Review on DNA Strand Algebra and its Application

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Abstract
Several technological limitations of traditional silicon based computing are leading towards the paradigm shift, from silicon to carbon, in computational world. Among the unconventional modes of computing evolved in past several decades, DNA computing has been considered to be quite promising in solving computational and reasoning problems by using DNA strands. Along with the sequential operations, the huge parallelism of DNA computing methodologies engaging numerous numbers of DNA strands induce the consideration of concurrent high-level formalisms. In this paper we have reviewed the algebraic explanation of concurrent DNA processes using DNA strand algebra, process calculus and DNA strand graph. We have demonstrated the application of syntax and semantics of the illustrated methodologies in the domains of reasoning and theorem proving with resolution refutation. Finally, we have presented DNA cryptography as one of the prominent areas for the future scope of research work where DNA strand algebra can be used as formal modelling tool to authenticate the security, logic and reasoning of the existing protocols.

Keywords: DNA strand algebra; DNA gate; DNA signal; process algebra; process calculus; DNA strand graph; DNA computing; strand displacement; logical inference, modus ponens; syllogistic reasoning; disposition; theorem proving; resolution refutation; DNA cryptography.

1. Introduction
The traditional technique of computing has been successfully evolved through past several decades and now landed up at its mature stage which is fast, adjustable, and well-documented. But research and application of conventional silicon based technology is
approaching towards the point where there are certain restrictions in the domains of design complexity, memory, processing power, energy consumption and heat dissipation. To overcome these limitations several unconventional computational techniques are being proposed amongst which molecular computing, has achieved substantial attention. DNA computing, a branch of molecular computing is based on Watson-Crick base pairing which is the unique property of DNA molecule. In 1994 Leonard Adleman, the pioneer of DNA computing first solved seven point Hamiltonian path problem using DNA strands. The possibility of computing directly with molecules was first explored by his work. Since then, different research works are being performed across the globe either to enhance the available DNA computing methodologies [Adleman, 1994; Benenson et al., 2001; Green et al., 2006; Winfree et al., 1996] or to propose innovative and novel approach towards solving problems using DNA computing.

After 25 years of research, the domain of DNA computation has been reached to the level where the researchers have developed DNA self assembly [Winfree et al., 1996] i.e. automation using DNA strands. The massive parallelism of the molecular operations viz. DNA synthesis, melting and annealing, amplification, extraction, separation, cutting, ligation, substituting, reading or sequencing, by which DNA strands can be manipulated, is one of the advantages of DNA computing. Along with the sequential operations, the huge parallelism of DNA computing methodologies engaging numerous numbers of DNA strands induce the consideration of concurrent high-level formalisms. In this review report we will demonstrate the algebraic explanation of concurrent DNA programs by DNA strand algebra [Cardelli, 2009], which can be defined as a subdivision of process algebra [Baeten, 2004]. The algebraic study of formal semantics of concurrent communicating processes is defined as process algebra. The tool of process algebra is the algebraic language which provides the high-level description of communications, interactions, and synchronizations between a collection of independent agents or processes. The algebraic laws presented by process algebra can manipulate and analyze the process descriptions and generate formal reasoning to control the equivalences between processes.

Generative grammar of formal language theory has a resemblance with the DNA self-assembly and DNA strand ligation. Both generate new strings from previous string following certain pre-defined rules. Thus, to represent the architecture of a model of DNA computation, formal language is widely appreciated. The mechanism of DNA strand displacements using DNA strands with rich secondary structures can be modeled, simulated and analyzed by a newly defined language by Petersen, Lakin and Phillips [Petersen et al., 2016], termed as process calculus. But there are some limitations of process calculus in implementation of different rules in the context of complexity of pattern matching. To overcome this problem Petersen et al. [Petersen et al., 2016] introduces the concept of DNA strand graph.

2. Methodology

In this paper we will deal with formal presentation of concurrent and communicating processes involved in DNA computing which is presented through DNA strand algebra. DNA
strand algebra is essentially dependent on process algebra. We will also focus on process calculus in the context of DNA computation and DNA strand graph. Before exploring the key topic, the first thing we have to know the difference between syntax and semantics of formal language.

In mathematical theory, formal language is defined by a set of strings of symbols which are constrained by specific rules. A language is constructed using the set of valid sentences. Syntax and semantics are used to verify the validity of the language. Syntax of the formal language can be defined as the grammatical structure of a language. It doesn’t concern about the meaning associated with the sentence. On the other hand, semantics refers to the meaning of the syntactically arranged vocabulary symbols and generally it is related to the truth and falsehood of the language. If a language is syntactically valid, it does not imply that it is also semantically correct.

2.1. Process Algebra

In computer science, process algebra can be defined as the algebraic study of formal semantics of concurrent communicating processes. The tool of this discipline is the algebraic language which provides the high-level description of communications, interactions and synchronizations between a collection of independent agents or processes. The algebraic laws of process calculi manipulate and analyze the process descriptions and control the equivalences between processes by generating formal reasoning.

Process calculi [Berry and Boudol, 1989] express chemistry of diluted well-mixed solutions where floating molecules can interact according to certain pre-defined reaction rules. The fundamental operators of process calculi permit the following operations;

i. **Parallel composition**: The simultaneous and independent progress of the processes is achieved by parallel composition of the processes. The parallel composition of two independent processes $P$ and $Q$ can be expressed as $P|Q$. It permits the synchronization and flow of information between the processes.

ii. **Compatibility**: Process algebra specifies the channels used for the communication and/or synchronization of input-output data. One of its fundamental features is compatibility, i.e. internal actions are not used for communication and every action is controlled by at most one process.

iii. **Sequential Composition**: The concurrent processes can be sequentially ordered. Generally, the sequential operator is integrated with the input and/or output information. In process calculi, the expression $f(x).P$ (where, $f(x)$ is input operator and $P$ is a process) indicates that $P$ will be activated after receiving the information through $f$ substituted for identifier $x$. 

iv. *Hiding of the points of interaction:* During parallel composition of agents in concurrent processes, the connections made at the points of interactions are controlled by hiding operations. This operator is vital as the interaction points are susceptible to interference.

v. *Recursion and replication:* The infinite behavior of the finite process is demonstrated by recursion and replication. The recursion operation can be expressed as \( \mu X.P \), where \( P \) has occurrences of \( X \). \( P \) in this expression can again be replaced by \( \mu X.P \) and so on. The replication operation is denoted by \( !P \) which represents the parallel composition of unbounded number of \( P \) processes i.e. \( P \mid P \mid \ldots \).

The binary relations *mixing* and *reaction* can be defined on a set of chemical process calculi. If \( P \), \( Q \) and \( R \) are three chemical solutions in a set; then *mixing* \( (P \equiv Q) \) syntactically brings the floating molecules close enough so that they can interact i.e. it creates equivalence; *reaction* \( (P \rightarrow Q) \) demonstrates the change occurs in the chemical solution. The sequence of reactions is denoted by the symmetric and transitive closure, \( \rightarrow^* \).

The general laws of chemistry demonstrated through process calculi are listed below;

\[
\begin{align*}
P &\equiv P; & P \equiv Q \Rightarrow Q \equiv P; & P \equiv Q, Q \equiv R \Rightarrow P \equiv R & \text{equivalence} \\
P &\equiv Q \Rightarrow P + R \equiv Q + R & \text{in context} \\
P + Q &\equiv Q + P; & P + (Q + R) \equiv (P + Q) + R; & P + 0 \equiv P & \text{diffusion} \\
P &\rightarrow Q \Rightarrow P + R \rightarrow Q + R & \text{dilution} \\
P &\equiv P', & P' \rightarrow Q', & Q' \equiv Q \Rightarrow P \rightarrow Q & \text{well mixing}
\end{align*}
\]

2.2. **DNA Strand Algebra [Cardelli 2009; 2013]**

Luca Cardelli from Microsoft Research first proposed DNA strand algebra [Cardelli, 2009] which he described as a branch of process algebra. DNA strands, DNA gates, and their interactions [Cardelli, 2009; 2013] are the key apparatus of DNA strand algebra. The formulations of process algebra are perfectly applicable for DNA strand algebra as all the mechanisms and active elements of strand algebra are the part of the system and consumed by their own activity.

The essential atomic elements based on which the structure of DNA strand algebra is developed are;

- **Signals:** These are oligonucleotides i.e. single stranded short DNA sequences. In this paper the signal strand is denotes by \( x \).
- **Gates:** These are generally single stranded or partially double stranded DNA structures. Gates act as operators which take signal as input and generates either one/more signals or nothing (0) as output.

The combinators of strand algebra are;

- *parallel (concurrent) composition* \( (P \mid Q) \)
- *populations* \( (P') \)
The ‘soup’, where the concurrent communicating processes occur, is actually the combination of signals and gates. The molecules floating in the soup can interact with each other without any interference.

2.2.1. Syntax of DNA strand Algebra

When the signal strand is added to the soup, it attaches with the complementary input segment of the gate. Here, the complementary denotes the Watson-Crick complement. For example, a signal strand \( x \) has three segments, viz. \( b, c, d \) (in 5’ to 3’ direction). The complementary strand of \( x \) is represented by \( x^\perp = (b^\perp, c^\perp, d^\perp) \) (in 5’ to 3’ direction). The signal strand \( x \) hybridizing with \( x^\perp \) is shown in Fig. 1.

![Figure 1. Signal strand \( x \) hybridizing with \( x^\perp \)](image)

Now, we will show the representation of the gates. \([x_1, ...., x_n], [x^\perp_1, ...., x^\perp_m]\) is a gate where input signals are \( x_1, ...., x_n \) and output signals are \( x^\perp_1, ...., x^\perp_m \). These are all consumed by the process. The gate joins \( n \) number of signal strands and forks \( m \) number of signal strands. Table 1 explains the syntax and abbreviations used in DNA strand algebra.

| Syntax | Description |
|--------|-------------|
| \( x \) | Signal |
| 0 | Inert |
| \( P_1 \parallel P_2 \) | parallel compositions |
| \( P^* \) | unbounded population |
| \( x_1 \cdot x_2 \equiv [x_1] \cdot [x_2] \) | transducer gate |
| \( x \cdot [x_1, ...., x_n] \equiv [x] \cdot [x_1, ...., x_n] \) | fork gate |
| \( [x_1, ...., x_n] \cdot x \equiv [x_1, ...., x_n] \cdot [x] \) | join gate |

Table 1. Syntax and abbreviations used in DNA strand algebra

The inert component (0) which the gate generates, the infinite populations \( P^* \), the parallel compositions \( P_1 \parallel P_2 \) all are the components of the system i.e. the parts of signals and gates assemblies. The syntax expressing this statement is:

\[
P := x : [x_1, ...., x_n] \cdot [x^\perp_1, ...., x^\perp_m] : \{0 : P_1 \parallel P_2 : P^*\ \text{where, } n \geq 1; m \geq 0 \} \quad (1)
\]

2.2.2. Permissible Relations of DNA strand Algebra
The relations applicable in DNA strand algebra are mixing and reaction [Cardelli, 2009]. The relation ‘mixing’ is denoted by ‘≡’. The set of rules which this relation follows is given in Table 2.

| Rule | Description |
|------|-------------|
| \( P \equiv P \) | equivalence |
| \( P \equiv Q \Rightarrow Q \equiv P \) | |
| \( P \equiv Q, Q \equiv P \Rightarrow P \equiv R \) | |
| \( P \mid 0 \equiv P \) | diffusion |
| \( P \mid Q \Rightarrow Q \mid P \) | |
| \( P \mid (Q \mid R) \equiv (P \mid Q) \mid R \) | |
| \( P \equiv Q \Rightarrow P \mid R \equiv Q \mid R \) | in context |
| \( P \equiv Q \Rightarrow P^* \equiv Q^* \) | |

