A20-C1 and A22-C1 as inputs and the mixture of 2AP-T20, AA, and Cu\textsuperscript{2+} as platform; (B) equivalent logic symbol of “OR/NOR” logic pair; (C) truth table of “OR/NOR” logic pair; (D) normalized fluorescent column bars of the OR (blue, 2AP) and NOR (yellow, CuNPs) gates under different input combinations.

![Figure 5](image_url)

**Figure 5.** (A) Scheme of the A25 fluorescent detection platform; (B) fluorescence spectra of 2AP and CuNPs with the different concentrations of A25; (C) corresponding calibration graph for the A25 detection. Linear relationship between the logarithmic values of the $FI_{370}/FI_{625}$ and A25 concentration in the range from 12 nM to 250 nM. The error bars were obtained via three independent experiments.
3. Conclusions

To summarize, we, for the first time, constructed a rapid and enzyme-free platform for constructing DNA CLPs by integrating poly-T CuNPs and 2AP as universal dual output generators. Surprisingly, the YES/NOT and OR/NOR CLPs can be operated in just less than 20 min without the participation of any enzymes. Additionally, the ratiometric analysis of poly-A DNA was also realized based on the same platform by taking advantage of the high reliability and accuracy of the D-CLPs. This work not only provided a low-cost, fast-response, and typical paradigm for DNA computing, but also demonstrated the fabrication of novel ratiometric fluorescent sensors for the analysis of nucleic acids and diagnosis of diseases in the future.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry5030108/s1, Table S1: Sequences of DNA strands used in this work; Figure S1: Fluorescence kinetics of CuNPs after adding 300 nM A20-C1 to the solution of 250 nM 2AP-T20 strand; Figure S2: Fluorescence spectra of YES/NOT logic gate under different inputs; Figure S3: Optimization of the concentration of A20-C1 used in D-CLPs via recording the fluorescence signal of 2AP and CuNPs; Figure S4: Fluorescence spectra of OR/NOR logic gate under different inputs; Figure S5: The different poly-As are set as control sequences to demonstrate the specific response of 2AP-T20 system. Figure S6. Different single bases are inserted into the poly-A tail to clarify the T30-2AP system’s specificity.

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