Cascadable Stochastic Logic for DNA Storage

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***Abstract*—Ever since Watson and Crick first described the molecular structure of DNA, its information-bearing potential has been apparent to computer scientists. This has led to a concerted effort in academia and industry to deliver practical DNA data storage systems. This paper presents a novel approach for both storage and computation with DNA. Data is stored in the form of analog values of the relative concentration of different DNA molecules. Computation is in the form of cascadable NAND operations, effected via toehold-mediated strand displacement reactions operating on these concentration values. Results were verified with the "Peppercorn Enumerator," a recent software tool for analyzing domain-level strand displacement. In all cases, the relative error in output concentration was less than 0.03%. The approach is robust to encoding errors and cross-hybridization. It does not rely on long DNA strands, which are expensive to synthesize. It opens new avenues for storage and computing, including the implementation of a wide range of useful mathematical functions *in vitro*.**

I. Introduction

A. The Biology

Deoxyribonucleic Acid (DNA) is a polymerized macromolecule that stores genetic information in nearly all living things in a directed sequence of adenines (A), cytosines (C), guanines (G), and thymines (T). DNA primarily exists as an antiparallel double stranded molecule forming a double helical ladder structure, in which the rungs of the ladder are *nucleotide pairs* (A binds to T, C to G and vice versa) while the side rails are the *phosphodiester backbones* [1]–[3].

In our synthetic storage system, we concatenate smaller single stranded DNA sequence units, called *domains*, to form longer strands. All domains are bounded to less than 30 nucleotides in length. Each domain binds with its complement. In Figure 1, domain 1 is shown in pink, domain 2 is shown in blue, and domain 3 is shown in yellow. The complementary domains are 1^*, 2^*, and 3^*, respectively. All domains are assumed to be *orthogonal* in sequence to each other, i.e. strands from different domains must exhibit negligible binding to each other. Orthogonality can be achieved by maximizing the *Hamming* distance for every pair of domains [4].

A *toehold* is an exposed domain, generally 10 nucleotides in length, on one of the strands in a double-stranded DNA (dsDNA) complex. Toeholds can be created with DNA nicking enzymes such as CRISPR-Cas9 [5] as in Figure 2. With two separate applications of guided CRISPR-Cas9, the backbone of the dsDNA can be nicked before and after the toehold. At this point the strand covering the toehold can be released by mild denaturing and elution [6]. For this process, the dsDNA is held in solution by the use of magnetic beads attached to the DNA backbone. A magnetic field is applied during the washing process [7]–[9].

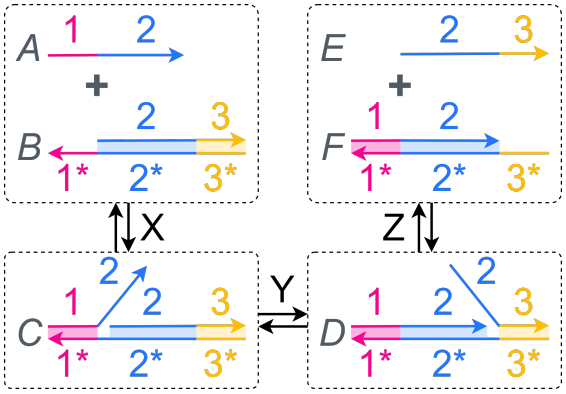

Fig. 1: The steps of toehold-mediated strand displacement. Each stage of the reaction is shown as a dashed bubble. The reaction starts in the upper left with molecules A and B, goes down to molecule C through reaction X, goes right to D through reaction Y, and finally produces E and F after reaction Z.

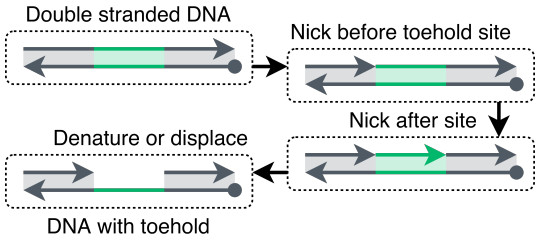

Fig. 2: Creating a toehold on a domain of interest (in green) in double-stranded DNA with the use of nicking enzymes like CRISPR-Cas9. Here, hybridized double-stranded domains are colored solid.