Table 2. Set of rules followed by the relation mixing

The relation ‘reaction’ is denoted by ‘\( \rightarrow \)’. The set of rules which this relation follows is given in Table 3.

| Rule | Description |
|------|-------------|
| \( x_1 \mid \ldots \mid x_n \mid [x_{i_1}, \ldots, x_{i_n}] \cdot [x_{i_1}, \ldots, x_{i_m}] \rightarrow x_{i_j} \mid \ldots \mid x_{i_m} \) | gate (\( n \geq 1, m \geq 0 \)) |
| \( P \rightarrow Q \Rightarrow P \mid R \rightarrow Q \mid R \) | dilution |
| \( P \equiv P', P' \rightarrow Q', Q' \equiv Q \Rightarrow P \rightarrow Q \) | well mixing |

Table 3. Set of rules followed by the relation reaction

2.2.3. Toehold Mediated Branch Migration and Strand Displacement

In DNA strand algebra the mechanism of the system i.e. the interaction between gate and signal strands is generally dependent on toehold mediated branch migration and strand displacement [Cardelli, 2013; Green and Tibbetts, 1981; Zhang and Winfree, 2009]. The process through which two DNA strands with partial or full complementarity hybridize to each other, displacing one or more pre-hybridized strands is called DNA strand displacement [Ray and Mondal, 2016]. Branch migration occurs when a DNA strand, partially paired to its complementary sequence in a DNA duplex, extends its pairing by displacing other pre-hybridized DNA strand. The single stranded segment of a DNA strand which initiates the branch migration process is termed as toehold.

In DNA strand algebra the signal strand \( x \) is designed in such a way so that it can hybridize with the desired gate structure. Structurally the signal strand has three segments, viz. \( x_h, x_p, x_b \); where, \( x_h \equiv history \) (accumulate the history of previous hybridizations and other interactions), \( x_t \equiv toehold \) (initiates toehold mediated branch migration and strand displacement and reversibly binds with the gate structure), \( x_b \equiv binding \) (hybridizes with the gate). Fig. 2 represents the schematic diagram of the DNA signal strand.
2.2.4. Semantics of DNA Strand Algebra

We will explain the semantics of DNA strand algebra by presenting certain models of DNA implementation of the combinatorial strand algebra, $\mathcal{P}$ [Cardelli, 2009]. These DNA models can be represented by expressions from DNA strand algebra. In a DNA system, the signals can interact with the gates; but interactions between the signals and between the gates are not allowed.

Fig. 3 shows the schematic diagram illustrating the mechanism of annihilator [Cardelli, 2009]. The signal strand $x$ hybridizes with the gate $G$ by toehold mediated branch migration process and displaces the strand $x_h$. This reaction produces nothing (0). The gate can be called ‘$x_h$ generic’ as the performance of the gate does not depend on $x_h$. The expression representing the mechanism is;

$$x \mid x \cdot [h] \rightarrow 0$$  \hspace{1cm} (2)

Fig. 4 shows the schematic diagram illustrating the mechanism of transducer. The DNA implementation of transducer model assigns the gate $x.y$ which transduces the signal $x$ into a signal $y$. The model depends on two reactions, one is reversible and the other is irreversible using two separate gate structures; gate backbone ($G_b$) and gate trigger ($G_t$). In the forward reversible reaction, the signal $x$ hybridizes to $G_b$ by displacing signal $y$. After adding $G_t$ to the soup, the second irreversible reaction occurs which locks the gate structure in the situation where the signal $x$ is consumed and $y$ is generated. This reaction produces nothing (0). The expression representing the mechanism is;
Figure 4. Mechanism of transducer

Following the same design strategy 2-way fork gate, $x. [y, z]$ can be developed which generate two output signals. The expression of the DNA system is represented as;

$$x | x.y \rightarrow y$$

(3)

By using longer trigger strands, this model can be extended to develop $n$-way fork which is capable of producing $n$ number of DNA signal strands.

Fig. 5 represents the schematic diagram of 2-way join-core function which joins two signals ($x$ and $y$) and produces another signal ($z$). The expression of the join gate model is;

$$x | y | [x, y]. z \rightarrow z$$
Figure 5. Mechanism of 2-way join-core function

Cardelli [Cardelli, 2009] also extended DNA strand algebra to develop a DNA model termed as *curried gates* which can produce other gates. Let us assume that \( H(y) \) is a transducer \( y.z \) as shown in Fig. 4. Using the same mechanism, curried gate \( x.y.z \) can be generated which is represented by the expression:

\[
x \mid x.y.z \rightarrow y.z
\]

By using these DNA implementations, all the other formal languages and interacting automata can be mapped to DNA strand algebra.

2.2.5. Nested DNA Strand Algebra

Cardelli [Cardelli, 2009] also introduced *nested DNA strand algebra* \((nP)\) to compile high-level language in form of DNA strand algebra. Using nested join or fork operators of DNA
strand algebra compound expressions can be presented. The sign ‘?’ denotes the input to the DNA system and ‘!’ denotes the output of the input system. Thus, the model which takes \( x_1 \) and \( x_3 \) as input signal strand and produces \( x_2 \) can be expressed in the following form;

\[
? x_1, ! x_2, ? x_3 \equiv x_1, [x_2, x_0][x_0, x_3].[]
\]  

(6)

where,

\( x_0 \equiv \) fresh signal strand which does not obstruct the system reaction

Nesting operators lead to the nested population, for example, \( ? x.(P^*) \). Now, the new syntax modified from expression (1) is;

\[
P := x : ?[x_1, ..., x_n].P : ![x_1, ..., x_n].P : 0 : P_1 | P_2 : P^* \quad \text{where,} \ n \geq 1
\]

(7)

In the modified version of DNA strand algebra the mixing relation is unchanged, but the for gate rule the reaction relation (Table 3) is altered as given in Table 4.

| \( ? [x_1, ..., x_n].P \) | \( x_1 \) ... \( x_n \) \( \rightarrow P \) | Input gate (for example, \( ? x.0 \rightarrow x \)) |
| \( ![x_1, ..., x_n].P \rightarrow x_1 \) ... \( x_n \) \( P \) | Output gate (for example, \( ! x.0 \rightarrow x \)) |

Table 4. Modified gate rules followed by reaction relation in nested DNA strand algebra

Cardelli also presented the unnest algorithm to compile nested DNA strand algebra to DNA strand algebra. The algorithm is given below [Cardelli, 2009];

\[
\begin{align*}
U(P)_\mathcal{X} & \equiv X_0|U(X_0, P)_\mathcal{X}_2 \\
U(X, x)_\mathcal{X} & \equiv X, x \\
U(X, ?[x_1, ..., x_n], P)_\mathcal{X} & \equiv [X, x_1, ..., x_n].X_0|U(X_0, P)_\mathcal{X}_2 \\
U(X, ![x_1, ..., x_n], P)_\mathcal{X} & \equiv X.[x_1, ..., x_n, x_0]|U(X_0, P)_\mathcal{X}_2 \\
U(X, 0)_\mathcal{X} & \equiv X.[] \\
U(X, P'|P'')_\mathcal{X} & \equiv X,[X_0, x_1]|U(X_0, P')_{\text{evn}(x_2)}|U(X_1, P'')_{\text{odd}(x_2)} \\
U(X, P^*)_\mathcal{X} & \equiv (X,[X_0, x]|U(X_0, P)_\mathcal{X}_2)^*_1
\end{align*}
\]

where,

\( \mathcal{X} \) \equiv unbounded list of distinct signal strand
\( \text{evn}(\mathcal{X}) \) \equiv even elements of \( \mathcal{X} \)
\( \text{odd}(\mathcal{X}) \) \equiv odd elements of \( \mathcal{X} \)
\( U() \) \equiv function for innerloop

2.2.6. Stochastic DNA Strand Algebra

By associating the stochastic rates to the DNA gate, stochastic DNA strand algebra is formed. If the numbers of the input strands are same, then the stochastic rates of the gates \( g_n \) are also identical. The population \( P^* \) of strand algebra is infinite; thus, to get stable rate ratio of the DNA system the size of the population should be stable. This can be achieved by dropping \( P^* \) construct. While developing stochastic rates, instead of considering \( P^* \), restricted population,
$P^k$ is taken under consideration which is the $k$ parallel copies of $P$ ($P$ is the global state). $P^=k$ i.e. the restricted population of constant size $k$, can be defined as,

$$P^=k \equiv ([x, y]. [z, X])^k ([X, [x, y], [z, X]])^f(k)$$ (8)

where,

$X \equiv$ unused signal

$f(k) \equiv$ size of buffer solution which is adequately large (buffer population is used to keep $P^=k$ constant; it can be refilled without interrupting the ongoing reactions)

For the gate $[x_1, \ldots, x_n]. [y_1, \ldots, y_m]$ with stochastic rate $g_n$, the global transition from a global state $P$ to a next global state can be defined by,

$$P \rightarrow (P \text{ choose } (x_1\ldots x_n[x_1,\ldots,x_n],[y_1,\ldots,y_m])) \times g_n \equiv \text{ propensiety of gate reaction}$$ (9)

where,

$\text{ comp}(r) \equiv r^\bot$ and $\text{ comp}(r^\bot) \equiv r$.

$\text{ toehold}(r) \equiv$ true if $r$ is a toehold domain.

Though there is no direct correspondence between DNA strand algebra and stochastic DNA strand algebra, but the abstract stochastic model is required for better understanding of the DNA system.

### 2.3. Process Calculus [Petersen et al., 2016]

In process calculus, a multiset consists of DNA strands $<S>$ is termed as a process or program $P$. The program can be defined by the following expression;

$$P ::= <S_1> \ldots <S_i>$$ (10)

where, $i \geq 0$

Each strand $<S>$ contains one or more domains $d$. Domain is actually a sequence of DNA bases or nucleotides i.e. A, T, G, C.

$$S ::= d_1 \ldots d_i$$ (11)

where, $i \geq 0$

A domain $d$ in a DNA strand is either free or bound with the complementary domain of any other DNA strand or to the same strand. A free domain is denoted by $d$. If the domain is bound by bond $x$, the bound domain is denoted by $d!x$. Let, an arbitrary domain is named $r$. The complementary domain of $r$ is denoted by $r^\bot$. A domain is called toehold ($r^\wedge$) if it is short enough to spontaneously attach with and detach from its complement $r^\wedge$.

The semantics of process calculus depends on certain functions which determine whether a rule is permissible in a particular process. The functions are listed below;

- $comp(r)$ is a function which returns the complementary domain of domain $r$. Thus, it can be said that, $comp(r) = r^\bot$ and $comp(r^\bot) = r$
- $toehold(r)$ is a function which returns true if $r$ is a toehold domain. Then the domain $r$ can be represented as $r^\wedge$. 
• \textit{adjacent}(x, P) is a function which returns the set of bonds that are adjacent to bond \( x \) in program \( P \).
• \textit{hidden}(x, P) is a function which returns true if one end of bond \( x \) occurs within a closed loop in program \( P \).
• \textit{anchored}(x, P) is a function which returns true if both ends of bond \( x \) are held “close” to each other in program \( P \). Thus, bond \( x \) is a part of a stable junction.
• \( C(S_1, ..., S_i) \) is a context defined as a process \( P \) having the sequences \( S_1, ..., S_i \).
• \( \text{permute}(S_1, ..., S_i) \) is a function which returns any possible permutation of sequences \( S_1, ..., S_i \).

