Four-Analog Computation Based on DNA Strand Displacement

Chengye Zou,† Xiaopeng Wei,‡† Qiang Zhang,‡*,† Chanjuan Liu,† Changjun Zhou,‡ and Yuan Liu‡

†Faculty of Electronic Information and Electrical Engineering, Dalian University of Technology, Dalian 116024, China
‡Key Laboratory of Advanced and Intelligent Computing, Dalian University, Ministry of Education, Dalian 116622, China

ABSTRACT: DNA strand displacement plays an important role in biological computations. The inherent advantages of parallelism, high storability, and cascading have resulted in increased functional circuit realization of DNA strand displacement on the nanoscale. Herein, we propose an analog computation with minus based on DNA strand displacement. The addition, subtraction, multiplication, and division gates as elementary gates could realize analog computation with minus. The advantages of this proposal are the analog computation with negative value and division computation. In this article, we provide the designs and principles of these elementary gates and demonstrate gate performance by simulation. Furthermore, to show the cascade property of gates, we computed a polynomial as an example by these gates.

1. INTRODUCTION

The advancement of science and technology has necessitated higher requirements for computing speed and size of computer; however, these requirements may be limited by budget speed and computer size that are at maximal capacity. Therefore, new computer types are urgently needed to break through the bottleneck. Biological computers may satisfy the need in the future due to their parallelism and high storability. At present, biological calculation and DNA computation have attracted research interest, and increasing attentions have resulted in increased functional circuit realization of DNA strand displacement on the nanoscale. Herein, we propose an analog computation with minus based on DNA strand displacement. The addition, subtraction, multiplication, and division gates as elementary gates could realize analog computation with minus. The advantages of this proposal are the analog computation with negative value and division computation. In this article, we provide the designs and principles of these elementary gates and demonstrate gate performance by simulation. Furthermore, to show the cascade property of gates, we computed a polynomial as an example by these gates.

Song et al. have researched analog computation by DNA strand displacement circuits, and they proposed three elementary arithmetic operations: addition, subtraction, and multiplication. Analog circuits are suitable for positive analog computation because the concentration of DNA strands is the value of the input and the output. The concentration of DNA strands can only be positive; thus, in their article, they have implemented only positive analog computation. The subtraction gate in particular permits the use of larger numbers and allows smaller values to be removed. In addition, their element gates are without the division gate; as a result, they utilize Newton iteration to realize the division computation, but the error is large. In this article, we proposed four new elementary arithmetic operations based on their three element gates, addition, subtraction, multiplication, and division, which can carry out analog computation with negative and positive values through a dual-rail system and compared the properties of our DNA analog circle with their design. The chemical reaction networks (CRNs) of the four element gates are originated from ref 5. We have simplified the CRNs of their three element gates and reduce reversible reactions.

2. RESULTS

2.1. Abstractions of the Gates. Every gate has four inputs and two outputs, the high corner marks + and to distinguish — here indicate positive and negative values. For example, when input values $a_1$ and $a_2$ are positive numbers, $a'_1$ and $a'_2$ are nonzero but $a'_1$ and $a'_2$ are zero; when input values $a_1$ and $a_2$ are negative numbers, $a'_1$ and $a'_2$ are zero but $a'_1$ and $a'_2$ are...
nonzero; when output value $P_a$ is positive, $P_a^+$ is nonzero but $P_a^-$ is zero; and when output value $P_a$ is negative, $P_a^+$ is zero but $P_a^-$ is nonzero (Figure 1).

2.2. Addition Gate. CRNs 1a–1f5 of the addition gate can be described as follows

$+ \rightarrow + Ia \text{ Ga } Sp_k^1$ \hspace{1cm} (1a) \\
$+ \rightarrow + Ia \text{ Ga } Sp_k^2$ \hspace{1cm} (1b) \\
$+ \rightarrow − Ia \text{ Ga } Sp_k^2$ \hspace{1cm} (1c) \\
$+ \rightarrow − Ia \text{ Ga } Sp_k^2$ \hspace{1cm} (1d) \\
$+ \rightarrow + S_pC a M a M a_k^1$ \hspace{1cm} (1e) \\
$+ \rightarrow + S_pC a M a_k^2$ \hspace{1cm} (1f)