Toehold-mediated strand displacement (TMSD) is a particular class of *in vitro* reactions that allows for rate-controlled reactions of DNA molecules with toeholds [10]–[12]. A single-stranded DNA (ssDNA) containing the complementary sequence to a toehold can bind at that location. If the ssDNA is longer than the toehold there will be an overhanging *flap*. This flap can displace the adjacent domains in the dsDNA through a process termed *branch migration*. The original ssDNA can completely displace the originally bound portion of the dsDNA releasing a new ssDNA. This new ssDNA can then participate in further displacement reactions, creating a cascade of displacement reactions.

Figure 1 illustrates the different steps involved in TMSD: the dsDNA B has 3 domains, of which 1^* is a toehold. The ssDNA A contains domain 1 and can bind to B in reaction X, resulting in molecule C containing an overhanging flap from A. Through branch migration, shown in reaction Y, the A flap can fully bind and displace the original strand to produce D. Eventually this strand can be displaced off entirely in reaction Z to produce ssDNA E and dsDNA F, which now has a new toehold in 3^*. The ssDNA E can also participate in TMSD reactions through domains 2 or 3. The rates and directions for all reactions X,Y, and Z can be controlled by factors such as the length of domains (the binding of longer domains is favorable), the C-G percentage of domains (C-G bonds consist of 3 hydrogen bonds compared to the 2 in A-T bonds and thus favors binding), temperature (denaturing is favorable at higher temperatures), elution and magnetic purification (reducing product concentration drives a reaction forward), and through enzymes (DNAse can degrade DNA to reduce product concentration).

B. The Computer Science

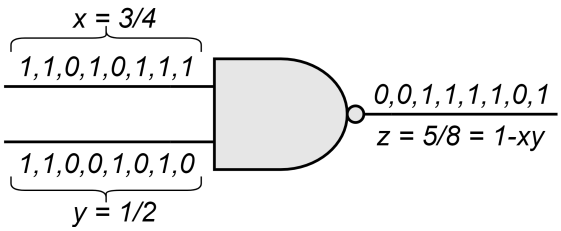

Fig. 3: A NAND gate operating on inputs $x = 3/4$ and $y = 1/2$. These are the probabilities of seeing 1's in streams of randomized bits. Recall that a NAND gate only outputs 0 if both inputs are 1. Here the gate computes a new bit stream where the probability of seeing a 1 is $z = 1 - xy$. Note that all randomized bit streams must be generated independently.

Stochastic logic is a paradigm for the design of electronic circuits in which digital gates operate on probabilities, i.e. analog values between 1 and 0 [13]. These values are represented as streams of random bits of 0 and 1, with the encoded value equal to the probability of a randomly chosen bit being 1, as shown in Figure 3 (we refer to such values as *stochastic values*). In contrast to conventional digital design in which numbers are represented in a binary radix format, complex functions can be computed with remarkably simple circuits with stochastic logic. For instance, multiplication can be implemented with a single AND gate. More complicated functions such as the exponential, absolute value, square roots, and hyperbolic tangent can each be computed with a very small number of gates [14]. Recall that in Boolean logic, a NAND gate is functionally complete. That is, all Boolean circuits can be constructed using cascades of these NAND gates. Similarly, any stochastic function can be computed with a cascade of NAND gates [15]. Figure 6 illustrates a more complex example of stochastic computation.

II. Methods

Our encoding is based on storing stochastic values in the form of relative concentrations of different dsDNA molecules

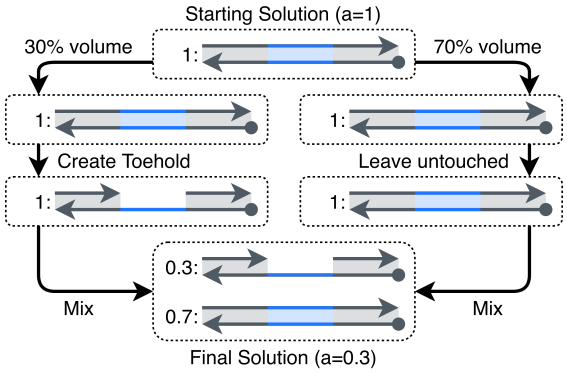

Fig. 4: Storing the stochastic value $a = 0.3$ in a fresh solution by performing a split by volume, and then creating a toehold in only one of the resulting two solutions.