Now, we will define the semantics of some rules of process calculus by the following figures and corresponding expression.

![Figure 6. Rule (RB)](image)

The semantics of rule (RB) as shown in Fig. 6 can be presented as,

\[
\frac{\neg \text{hidden}(j, P)}{C(r, r^\perp) \xrightarrow{RB,(j)} C(r! j, r^\perp! j) = P}
\] (12)

![Figure 7. Rule (RU)](image)

The semantics of rule (RU) as shown in Fig. 7 can be presented as,

\[
\frac{\neg \text{anchored}(j, P) \quad \text{toehold}(r)}{P = C(r! j, r^\perp! j) \xrightarrow{RU,(l)} C(r, r^\perp)}
\] (13)
The semantics of rule (R3) as shown in Fig. 8 can be presented as,

\[
(RU) \quad \frac{\text{anchored}(j, P)}{\text{anchored}(j, P)} \quad C(r, r!j, r^\perp!j) \xrightarrow{\text{R3}, [j]} C(r!j, r, r^\perp!j) = P
\]

(14)

The semantics of rule (RM) as shown in Fig. 9 can be presented as,

\[
(RM) \quad \frac{\text{anchored}(j_1, P') \ldots \text{anchored}(j_i, P')}{\text{anchored}(j_1, P') \ldots \text{anchored}(j_i, P')} \quad C(r!j_1, r'!j_1, r!j_2, r'!j_2, \ldots, r!j_i, r'!j_i) \xrightarrow{\text{RM}, [j_1 \ldots j_i]} C(r!j_1, r'!j_2, r!j_2, r'!j_3, \ldots, r!j_i, r'!j_i) = P'
\]

(15)

Now we will illustrate the reduction rules of process calculus by the help of an example. We take hairpin toehold exchange program with two invader strands as the example. The pictorial representation of the program is shown in Fig. 10.
Figure 10. Hairpin toehold exchange program with to invader strands
In the illustrated example of Fig. 10 there are two invader strands and one template strand. One of the two single stranded invader strands has two domains \( t^\perp, p \) and the other has three domains \( p, q, r, q^\perp, p^\perp, t^\perp \). The template strand with secondary hairpin structure contains five domains \( p, q, r, q^\perp, p^\perp, t^\perp \). The program codes of the strands are given below:

\[
\text{invader} = < t^\perp p > | \text{invader} = < r^\perp q^\perp p^\perp > | \text{template} = < p!y_1 q!z_1 r q^\perp!z_1 p^\perp!y_1 t^\perp >
\] (16)

The function \textit{toehold}(t) returns true for the single stranded invader strand. Thus, the domain at 5’ end of the strand is denoted by \( t^\perp \). This domain has a free complementary domain \( t^\perp \perp \) in the template strand as the program matches the context \( C(t, t^\perp \perp) \). It can be written that \( P = C(t^\perp x, t^\perp \perp x) \) as one end of the bond \( x \) is not in closed loop, i.e. \( \text{hidden}(x, P) \) returns false. Thus, the program \( P' \) can be produced by the rule \( (RB) \) which forms the new bond \( x \) between the single stranded invader strand and the template strand. The program code is shown below:

\[
< t^\perp p > | < r^\perp q^\perp p^\perp > | < p!y_1 q!z_1 r q^\perp!z_1 p^\perp!y_1 t^\perp \perp > \xrightarrow{(RB)} < t^\perp x p > | < r^\perp q^\perp p^\perp > | < p!y_1 q!z_1 r q^\perp!z_1 p^\perp!y_1 t^\perp \perp x >
\] (17)

As domain \( t \) is toehold, it is short enough to unbind spontaneously. Here the program \( \text{anchored}(x, P) \) returns false as the bond \( x \) is not a part of a junction that holds both ends of the bond close to each other. Thus, the rule \( (RU) \) can also occur which breaks the bond \( x \) between the single stranded invader strand and the template strand to generate the program \( C(t, t^\perp \perp) \). It is reversible of rule \( (RB) \). The program code is shown below:

\[
< t^\perp x p > | < r^\perp q^\perp p^\perp > | < p!y_1 q!z_1 r q^\perp!z_1 p^\perp!y_1 t^\perp \perp x > \xrightarrow{(RU)} < t^\perp p > | < r^\perp q^\perp p^\perp > | < p!y_1 q!z_1 r q^\perp!z_1 p^\perp!y_1 t^\perp \perp >
\] (18)

In the next step toehold mediated branch migration and strand displacement occurs. The free domain \( p \) of the invader strand has complementary domain \( p^\perp \) in the template strand which is already bound by the bond \( y_1 \). In this step the program matches the context \( C(p, p!y_1, p^\perp!y_1) \). We have to check if an anchored bond can be formed between the invader strand and the template strand to generate the program \( P' = C(p!y_2, p, p^\perp!y_2) \). The formation of the new bond \( y_2 \) is possible by applying rule \( (R3) \) as bond \( x \), which holds the both ends of bond \( y_2 \) close to each other, exists as the immediate neighbor of \( y_2 \) in \( P' \).

\[
< t^\perp x p > | < r^\perp q^\perp p^\perp > | < p!y_1 q!z_1 r q^\perp!z_1 p^\perp!y_1 t^\perp \perp x > \xrightarrow{(R3)} < t^\perp x p!y_2 > | < r^\perp q^\perp p^\perp > | < p!y_1 q!z_1 r q^\perp!z_1 p^\perp!y_2 t^\perp \perp x >
\] (19)

Next, the other invader strand comes in action. There is a free domain \( p^\perp \) at 3’ end of the invader strand. This domain has a free complementary domain \( p \) in the 5’ end of the template strand. The formation of a new bond \( y_3 \) is possible as one end of the bond does not occur in closed loop, i.e. the bond is not hidden. The formation of the bond according the rule \( (RB) \) is shown in the following program code;
This reaction is a reversible reaction. The previous step can be restored by rule (RU).

\[
\begin{align*}
< t^\dagger x \ p! y_2 > | < r^\perp \ q^\perp \ p^\perp > | < p \ q! z_1 \ r \ q^\perp ! z_1 \ p^\perp ! y_2 \ t^\perp ! x > \\
\xrightarrow{(RB)} < t^\dagger x \ p! y_2 > | < r^\perp \ q^\perp \ p^\perp ! y_3 > | < p! y_3 \ q! z_1 \ r \ q^\perp ! z_1 \ p^\perp ! y_2 \ t^\perp ! x >
\end{align*}
\]

(20)

The formation of the new bond \( y_2 \) is possible by applying rule (R3) as bond \( x \), which holds the both ends of bond \( y_2 \) close to each other, exists as the immediate neighbor of \( y_2 \) in \( P' \).

\[
\begin{align*}
< t^\perp x \ p! y_2 > | < r^\perp \ q^\perp \ p^\perp ! y_3 > | < p! y_3 \ q! z_1 \ r \ q^\perp ! z_1 \ p^\perp ! y_2 \ t^\perp ! x > \\
\xrightarrow{(R3)} < t^\perp x \ p! y_2 > | < r^\perp ! u \ q^\perp ! z_2 \ p^\perp ! y_3 > | < p! y_3 \ q! z_2 \ r^\perp ! u \ q^\perp \ p^\perp ! y_2 \ t^\perp ! x >
\end{align*}
\]

(22)

2.4. Strand Graph [Petersen et al., 2016]

Graphs are mathematical structures for modelling pair-wise relations between objects. The graphical structures are formed by vertices or nodes which are connected by edges. In a graph if there is no distinction between the two nodes associated with each edge, the graph is said to be undirected. In directed graph each edge has a specific direction from one node to another. Strand graph is used for representation of the rich secondary structures of DNA molecules and implementation of the complex rules to conduct a process. Now we will summarize the notation for strand graph theory as demonstrated in the paper [Petersen et al., 2016].

Strand graph is defined by \( G = (V, \text{length}, \text{colour}, A, \text{toehold}, E) \), where, \( V = \{1, \ldots, N\} \) denotes the set of vertices of the graph. Each vertex, shown by natural number, represents a DNA strand. There are different sites in a vertex. Each site \( s \) denotes a specific domain of that strand. The vertices are drawn as circular arrow with a specific direction i.e. from 5’ to 3’ of a DNA strand. The sites are placed in a vertex according to the occurrences of the corresponding domain in the specific strand. Site is represented as \( s = (s, n) \), where \( v \) is a vertex and \( n \) is the position of site \( s \) in vertex \( v \). Both \( v \) and \( n \) are natural numbers.
**length**: denotes a function by which a specific length is assigned to each vertex. Lengths are represented by natural numbers.

**colour**: denotes a function by which a specific colour is assigned to each vertex. Colours are also represented by natural numbers. Thus, it would be easier to identify a particular vertex representing a specific DNA strand. Colour is actually a function of the length. If \( v_1 \) and \( v_2 \) are two vertices of a strand graph, then, \( \text{length}(v_1) = \text{length}(v_2) \Rightarrow \text{colour}(v_1) = \text{colour}(v_2) \).

\( A \) is the set of admissible edges of the strand graph. If two domains of the DNA strands are complementary, they are able to hybridize with each other by forming a bond. Then an edge can be drawn between the sites of the vertices representing those domains. Throughout the performance of the whole program, all bonds those are allowed to be formed are represented by the set of admissible edges. Edge is represented as \( e = \{s_1, s_2\} \) where \( s_1 \) and \( s_2 \) are two sites and \( s_1 \neq s_2 \). Again, we can write that, \( e = \{(v_1, n_1), (v_2, n_2)\} \).

**Toehold** is a function that returns true if permissible edges exist between the short toehold domains and returns false for permissible edges between the long domains.

\( E \) is the set of current edges of the strand graph which is expressed as \( \{e_1, \ldots, e_I\} \subseteq A \). In the contrary of other above mentioned information to define strand graph, \( E \) is non-static information. During the execution of the program the set of current edges changes with the change in reduction rules. A domain in a DNA strand cannot bind with more than one domain at any given instant i.e. only one edge can be drawn from a given site at that point of time. This is can be expressed as, \( (i \neq j) \Rightarrow e_i \cap e_j = \emptyset \).

Now, we will illustrate the representation of DNA strand graph by an example. Fig. 11 shows the mechanism of toehold-mediated four-way strand displacement and branch migration. This mechanism consists of four DNA strands. In this program two partially double stranded DNA sequences simultaneously exchange the strands. Four-way strand displacement method is initiated by unhybridized toehold domains. The intermediate structure of this program is called **Holliday junction**.
The program codes of the DNA strands of the above described mechanism in the initial state are formed by process calculus. The codes of four strands are given below;

Strand 1 < S₁ >: < a^ı i b^ı j₁ c^⊥ >
Strand 2 < S₂ >: < d^⊥ b^⊥ j₁ a^⊥ i >
Strand 3 < S₃ >: < c^⊥ b^⊥ j₂ e^⊥ k >
Strand 4 < S₄ >: < e^⊥ k b^⊥ j₂ d^⊥ >

(23)

The DNA strand graph representing the initial state of toehold-mediated four-way strand displacement and branch migration mechanism is shown in Fig. 12.
Each DNA strand in the process of toehold-mediated four-way strand displacement and branch migration (Fig. 8) is represented by vertex in the DNA strand graph as shown in Fig. 12. The arrowheads of the vertices which are drawn as circular arrows indicate the 3’ end of the DNA strand. Different arbitrary colours are assigned for the vertices in the graph. For example, vertex 1 which represents the strand type $< a^\wedge i \ b^!j_1 \ c^\wedge >$ is assigned the colour pink. The domains of the DNA strands are presented by the sites which are placed on the vertices according to their occurrences. All the admissible edges are drawn in the strand graph. The current edges are represented by red lines and rests of the edges are represented by blue lines. The toehold edges are drawn by dashed lines.