$Ia_1^+, Ia_2^+, Ia_1^-, Ia_2^-$ are the input chemical species to the addition gate, where their initial concentrations $[Ia_1^+]_0$, $[Ia_2^+]_0$, $[Ia_1^-]_0$, and $[Ia_2^-]_0$, respectively. Therefore, $a_1^+ = [Ia_1^+]_0$, $a_2^+ = [Ia_2^+]_0$, $a_1^- = [Ia_1^-]_0$, and $a_2^- = [Ia_2^-]_0$ where $a_1^+, a_2^+, a_1^-$, and $a_2^- \in (0, r_a)$ and $Ga_i (i = 1, 2)$ and $Ca_3$ are the chemical species; we define the initial concentrations as $[Ga_1]_0 \geq 2r_a$ and $[Ca_3]_0 \geq 2r_a$. $Ma_1$ and $Sp_2$ are the output chemical species of this gate, and their concentrations at equilibrium, $[Ma_1]_\infty$ and $[Sp_2]_\infty$, represent $P_a^+$ and $P_a^-$, respectively. When $Ia_1^+, Ia_2^+, Ia_1^-$, and $Ia_2^-$ are reacted eventually, addition gate computers can be described as follows

$$P_a = a_1 + a_2$$

$$= [Ia_1^+]_0 + [Ia_2^+]_0 - [Ia_2^-]_0$$

$$= [Ia_1^+]_0 + [Ia_2^+]_0 - ([Ia_1^-]_0 + [Ia_2^-]_0)$$

$$= [Ma_1]_\infty - [Sp_2]_\infty$$ \hspace{1cm} (2)

The output of the addition gate can be described as follows

$$|P_a| = |a_1 + a_2|$$

$$= |[Ma_1]_\infty - [Sp_2]_\infty|$$

$$= $$

$$= \begin{cases} [Ma_1]_\infty - [Sp_2]_\infty, & \text{if } [Ia_1^+]_0 + [Ia_2^+]_0 > [Ia_1^-]_0 + [Ia_2^-]_0 \\ [Sp_2]_\infty - [Ma_1]_\infty, & \text{if } [Ia_1^+]_0 + [Ia_2^+]_0 < [Ia_1^-]_0 + [Ia_2^-]_0 \end{cases}$$ \hspace{1cm} (3)

When $[Ia_1^+]_0 + [Ia_2^+]_0 > [Ia_1^-]_0 + [Ia_2^-]_0$, $[Ma_1]_\infty$ is nonzero and $[Sp_2]_\infty$ is zero; otherwise, $[Ma_1]_\infty$ is zero and $[Sp_2]_\infty$ is nonzero. There are no constraints on rate constants, $k_i (i = 1, \ldots, 6)$.

The DNA reactions in the addition gate are shown in Figures 2 and 3.

2.3. Subtraction Gate. The subtraction gate is inspired by CRNs 5a–5f. CRNs 5a–5f of the subtraction gate can be described as follows

$+ \rightarrow + Is \text{ Ga } Sp_k^1$ \hspace{1cm} (5a) \\
$+ \rightarrow + Is \text{ Ga } Sp_k^2$ \hspace{1cm} (5b)
Figure 3. List of the DNA reactions in the addition gate; CRN 4 is adapted from ref 5.

\[ \text{Is}_1^- + \text{Ga}_2 \xrightarrow{k_1} \text{Sp}_2 \]  
\[ \text{Is}_2^+ + \text{Ga}_2 \xrightarrow{k_2} \text{Sp}_2 \]  
\[ \text{Sp}_1 + \text{Ca}_3 \xrightarrow{k_3} \text{Ma}_1 + \text{Ma}_2 \]  
\[ \text{Sp}_2 + \text{Ma}_1 \xrightarrow{k_4} \emptyset \]

where \( \text{Is}_1^+ \), \( \text{Is}_2^- \), \( \text{Is}_1^- \), and \( \text{Is}_2^+ \) are the inputs of the subtraction gate; when they are reacted eventually, subtraction gate computers can be described as follows

\[ P_i = s_1 - s_2 \]
\[ = [\text{Is}_1^+]_0 - [\text{Is}_1^-]_0 - ([\text{Is}_2^+]_0 - [\text{Is}_2^-]_0) \]
\[ = [\text{Is}_1^+]_0 + [\text{Is}_2^-]_0 - ([\text{Is}_1^-]_0 + [\text{Is}_2^+]_0) \]
\[ = [\text{Ma}_1]_\infty - [\text{Sp}_2]_\infty \]

The output of the addition gate can be described as follows.
The DNA reactions in the subtraction gate are similar to those in the addition gate; therefore, we exclude the diagram and the list of DNA reactions in the subtraction gate.

2.4. Multiplication Gate. Considering the symbols + and −, multiplication computation is classified as follows

\[ P_m = m_1 m_2 \]

\[
\begin{align*}
&\begin{cases}
m_1^+ m_2^+ = p_m^- \\
m_1^- m_2^- = p_m^+
\end{cases} \\
\end{align*}
\]

\[ (8a) \]

\[
\begin{align*}
&\begin{cases}
\tilde{m}_1^+ \tilde{m}_2^+ = p_m^- \\
\tilde{m}_1^- \tilde{m}_2^- = 0
\end{cases} \\
\end{align*}
\]

\[ (8b) \]

According to eq 8, we should split four inputs into eight inputs, as shown in Figure 4.

\[
\begin{align*}
m_1^+ \rightarrow \{\tilde{m}_1^+, m_1^-, \tilde{m}_1^-, m_2^+ \} \rightarrow \{\tilde{m}_2^+, m_2^- \} \rightarrow \{\tilde{m}_2^+, m_2^- \}
\end{align*}
\]

Figure 4. Splitting of four inputs in the multiplication gate.