in a single solution. (We call these stochastic values by analogy; it fact, these values are fully deterministic). Computation on the stored values is achieved through TMSD reactions. For a solution containing a standard volume and concentration (called a *fresh* solution) of dsDNA molecules, the relative concentration of dsDNA molecules containing toeholds to the total dsDNA concentration will be a fraction between 0 and 1. We treat this as a stochastic variable. In our figures, a dotted bubble represents a single solution of DNA, and the number to the left of a molecule in the solution represents its relative concentration with respect to all dsDNA molecules (note that ssDNA molecules are not included in calculating the total concentration). Fully hybridized double-stranded domains are shown as solid colors between the strands. A circle on the end of a DNA strand denotes the attachment of a magnetic bead.

A. Formation

We start with a fresh solution of dsDNA, shown in Figure 4 with a blue toehold domain. It is split by volume into two, according to the desired stochastic value. The figure illustrates a value of $a = 0.3$. One of resulting solutions, shown on the right in the figure, is left untouched. In the other, shown on the left in the figure, a toehold is exposed. A magnetic bead is used to hold the dsDNA in place while the released ssDNA is washed away. When the two solutions are mixed back together, the relative concentration of dsDNA with an exposed toehold to the total concentration of dsDNA will be exactly the split ratio. In this way, we have set a stochastic value. For a larger dsDNA molecule with several domains, multiple stochastic variables can be stored in different toehold domains independently.

B. NAND gate

Our reaction sequence for a NAND gate is shown in Figure 5. It computes the mathematical function $1 - a \times b$ for two stochastic variables a and b. By setting multiple variables together, a specific dsDNA molecule is prepared with concentration $a \times b$, containing a domain shown in yellow, flanked by two toeholds, shown in pink and blue. A single displacing strand of DNA is then mixed in the solution to initiate a TMSD