The strand graph as shown in Fig. 12 is defined by $G = (V, length, colour, A, toehold, E)$, where,

$$V = \{1, 2, 3, 4\}.$$  

$$length = \{1 \rightarrow 3, 2 \rightarrow 3, 3 \rightarrow 3, 4 \rightarrow 3\}.$$  

$$colour = \{1 \rightarrow 1, 2 \rightarrow 2, 3 \rightarrow 3, 4 \rightarrow 4\}.$$  

$$A = \{(1, 1), (2, 3), ((1, 2), (2, 2)), ((1, 2), (3, 2)), ((1, 3), (3, 1)), ((2, 1), (4, 3)), ((2, 2), (4, 2)), ((3, 2), (4, 2)), ((3, 3), (4, 1))\}.$$  

$$toehold = \{(1, 1), (2, 3)\} \rightarrow true, \{(1, 3), (3, 1)\} \rightarrow true, \{(2, 1), (4, 3)\} \rightarrow true, \{(3, 3), (4, 1)\} \rightarrow true, \{\text{other} \rightarrow false\}.$$  

$$E = \{(1, 1), (2, 3), ((1, 2), (2, 2)), ((3, 2), (4, 2)), ((3, 3), (4, 1))\}.$$  

Now, we will illustrate some functions which are used to define DNA strand graph. Let, the program of toehold-mediated four-way strand displacement and branch migration is denoted by $P$.

$$P = < S_1 > | < S_2 > | < S_3 > | < S_4 >$$

$$= < a^\wedge i \ b^!j_1 \ c^\wedge > | < d^\wedge * \ b^*j_1 \ a^\wedge > | < c^\wedge * \ b^!j_2 \ e^!*k > | < e^\wedge *k \ b^!j_2 \ d^\wedge >$$

(24)
The DNA strand graph representing program $P$ is $G = (V, \text{length, colour, } A, \text{toehold, } E)$. The function $tp$ omits all the bonds from a specific domain. For example $tp(b!j_1) = b$.

The first strand, $<S_1> = <a^\dagger i \ b ! j_1 \ c^\perp >$ has three domains. It can be written that the type $tp(S_1) = tp(a^\dagger i), tp(b!j_1), tp(c^\perp) = a^\dagger, b, c^\perp$. The function representing the length of $S_1$ is $\text{len}(S_1) = 3$.

The strand types are numbered according to their appearance in the given program (for example, $t_1, t_2, t_3, t_4$) depending on which the colour function is defined.

The domain function $\text{dom}$ indicates a specific domain of the strand graph. For the DNA strand graph $G$ corresponding to program $P$, $\text{dom}(2, 3)$ indicates the 3rd domain of $S_2$. Another domain function $\text{ndom}(2, 3)$ indicates the name of $\text{dom}(2, 3)$ after omitting all bonds.

The toehold function $\text{toe}$ defines the toehold of a specific DNA strand. For strand graph $G$, $\text{toe}(3, 1)$ returns true which indicates $\text{ndom}(3, 1)$ is a toehold domain.

$A$ is the set of admissible edges of $G$. $\{(3, 3), (4, 1)\}$ is the edge joining the 3rd domain of $S_3$ and the 1st domain of $S_4$ and $\{(3, 3), (4, 1)\} \in A$. Then, it can be written that, $\dagger (3, 3) \leftrightarrow (4, 1)$.

The following definition can be written to define a DNA strand graph [Petersen et al., 2016] using the above explained function:

\[
V = \{1, \ldots, N\} \quad \text{where, } N \text{ is natural number}
\]

\[
\text{length}(v) = \text{len}(Sv)
\]

\[
\text{colour}(v) = i \quad \Leftrightarrow \quad tp(Sv) = t_i
\]

\[
(v_1, n_1) \leftrightarrow (v_2, n_2) \quad \Leftrightarrow \quad \text{ndom}(v_1, n_1) = \text{comp}(\text{ndom}(v_2, n_2))
\]

\[
\text{toehold}((s_1, s_2)) \quad \Leftrightarrow \quad \text{toe}(s_1)
\]

\[
(v_1, n_1) \leftrightarrow (v_2, n_2) \quad \Leftrightarrow \quad \exists d,j. \text{dom}(v_1, n_1) = d^j \wedge \text{dom}(v_2, n_2) = \text{comp}(d)!j
\]

where, $d$ denotes the domain and $j$ denotes the bond between $(v_1, n_1)$ and $(v_2, n_2)$.

In the next section we will illustrate the semantics of reduction rules.

### 2.4.1. Semantics of reduction rules

DNA strand graph transits from one state to another by following the reduction rules. The change in state of the strand graph is indicated by the change in colours of the edges among vertices. The semantics of the reduction rules need definitions of few functions [Petersen et al., 2016].

The function $\text{sites}(E)$ returns the set of sites in set of current edges $E$ which can be expressed by $\{s | \exists e \in E. s \in e\}$.

If two edges in a strand graph not only exist between the same pair of vertices but also the corresponding sites are adjacent to each other, the two edges are said to be adjacent. The function $\text{adjacent}(e, E)$ returns the set of edges adjacent to the edge $e$ from the set $E$.

The function $\text{hidden}(e, E)$ returns true if one of the ends of edge $e$ from the set $E$ occurs within a closed loop.
The function $\text{anchored}(e, E)$ returns true if the edge $e$ from the set $E$ is a part of a stable junction by holding the corresponding sites close to each other.

Now we will describe the semantics of reduction rules [Petersen et al., 2016] through which the process occurs and reaches to its final state.

**Rule (GB):** Let the sites of two vertices of a DNA strand graph is joined by admissible edge $x$ which is not current at that instant. If those two sites are not preoccupied and open to each other, according to rule (GB) $x$ can be converted into current edge. The semantics of rule (GB) is given below;

$$
(GB) \frac{x \in A \setminus E \quad x \cap \text{sites}(E) = \emptyset \quad \neg\text{hidden}(x, E)}{E \xrightarrow{\text{GB},[x]} E \cup \{x\}}
$$

**Rule (GU):** Let the sites of two vertices of a DNA strand graph is joined by admissible edge $e$ and the sites represent toehold domain. Toehold domains are short enough to spontaneously unbind from its complement. Thus according to rule (GU) if the toehold domains are not anchored, the edge $e$ can be removed from the current set $E$ of the corresponding strand graph. The semantics of rule (GU) is given below;

$$
(GU) \frac{e \in E \quad \text{toehold}(e) \quad \neg\text{anchored}(e, E)}{E \xrightarrow{\text{GU},[e]} E \setminus \{e\}}
$$

**Rule (G3):** Let the sites of two vertices of a DNA strand graph is joined by admissible edge $x$ which is not current at that instant. $x$ can be joined to the set of current edges $E$ even though one of the end sites is preoccupied by some other site forming a current edge $e$. $x$ becomes current edge by removing $e$ if the function $\text{anchored}(x, E)$ returns true. This mechanism is termed as displacing path. The swapping of single bonds can form a long chain through the whole program. This mechanism is performed by reduction rule (G3). The semantics of rule (G3) is given below;

$$
(G3) \frac{e \in E \quad x \in A \setminus E \quad e = \{s, s'\} \quad x = \{s, s''\} \quad s'' \not\in \text{sites}(E) \quad \text{anchored}(x, E)}{E \xrightarrow{\text{G3},[x]} (E\{e\}) \cup \{x\}}
$$

**Rule (GM):** By the reduction rule (GM) the mechanism of displacing path i.e. swapping of single bonds makes a loop. The semantics of rule (GM) is given below;

$$
(GM) \frac{i \in \{1, \ldots, N\} \quad e_i \in E \quad x_i \in A \setminus E \quad e_i = \{s_i, s'_i\} \quad x_i = \{s_{i-1}, s_i\} \quad s'_0 = s'_N \quad \text{anchored}(x_i, E)}{E \xrightarrow{\text{GM},[x_1, \ldots, x_N]} (E\{e_1, \ldots, e_N\}) \cup \{x_1, \ldots, x_N\}}
$$

2.4.2. Graphical illustration of reduction rules

In Fig. 11 the entire mechanism of toehold-mediated four-way strand displacement and branch migration, which is graphically interpreted in Fig. 12, is shown. In this section we will
pictorially describe (Fig. 13) how the reduction rules work in DNA strand graph $G$ as shown in Fig. 12.

Figure 13. DNA strand graph with reduction rules conducting the program of toehold-mediated four-way strand displacement and branch migration.

So far we have discussed the theoretical aspects DNA strand algebra, process calculus and strand graph. In the next section we will explore the applications of the above discussed methodologies.

3. Applications of DNA Strand Algebra

In this section we will discuss the applications of DNA strand algebra in different expert system. In the first application (section 3.1) we have applied DNA strand algebra to develop an expert system based modus-ponens inference mechanism which is capable of drawing consequences from observed fact. In another application (section 3.2) we have developed a DNA system based on DNA strand algebra to perform syllogistic reasoning with DNA tweezers. The reduction rules of this DNA model using process calculus and DNA strand graph are also demonstrated. In section 3.3 we have presented theorem proving with resolution refutation using the semantics of process calculus and strand graph.

3.1. Logical Inference by the Syntax of Semantics of DNA Strand Algebra [Ray and Mondal, 2016]

We have designed an expert system developed on the notion of DNA strand algebra and DNA strand displacement. We have actually proposed a DNA model for logical reasoning using modus-ponens inference mechanism. In propositional logic, modus ponens is valid for two-value based exact reasoning. The laws of modus ponens are formulated in the format of If….Then rules and are applied to conventional two-valued logic. The simple form of this inference mechanism is given below;
Premise 1: If X is A Then Y is B
Premise 2: If X is A

Consequence: Y is B.

In the generalized form of modus ponens several conditional propositions are combined with else.

Premise 1: If X is $A_1$ and Y is $B_1$ then Z is $C_1$ else
Premise 2: If X is $A_2$ and Y is $B_2$ then Z is $C_2$ else

. . .

Premise n: If X is $A_n$ and Y is $B_n$ then Z is $C_n$ else
Premise n+1: If X is $A'$ and Y is $B'$

Consequence: Z is $C'$.

3.1.1. Expert rules and given problem

We have shown the deduction of logical inference by using the syntax and semantics of DNA strand algebra with the help of a worked out example of calculating BMI (body mass index) where each rule has two antecedent clauses and one consequent clause. The two domains of antecedent part are height (Ht) and weight (Wt) and one domain in the consequent part is BMI. Thus, the generalized form of modus ponens is reduced to a specific form having 100 expert rules. In this worked out example, observed antecedent data is given; the proposed expert system has to deduce the consequence form the given antecedent clauses. Sample expert rules (10 rules) and the given problem are shown in Table 8. The system searches the knowledgebase to select the desired rule by exact matching of the antecedent clauses. From the selected rule the consequence can be derived following the proposed methodology.