CRNs 9a—9d, 10a—10h, 11a—11h, and 12a,12b of the multiplication gate are given by

\[
\begin{align*}
\text{Im}_1^+ + \text{splitter}_1 \xrightarrow{k_1} \text{Gd}_1 + \text{Ht}_2 \\
\text{Im}_1^- + \text{splitter}_2 \xrightarrow{k_2} \text{Gd}_2 + \text{Ht}_1 \\
\text{Im}_2^+ + \text{splitter}_3 \xrightarrow{k_3} \text{G}_1 + \text{I}_1 \\
\text{Im}_2^- + \text{splitter}_4 \xrightarrow{k_4} \text{G}_2 + \text{I}_2 \\
\end{align*}
\]

\[ (9a) \]

\[ (9b) \]

\[ (9c) \]

\[ (9d) \]

where \( \text{Im}_1^+ \), \( \text{Im}_1^- \), and \( \text{Im}_2^+ \) are the input chemical species to the gate; \( \text{At} \) and \( \text{Bt} \) are the output chemical species to the gate; \( \text{Gd}_1 \), \( \text{Gd}_2 \), \( \text{Ht}_1 \), \( \text{Ht}_2 \), \( \text{G}_1 \), \( \text{G}_2 \), \( \text{I}_1 \), and \( \text{I}_2 \) are the breakup products of the input chemical species. \( \text{[Im}_1^+]_0 \), \( \text{[Im}_1^-]_0 \), and \( \text{[Im}_2^+]_0 \) are the initial concentrations of the input chemical species, so that, \( \text{[Im}_1^+]_0 = m_1^+ \), \( \text{[Im}_1^-]_0 = m_1^- \), \( \text{[Im}_2^+]_0 = m_2^+ \), and \( \text{[Im}_2^-]_0 = m_2^- \). \( \text{Sy}_1, \text{Sy}_2, \text{Nd}_1, \text{Nd}_2, \text{Sx}_1, \text{Sx}_2, \text{Nt}_1, \text{Nt}_2, \text{amplifier}, \text{splitter}_1, \text{splitter}_2, \text{splitter}_3, \text{splitter}_4, \text{amplifier}_1, \text{amplifier}_2 \) are the composed chemical species of the multiplication gate, and \( 0 < r_m \) is the input range; this implies that \( m_1^+, m_1^-, m_2^+, m_2^- \in (0, r_m) \), and initial concentrations of the other composed chemical species are \( \text{Sy}_1, \text{Sy}_2, \text{Nd}_1, \text{Nd}_2, \text{Sx}_1, \text{Sx}_2, \text{Nt}_1, \text{Nt}_2, \text{splitter}_1, \text{splitter}_2, \text{splitter}_3, \text{splitter}_4, \text{amplifier}_1, \text{amplifier}_2 \) are set to \( r_m \), where \( r_m = 10^{N} (N = 0, 1, 2, 3, ...) \).

When \( \text{Im}_1^+, \text{Im}_1^-, \text{Im}_2^+ \), and \( \text{Im}_2^- \) are reacted at equilibrium, \( \text{[At]}_\infty \) and \( \text{[Bt]}_\infty \) represent \( P_m^+ \) and \( P_m^- \) respectively. All other chemical species are intermediate products.

According to eq 8, eqs 8a and 8b cannot be satisfied simultaneously. When the inputs are \( \text{Im}_1^+ \) and \( \text{Im}_1^- \) or \( \text{Im}_2^+ \) and \( \text{Im}_2^- \)
Im2, the products of splitter are Gd1, G1, Ht2, and I1 or Gd2, G2, Ht1, and I2, respectively, which can produce Idn6. This means that [At]∞ is nonzero, but [Bt]∞ is zero; otherwise, [At]∞ is zero, but [Bt]∞ is nonzero.

The reaction rate constant must meet the following requirements:

\[
\begin{align*}
&k_1, k_2 \ll k_3, k_4 \\
&k_1, k_2 \ll k_5 = k_7 \\
&k_1, k_2 \ll k_9 = k_{11} \\
&k_1, k_2 \ll k_{13} = k_{15} \\
&k_1, k_2 \ll k_{17} = k_{19}
\end{align*}
\]

Therefore, reactions 10a, 10c, 10e, 10g, 11a, 11c, 11e, and 11g must be completed before reactions 9a and 9b can start. Because reactions 10a and 10c are completed before reaction 9a, the concentration ratio of Gy1 and Nd1 satisfied

\[
\frac{[Gy_1]}{[Nd_1]} = \frac{[Im_1^+]_0}{[Im_2^+]_0} = \frac{m_2^+}{m_2^+ + (r_m - m_2^+)}
\]