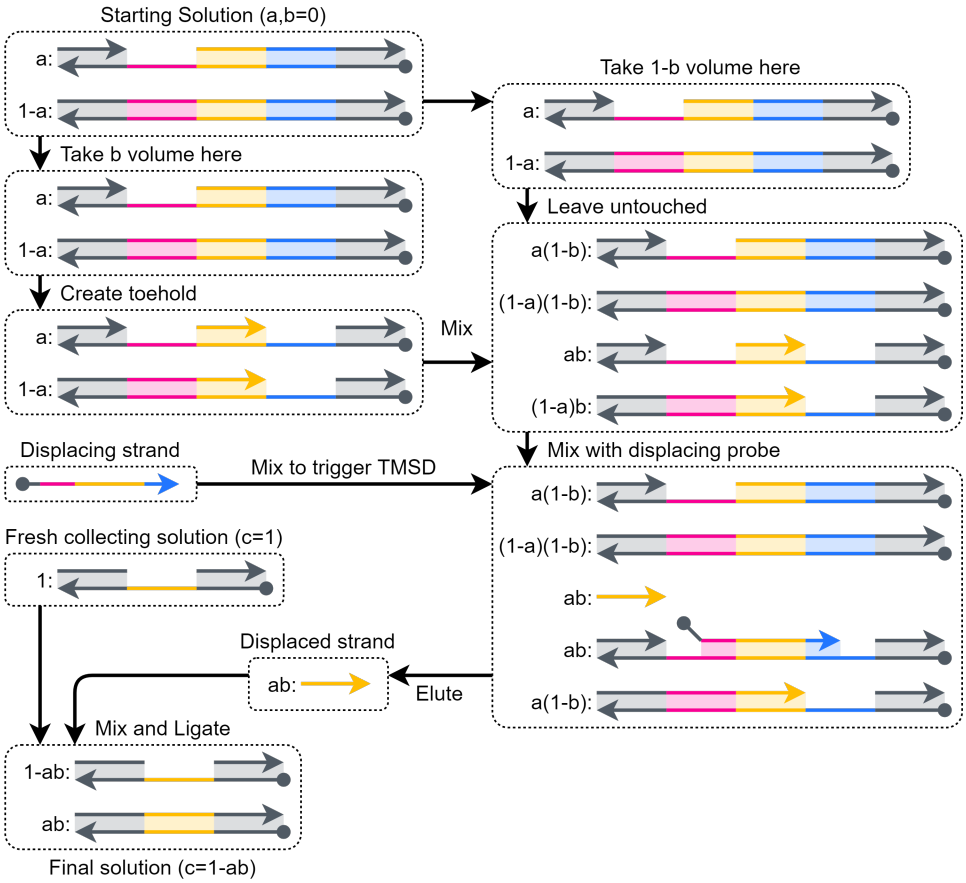

Fig. 5: A cascadable binary NAND gate, that computes the stochastic function $c = 1 - a \times b$. From a starting solution storing an arbitrary value a in a domain, shown in pink, and a domain storing a value $b = 0$, shown in blue, a volume split is performed followed by toehold creation to store a new arbitrary value b. When the two solutions are mixed back together, the concentration of dsDNA containing both toeholds shown in pink and blue is $a \times b$. (Note that we are computing a fraction of a fraction here.) A ssDNA called a *displacing strand* is mixed in the solution. It initiates a TMSD reaction that displaces the ssDNA shown in yellow from the dsDNA. All dsDNA are held in place by magnetic beads. The displaced strand is then eluted. It is then bound and ligated to a fresh solution of dsDNA with the complementary toehold, shown in yellow. The result is a solution where the relative concentration of dsDNA with the toehold shown in yellow is $1 - a \times b$.

reaction that displaces the ssDNA shown in yellow from the dsDNA. All dsDNA (and the extraneous displacing strands) are held in place by magnetic beads. The displaced ssDNA shown in yellow is eluted. It is mixed in with a fresh solution with complementary toeholds, and hybridization occurs. The resulting dsDNA is ligated to complete the reaction sequence [16]. The final solution stores a single stochastic variable that equals the NAND of the two input variables.

C. Simulations

We performed domain-level simulation using the tool Peppercorn Enumerator [17]. We set the initial concentration to 100 nM and the time period for each reaction to 100 seconds. A stochastic value a therefore had concentration $100a$ nM for dsDNA with toeholds. Unless explicitly specified, the length of a toehold was set to 10 nucleotides. For each simulated reaction, we have listed the domains, toeholds, and starting concentrations of all DNA molecules. We saw less than 0.03 nM relative error in concentration for the output. This confirmed the robustness of our NAND gate design. In detail, we tested:

1) Single Domain Hybridization: The reaction was $C_1 + S_1 \rightarrow S_2$. The highest relative error for binding $(100 - [S_1] - [S_2])$ was 0.03 nM. With toehold lengths of 30, this dropped to 0.01 nM. This translates to a 0.01% error in computation. Longer toeholds decreased the error in binding. The error rate was less than 1×10^{-4} when $[C_1] < 73$ nM. This simulation confirmed that it is feasible to set an arbitrary stochastic variable a into a solution.

TABLE I: Single Domain Hybridization molecules

Name	Type	Domains	Toeholds	Concentration
C_1	ssDNA	2	-	$100(1-a)$ nM
S_1	dsDNA	1,2,3	2^*	100 nM
S_2	dsDNA	1,2,3	-	0 nM

2) Multiple Domain Hybridization: The reaction was

$C_1 + C_2 + S_0 \rightarrow S_1 + S_2 + S_3$, and the measured concentration was $[S_0]$. The largest absolute error in concentration was observed to be 0.032 nM for $a = 1$ and $b = 0$ (and vice versa), while the majority cases exhibited error less than 0.01 nM. This confirmed that setting multiple stochastic variables a and b simultaneously resulted in an accurate storage.

