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Approaching mathematical model of the immune network based DNA Strand Displacement system

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ABSTRACT

One biggest obstacle in molecular programming is that there is still no direct method to compile any existed mathematical model into biochemical reaction in order to solve a computational problem. In this paper, the implementation of DNA Strand Displacement system based on nature-inspired computation is observed. By using the Immune Network Theory and Chemical Reaction Network, the compilation of DNA-based operation is defined and the formulation of its mathematical model is derived. Furthermore, the implementation on this system is compared with the conventional implementation by using silicon-based programming. From the obtained results, we can see a positive correlation between both. One possible application from this DNA-based model is for a decision making scheme of intelligent computer or molecular robot.

1. Introduction

Both theoretical studies and experimental results have been demonstrated regarding the DNA nanomachine device (Seelig et al., 2006; Zhang et al., 2007; Yurke et al., 2000; Rothemund, 2006; Soloveichik et al., 2010; Qian and Winfree, 2011; Qian et al., 2011). A toehold mediated strand displacement and branch migration has been treated as a promising methodology to deliver a dynamical system, which enables a bio-chemical circuit to approach the functionality of a silicon-based machine. While most attentions have been paid to the development of mechanical function of the nucleic-acid based molecular agent, such as DNA motor or walker (Sherman and Seeman, 2004; Shin and Pierce, 2004; Yin et al., 2004, 2008; Venkataraman et al., 2007; Omabegho et al., 2009), there is still a big gap where not so many references can be found regarding the computational design and information processing strategy by using DNA itself.

One biggest drawback of the DNA-based information processing system is because it is simply not easy to perform a computation above the DNA strands. Even the nucleotides can store the information in the similar manner with binary numbers, the manipulation can be done is restricted. This makes the coding of mathematical operation is not as trivial as in the dry computer. Instead, the predictable behavior of the Watson–Crick complementary and simple hybridization can be utilized as mechanism to programming in molecular level (Qian and Winfree, 2009, 2011; Qian et al., 2010; Soloveichik et al., 2010; Mardian et al., 2011). In Qian et al. (2011), a nature inspired computational method, such as neural network and natural immune system, have been employed as a strategy to develop an action-taking capable DNA system. These open the possibility for DNA to carry more complex task in many intelligent applications. However, the design of the DNA reaction and motif itself is still restricted to the specific problem. This leaves a question: given an arbitrary mathematical model to solve a computational problem, can we directly establish a DNA-based system with the same behavior?

In this work, we extend the idea of a self-organizing algorithm, namely Immune Network Theory, to describe a DNA-based interaction system. This model has been used to solve various computational problems, including decision making, reinforcement learning (Perelson, 1986; Castro and Timmis, 2003) in machine learning, robotics and artificial intelligence. Here, we derive the correlation between the DNA-based implementation with its mathematical formulation, in order to seek a more schematic way to compile the DNA Strand Displacement reaction.

To approach the solution to this problem, we express the DNA reaction above a mathematical notation referred to as Chemical Reaction Network (CRN). For decades, CRN has been employed to describe and analyze the kinetics of chemical reaction system. Given an arbitrary chemical reaction, where substrate of chemical reactants well-mix each other in a defined reaction rate constant to produce other chemical products, we can derive the instantaneous change of substrate's population over time, in terms of differential equation. The CRN has also been demonstrated as a powerful tool for molecular programming as it can model various complex dynamical systems implemented by DNA Strand Displacement reaction, including the oscillator (Soloveichik et al., 2010).

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In general, our contributions can be divided into two. First is to develop a new DNA-based computational algorithm that is based on swarm intelligence principle and interaction between DNA strands within a tube. Second is to bridge the current DNA computational system to any existed mathematical model, so that in future a gap between molecular and traditional computing can be minimized.

The rest of the paper will be organized as the following. Section 2 briefly introduces the DNA Strand Displacement reaction. Section 3 explains about the Chemical Reaction Network. Section 4 as the main contribution of this paper, we implement the Immune Network Theory model by using DNA-based system. Section 5 discusses the results obtained from the software-based simulation. Section 6 depicts the conclusion and any possible consideration in the future.

2. Chemical Reaction Network

Chemical Reaction Network (or CRN) is an applied mathematics theory that models the behavior of the biochemical reaction system in terms of ordinary differential equation. Suppose there are chemical species A, B, and C; it happens chemical reactions as in Eq. (1).

$$A + B \underset{k2}{\overset{k1}{\rightleftharpoons}} C \tag{1}$$

The kinetics of the reaction can be observed by the instantaneous change of the each species as in Eq. (2).