Because \( k_6 = k_7 \), Gd1 will be consumed by Gy1 and Nd1 at the same time and the concentration of Idn6 at equilibrium is

\[
[Idn_6]_\infty = m_1^+ m_2^+ m_2^+ (r_m - m_2^+) = m_1^+ m_2^+ r_m
\]

Then, to take advantage of amplification reaction 38, the concentration of At at equilibrium will be

\[
[At]_\infty = r_m m_1^+ m_2^+ r_m = [Im_1^+]_0 [Im_2^+]_0
\]

Similarly, we have

\[
\begin{align*}
&[At]_\infty = r_m m_1^+ m_2^+ r_m = [Im_1^+]_0 [Im_2^+]_0 \\
&[Bt]_\infty = r_m m_1^+ m_2^+ r_m = [Im_1^+]_0 [Im_2^+]_0 \\
&[Bt]_\infty = r_m m_1^+ m_2^+ r_m = [Im_1^+]_0 [Im_2^+]_0
\end{align*}
\]
The diagrams of the DNA reactions of the splitter and amplifier are shown in Figure 5 and Figure 6, respectively. Figure 6 shows the reaction diagrams of the two-fold amplifier; we can increase the length of DNA strands of \(Pm_1, Pm_2, Qm_1, Qm_2, Qd_1,\) and \(Qd_2\) to achieve multiple amplification. The DNA reactions in the multiplication gate are shown in Figure 7.

2.5. Division Gate. 2.5.1. Basic Division Gate. For the division computation with minus, division computations are classified as follows

\[
\begin{align*}
R_1 &= d_1d_2 = \begin{cases} \\
\frac{d_1^+/d_2^+}{d_1^-/d_2^-} = P_d^+ \\
\frac{d_1^+/d_2^-}{d_1^-/d_2^+} = P_d^- \\
\end{cases}
\end{align*}
\]

(20a)

\[
\begin{align*}
\frac{\dot{d}_1^+/\dot{d}_2^+}{\dot{d}_1^-/\dot{d}_2^-} &= P_d^+ \\
\frac{\dot{d}_1^+/\dot{d}_2^-}{\dot{d}_1^-/\dot{d}_2^+} &= 0 \\
\frac{\dot{d}_1^+/\dot{d}_2^+}{\dot{d}_1^-/\dot{d}_2^-} &= 0 \\
\frac{\dot{d}_1^+/\dot{d}_2^-}{\dot{d}_1^-/\dot{d}_2^+} &= P_d^- \\
\end{align*}
\]

(20b)

where \(|d_1| \geq |d_1|, |d_1| \geq 1.\)

According to eq 20, we should split four inputs into eight inputs, as shown in Figure 8.

The following CRNs, 21a–21d, 22a–22j, 23a–23j, and 24a–24d, are given for the division gate

\[
\begin{align*}
\text{Id}_1^+ + \text{split}_1 &\rightarrow \text{Id}_1 + \text{Ih}_2 \\
\text{Id}_1^+ + \text{split}_2 &\rightarrow \text{Id}_2 + \text{Ih}_1 \\
\text{Id}_1^+ + \text{split}_3 &\rightarrow \text{Xb}_2 + \text{Xm}_2 \\
\text{Id}_1^+ + \text{split}_4 &\rightarrow \text{Md}_2 + \text{Bm}_2 \\
\text{Id}_1 + \text{Id}_2 &\rightarrow \text{Xb}_1 + \text{Ng}_1 + \text{Xb}_1 \\
\text{Gi}_1 + \text{Xb}_1 &\rightarrow \text{Bi}_1 + \text{Ig}_1 \\
\text{Xb}_2 + \text{Bi}_1 &\rightarrow \emptyset \\
\text{IM}_1 + \text{Ng}_1 &\rightarrow \emptyset \\
\text{IM}_1 + \text{Xb}_2 &\rightarrow \text{Pg}_1 + \text{I}_2\text{d}_1 \\
\text{Id}_2 + \text{Id}_2 &\rightarrow \text{Xg}_2 + \text{Ng}_2 + \text{Md}_1 \\
\text{Gi}_2 + \text{Md}_1 &\rightarrow \text{Bi}_2 + \text{Ig}_2 \\
\text{Md}_2 + \text{Bi}_2 &\rightarrow \emptyset \\
\text{IM}_2 + \text{Ng}_2 &\rightarrow \emptyset \\
\text{IM}_2 + \text{Md}_2 &\rightarrow \text{Pg}_2 + \text{I}_2\text{d}_1 \\
\text{Ih}_1 + \text{Ih}_1 &\rightarrow \text{Xh}_1 + \text{Nh}_1 + \text{Xm}_1 \\
\text{Xm}_1 + \text{Hm}_1 &\rightarrow \text{Bh}_1 + \text{Mh}_1 \\
\text{Xm}_2 + \text{Bh}_1 &\rightarrow \emptyset \\
\text{IM}_3 + \text{Nh}_1 &\rightarrow \emptyset \\
\text{IM}_3 + \text{Xm}_2 &\rightarrow \text{Qb}_1 + \text{M}_3\text{t}_1 \\
\end{align*}
\]
\[
\begin{align*}
\text{Ih}_2 + \text{IH}_2 & \xrightarrow{k_w} \text{Xh}_2 + \text{Nh}_2 + \text{Bm}_1 \quad \text{(23f)} \\
\text{Bm}_1 + \text{Hm}_2 & \xrightarrow{k_w} \varnothing \quad \text{(23h)} \\
\text{Bm}_1 + \text{Hm}_2 & \xrightarrow{k_w} \text{Bh}_2 + \text{Mh}_2 \quad \text{(23g)} \\
\text{IM}_1 + \text{Nh}_2 & \xrightarrow{k_w} \varnothing \quad \text{(23i)}
\end{align*}
\]

