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Graphene oxide/silver nanoclusters based logic devices and their application to multiplexed analysis of miRNA

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ABSTRACT

Molecular-level logic gates have drawn increasing attention in nonarithmetic information processing, data transmission, logic computation and multiplexed analysis. Based on the characteristic of the graphene oxide (GO) and DNA-stabilized silver nanoclusters (AgNCs), a simple and universal platform is developed for integration of multiple logic gates to achieve parity generator and parity checker functions. The parity generator/checker can detect the inevitable bit errors during any type of binary data transmission. Moreover, the GO/AgNCs platform has the ability to construct analog OR and INHIBIT logic gates. And the integration of OR and INHIBIT logic gates provide an interesting approach for distinguishing multiple target miRNAs, presenting great application in development of rapid and intelligent detection. The function of a parity generator/checker and advanced sensor has been realized with fluorescent molecular switches taking advantage of the efficient adsorption/quenching ability of GO toward AgNCs, preventing laborious modification of biomolecules. Furthermore, as the fluorescence quencher consists of biocompatible nanomaterials, the devices can stably perform their logic operations in a biological matrix, which holds great potential application in future clinical diagnosis.

1. Introduction

Boolean logic gates have played a key role in traditional silicon-based computers over the past few decades. This binary logic, referred to as two-value, is a set of rules for dealing with propositions that must be either true or false. The logic value is coded by 0 or 1, which represents two output states (on/off, corresponding to "1/0", respectively) under different inputs. To date, traditional silicon-based computers have exhibited unprecedented performance and thus revolutionized computation. Inspired by the successful use of semiconductor-based computers, scientists have pursued efficient materials to mimic Boolean logic gates [1,2]. In recent years, nontraditional molecular logic devices have received a great deal of attention and witnessed significant advancements. The research efforts can be divided into two different directions; firstly, the exploitation of relatively simple logic gates, such as AND, OR, NOT, XOR, INHIBIT and IMPLICATION for bioinspired applications (biochemical analysis [3–7], disease diagnostics and therapy [8–10], controlling the process of life [11], and biomedical imaging [12]); and, secondly, exploration of the challenging task of integrating complex functions into purpose-designed molecular devices [13–15]. The goal of the two directions is to further the progress of molecular logic computing and to investigate more applications of logic gates in life and chemical sciences.

Among the various materials that are able to mimic Boolean operations, DNA is considered to be the most prominent engineering material for addressing the central problems of molecular computing owing to its inherent advantages, such as easy synthesis, low cost, structural simplicity, high flexibility, excellent biocompatibility, and predictable molecular behavior [16–18]. At present, various basic and advanced DNA devices with diverse functions have been developed, including half adder/half subtractor [19], full adder/full subtractor [20], encoder/decoder [21], multiplex/demultiplex circuit [22], digital comparator [21], majority voting logic circuit [23], keypad lock [24], multiple-cascade logic circuit [25] and automata [26]. With regard to further development of DNA computing, the construction of a universal platform to satisfy the requirements of increasing computational complexity and cost-effectiveness is still a great challenge; most circuits for advanced logic gates are realized with the help of dye-labeled or redox-labeled DNA strands, or the interaction between enzymes and DNA, resulting in high cost and more complicated operation processes [19]. Taking advantage of the various DNA secondary structures and smart functional nanomaterials, we have attempted to construct a label-free and enzyme-free platform. In particular, DNA-templated silver nanoclusters (AgNCs), which are a new class of fluorophores that exhibit

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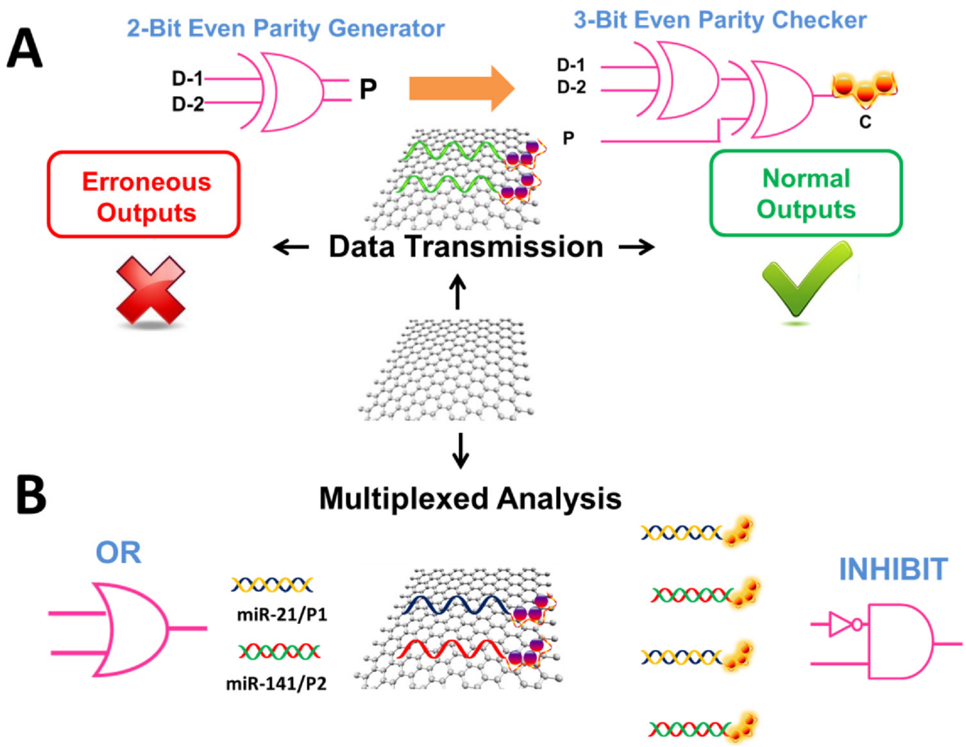