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -k1[A][B] + k2[C] \tag{2}$$

$$\frac{d[C]}{dt} = k1[A][B] - k2[C]$$

where $[A]$, $[B]$, and $[C]$ is the population number of the species at any time t. The reaction can be divided into two different reactions. First, the reaction where species A and B act as the reactants, and C as the product (forward reaction with constant rate $k1$). Second, the reaction where species C acts as the reactant, and A and B as the products (backward reaction with constant rate $k2$). The number of products depends on how many reactant's molecules collide each other throughout the reaction, which is denoted by the reaction rate. Therefore, in the case of forward reaction, it is shown by the first-line of Eq. (2). The second-line depicts the backward reaction. The plus and minus sign distinguish the product from the reaction, which should be positive when the species is produced and negative if it is consumed.

Soloveichik et al. (2010) showed that CRN can be utilized as a formulating tool in programming a DNA-based system with complex behavior. Since DNA is basically a biochemical material, its reaction kinetics also follows the CRN principle. By seeing this as a reverse problem, a corresponding DNA operation can be designed to achieve the intended behavior of the chemical system. For example, in Soloveichik et al. (2010) a DNA-based Lotka–Volterra model and limit cycle oscillator are successfully implemented.

3. DNA Strand Displacement

3.1. Basic DSD reaction

DNA Strand Displacement (or DSD) is a stochastic bio-chemical reaction, in which a single strand DNA reacts with a multi strand DNA complex to produce another single strand DNA (Seelig et al., 2006). This process can be viewed as a computational mechanism, with DNA as medium to carry the structure as well as the information. Among all DNA manipulation techniques available so far, DSD is said to be superior as it does not require any different molecules design except the strands, such as the restriction enzyme. Therefore, it is suitable for a large application design (Qian and Winfree, 2009, 2011).

The basic DSD reaction is shown in Fig. 1. Abstractly, a DNA strand is seen as consecutive sub-sequences (or called domains) with arbitrary alphanumeric character to represent the coding. By doing this, we can avoid the need to work with the nucleotide sequences. Instead, we treat the domains as the simplest functional unit in the computation. One character consistently represents the exact sequence, with the *-mark represents the complements (A with T, C with G and vice versa). We categorize the domains into two different types depending on the sequence length. The shorter (around 4–5 nucleotides) is referred to as toehold which is represented by the colored line. The longer (around 20 nucleotides or more) is called as non-toehold which is represented by the gray line. As the reaction occurs by chance, the toehold will reversibly bind faster than the non-toehold. Therefore, a free toehold in the system can trigger the whole DSD reaction to begin, while the non-toehold will provide the binding power as it does not easily unbind. Once a toehold from a single strand DNA binds to its free complement in a multi strand DNA complex, it will alter the adjacent domain to also bind with the following sequences by entropy difference. In this step, only if all the nucleotides match then the reaction can irreversibly proceed. As the result, a new single strand DNA will be released and replaced from the multi strand DNA complex through the process referred to as branch migration (Seelig et al., 2006).

In Fig. 1, the reaction is equivalent to a computational procedure that transforms signal A (consisting of domain t and a) into signal B (consisting of domain a and u) through the binding with a complex T_1 (which in turn is transformed into T_2). In the end, signal B can also perform a different reaction to complex T_2 to produce signal A and complex T_1 again. Thus, this reaction is considered as a reversible reaction. An irreversible DSD reaction can be achieved by making sure that there is no free toehold in the end of the process, so the multi strand DNA complex will become a waste after the reaction. For example, by adding another domain to signal A (for example $A = (t, a, u)$).

$$A + T_1 \underset{k2}{\overset{k1}{\rightleftharpoons}} T_2 + B \tag{3}$$

Eq. (3) shows the equivalent chemical reaction to the DNA Strand Displacement process in Fig. 1, assuming all the sequences matches the coding and the branch migration happens instantaneously.

3.2. DSD-based computational operator

There are many ways to compile DNA Strand Displacement reaction into a computational procedure. Among all design available so far, the principle is to encode every signal as a single strand DNA uniformly, for example in 3-domains (Cardelli, 2009; Mardian et al., 2011) or 4-domains coding (Soloveichik et al., 2010). On the other hand, a multi strand DNA complex will be treated as the fuel for the reaction as its design can vary depending on the input and output signals. We assume the multi strand DNA species is available in a very large number that it will not be exhausted within the given time, in order to maintain the reaction long enough.

In this paper, we implement our DSD-based computational operator (or simply DNA operator) by following the outline in (Soloveichik et al., 2010). We encode the signal in 4-domains coding, consisting of two non-toehold domains and two toehold domains reside alternating. The first non-toehold is the history domain. It stores the information to which multi strand DNA complex, that signal bound previously. Two single strand DNA with a different history domain are treated as the same signal, as they may