Figure 7. continued
Figure 7. List of the DNA reactions in the multiplication gate; CRNs 19 and 20 are adapted from ref 5.

Figure 8. Splitting of four inputs in the division gate.
Figure 9. continued
Figure 9. List of the DNA reactions in the basic division gate; CRNs 30–32 are adapted from refs 4, 5.

\[
\text{I}_2\text{d}_2 + \text{Pn} \xrightarrow{k_{24}} \emptyset \tag{24b}
\]

\[
\text{Bn} + M_3t_1 \xrightarrow{k_{25}} Qn + N_jb \tag{24c}
\]

\[
M_3t_2 + Qn \xrightarrow{k_{24}} \emptyset \tag{24d}
\]

where \([\text{Id}_1^+]_0\), \([\text{Id}_1^-]_0\), \([\text{Id}_2^+]_0\), and \([\text{Id}_2^-]_0\) are the input chemical species to the gate; \([\text{Id}_3^+]_0\), \([\text{Id}_3^-]_0\), \([\text{Id}_4^+]_0\), and \([\text{Id}_4^-]_0\) are the output chemical species to the gate; and \([\text{Id}_1]\), \([\text{Ih}_2]\), \([\text{Ih}_3]\), \([\text{Xb}_2]\), \([\text{Xm}_2]\), \([\text{Md}_2]\), and \([\text{Bm}_2]\) are the breakup products of the input chemical species. 

\([\text{Id}_1^+]_0\), \([\text{Id}_1^-]_0\), \([\text{Id}_2^+]_0\), and \([\text{Id}_2^-]_0\) are the initial concentrations of the input chemical species, so that, \([\text{Id}_1^+]_0 = d_1^+, [\text{Id}_1^-]_0 = d_1^-, \ldots\), and \([\text{Id}_2^+]_0 = d_2^+, [\text{Id}_2^-]_0 = d_2^-\), where \([\text{Id}_1]\), \([\text{Id}_2]\), \([\text{Gl}_1]\), \([\text{Gl}_2]\), \([\text{IH}_1]\), \([\text{IH}_2]\), \([\text{Hm}_1]\), \([\text{Hm}_2]\), \([\text{M}_{12}^+]\), and \([\text{M}_{12}^-]\) are the chemical species in the system.
IMM, IM2, IM3, IM4, I2d2, M2t2, split1, split2, split3, and split4 are composed of the chemical species of the division gate, \((0, r_m)\) is the input range, meaning that \(d_1^+, d_1^-, d_2^+, d_2^- \in (0, r_m)\), and initial concentrations of the other composed chemical species are

Figure 10. Main leak reactions according to ref 5 in the four analog computation gates: leak reactions 1a and 2 in the addition and subtraction gates; leak reactions 3–10a in the multiplication gate; and leak reactions 11a–14 in the basic division gate. The forward and backward leak reaction rates are \(5 \times 10^{-9}/\text{nM/s}\).
defined as $[\text{ID}_1^0] = [\text{ID}_2^0] = [\text{G}_1]_0 = [\text{G}_2]_0 = [\text{I}_1]_0 = [\text{I}_2]_0 = [\text{H}_1]_0 = [\text{H}_2]_0 = [\text{I}_m]_0 = [\text{I}_m]_0 = [\text{H}_m]_0 = [\text{H}_m]_0 = [\text{A}_n]_0 = [\text{B}_n]_0 = r_{\text{sw}} [\text{I}_m]_0 = [\text{I}_m]_0 = [\text{I}_m]_0 = [\text{M}_t]_0 = [\text{M}_t]_0 = 1$.

When $\text{Id}_1^+$, $\text{Id}_1^−$, $\text{Id}_2^+$, and $\text{Id}_2^−$ are reacted at equilibrium, $[\text{I}_2d_1]_0$ and $[\text{M}_t]_0$ represent $P_d^+$ and $P_d^−$, respectively. All other chemical species are intermediate products.