Let, the Universe of Height (domain A of antecedent clause) is denoted by Ht, Universe of Weight (domain B of antecedent clause) is denoted by Wt and the Universe of Body Mass Index (domain C of consequent clause) is denoted by BMI. Quantization of Universes of Ht, Wt and BMI are shown in Fig. 5, 6 and 7.

| Quantized Universe | Oligonucleotide Sequences (5’-3’) | Linguistic Value |
|--------------------|----------------------------------|-----------------|
| Ht < 4’3”          | CTGGA                            | Very Short(I)   |
| 4’3” ≤ Ht < 4’6”   | TAATT                            | Very Short(II)  |
| 4’6” ≤ Ht < 4’9”   | GATCC                            | Short(I)        |
| 4’9” ≤ Ht ≤ 5’     | ATTTT                            | Short(II)       |
| 5’ ≤ Ht < 5’3”     | TCAGC                            | Medium Height(I)|
| 5’3” ≤ Ht < 5’6”   | CGAAT                            | Medium Height(II)|
| 5’6” ≤ Ht < 5’9”   | AATGT                            | Tall(I)         |
| 5’9” ≤ Ht ≤ 6’     | CCGGA                            | Tall(II)        |
| 6’ ≤ Ht < 6’3”     | ATCGT                            | Very Tall(I)    |
| 6’3” ≤ Ht           | TTAGA                            | Very Tall(II)   |
Table 5. Quantization of Height (A Domain)

| Quantized Universe | Oligonucleotide Sequences (5'-3') | Linguistic Value |
|--------------------|-----------------------------------|------------------|
| Wt < 90 lb         | ATTCA                             | Very Light(I)    |
| 90 lb ≤ Wt < 100 lb| GCCAA                             | Very Light(II)   |
| 100 lb ≤ Wt < 110 lb| TTCGT                          | Light(I)         |
| 110 lb ≤ Wt < 120 lb| CAAAC                           | Light(II)        |
| 120 lb ≤ Wt < 130 lb| CGGAA                           | Medium Weight(I) |
| 130 lb ≤ Wt < 140 lb| ATCCG                           | Medium Weight(II)|
| 140 lb ≤ Wt < 150 lb| GGAAT                           | Heavy(I)         |
| 150 lb ≤ Wt < 160 lb| GTAGC                           | Heavy(II)        |
| 160 lb ≤ Wt < 170 lb| ATCCC                           | Very Heavy(I)    |
| 170 lb ≤ Wt         | TAGGA                             | Very Heavy(II)   |

Table 6. Quantization of Weight (B Domain)

| Quantized Universe | Oligonucleotide Sequences (5'-3') | Linguistic Value |
|--------------------|-----------------------------------|------------------|
| BMI < 18.5         | CTAAG                             | Under Weight     |
| 18.5 ≤ BMI < 25    | AGGAA                             | Normal Weight    |
| 25 ≤ BMI < 30      | TAGCT                             | Over Weight      |
| 30 ≤ BMI < 35      | GCGCG                             | Obesity (Class I)|
| 35 ≤ BMI < 40      | GTAAC                             | Obesity (Class II)|
| 40 ≤ BMI           | AAATA                             | Morbid Obesity   |

Table 7. Quantization of Body Mass Index (C Domain)

| Sl. No. | Antecedent Clause (A) | Antecedent Clause (B) | Consequent Clause (C) |
|---------|------------------------|-----------------------|-----------------------|
| 1       | A₁ → Medium Ht(I)      | B₁ → Very Light(II)   | C₁ → Under Wt         |
| 2       | A₂ → Short(I)          | B₂ → Very Heavy(II)   | C₂ → Obesity (Class II)|
| 3       | A₃ → Very Tall(I)      | B₃ → Heavy(I)         | C₃ → Normal Wt        |
| 4       | A₄ → Very Short(I)     | B₄ → Heavy(II)        | C₄ → Morbid Obesity   |
| 5       | A₅ → Short(II)         | B₅ → Very Heavy(II)   | C₅ → Obesity (Class II)|
| 6       | A₆ → Very Short(II)    | B₆ → Medium Wt(II)    | C₆ → Obesity (Class I) |
| 7       | A₇ → Tall(I)           | B₇ → Very Heavy(I)    | C₇ → Over Wt          |
| 8       | A₈ → Medium Ht(I)      | B₈ → Heavy(I)         | C₈ → Over Wt          |
| 9       | A₉ → Very Tall(II)     | B₉ → Medium Wt(I)     | C₉ → Under Wt         |
| 10      | A₁₀ → Very Short(II)   | B₁₀ → Very Light(II)  | C₁₀ → Normal Wt       |
| problem | Ht (A') → Medium Ht(I)| Wt (B') → Heavy(I)    | C' → ?                |

Table 8. Expert rules and given problem

3.1.2. Design strategy and formulation of logical inference by DNA strand algebra

The DNA model for deduction of the given logical inference is developed using two gate structures viz. gate backbone ($G_b$) and gate trigger ($G_t$); and three signal strand viz. signal $A$, signal $B$ and signal $C$.

All the 100 expert rules are encoded in form of 100 separate gate backbones ($G_b$). Fig. 14 shows the structure of one sample gate structure.
ant $\equiv$ 5 bases long fixed sequence (AAAAA) indicating the start of the antecedent clauses.

$\con$ $\equiv$ 5 bases long fixed sequence (CCCCCC) indicating the start of the consequent clause.

$A_x \equiv$ 5 bases long variable sequence indicating the Ht domain ($A$) of rule $x$.

$B_x \equiv$ 5 bases long variable sequence indicating the Wt domain ($B$) of rule $x$.

$C_x \equiv$ 5 bases long variable sequence indicating the BMI domain ($C$) of rule $x$.

$\text{rule}_x\_\ant \equiv$ 10 bases long variable sequence attached to the antecedent clauses of a particular expert rule (in signal $B$); it represents the rule number associated with the antecedent.

$\text{rule}_x\_\con \equiv$ 10 bases long variable sequence attached to the consequent clause of a particular expert rule (in signal $C$); it represents the rule number associated with consequence.

The given problem (i.e. observed data) from which the consequence has to be deduced is represented by the signal strand $A$ (Fig. 15).

\[ \text{obs} \equiv 10 \text{ bases long variable DNA sequence which is unique for any observed data.} \]

$\ant^\perp \equiv$ complementary sequence (TTTTT) to the segment $\ant$.

$A' \equiv$ domain $A$ of the observed data as given in the problem.

Another gate structure i.e. gate trigger ($G_t$) is shown in Fig. 16.

\[ \text{B'} \equiv \text{domain B of the observed data as given in the problem.} \]

$\con^\perp \equiv$ complementary sequence (GGGGG) to the segment $\con$.

$C'_y \equiv$ variable domain representing the possible consequence of the given antecedent clauses.
In the proposed DNA system (Fig. 17) the gate structures consume one input signal A and produces two outputs signal B and signal C. The deduced consequence of the given observation is encoded by signal C. The mechanism of deduction of logical inference can be represented by the following expression:

\[ A \land [B, C] \rightarrow B \land C \quad (30) \]

Figure 17. Pictorial representation of the DNA system for deduction of logical inference

By the proposed system we have illustrated the DNA implementation of the well established inference mechanism modus ponens. In this application we have replaced the notion of classical logic by DNA strand algebra.
3.2. Syllogistic Reasoning by the Semantics of Strand Algebra, Process Calculus and Strand Graph

We will show another application of DNA strand graph in the domain of commonsense reasoning. We have modelled the dynamic DNA device, termed as DNA tweezers, to perform syllogistic reasoning using the methodology of DNA strand algebra [Mondal and Ray, 2017]. In the paper [Yurke et al., 2000] Yurke et al. first introduced the mechanism of this DNA-fuelled molecular machine and we have solved syllogistic reasoning using DNA tweezers [Ray and Mondal, 2012] using the methodologies of conventional DNA computation. We have considered the fuzzy syllogistic reasoning. The simple form of the example where plausible consequence has to be deduced from dispositional premises is given below;

\[
\begin{align*}
\text{icy roads are slippery} \\
\text{slippery roads are risky} \\
\text{risky roads are accident prone} \\
\text{icy roads are accident prone.}
\end{align*}
\]

We have fuzzified each domain and attach the membership values to make explicit the implicit fuzzy quantifier [Mondal and Ray, 2017]. The dispositions which are considered in this section are based on fuzzy logic which uses the whole interval between 0 (false) and 1 (true) to describe human reasoning. Fuzzy logic resembles human decision making and has an ability to draw a precise conclusion from approximate data. The example which we will consider in this application (dispositional premises given above) has four domains represented as four primary fuzzy sets, \textit{viz.} icy (\(i\)), slippery (\(s\)), risky (\(r\)) and accident prone (\(a\));

The commonsense knowledge about the icy road and its adverse consequence is represented as the set of rules (Table 8). Using each set (of dispositions) a unique DNA tweezers can be formed (Fig. 18). Finally, an observed data (here, \textit{less icy (II)}) is given from which the possible consequence has to be deduced.

| Set   | Commonsense knowledge about icy road and its adverse consequence |
|-------|---------------------------------------------------------------|
| Set 1 | Very less icy (I) roads are very less slippery (I).           |
|       | Very less slippery (I) roads are very less risky (I).         |
|       | Very less risky roads (I) are very less accident prone (I).   |
| Set 2 | Very less icy (II) roads are very less slippery (II).         |
|       | Very less slippery (II) roads are very less risky (II).       |
|       | Very less risky roads (II) are very less accident prone (II). |
| Set 3 | Less icy (I) roads are less slippery (I).                     |
|       | Less slippery (I) roads are less risky (I).                   |
|       | Less risky roads (I) are less accident prone (I).            |
| Set 4 | Less icy (II) roads are less slippery (II).                   |
|       | Less slippery (II) roads are less risky (II).                 |
|       | Less risky roads (II) are less accident prone (II).           |
| Set 5 | More or less icy (I) roads are more or less slippery (I).     |
|       | More or less slippery (I) roads are more or less risky (I).   |
|       | More or less risky (I) roads are more or less accident prone (I). |
|       | More or less icy (II) roads are more or less slippery (II).   |
| Set 6  | More or less slippery (II) roads are more or less risky (II). More or less risky (II) roads are more or less accident prone (II). |
| Set 7  | Icy (I) roads are slippery (I). Slippery (I) roads are risky (I). Risky (I) roads accident prone (I). |
| Set 8  | Icy (II) roads are slippery (II). Slippery (II) roads are risky (II). Risky (II) roads accident prone (II). |
| Set 9  | Very icy (I) roads are very slippery (I). Very slippery (I) roads are very risky (I). Very risky (I) roads are quite accident prone (I). |
| Set 10 | Very icy (II) roads are very slippery (II). Very slippery (II) roads are very risky (II). Very risky (II) roads are quite accident prone (II). |

Table 8. Representation of set of dispositional premises

Figure 18. DNA tweezers encoding a set of disposition

3.2.1. Formulation of syllogistic reasoning by strand algebra

We have presented the algorithm to deduce conclusion DNA strand algebra. First, the database, presented in the form of disposition sets, is searched. Following the backward chaining procedure we proceed from a tentative conclusion backward to the premise to verify if the data supports that conclusion. Finally the specific disposition with possible conclusion has to be separated from the database.
Step 1. The three rules (denoted as rule $x$, $y$ and $z$ respectively) of each set of dispositions are coded in the form of DNA sequences and presented as signals. These are the structural components if DNA tweezers. The domains of the signals are given below;

\[
\begin{align*}
\text{Signal } x: & \quad \text{5'} \quad i \quad s \quad 3' \\
\text{Signal } y: & \quad \text{3'} \quad \text{spacer} \quad r \quad 5' \\
\text{Signal } z: & \quad \text{5'} \quad r \quad a \quad 3'
\end{align*}
\]

Step 2. The given observation is encoded by single stranded DNA sequence in 3' to 5' direction.

