Four-Way Junction-Driven DNA Strand Displacement and Its Application in Building Majority Logic Circuit

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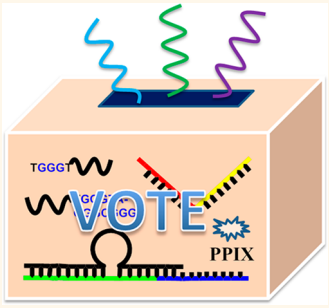
ABSTRACT We introduced a four-way DNA junction-driven toehold-mediated strand displacement method. Separation of the different functional domains on different strands in the four-way junction structure and usage of glue strand to recombine them for different logic gates make the design more flexible. On the basis of this mechanism, a majority logic circuit fabricated by DNA strands was designed and constructed by assembling three AND gates and one OR gate together. The output strand drew the G-rich segments together to form a split G-quadruplex, which could specifically bind PPIX and enhance its fluorescence. Just like a poll with three voters, the high fluorescence signal would be given off only when two or three voters vote in favor. Upon slight modification, the majority circuit was utilized to select the composite number from 0 to 9 represented by excess-three code. It is a successful attempt to integrate the logic gates into a circuit and to achieve desired functions.



KEYWORDS: DNA-based nanodevices · strand displacement · four-way junction · logic circuit · G-quadruplex

Unconventional computing is a burgeoning interdisciplinary field, in which the computing is done by a wide range of unusual methods and materials.[1] It may sound crazy to solve computational problems by molecules or even atoms, but many computing systems have been fabricated by various molecules,[2−5] especially biomolecules. Because of their unique properties, DNA, RNA, enzymes, and other biological components are all excellent building blocks for computer systems.[6−11] Since Adelman resolved seven-point Hamiltonian path problem using DNA strands as the basic computing materials, DNA computing has drawn widespread attention and made great progress in recent years.[12−15] Logic gates are the elementary building blocks of a computing system, each of which can implement their respective Boolean functions. Combining them into logic circuits would lead to more complicated functions. Many practical problems can be abstracted into logical relations and solved by the corresponding combinational logic circuits.[16,17] With the reliable prediction of hybridization behavior based on the Watson−Crick base-pairing principle, DNA becomes an ideal building material for molecular computing system. To design and construct logic DNA nanodevices based on DNA strands according to the actual need would be an exciting and challenging job.

Toehold-mediated DNA strand displacement reaction supplies us a superior tool to receive and transfer DNA input information without enzyme.[18,19] In this mode, both the toehold binding region and displacement region are on the input strand. When this strand is added, it can bind to the toehold end *via* the toehold binding region and replace the output strand by displacement region. A variety of logic gates, circuits, signal amplifiers and even neural networks have been constructed on the basis of this mechanism.[20−24] However, the traditional toehold based strand displacement mode is insufficient to meet the needs of more complex and powerful computing systems. Many efforts have been made to improve the design and provide new modes to solve

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various problems.[25−27] Holliday junction, a mobile four-way junction formed by four DNA strands, is widely used in the design of complex 2D and 3D DNA nanostructures.[28,29] In our work, formation of this four-way DNA junction is successfully applied to drive the strand displacement reaction (SDR) for the first time. Unlike the traditional toehold-mediated strand displacement mode, the displacement region and toehold binding region lie in two input strands, respectively, in this mode. Different functional regions are distributed in different strands, and thus, displacement of the target strand is impossible. A binding region is connected to these two input strands. The third strand works like glue to stick these two strands together through the binding region to form a three-strand structure, so that the toehold binding and displacement regions get close. Thus, this three-strand structure can bind to the forth strand *via* the toehold end and replace the output strand to form the four-way junction structure. In this molecular platform, due to the application of the multiarm DNA motif, more input information can be received at one time, different functional regions can be distributed in different strands, and these input strands can be recombined by glue strand for different gates, which make this SDR mode more versatile, flexible and efficient.