According to eq 20, eqs 20a and 20b cannot be satisfied simultaneously. When the inputs are $\text{Id}_1^+$ and $\text{Id}_2^+$, the products of the splitter are $\text{Id}_1$, $\text{I}_h$, $\text{X}_b$, $\text{X}_m$, and the concentration of $\text{M}_t$ at equilibrium will be $[\text{M}_t]_0 = 1$ corresponding to reaction 23e, where the reaction rate constant must meet the following requirements

$$
k_8 \ll k_{1a}, k_{1b}, k_{1c}, k_{1d}, k_7
$$

$$
k_{12} \ll k_{2a}, k_{2b}, k_{2c}, k_{2d}, k_{2e}, k_{11}
$$

$$
k_{10} \ll k_{1a}, k_{1b}, k_{1c}, k_{1d}, k_{1e}, k_{15}
$$

$$
k_{20} \ll k_{2a}, k_{2b}, k_{2c}, k_{2d}, k_{2e}, k_{19}
$$

(25)

Therefore, reactions 21a, 21c, 22a, 22b, and 22c must be completed before reactions 22d and 22e can start. Because reactions 22b and 22c are completed before reactions 22d and 22e, the concentration of $\text{X}_b$ approaches $[\text{Id}_2^+] = [\text{Id}_1^+]$ and then the concentration ratio of $\text{Ng}_1$ and $\text{X}_b$ is satisfied

$$
\frac{[\text{Ng}_1]}{[\text{X}_b]} = \frac{[\text{Id}_2^+]}{[\text{Id}_1^+]} = \frac{d_1^{+} - d_2^{+}}{d_1^{+} - d_1^{−}}
$$

(26)

Owing to the rate of reactions 22d and 22e being identical, $\text{I}_m$ will be consumed by $\text{Ng}_1$ and $\text{X}_b$ at the same time and the concentration of $\text{Id}_1$ at equilibrium is

$$
[\text{I}_2d_1]_0 = 1 - \frac{d_2^{−} - d_1^{+}}{d_1^{+} + (d_2^{+} - d_1^{−})} = 1 - \frac{d_1^{+}}{d_2^{+}}
$$

(27)

Next, to take advantage of amplification reactions 24a–24d, the concentrations of $\text{I}_2d_2$ and $\text{M}_t$ at equilibrium will be

$$
[\text{I}_2d_2]_0 = 1 - \left(1 - \frac{d_1^{−}}{d_2^{+}}\right) = \frac{d_1^{+}}{d_2^{−}}
$$

$$
[\text{M}_t]_0 = 1 - 1 = 0
$$

(28)

Similarly, we have

$$
[\text{I}_2d_2]_0 = 1 - \left(1 - \frac{d_1^{−}}{d_2^{+}}\right) = \frac{d_1^{+}}{d_2^{−}}
$$

$$
[\text{M}_t]_0 = 1 - \left(1 - \frac{d_1^{−}}{d_2^{+}}\right) = \frac{d_1^{−}}{d_2^{−}}
$$

(29)

The DNA reactions in the basic division gate are shown in Figure 9.

2.5.2. Improved Division Gate. In consideration of the limitations ($|\text{Id}_1| \geq |\text{Id}_1|$, $|\text{Id}_1| \geq 1$), we have taken the following actions to improve the analog computation of division

1. To satisfy $10^N|\text{Id}_1| \geq |\text{Id}_1|$ and $10^N(|\text{Id}_1| \geq 1$ ($N = 0, 1, 2, 3, ...$), we use a $10^N$-times amplifier to amplify the concentration of the input of $\text{Id}_1$ or $\text{Id}_1^−$, when $N = 0$, the improved division gate will be reduced to the basic division gate.

2. Amplified $\text{Id}_1^+$ or $\text{Id}_1^−$ is involved in the reactions of the splitter and basic division gate; thus, the concentration of $\text{I}_2d_1$ at equilibrium is

$$
[\text{I}_2d_1]_0 = \frac{1}{d_1^{+} + (d_2^{+} - d_1^{−})} = 1 - \frac{d_2^{+}}{10^N d_2^{+}}
$$

(33)

Then, the concentration of $\text{I}_2d_2$ at equilibrium will be

$$
[\text{I}_2d_2]_0 = 1 \left(1 - \frac{d_1^{−}}{10^N d_2^{+}}\right) = \frac{d_1^{−}}{10^N d_2^{+}}
$$

(34)

Similarly, we have

$$
[\text{M}_t]_0 = 1 \left(1 - \frac{d_1^{−}}{10^N d_2^{+}}\right) = \frac{d_1^{−}}{10^N d_2^{−}}
$$

(35)

3. Finally, we use a $10^N$-times amplifier to amplify the output of the basic division gate.

Therefore, we can extend the division analog computation to a real number range through the above actions.

3. LEAK REACTIONS

Figure 10 depicts the main leak reactions in the four analog computation gates. The reason of the main leak is that the base pairs in the circular portion of DNA strand can be temporarily broken and create a toehold for an invaded strand. For example, $\text{M}_2$ can invade $\text{S}_3$, and displace the $q_1$ domain in the addition and subtraction gates, which is a typical reaction existing in the multiplication and division gates without splitter and amplifier.