Step 3. The gate is developed using single stranded DNA sequences representing the possible consequence i.e. hypotheses (signal $c$) are shown below;

\[
\text{Signal } c: \quad \text{3'} \quad i^\perp \quad a^\perp \quad r^\perp \quad 5'
\]

The ten possible sequences of signal $c$ are shown in Fig. 19.

![Figure 19. Signal $c$: DNA sequences representing observed data, hypotheses and toehold domain](image)

Step 4. The signals $x$, $y$ and $z$ are combined into a soup by parallel composition to form the 10 different open complexes. Again, in this soup sequences representing signal $c$ are combined by parallel composition to form the desired gate, $G(xyz)$ (Fig. 20). At initial state, it is a closed complex. The assembly of the signals can be represented by the following expression:

\[
x \mid y \mid z \mid c \mid \{x, y, z, c\} . [] \rightarrow 0
\]  

(31)
Only one sequence from 10 sequences presenting signal $c$ (Fig. 19) hybridizes to a rule. The single stranded segment of the open complex which is completely complementary to one of the input signals (signal $c$ in Fig. 19) binds with it. This leads to the formation of closed complex.

**Step 5.** Again, single stranded DNA sequences, signal $c'$, are added in the *soup* as input. As a result, the gate $G(\text{xyz})$ is formed. The sequences representing signal $c'$ are the complementary to signal $c$. Therefore, 10 single stranded DNA sequences are added as signal $c'$.

The signal $c'$ completely binds with $c$ by toehold mediated branch migration and strand displacement to form a complete double stranded DNA by-product. The gate $G(\text{xyz})$ again returns to its previous open form. This reaction is expressed as:

$$c' \mid c'. \ G(\text{xyz}) \rightarrow G(\text{xyz})$$  \hspace{1cm} (32)

The expression (32) is pictorially represented by Fig. 21.
Step 6. The order of the bases of the double stranded DNA by-product can be known from DNA sequencer. The decoded linguistic value is the deduced consequence of the syllogistic reasoning example performed by DNA strand algebra.

3.2.2. Formulation of syllogistic reasoning by process calculus

Let the $P$ is the program which performs syllogistic reasoning by DNA tweezers. The program $P$ consists of five DNA strands. Three of these strands ($S_1$, $S_2$ and $S_3$) codes the set of premises ($S$) i.e. $p_1$, $p_2$ and $p_3$. The remaining two strands, $S_4$ and $S_5$, code input $A$ and input $B$ respectively. Thus, $P$ can be defined as the multiset of five DNA strands.

$$P = \langle S_1 \rangle | \langle S_2 \rangle | \langle S_3 \rangle | \langle S_4 \rangle | \langle S_5 \rangle$$

Therefore, $P$ can be written as,

$$P = \langle i \ s! x \rangle | \langle r^{-1}! y \ sp \ s^{-1}! x \rangle | \langle r! y \ a \rangle | \langle t^{-1} \ a^{-1} \ i^{-1} \rangle | \langle i \ a \ t^\perp \rangle$$

(33)
where, all the strands are shown in 5’ to 3’ direction.

The literals are encoded by arbitrarily chosen ten bases long single-stranded DNA sequence representing the domains of the corresponding DNA strands. But, the toehold domain, i.e. \( t^\perp \) and \( t'^\perp \), is five bases long DNA oligonucleotide. It is short enough to spontaneously attach and detach from its complementary sequence. The given program code (expression 33) shows that domain \( s \) at the 3’ end of \( <S_1> \) is bound to domain \( s^\perp \) of \( <S_2> \) by bond \( x \). The domain \( r^\perp \) of \( <S_2> \) is bound to domain \( r \) of the DNA strand \( <S_5> \) by bond \( y \). Thus, the DNA tweezers is formed by partially hybridized strands \( <S_1> \), \( <S_2> \) and \( <S_5> \). At this stage the tweezers are in open form. \( <S_4> \) codes input \( A \) and \( <S_5> \) codes input \( B \). Initially, \( <S_4> \) and \( <S_5> \) are single stranded as all the domains of the corresponding strands are free.

As the domain \( i \) of \( <S_1> \) and the domain \( i^\perp \) of \( <S_5> \) are not bound with any other domain, the program matches the context \( C(i, i^\perp) \). It can be written that \( P' = C(i!u_1, i^\perp!u_1) \) as one end of the bond \( u_1 \) is not in closed loop, i.e. hidden\((u_1, P)\) returns false. Thus, the program \( P' \) can be produced by the rule \((RB)\) which forms the new bond \( u_1 \) between the complementary domains \( i \) and \( i^\perp \). The program code is given below;

\[
\begin{align*}
&<i \ s!x> | <r^\perp!y \ sp \ s^\perp!x> | <r!y \ a> | <t^\perp 1 \ a^\perp \ i^\perp> | <i \ a \ t^\perp> \\
&\rightarrow <i!u_1 \ s!x> | <r^\perp!y \ sp \ s^\perp!x> | <r!y \ a> | <t^\perp 1 \ a^\perp \ i^\perp!u_1> | <i \ a \ t^\perp>
\end{align*}
\]

(34)

Again, the domain \( a \) of \( <S_2> \) and the domain \( a^\perp \) of \( <S_5> \) are free. Thus, the program matches the context \( C(a, a^\perp) \). New bond \( v_1 \) can be formed by the rule \((RB)\) between the complementary domains \( a \) and \( a^\perp \). The formation of bond \( v_1 \) is possible, if and only if the program hidden\((v_1, P)\) returns false. This step leads the formation of closed configuration of the DNA tweezers. The program code is given below;

\[
\begin{align*}
&<i!u_1 \ s!x> | <r^\perp!y \ sp \ s^\perp!x> | <r!y \ a> | <t^\perp 1 \ a^\perp \ i^\perp!u_1> | <i \ a \ t^\perp> \\
&\rightarrow <i!u_1 \ s!x> | <r^\perp!y \ sp \ s^\perp!x> | <r!y \ a!v_1> | <t^\perp 1 \ a^\perp !v_1 \ i^\perp!u_1> | <i \ a \ t^\perp>
\end{align*}
\]

(35)

Now, \( <S_5> \) i.e. input \( B \) comes into action. The function toehold\((t)\) returns true for \( <S_5> \). The toehold domain \( t^\perp \) at the 3’ end of \( <S_5> \) has a free complementary domain \( t'^\perp \) in \( <S_5> \). The program matches the context \( C(t^\perp, t'^\perp) \). Thus, it can be written that \( P' = C(t^\perp!w, t'^\perp!w) \) as one end of the bond \( w \) is not in closed loop, i.e. hidden\((w, P)\) returns false. Thus, according to rule \((RB)\) the program \( P' \) can be generated which forms the new bond \( w \) between the toehold and its complementary domain. The program code is shown below;

\[
\begin{align*}
&<i!u_1 \ s!x> | <r^\perp!y \ sp \ s^\perp!x> | <r!y \ a!v_1> | <t^\perp 1 \ a^\perp !v_1 \ i^\perp!u_1> | <i \ a \ t^\perp> \\
&\rightarrow <i!u_1 \ s!x> | <r^\perp!y \ sp \ s^\perp!x> | <r!y \ a!v_1> | <t^\perp 1 \ w^\perp a!v_1 \ i^\perp!u_1> | <i \ a \ t'^\perp!w>
\end{align*}
\]

(36)

The toehold domain \( t^\perp \) is short enough to unbind spontaneously. As the newly formed bond \( w \) is not a part of a junction that holds both ends of the bond close to each other, the program anchored\((w, P)\) returns false. Thus, according to rule \((RU)\) the bond \( w \) between the toehold and its complementary domain can be broken to generate the program \( C(t^\perp, t'^\perp) \). It is reversible of rule \((RB)\). The program code is shown below;
Because of the hybridization of toehold domains, toehold mediated branch migration and strand displacement occurs. The free domain $a$ of $S_5$ has a complementary domain $a^\perp_1$ in $S_4$ which is already bound by the bond $v_1$. In this step the program matches the context $C(a/v_1, a^\perp_1, a)$. It should be checked that, if an anchored bond can be formed between domains mentioned above to generate the program $P' = C(a, a^\perp_1, a^\perp_1)$. In this step, a new bond $v_2$ can be generated by applying rule (R3) as there is a bond $w$ that is immediately adjacent to $v_2$ in $P'$, holding both ends of bond $v_2$ close to each other.

The resultant code of the program $P$ shows that, again the DNA tweezers return to its open configuration. The DNA strands $S_4$, i.e. input $A$, and $S_5$, i.e. input $B$, are completely bound to each other by three newly formed bonds $w$, $v_2$ and $u_2$. The complete double stranded DNA sequence formed by the hybridization is the by-product of the entire program coded above (expression 33-39). The domains of the by-product encode the conclusion of the set of propositions $S$. The chaining syllogism has been solved using strand displacement mechanism of DNA tweezers and in this section the entire procedure is formally coded by process calculus.

3.2.3. Formulation of syllogistic reasoning by strand graph and reduction rules

In this section we will graphically represent the wet lab algorithm to perform syllogistic reasoning by DNA tweezers. By DNA strand graph, the architecture of tweezers model can be analyzed more expressively. We are deducing conclusion from a given set of proposition $S$. The reasoning aspect has been replaced by DNA chemistry which is coded by program $P$ (expression 33).

The graphical depiction of program $P$ is the DNA strand graph $G$ shown in Fig. 22.
Each of the five strands in program $P$ is represented by the vertices in graph $G$ (Fig. 22). Arbitrary colours are assigned for the vertices in the graph. The vertices are represented by circular arrows and the arrowhead indicates the 3’ end of the DNA strand. The domains of the DNA strands are presented by the sites which are placed on the arrow-headed vertices according to their occurrences. All the admissible edges are drawn connecting the corresponding sites of the vertices. The current edges are represented by red lines and the remaining edges are represented by blue lines. The toehold edges are shown by dashed lines.

The initial state of DNA strand graph, shown in Fig. 22, is defined by $G = (V, length, colour, A, toehold, E)$, where,

$$V = \{1, 2, 3, 4, 5\}.$$  
$$length = \{1 \to 2, 2 \to 3, 3 \to 2, 4 \to 3, 5 \to 3\}.$$  
$$colour = \{1 \to 1, 2 \to 2, 3 \to 3, 4 \to 4, 5 \to 5\}.$$  
$$A = \{(1, 1), (4, 3)\}, \{(1, 2), (2, 3)\}, \{(2, 1), (3, 1)\}, \{(3, 2), (4, 2)\}, \{(4, 1), (5, 3)\}, \{(4, 2), (5, 2)\}, \{(4, 3), (5, 1)\}.$$  
$$toehold = \{(4, 1), (5, 3)\}.$$  
$$E = \{(1, 2), (2, 3)\}, \{(2, 1), (3, 1)\}.$$  

Fig. 23 is the graphical representation of program $P$ which performs syllogistic reasoning using DNA strands. Each step of the program changes according to suitable reduction rule.
Initially only the admissible edges connecting the sites of first three vertices are included in the set of current edges $E$. Thus, the DNA tweezers are in open configuration; and input $A$ (represented by vertex 4) and input $B$ (represented by vertex 5) are in single stranded form. The 1st site (domain $i$) of vertex 1 and the 3rd site (domain $i\perp$) of vertex 4 are not preoccupied and open to each other. Thus, according to rule (GB) in the first step of the program the admissible edge joining these two sites is converted to current edge. Thus, the colour of the edge changes from blue to red. Similarly, in the next step the admissible edge joining 2nd site (domain $a$) vertex 3 and the 2nd site (domain $a\perp$) of vertex 4 becomes current according to reduction rule (GB). This step leads to the closed configuration of the DNA tweezers.