In Boolean logic, the circuit with majority function returns true only when more than 50% of its inputs are true, and false otherwise.[30] The majority function can be used to realize complex functions in some logic devices. For example, in a full adder, the carry output is performed by a three-input majority circuit.[31] Some groups have constructed three-input majority gates by nanomagnetic materials[32] and even DNA materials,[33] whereas requirement of long signal strand, DNA ligase and fluorescence label limit its flexibility in design and simplicity of operation. Herein, we built a new label-free DNA logic circuit with majority function based on the DNA four-way junction-driven SDR. This three-input majority logic circuit was realized through assembling three AND gates and one OR gate. The advantage of DNA four-way junction-driven SDR is fully demonstrated in building the majority logic circuit. The three AND logic gates were all constructed based on this strand displacement mode. For OR logic gates, a pool of G-rich DNA segments were set up to capture the output signals from the upper gates. The input strand could draw two G-rich strands together to form a split G-quadruplex.[34,35] The unique structure of G-quadruplex enables it to bind to various porphyrins, *e.g.*, protoporphyrin IX (PPIX), mesoporphyrin IX (MPIX) and *N*-methyl mesoporphyrin IX (NMM).[36−38] For PPIX, it usually aggregated into micelles with low fluorescence in aqueous solution, whereas its fluorescence was dramatically enhanced after binding to G-quadruplex.[34,39] We took PPIX as a readout tool to transfer the final output signal in this work. Application of the split G-quadruplex enhanced fluorescence here not only simplifies the design of the three-input OR logic gate, but also avoids the expensive exogenous fluorescent label. This intelligent molecular platform can give a sound judgement after the addition of input strands. Like a poll with three voters, the high fluorescence signal would be given off only when two or three vote in favor. Furthermore, upon slight modification, the majority circuit was utilized to select the composite number from 0 to 9 represented by excess-three (XS-3) code. It is a successful attempt to integrate the logic gates into a circuit and to achieve desired function. The application of this DNA four-way junction-driven strand displacement mode in building logic circuit with specific function demonstrates its outstanding properties and application prospects. Combined with aptamer or nanomaterials, the computing system based on this new SDR mode would be well applied in biosensor, environment monitoring, disease diagnosis and intelligent therapy.[40,41]

RESULTS AND DISCUSSION

At first, we introduced a four-way junction-driven strand displacement mode, which was the core reaction of our majority circuit. The mechanism of the four-way junction based toehold-mediated SDR is shown in Figure 1. Strand S, which can hybridize with two G-rich strands G1 and G2 to guide the formation of split G-quadruplex, was blocked by strand H4 in the stem-loop form. The displacement domain and toehold binding domain were distributed on strand H1 and H2, respectively. Even though H1 and H2 were both added, S would still be reserved on H4, which was due to the separation of these two important function domains. However, when strand H3 was present, the two domains were drawn together by hybridization of the binding domains. H3 worked like glue to stick H1 and H2 into a complex with the intact function to bind toehold end and replace the output strand. Upon the mediation of the toehold end on H4, this newly formed three-strand complex could hybridize with H4 to form the four-way junction structure and then release strand S. The output S would induce the formation of split

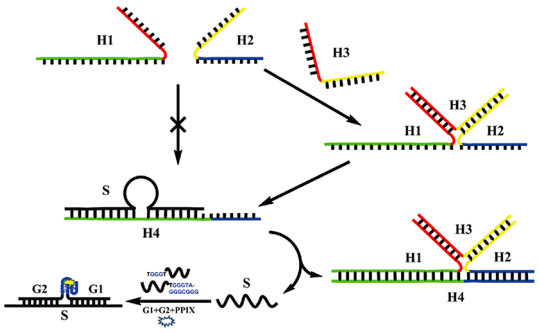

Figure 1. Schematic diagram of DNA four-way junction based toehold-mediated SDR.