We have analyzed the leak reactions of the four gates to evaluate the affection of the leak reactions for the output of the gates as follows:

(a) Affection of leak reactions in addition gates:

(i) When the symbols of $a_1$ and $a_2$ are different, leak reaction 1a in the addition gate is absent. The reaction rate of leak reaction 2 (reaction 37) is reduced compared to that of reaction 1f; therefore, affection of leak reaction 2 can be ignored.
When the symbols of $a_1$ and $a_2$ are the same, leak reaction 1a (reaction 38) will delay the concentration of the output reaching to valid range.

$$\begin{align*}
S_x + Ma_2 & \rightarrow Aq_1 + Sp_1 \\
Aq_1 + Sp_1 & \rightarrow S_x + Ma_2
\end{align*}$$

(II) When the symbols of $a_1$ and $a_2$ are the same, leak reaction 1a (reaction 38) will delay the concentration of the output reaching to valid range.

$$\begin{align*}
S_x + Ma_2 & \rightarrow Aq_1 + Sp_1 \\
Aq_1 + Sp_1 & \rightarrow S_x + Ma_2
\end{align*}$$

(b) Effect of leak reactions in subtraction gates:

(I) When the symbols of $s_1$ and $s_2$ are the same, the affection of leak reaction can be ignored.

(II) When the symbols of $s_1$ and $s_2$ are different, leak reaction 1a will delay the concentration of the output strand at equilibrium without affecting the value of output.

(c) Effect of leak reactions in multiplication gates:

Although the production of leak reactions 3, 5a, 7, and 9a will increase the value of output, we can neglect the affection of leak reactions in multiplication gates because these leak reactions have much less reaction rates compared to those of reactions 10b, 10f, 11b, and 11f.

(d) Effect of leak reactions in division gates:

In view of surplus of $X_{b_2}$, $M_d_2$, $X_m_2$, and $B_m_2$ in reactions 22c and 22e; reactions 23h and 23j; reactions 23c and 23e; reactions 23h and 23j, respectively, the production of leak reactions 11a–14 will increase the concentrations of [I2d1] and [M2t1] slowly, which will reduce the value of output gradually.

Above all, we use a valid range to show the performance of a gate under particular inputs; thus, $p_1 - r \leq$ output value $\leq p_1 + r$, $p_1 - r \leq$ output value $\leq p_1 + r$, $p_m - r \leq$ output value $\leq p_m + r$, and $p_u - r \leq$ output value $\leq p_u + r$ are fixed to define the valid output range of the addition gate, subtraction gate, multiplication gate, and division gate, respectively, where $0.02 \leq r \leq 0.04$ nM.

4. SIMULATION RESULT OF THE GATES

To test the effectiveness of these four gates, we simulated three input ranges (0, 1), (0, 2), and (0, 4), where the ranges between the pink and green lines were the valid output ranges. The simulation performance for the addition gate is given in Figure 11. When the symbols of $a_1$ and $a_2$ are different, the output stays in the valid range for a longer time because the inputs are larger and the effect of leak is relatively smaller. When the symbols of $a_1$ and $a_2$ are the same, the period for outputs in the valid range is constant. Figure 12 shows the performance of the simulation for the subtraction gate. When the symbols of $s_1$ and $s_2$ are the same, the output stays in the valid range for a longer time because the inputs are larger and the effect of leak is relatively smaller. When the symbols of $s_1$ and $s_2$ are different, the period for outputs to stay in the valid range is constant. The simulation performance for the multiplication gate is shown by Figure 13; because the period for outputs to stay in the valid range is constant, the influence of leak for multiplication gates can be ignored. Figure 14 shows the simulation performance for the division gate; the period for output to stay in the valid range increases with increasing concentrations of inputs because the influence of leak decreases with increasing inputs.

5. ANALOG DNA CIRCUIT TO COMPUTE

$$g(x, y) = \frac{xy}{x^2 + y^2}$$

5.1. Principle of the Analog Circuit. The input and output strands have same properties, so our four analog gates are modular; therefore, we can build DNA circuits by the four analog gates. For the addition and subtraction gates, early arrivals will wait for latecomers. When the cancellation between $Sp_1$ and $Sp_2$ is finished, the remaining $Sp_1$ or $Sp_2$ will be the
output strands. For the multiplication gate, the concentration ratios of Gy1 and Nd1, Gy2 and Nd2, Gx1 and Nt1, and Gx2 and Nt2 are obtained as early as possible because the ratios of reactions 18 and 19 are much smaller than those of the other reactions. Furthermore, Im1+ and Im1− or Im2+ and Im2− can be freely chosen for preparation in a “dynamic” fashion by other gates. For the division gate, inputs IM1, IM2, IM3, and IM4 can be prepared in a “static” fashion and ratios of reactions with IM1, IM2, IM3, and IM4 can be prepared in advance and they will react with other DNA strands of below gates.