Now, the toehold domain $t^\perp$ (3rd site) of vertex 5 hybridizes to the complementary domain $t^\perp$ (1st site) of vertex 4 and the blue dashed line is converted to red. This step is reversible. After the hybridization of the toehold domains, the branch migration and strand displacement occurs. The 2nd site (domain $a\perp$) of vertex 4 is preoccupied by the 2nd site (domain $a$) of vertex 3. The edge joining these two sites is omitted from the set of current edge and the admissible edge joining 2nd site (domain $a\perp$) of vertex 4 and 2nd site (domain $a$) of vertex 5 is included in the set of current edges. The strand displacement continues as the red edge joining the 1st site (domain $i$) of vertex 1 and the 3rd site (domain $i\perp$) of vertex 4 becomes blue; and the blue edge joining the 3rd site (domain $i\perp$) of vertex 4 and 1st site (domain $i$) of vertex 5 becomes blue. The strand displacement occurs by the reduction rule (G3).

Now, all the admissible edges joining the corresponding sites of vertex 4 and vertex 5 are included in the set of current edges. Thus, it can be said that input $A$ (vertex 4) is completely bound with input $B$ (vertex 5). The complete double stranded DNA sequence formed by the hybridization is the resultant by-product of the program $P$ and the deduced conclusion of the conclusion of the program.
chaining syllogism. The DNA tweezers returns to its initial open configuration. The cycle is repeated again and again as long as the fuel molecules, input $A$ and input $B$, is available.

3.3. Theorem Proving based on the Semantics of Process Calculus and DNA Strand Graph

This section presents one more application of DNA strand graph where we performed theorem proving with resolution refutation. Resolution, an important aspect of automated theorem proving and mathematical logic, can be defined as a rule of inference which leads to proof by contradiction technique for sentences in propositional logic and first-order logic. Proof by contradiction can also be called refutation theorem-proving. When two clauses contains complementary literals, a valid rule of resolution generates a new clause from these two clauses. A propositional variable or its negation (i.e., $P$, $\neg P$) is called a literal. Resolution is the only interference rule which needs to build a complete theorem prover, based on proof by contradiction and usually called resolution refutation [Chang and Lee, 1997].

3.3.1. The Resolution Principle in Propositional Logic

Theorem proving, a subfield of automated reasoning and mathematical logic, is used to develop computer programs. It proves that some statements (conjecture) is a logical consequence of a set of hypotheses. Theorem proving is applicable for several domains. In this paper we will perform theorem proving with resolution refutation in propositional logic [Chang and Lee, 1997].

A proposition is an assertion which is either true or false but not both. The propositional statements are made up of propositional variables and connectives. The propositional variables are variables having specified or unspecified truth value. These variables can be connected with logical connectives, for example, and (conjunction $\land$), or (disjunction $\lor$), not (negation $\neg$). A propositional variable or its negation is called a literal. For example, if $P$ is a propositional variable, then $P$ and $\neg P$ are both literals. An assertion which contains at least one propositional variable is called to be in propositional form. Propositional logic, the branch of logic, is the study of propositions that are formed by other propositions and logical connectives. Propositional logic is also concerned on how their value depends on the truth value of their components. Apart from the above mentioned logical operators there are two more operators which are used in logic. One is called implication ($\Rightarrow$) and other is equivalence ($\Leftrightarrow$).

Propositional resolution, a rule of inference, is capable of generating theorem prover in the domain of propositional logic. Before the application of resolution principle in propositional logic, the premises and conclusions must be expressed in clausal form. A clausal sentence is either a literal or a disjunction of literals. If $P$ and $Q$ are propositional variable, then the clausal sentences are:

$$
\begin{align*}
P \\
\neg P \\
\neg P \lor Q
\end{align*}
$$

36
A clause is the set of literals in a clausal sentence. The clauses of above mentioned clausal sentences are:

\[
\begin{align*}
\{P\} \\
\{\neg Q\} \\
\{\neg P, Q\}
\end{align*}
\]

The empty set {} is also a clause. It is equivalent to an empty disjunction and, therefore, is unsatisfiable. Thus, the clausal form and clauses in propositional logic can be defined as follows:

\[
(\text{clausal form}) := (\text{clause}) \land (\text{clause}) \land \cdots \land (\text{clause})
\]

\[
(\text{clause}) := (\text{literal}) \lor (\text{literal}) \lor \cdots \lor (\text{literal})
\]

The rules for conversion of arbitrary set of propositional logic sentences to equivalent set of clauses are given below:

1. Implications:

\[
P \Rightarrow Q \quad \rightarrow \quad \neg P \lor Q
\]

\[
P \Leftarrow Q \quad \rightarrow \quad P \lor \neg Q
\]

\[
P \iff Q \quad \rightarrow \quad (\neg P \lor Q) \land (P \lor \neg Q)
\]

2. Negations:

\[
\neg \neg P \quad \rightarrow \quad P
\]

\[
\neg (P \land Q) \quad \rightarrow \quad \neg P \lor \neg Q
\]

\[
\neg (P \lor Q) \quad \rightarrow \quad \neg P \land \neg Q
\]

3. Distribution:

\[
P \lor (Q \land R) \quad \rightarrow \quad (P \lor Q) \land (P \lor R)
\]

\[
(P \land Q) \lor R \quad \rightarrow \quad (P \lor R) \land (Q \lor R)
\]

\[
P \lor (P_1 \lor \cdots \lor P_n) \quad \rightarrow \quad P \lor P_1 \lor \cdots \lor P_n
\]

\[
(P_1 \lor \cdots \lor P_n) \lor P \quad \rightarrow \quad P_1 \lor \cdots \lor P_n \lor P
\]

\[
P \land (P_1 \land \cdots \land P_n) \quad \rightarrow \quad P \land P_1 \land \cdots \land P_n
\]

\[
(P_1 \land \cdots \land P_n) \land P \quad \rightarrow \quad P_1 \land \cdots \land P_n \land P
\]

4. Operators (O):

\[
P_1 \lor \cdots \lor P_n \quad \rightarrow \quad \{P_1, \ldots, P_n\}
\]

\[
P_1 \land \cdots \land P_n \quad \rightarrow \quad \{P_1\}, \ldots, \{P_n\}
\]

Resolution principle states that: "For any two clauses \(C_1\) and \(C_2\), if there is a literal \(L_1\) in \(C_1\) that is complementary to a literal \(L_2\) in \(C_2\), then delete \(L_1\) and \(L_2\) from \(C_1\) and \(C_2\), respectively, and construct the disjunction of the remaining clauses. The constructed clause is a resolvent of \(C_1\) and \(C_2\)." [Chang and Lee, 1997]

For example, let,

\[
C_1: \quad P
\]

\[
C_2: \quad \neg P \lor Q.
\]
According to the resolution principle, the complementary pair of literal, i.e. $P$ in $C_1$ and $
eg P$ in $C_2$, should be deleted to construct the resolvent $C_3$. The resolvent $C_3$ is:

$$C_3: Q.$$  

Another example is given below,

$$C_1: \neg Q \lor R$$
$$C_2: \neg P \lor Q \lor \neg S$$

The resolvent of $C_1$ and $C_2$ is:

$$C_3: R \lor \neg P \lor \neg S$$

If there is no complementary literal in $C_1$ and $C_2$, the no resolvent can be constructed from given clauses. For example,

$$C_1: \neg R \lor S$$
$$C_2: \neg R \lor Q \lor T$$

Another property of resolution principle is, "if two clauses $C_1$ and $C_2$ are given, a resolvent $C$ of $C_1$ and $C_2$ is a logical consequence of $C_1$ and $C_2"$. [Chang and Lee, 1997]

We have previously mentioned that, if the resolution principle generate empty clause $\{}$ from a set of clauses $S$, then it can be said that $S$ is unsatisfiable. The following definition can be drawn from the principle of resolution:

"Given a set of clauses $S$, a (resolution) deduction of $C$ from $S$ is a finite sequence $C_1$, $C_2$, ..., $C_k$ of clauses such that each $C_i$, either is a clause in $S$ or a resolvent of clauses preceding $C_i$, and $C_k = C$. A deduction of $\{}$ from $S$ is called a refutation, or a proof of $S"$. [Chang and Lee, 1997]

Thus, the resolution principle can be used to prove the unsatisfiability of a set of clauses. This can be explained by the following examples.

Let $S$ is a set containing six clauses,

$$\begin{align*}
(i) & \quad P \lor \neg Q \lor R \\
(ii) & \quad \neg U \lor V \lor \neg R \\
(iii) & \quad Q \\
(iv) & \quad \neg V \\
(v) & \quad \neg P \\
(vi) & \quad U
\end{align*}$$

$$\left\{ \begin{array}{l}
S
\end{array} \right\}$$

(40)

From (i) and (iii) of expression (40), the generated resolvent is,

$$\text{(vii)} \quad P \lor R$$

From (ii) and (iv), the generated resolvent is,

$$\text{(viii)} \quad \neg U \lor \neg R$$

From (vii) and (viii), the generated resolvent is,

$$\text{(ix)} \quad P \lor \neg U$$

From (ix) and (v), the generated resolvent is,

$$\text{(x)} \quad \neg U$$

From (x) and (vi), the generated resolvent is,

$$\text{(xi)} \quad \{}$$
Since \{\} is derived from the set of clauses \(S\) by resolution, it can be said that the empty clause \{\} is the logical consequence of \(S\). Only an unsatisfiable set of clauses can have empty clause \{\} as the logical consequence. Hence, it is proved that \(S\) is unsatisfiable. Fig. 24 shows the corresponding deduction tree.

Figure 24. Deduction tree

Thus, it can be said that resolution refutation or proof by contradiction proves a theorem by negating the statement to be proved. The negated statement is added to the set of premises which are known to be true. The theorem prover, generated by propositional resolution, proves the consistency of the negated goal. The inconsistency of the negated goal with the given set of premises implies that the original goal is consistent.

Let, we want to prove a premise or axiom \(X\) is true from a set of axioms \(Z\). The flowchart of resolution refutation for proving the truth value of \(X\) is shown in Fig. 25.
In this section the process of theorem proving with resolution refutation by DNA strands is represented by the formal language of process calculus and strand graph semantics.

3.3.2. Formulation of theorem proving by conventional DNA computing

In this section we will discuss theorem proving by resolution refutation using DNA strands with the help of some elementary operations to manipulate the strands performed by Lee, Park, Jang, Chai and Zhang [Lee et al., 2002]. To prove the unsatisfiability of the set of clauses $S$ (expression (40)) by resolution refutation in DNA computation, few steps should be followed.