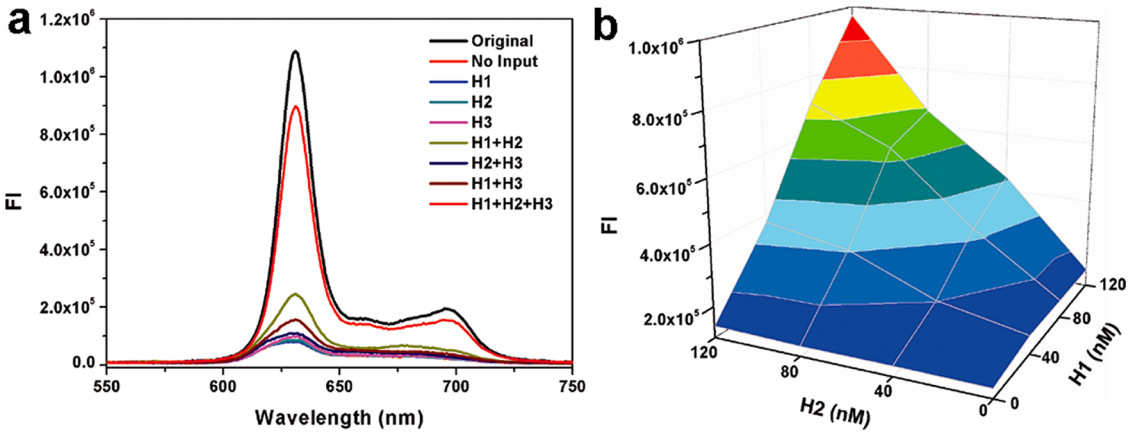

Figure 2. (a) Fluorescence emission spectra result of the SDR induced by the different combinations of three inputs H1, H2, and H3. (b) Fluorescence intensity at 630 nm plotted against the concentrations of H1 and H2. Strand H3 keeps at the concentration of 120 nM in all groups.

G-quadruplex and enhance the fluorescence intensity of PPIX. The fluorescence spectra are shown in Figure 2a. The theoretical design and actual measurements fitted together neatly. Only when the three input strands were all present, would a high fluorescence signal be given off. Furthermore, the effect of the input quantity of three different strands for the release of S was investigated (Figure 2b). First, we added enough H3 and observed the change of fluorescence intensity with the concentration of H1 and H2. Obviously, the two input strands both played important roles in the displacement of strand S. Only when enough H1 and H2 were added would the fluorescence intensity reach the climax. Subsequently, we inspected the effect of initial concentration of H3 for the final fluorescence signal. As shown in Figure S1, the fluorescence intensity also increased with the addition of H3, which supported the hypothesis that integrity of three input DNA strands was essential to the release of S.

The mechanism of four-way junction based toehold-mediated SDR is verified by native polyacrylamide gel electrophoresis (PAGE). In Figure 3, the DNAs contained in different bands have been figured out. We first identified the formation of the four-way junction structure. From lane 4 to lane 7, each time a DNA strand was added, the mobility of the bands got lower, which was caused by the increase of length, weight, and volume of the DNA complex. The band in lane 7 should be mainly composed of DNA four-way junction structure. Effects of the input strands for S/H4 hybrid were also investigated. The bands of S/H4 double-stranded complex were stable in lane 9−12, whereas the band obviously was weak in lane 13 and a new band appeared in this lane in the same position of four-way junction. This phenomenon proved that the four-strand DNA complex was formed and the S/H4 hybrid was disbanded when the three input strands were present. Thus, it is a reliable molecular device that functions as designed.

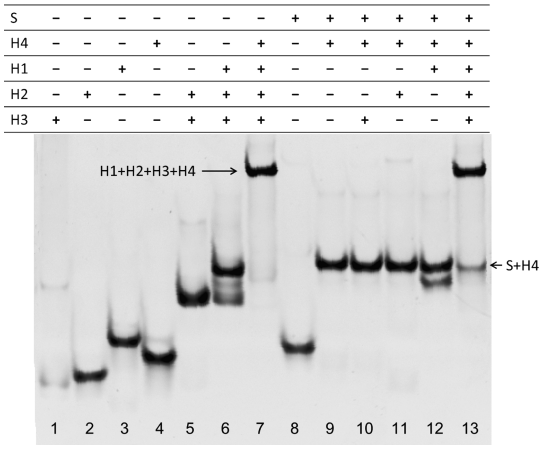

Figure 3. Native 15% polyacrylamide gel analysis of the formation of four-way junction structure and SDR. DNA strands added in every lane are indicated in the table. Concentrations for each DNA in PAGE are all 0.2 μM.

To prove the application potential of this DNA four-way junction based SDR mode in construction of DNA computing system and realization of specific function, we built a DNA logic circuit with majority function based on this SDR mode to count the inputs. The truth table and circuit diagram were shown in Figure S2. For a majority circuit with three inputs, a high positive signal should be given off when there were two or more positive inputs. In our design, three parallel two-input AND logic gates were set up to receive the input signals. Any two inputs would trigger an AND gate to produce an output signal. Then, a three-input OR logic gate was cascaded to the three AND gates. Thus, any positive signals input into the OR gate from the upper gates would induce a high output signal from the OR gate.