TABLE II: Multiple Domain Hybridization molecules

Name	Type	Domains	Toeholds	Concentration
C_1	ssDNA	2	-	$100(1-a)$ nM
C_2	ssDNA	4	-	$100(1-b)$ nM
S_0	dsDNA	1,2,3,4,5	$2^*, 4^*$	100 nM
S_1	dsDNA	1,2,3,4,5	2^*	0 nM
S_2	dsDNA	1,2,3,4,5	4^*	0 nM
S_3	dsDNA	1,2,3,4,5	-	0 nM

3) Dual Toehold Displacement: The reaction was $P_1 + S_0 + S_1 + S_2 + S_3 \rightarrow R_1 + C_1$, and the target concentration was $[C_1]$. This simulation tested whether using a displacing strand allowed for efficiently displacing off the ssDNA shown in yellow in Figure 5. However, this simulation did not investigate the efficiency of the elution. The largest error observed was 0.01 nM while the rest of the cases had unobservable error. This minor peak in error was completely flattened by setting $[P_1] = 200$ nM. This confirmed that using a displacing strand in high concentration to displace the $a \times b$ ssDNA in our NAND gate is highly efficient.

TABLE III: Dual Toehold Displacement molecules

Name	Type	Domains	Toeholds	Concentration
P_1	ssDNA	2,3,4	-	100 nM
S_0	dsDNA	1,2,3,4,5	$2^*, 4^*$	$100ab$ nM
S_1	dsDNA	1,2,3,4,5	2^*	$100a(1-b)$ nM
S_2	dsDNA	1,2,3,4,5	4^*	$100(1-a)b$ nM
S_3	dsDNA	1,2,3,4,5	-	$100(1-a)(1-b)$ nM
R_1	dsDNA	1,2,3,4,5	-	0 nM
C_1	ssDNA	2	-	0 nM

III. Discussion

Note that our reaction sequence for a NAND gate results in dsDNA with exactly the same form of encoding as the inputs, namely the encoding shown in Figure 4. This allows the cascading of these NAND gates and thus the computation of any stochastic circuit. Complex polynomial functions can be computed this way [15]. Nonlinear functions such as e^{-x} can be approximated through polynomial approximations [18], as illustrated in Figure 6. The only limitation is that all functions must map the unit interval $[0, 1]$ to the unit interval $[0, 1]$, since the computation is on probabilities, in the case of stochastic logic, and fractional concentrations, in the scheme proposed in this paper.

Most prior work on DNA storage has focused on synthesizing DNA, with the information stored in the sequence of the nucleotides [19]. Indeed, this is how life stores genetic information. Such storage is compelling in terms of the density: up to 200 petabytes (that is one million gigabytes, or 2^{50} bytes) can theoretically be stored in a single gram of DNA [20]. However, this approach requires expensive *de novo* synthesis, the use of enzymes for purification and amplification, and single-nucleotide precision in sequencing. Furthermore, it is limited to storage only and is not a good fit for *in vitro* computation.

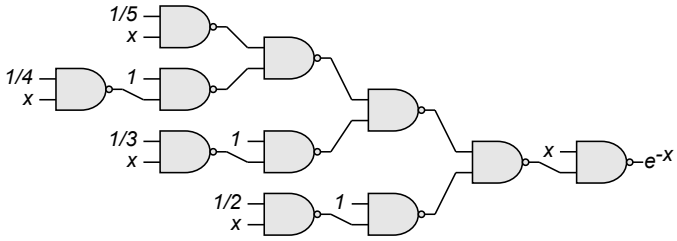

Fig. 6: A 5^{th} order polynomial approximation of the exponential function e^{-x} using just stochastic NAND gates.

The approach that we advocate in this paper, namely storing values in terms of concentrations, provides much lower densities of storage, per mass or per volume. However, computation on concentration values is possible with TMSD reactions. A recent research thrust is the design of arrays of toeholds for parallel TMSD operations [21]. The concepts in this paper could open new avenues for computing on such arrays, with analog concentration values.

We note that the dsDNA molecules in our scheme can be synthesized en masse by concatenating DNA domains using Gibson assembly [22]. Toehold manipulations allow for fine control of reaction rates. Our dsDNA molecules are not likely to exhibit large variance in reaction rates as we do not limit concentrations when creating toeholds.

In current and future work we are investigating: 1) the development of a reaction sequence for a ternary NAND gate; 2) detailed simulations of multi-NAND gate cascades, such as the one shown in Figure 6; 3) investigating the reaction time dependence in our designs; and 4) performing *in vitro* experiments for verification.

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