Scheme 1. (A) Scheme of the 2-bit even parity generator and 3-bit even parity checker for error detection through data transmission (the red "×" represents the erroneous outputs and the green "√" indicates the normal outputs); (B) Scheme of the OR and INHIBIT logic gates for the intelligent detection of miR-21 and miR-141 based on AgNCs and GO.

subnanometer size, high photostability, non-toxicity, and remarkable biocompatibility [27–29], are suitable to be used as fluorescent probes in biochemical analysis [30]. More importantly, DNA-templated AgNCs overcome the shortcomings of DNA modification and are appropriate candidates to act as label-free fluorescence signal reporters. In addition, graphene oxide (GO), a water-soluble nanomaterial, has been demonstrated to be one of the best choices of label-free quenchers for the construction of bioelectronic devices and advanced biosensors.

Herein, by employing DNA-templated AgNCs and GO as the building blocks and using the fluorescence of AgNCs as the outputs, we experimentally construct a series of multifunctional logic devices to perform nonarithmetic information processing and data transmission including a parity generator and checker. Different from the reported paper [14], the pG/pC system can be easily constructed without the help of enzymes and label DNA. What's more, taking advantages of the extraordinarily high quenching efficiency of GO and the DNA-templated silver nanoclusters (AgNCs), we have developed a new platform to construct analog INHIBIT-OR logic gate which was utilized for distinguishing miR-21 and miR-141 from each other for the first time. The method was further applied to the determination of miRNA spiked serum samples. More importantly, the proposed label-free logic circuits can be completed in a single tube rapidly, and all of them share the same threshold values. In addition, the devices can perform well in 5% serum, indicating that they may have potential applications in bioimaging and intelligent disease diagnostics.

2. Experimental

2.1. Chemicals and materials

All DNA oligonucleotides were purchased from Sangon Biotechnology Co., Ltd (Shanghai, China) and the sequences are provided in Table S1. The DNA strands were dissolved in ultrapure water as stock solutions and measured by UV–vis absorption spectroscopy throughout the experiments for future use. Silver nitrate, sodium borohydride, and other analytical pure chemicals were purchased from Aladdin Ltd. (Shanghai, China). Fetal bovine serum serum was purchased from Gibco(USA). GO was synthesized according to a modified Hummer's method.

2.2. Synthesis of silver nanoclusters (AgNCs)

The AgNCs were synthesized according to a previous report [31]. The AgNC-nucleation sequences (S-DNA, Ag-DNA1 or Ag-DNA1) were dissolved in PBS buffer (10 mM Na_2HPO_4/NaH_2PO_4, 100 mM CH_3COONa, 5 mM $Mg(CH_3COO)_2$, pH 7.5). Then, 1 mM $AgNO_3$ was added with vigorous shaking for 30 s. The solution mixture was kept in the dark at room temperature for 30 min. Subsequently, 1 mM $NaBH_4$ was added to the above solution, followed by vigorous shaking for 1 min. The final concentrations were 100 nM AgNC-nucleation sequences (S-DNA, Ag-DNA1 or Ag-DNA1), 600 nM $AgNO_3$, and 600 nM $NaBH_4$. Finally, the mixture was kept in the dark at room temperature and the reaction was allowed to proceed for 2 h prior to use of the product.

2.3. Construction of the logic devices for PC/PG and multiplexed analysis

The detailed procedure for the construction of the logic devices for parity generating/checking and multiplexed analysis are listed in the Supporting Information.

3. Results and discussion

3.1. Construction of the 2-Bit even parity generator

In any type of data transmission, the occurrence of bit errors is an inevitable and frequent issue. These failures have fatal effects on correct logic computations, especially in sophisticated circuits. Fortunately, the errors can be detected by parity generating and checking[32]. Typically, a parity bit (P) is generated and added to the data bits to make the total number of 1's (Σ) either even or odd. Thus, the parity bit can be utilized to detect errors in binary data transmission. The message, which contains the data bits along with the parity bit, is conveyed from the transmitting end to the receiving end. Then, the total number of 1's