The schematic diagram of the three-input majority logic circuit fabricated by DNA strands was shown in Figure 4. For the first AND gate, the two input strands A and B carried the displacement and toehold binding domain, respectively. La and Sa/Ia hybrid worked as

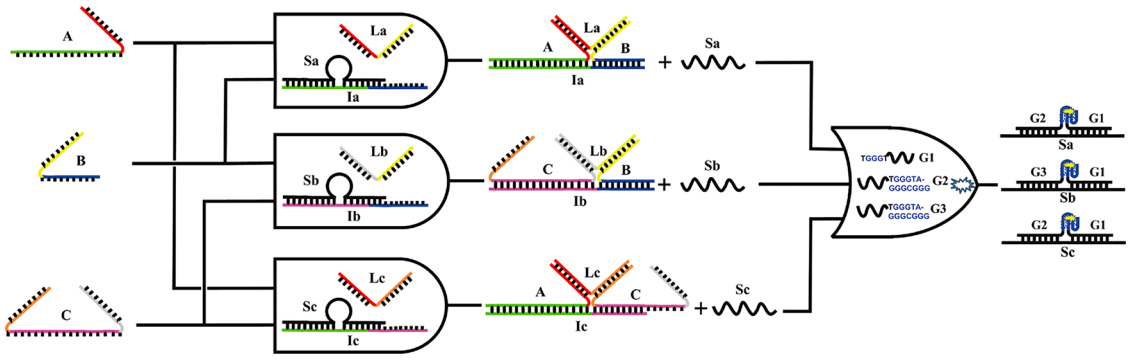

Figure 4. Schematic diagram of the three-input majority circuit fabricated by DNA strands.

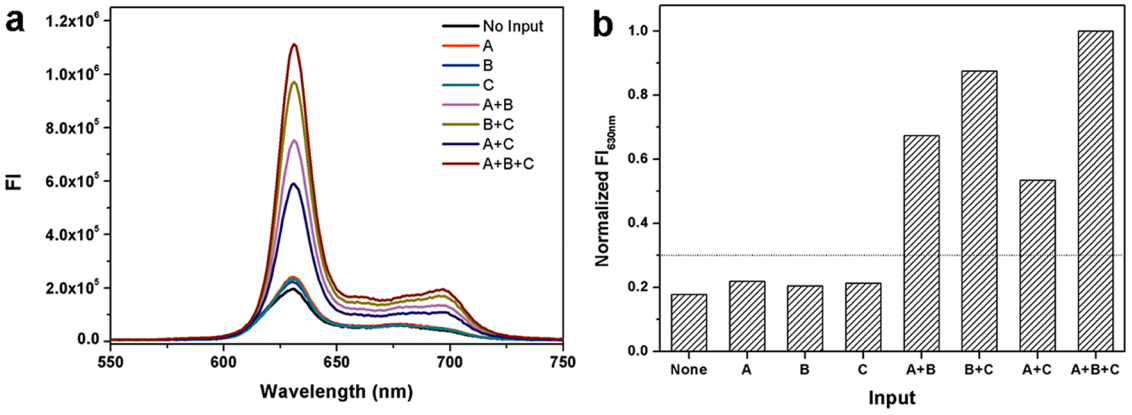

Figure 5. (a) Fluorescence emission spectra result of the majority logic circuit. (b) Normalized fluorescence intensity result at 630 nm of the majority logic circuit. Threshold value is set at 0.3 to judge the positive and negative output signals.