Figure 15 shows an analog DNA circuit to compute $g(x, y) = \frac{xy}{x^2 + y^2}$, for $x \in \mathbb{R}, |y| \geq 1$.

5.2. Simulation of the Circuit to Compute $g(x, y)$. In the simulation of $g(x, y)$, $x \in \{-2, -1.75, -1.5, -1.25, -1, \}$, $y \in \{-2, -1.75, -1.5, -1.25, -1, \}$.
To quantify the performance of the circuit, we fixed the valid range between 0.95 \( g(x, y) \) and 1.05 \( g(x, y) \) during the 10^6 s. Figure 16a gives an example of the computation of \( g(x, y) \), where \( x = 1 \) and \( y = -2 \). The figure of evolution of \( g(x, y) \) is similar to division gate, but the outputs of \( g(x, y) \) reach the valid range slower than division gate (\([\text{Id1}]_0 = 1\), \([\text{Id1}]_0 = [\text{Id2}]_0 = 0\), \([\text{Id2}]_0 = 2\)), which is the result of operations of add and multiplication gates. In simulation, when \( y \in \{1, 1.5, 2, 2.5, 3\} \), the outputs stay in the valid range for a longer time, as shown in Figure 16b, which is irrelevant to the value of outputs because the affection of leak reaction is reduced with enlargement of inputs. Consequently, time for outputs to stay in the valid range has positive and negative symmetries, which means that time for outputs to stay in the valid range is the same for identical absolute values of inputs. When \( y \in \{4, 5\} \), the outputs cannot stay in the valid range, meaning that the enlargement of error for outputs, rather than decrease of time for outputs, stays in the valid range.

6. COMPARISON AND ANALYSIS

In this article, we not only added the division gate but also realized analog computation by DNA strand displacement circuits with minus; furthermore, we made some improvements in DNA analog computation.

6.1. Reduce the Influence of Leak Reactions of the Amplifier. As Figure 18 shows, \( \text{Om} \) is a production of main leak reactions in the amplifier designed by Song et al. and will increase the output of the multiplication gate. The larger \([\text{Id1}]_0\) is more influential to the output, as shown in Figure 17, when \([\text{Im1}]_0 = 1.5\) and \([\text{Im2}]_0 = 2\).

The leaks shown in Figure 18 were not evident in our amplifier, indicating that our multiplication gate was more stable and easier to operate.

6.2. Accuracy of Analog Division Computation. Although there was no division gate in the DNA analog com-
putation gates designed by Song et al., they achieved division computation \( r(x) = \frac{1}{x} \) \((0.5 < x < 1)\) by Newton iteration
\[
Y_{n+1} = 2Y_n - Y_n^2x
\]
(38)
where \( \lim_{n \to \infty} Y_n = \frac{1}{x} \).

Execution of the circuit to compute \( g(x, y) = 2y - y^2x \) is shown in Figure 19, when \( x = 0.5 \) and \( y = 1 \).

Considered that \( 10^3x > 1 \) in the computation of \( r(x) \), we can use the improved division gate to compute \( r(x) \). The performance of the improved division gate is shown in Figure 20a, when \([I_2d_2]_0 = 1\) and \([I_2d_3]_0 = 0.5\). Then, we chose a 10x amplifier to amplify the output of the improved division gate when the output of the improved division gate reached a valid range; otherwise, \( I_2d_2 \) and \( M_2t_2 \) will be amplified first because \( I_2d_2 \) and \( M_2t_2 \) are statically prepared in advance. The process of amplification is shown in Figure 20b, where \([I_2d_2]_0 = 0.1977\) and \( I_2d_3 \) is the output of the 10x amplifier.

On the basis of these principles, the results of our strategy were more accurate than those of the technique by Song et al.

7. CONCLUSIONS

We proposed four DNA analog computation gates and extended the computation range to real numbers. On the basis of the same properties of these gates, we constructed a DNA circuit to compute the polynomial function of inputs. Simulations showed that the time for outputs of circuit to reach a valid range was similar to that for a single basic division gate because DNA reactions are simultaneous; therefore, the
computations in the DNA circuit are parallel, which we aimed to achieve in this study.

Leak reaction is a common issue in a DNA strand displacement circuit, which was reduced in our work. In our amplifier and splitter, we eliminated the main leak reactions, similar to that of the main leak reactions in the amplifier designed by Song et al., which improved the computation of multiplication.

8. METHODS

The performances of the four element gates, the improved division gate, and the computation of a polynomial are simulated by Language for Biochemical Systems (LBS). To speed up the simulation, we used MATLAB to run the code produced from LBS by Visual GEC. All DNA figures are drawn by Visual DSD. The unit of the values of the code in the supporting information is nM.

AUTHOR INFORMATION

Corresponding Authors
*E-mail: xpwei@dlu.edu.cn (X.W.).
*E-mail: zhangq@dlu.edu.cn (Q.Z.).

ORCID
Qiang Zhang: 0000-0003-3776-9799

Author Contributions
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Notes
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