the basic gate device. When A and B were both input, the glue strand La would stick them together through hybridizing with the binding domain of them to form a three-strand complex. Subsequently, upon the help of toehold, three-strand complex bound Ia to displace Sa and became a four-way DNA junction. What was ingenious about the application of four-way junction based SDR in this circuit was that the glue strand can be flexibly adjusted according to the binding domain of the input strand, so the combination of toehold binding domains and displacement domains were decided by the glue strand. Different glue strands were designed for different gates to receive their corresponding input strands. For example, in the second AND gate strand, Lb was designed to stick strand B and C together to displace Sb on Ib. In contrast with La in the first gate, half of Lb was modified to draw the two functional domains on B and C together. Release of Sb was driven by the formation of a four-way junction composite of strand B, C, Lb and Ib. Similarly, in the third AND gate, in order to receive the input strand A and C, Lc was also adjusted accordingly. It was noteworthy that the middle domain of strand C played a dual role in this system. In the second AND gate, strand C was responsible for displacing Sb, whereas it was used to bind the toehold end on Ic in the third gate. The role conversion was attributed to the guidance of the glue strands in each gate. To perform the function of OR logic gate, a pool of G-rich short strands was built to capture the output strands from the upper AND gates. Any one of Sa, Sb and Sc could hybridize with two G-rich segments to form the split G-quadruplex, which can bind PPIX in solution to enhance its fluorescence.

The actual test results were shown in Figure 5. At first the three AND gates were tested separately. The strands used in the first AND gate were the same as the ones in Figure 1 and its results have been shown in Figure 2a. The spectra of the other two gates can be found in Figure S3. It is clear from these data that the three AND gates worked well by themselves. As shown in Figure 5a, when these gates were mixed together, the positive and negative signals still could be distinguished easily for their obvious differences, though the background signals got a bit higher after mixing. All the combinations of the three inputs were tested. When no strand or only one strand was input, the fluorescence values stayed at the low region under the threshold. However, when two or three strands were input, the output signals increased to a high stage above the threshold (Figure 5b). Seen from the fluorescence data, this molecular device did judge the results accurately and function well as designed.

To demonstrate the application prospect of the circuit with majority function, we have applied this

a

Decimal Number	XS-3 code				Output
	A	B	D	C	
0	0	0	1	1	0
1	0	1	0	0	0
2	0	1	0	1	0
3	0	1	1	0	0
4	0	1	1	1	1
5	1	0	0	0	0
6	1	0	0	1	1
7	1	0	1	0	0
8	1	0	1	1	1
9	1	1	0	0	1

b

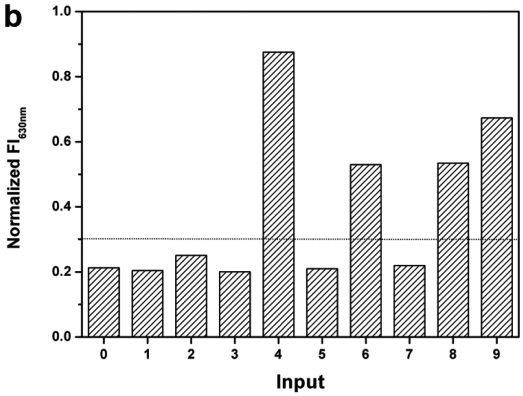

Figure 6. (a) Truth table of the circuit to select composite number less than 10 represented by XS-3 code. (b) Normalized fluorescence intensity result at 630 nm of the circuit. Fluorescence intensity of input ABC in Figure 3 is set as 1. Threshold value is set at 0.3 to judge the positive and negative output signals.

circuit with slight modification to screen out the composite number from natural numbers less than 10 represented by XS-3 code. As is well-known, XS-3 is an important binary code used to express decimal numbers, in which the decimal digit is represented by four bits as the digit value plus 3.[42] Since it overcomes the shortcomings emerged when taking the BCD code (Binary Coded Decimal) to add two decimal digits whose sum exceeds 9, it is particularly significant for arithmetic operations. Setting the XS-3 equivalent of these 10 numbers as input and the output of the four composite numbers as 1, the truth table was given in Figure 6a. According to this table, a circuit endowed with majority function was designed and shown in Figure S4. This circuit could be fabricated by making only little modification on the former majority circuit. As shown in Figure S5, Lb was taken out from the basic device and served as a new input D. Therefore, the second AND gate became a three-input AND gate with B, C, and D as input. The fluorescent result was shown in Figure 6b. The fluorescence intensities of these four composite numbers were obviously higher than the other numbers. This interesting phenomenon proved the circuit worked very well as expected.

CONCLUSIONS

In summary, we introduced a toehold-mediated strand displacement mode based on DNA four-way junction structure and utilized it to build a DNA logic circuit with majority function. Native PAGE has been employed to identify this strand displacement reaction. Introduction of the four-way junction structure in toehold-mediated SDR makes the displacement reaction controlled by more input strands. It provides a new mode to process and transfer input information. And the logic circuit fabricated based on this mode can be flexibly adjusted through modifying the binding domain of the glue strand. Application of this DNA majority circuit to select the composite number from 0 to 9 represented by XS-3 code demonstrates its value and prospects in DNA computing. Comparing with the conventional DNA logic devices, the strands used in this work are label-free and the device functions without enzymes, which dramatically reduces the cost in experiment. These advantages of the four-way junction-driven SDR determine its wide application perspective in the future. Furthermore, the positive output signal of the majority circuit could be controlled by more meaningful factors by building some relationships between the input strands and diseases, or assembling aptamer sequences into the circuits to sense special biomolecules. And if some relationships between the final output signals and drug release were established, a biomolecule sensitive smart drug delivery system based on logic DNA nanodevices could be expected to be realized.

EXPERIMENTAL SECTION

Materials and Reagents. DNA strands were purchased from Sangon Biotechnology Co., Ltd. (Shanghai, China). PPIX was purchased from Sigma-Aldrich. Other chemicals were of reagent grade and were used without further purification. The sequence of these strands was shown in Table S1. DNA strands were dissolved in water as stock solution and quantified by UV−vis absorption spectroscopy with the following extinction coefficients (ε260 nm, M^{-1} cm^{-1}): A = 15 400, G = 11 500, C = 7400, T = 8700. UV−vis absorbance measurements were performed on a Cary 500 Scan UV/vis/NIR Spectrophotometer (Varian, USA).

DNA Strand Displacement Reaction. The DNA were dissolved in water and diluted with TEK (abbreviation for Tris-EDTA-KCl) buffer (5 mM Tris-HCl, 0.5 mM EDTA, 100 mM NaCl, 20 mM KCl, 10 mM $MgCl_2$, pH 8.0) for hybridization of strands and formation of G-quadruplex. In strand displacement reaction, the solutions of strand S and H4 were mixed in TEK buffer and heated at 88 °C for 10 min, then slowly cooled down to room temperature (RT). Strand H1, H2 and H3 were added into it and the mixture was incubated at RT for 30 min. G1, G2 and PPIX diluted with TEK buffer were added last and the mixture was incubated for 60 min before fluorescent test. The fluorescent analysis was performed in the TEK buffer with a final concentration of 1.2 μM

for PPIX, 0.16 μM for G1, G2, 0.1 μM for S, and 0.12 μM for the other strands.

Operation of the DNA Circuit. Strands Sa, Sb, Sc, Ia, Ib, Ic, La, Lb and Lc were mixed in TEK buffer and heated at 88 °C for 10 min, then slowly cooled down to room temperature. After this, the solution was ready to receive the input strands. The solution was incubated at RT for 30 min after the addition of input. G1, G2 and PPIX diluted with TEK buffer were added last and the mixture was incubated for 60 min. The fluorescent analysis was performed in the TEK buffer with a final concentration of 1.2 μM for PPIX; 0.16 μM for G1 and G2; 0.1 μM for Sa, Sb, Sc, Ia, Ib, Ic; 0.12 μM for La, Lb, Lc; and 0.24 μM for the input strands. In the circuit for screening out composite number, strand Lb was operated as input and added with the final concentration of 0.12 μM.

Fluorescence Spectroscopic Analysis. Fluoromax-4 Spectrofluorometer (HORIBA Jobin Yvon, Inc., NJ) was used to collect the fluorescence emission spectra of DNA-PPIX complexes in TEK buffer at RT from 550 to 750 nm with the excitation wavelength of 410 nm.

Native Polyacrylamide Gel Electrophoresis (PAGE). The DNA solutions mixed with 6× loading buffer (TEK buffer, pH 8.0, 50% glycerol, 0.25% bromphenol blue) were analyzed in 15% native polyacrylamide gel. The electrophoresis was conducted in 1× TBE (pH 8.0) at constant voltage of 110 V for 1 h. The gels were scanned by a UV transilluminator after staining with Gel Red.

Conflict of Interest: The authors declare no competing financial interest.

Supporting Information Available: DNA sequences and parts of the experimental data. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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