**Step 1.** The clauses of set $S$ contain five propositional variables or literals. Each literal is encoded by arbitrarily chosen ten bases long single-stranded DNA oligonucleotide. The negation of each literal is encoded by the complementary sequence of the corresponding DNA strand (Table 9).
Step 2. All the clauses are encoded by single-stranded DNA oligonucleotides. To encode the clauses, the DNA strands representing literals of the corresponding clause are concatenated. The encoded clauses are listed in Table 10.

| Literal | Encoded DNA strand |
|---------|---------------------|
| $p$     | 5’ − ACGTAGTCAC − 3’ |
| $\neg p$ | 3’ − TGCATCAGTG − 5’ |
| $q$     | 5’ − CAGTCAATT − 3’ |
| $\neg q$ | 3’ − GTTCAGTTA − 5’ |
| $r$     | 5’ − TCAGTCGAAT − 3’ |
| $\neg r$ | 3’ − AGTCAGTTA − 5’ |
| $u$     | 5’ − CTAGGTCCAT − 3’ |
| $\neg u$ | 3’ − GATCAGGTA − 5’ |
| $v$     | 5’ − GATCGTGCAT − 3’ |
| $\neg v$ | 3’ − CTAGCACGTA − 5’ |

Table 9. Representation of literals by DNA strands

Step 3. All the single-stranded DNA oligonucleotides as shown in Table 10 are mixed in a test tube and allowed to hybridize with each other. In this step the principle of resolution refutation is implemented by DNA strand hybridization. The DNA strands encoding the clauses hybridize with each other to generate resolvent. The resolvent may be partially double-stranded or full double-stranded DNA sequence. Fully double-stranded DNA sequence denotes empty clause $\{\}$.

| Clause | Encoded DNA strand |
|--------|---------------------|
| $p \lor \neg q \lor r$ | 5’ − ACGTAGTCACGATTCAGTTA − 3’ |
| $\neg u \lor v \lor \neg r$ | 5’ − ATGGACTACGTAGTCAGTAAT − 3’ |
| $q$     | 5’ − CAGTCAATT − 3’ |
| $\neg q$ | 3’ − ATGCACGATC − 3’ |
| $\neg p$ | 3’ − CAGTCAATT − 3’ |
| $u$     | 5’ − CTAGGTCCAT − 3’ |

Table 10. Representation of clauses by DNA strands

Step 4. The resultant hybridized DNA strands are allowed to be ligated using specific ligase enzyme.

Step 5. The ligated sequences obtained from step 4 are amplified using specific primers by polymerase chain reaction. The primers are chosen specifically so that unwanted sequences are not amplified.

Step 6. To verify whether fully double-stranded DNA sequence is present in the resultant amplified sequences gel electrophoresis is performed. Complete double-stranded DNA sequence denotes empty clause $\{\}$. 
If an empty clause {} is derived from the set of clauses $S$ by resolution, it is proved that $S$ is unsatisfiable. Thus, the fully double-stranded resultant DNA sequence (resolvent) establishes the unsatisfiability of $S$. The given theorem is proved by contradiction. If all the resultant sequences are single-stranded or partially double-stranded, then it is proved that $S$ is satisfiable.

Fig. 26 is the pictorial representation of the process of theorem proving by resolution refutation with DNA strands. We also compare the process with deduction tree shown in Fig. 24.

3.3.3. Formulation of theorem proving by process calculus

In this section we will code theorem proving by resolution refutation by process calculus using the syntax and semantics described in section 2.3. We have to prove the unsatisfiability of the set of clauses $S$.

Let the entire program is denoted by $P$. The program $P$ consists of six clauses which are encoded by single-stranded DNA oligonucleotides. $P$ is defined as the multiset of six DNA strands.
\[ P = <S_1> | <S_2> | <S_3> | <S_4> | <S_5> | <S_6> \]  

(41)

Therefore,
\[ P = <P \quad Q^\perp \quad R > | <U^\perp \quad V \quad R^\perp > | <Q > | <V^\perp > | <P^\perp > | <U > \]  

(42)

Every literal is encoded by arbitrarily chosen ten bases long single-stranded DNA sequence. The DNA strand encoding the negation of each literal is the Watson-Crick complement of the corresponding literal. Thus, the DNA strand encoding the negation of literal \( P \), i.e. \( \neg P \), is named as \( P^\perp \). For all the literals the same rule has been followed. Each of the strands \(<S_1> \) and \(<S_2> \) contains three domains as given by the program code. The remaining strands, i.e. \(<S_3>, <S_4>, <S_5> \) and \(<S_6> \), contain one domain each. From the program code it is clear that at the initial state of the program all the domains of the strands are free. As the domain \( Q^\perp \) of \(<S_1> \) and the domain \( Q \) of \(<S_2> \) are not bound with any other domain, the program matches the context \( C(Q, Q^\perp) \). It can be written that \( P = C(Q^\perp, Q^\perp) \) as one end of the bond \( i \) is not in closed loop, i.e. hidden(i, P) returns false. Thus, the program \( P' \) can be produced by the rule (RB) which forms the new bond \( i \) between the second domain of \(<S_1> \) and the only domain of \(<S_2> \). The program code is given below;
\[
\begin{align*}
&P \quad Q^\perp \quad R > | <U^\perp \quad V \quad R^\perp > | <Q > | <V^\perp > | <P^\perp > | <U > \\
\text{(RB)} & \quad \Rightarrow <P \quad Q^\perp j \quad R > | <U^\perp \quad V \quad R^\perp > | <Q^\perp j > | <V^\perp > | <P^\perp > | <U >
\end{align*}
\]  

(43)

As the domains \( V \) of \(<S_2> \) and \( V^\perp \) of \(<S_1> \) are free, the program matches the context \( C(V, V^\perp) \). The new bond \( j \) can be formed joining these two domains by the rule (RB) as one end of the bond is not hidden. The program code is given below;
\[
\begin{align*}
&P \quad Q^\perp j \quad R > | <U^\perp \quad V \quad R^\perp > | <Q^\perp j > | <V^\perp > | <P^\perp > | <U > \\
\text{(RB)} & \quad \Rightarrow <P \quad Q^\perp j \quad R > | <U^\perp \quad V \quad R^\perp > | <Q^\perp j > | <V^\perp > | <P^\perp > | <U >
\end{align*}
\]  

(44)

Now, the second domains of the strands \(<S_1> \) and \(<S_2> \) are bound. The domains \( R \) and \( R^\perp \) at 3’ ends of the strands \(<S_1> \) and \(<S_2> \) are free. Thus, the program matches the context \( C(R, R^\perp) \). The new bond \( k \) can be formed between these domains by rule (RB). The ends of the bond do not occur in closed loop. The program code is given below;
\[
\begin{align*}
&P \quad Q^\perp j \quad R > | <U^\perp \quad V \quad R^\perp > | <Q^\perp j > | <V^\perp > | <P^\perp > | <U > \\
\text{(RB)} & \quad \Rightarrow <P \quad Q^\perp j \quad R \quad k > | <U^\perp \quad V \quad R \quad k > | <Q \quad j > | <V^\perp > | <P^\perp > | <U >
\end{align*}
\]  

(45)

Again, rule (RB) comes into action and a new bond \( l \) is formed between the free domains \( P \) of \(<S_1> \) and \( P^\perp \) of \(<S_2> \) as one end of the \( l \) is not hidden. The program code is given below;
\[
\begin{align*}
&P \quad Q^\perp j \quad R \quad k > | <U^\perp \quad V \quad j \quad R \quad k > | <Q \quad i > | <V^\perp > | <P^\perp > | <U > \\
\text{(RB)} & \quad \Rightarrow <P \quad Q^\perp j \quad R \quad k > | <U^\perp \quad V \quad j \quad R \quad k > | <Q \quad i > | <V^\perp > | <P^\perp > | <U >
\end{align*}
\]  

(46)
Except the domains $U_\perp$ of $<S_2>$ and $U$ of $<S_6>$, all the domains of program $P$ is bound. The program matches the context $C(U, U_\perp)$. New bond $m$ can be formed between these two domains by rule (RB). The program code is given below;

\[
\begin{align*}
&P|l \mid Q \mid l \mid R ! ! k > | < U \mid l \mid V ! j \mid R \mid l ! k > | < Q ! i > | < V \mid l ! j > | < P \mid l ! l > | < U > \\
&\xrightarrow{(RB)} P|l \mid Q \mid l \mid R ! ! k > | < U \mid l ! m \mid V ! j \mid R \mid l ! k > | < Q ! i > | < V \mid l ! j > | < P \mid l ! l > | < U ! m >
\end{align*}
\]

Form the program code it is clear that all the domains of the given program are bound. Thus, the resultant strand is complete double stranded DNA sequence which indicates empty clause $\{\}$. This proves the unsatisfiability of the set of clauses $S$.

3.3.3. Formulation of theorem proving by strand graph and reduction rules

This section is the graphical representation of program $P$ which has been described by process calculus using program codes in the previous section. The unsatisfiability of the set of clauses $S$ is demonstrated using DNA strand graph $T$. Initially the code of program $P$ is represented by the expression (42). Graphical depiction of program $P$ is shown in Fig. 27.

![Figure 27. DNA strand graph $T$ representing the initial state of program $P$](image)

Six strands of $P$ is represented by six vertices in $T$ (Fig. 27). Different arbitrary colours are assigned for the vertices in the graph. The domains of the DNA strands are presented by the sites which are placed on the arrow-headed vertices according to their occurrences. All the edges of the strand graph $T$ are admissible edges. Since, at the starting point of the program all the DNA sequences are single stranded i.e. initially the set of current edges is empty i.e. $E = \emptyset$. The admissible edges are drawn by blue lines.

The initial state of DNA strand graph as shown in Fig. 27 is defined by $T = (V, \text{length}, \text{colour}, A, \text{toehold}, E)$, where,

\[
\begin{align*}
V &= \{1, 2, 3, 4, 5, 6\}.
\text{length} &= \{1 \rightarrow 3, 2 \rightarrow 3, 3 \rightarrow 1, 4 \rightarrow 1, 5 \rightarrow 1, 6 \rightarrow 1\}.
\text{colour} &= \{1 \rightarrow 1, 2 \rightarrow 2, 3 \rightarrow 3, 4 \rightarrow 4, 5 \rightarrow 5, 5 \rightarrow 6\}.
\end{align*}
\]
\[
A = \{(1, 1), (5, 1)\}, \{(1, 2), (3, 1)\}, \{(1, 3), (2, 3)\}, \{(2, 1), (6, 1)\}, \{(2, 2), (4, 1)\}.
\]

\[
toehold = \emptyset.
\]

\[
E = \emptyset.
\]

In Fig. 28 the entire mechanism of theorem proving by resolution refutation using DNA strands is represented by strand graph \( T \) and reduction rules.

Figure 28. DNA strand graph with reduction rules conducting the program of theorem proving by resolution refutation using DNA strands

In Fig. 28, the admissible edges are drawn by blue lines. Initially the set of current edges \( E \) is empty, thus, all the edges are admissible. The 2\(^{nd}\) site (domain \( Q^1 \)) of vertex 1 and the only site (\( Q \)) of vertex 3 are not preoccupied and open to each other. Thus, according to rule (GB) in the first step of the program the admissible edge joining these two sites is converted into current edge. The current edge is drawn by red lines. All the remaining admissible edges of the strand graph are converted into current edges in next few steps following the reduction rule (GB). Finally, all the edges of the graph are included in set \( E \). No site in graph is free in the resultant graphical structure. This indicates that, the final strand is complete double stranded DNA sequence which implies empty clause \( \{\} \). Thus, the unsatisfiability of the set of clauses \( S \) has been proved.

4. Future Scope of Work

We have extensively studied the area of DNA strand algebra and suggested several real life applications in this paper. DNA cryptography is one of the prominent domains where DNA strand algebra can be applied. DNA molecules, having the capacity to store, process and transmit information, inspires the idea of DNA cryptography. It is the rapid emerging unconventional
techniques which combines the chemical characteristics of biological DNA sequences with classical cryptography to ensure non-vulnerable transmission of data.

We have surveyed the present state of art of DNA cryptography methodologies. To authenticate the security, logic and reasoning of the proposed protocols in this area formal modelling tool is needed. The formal representation of the existing algorithms leads to the formal verifications of the corresponding properties. DNA strand algebra and process calculus can be used as the modelling tool for formal representation of cryptographic algorithm, primitive operators and interaction between the agents of a process. This formal approach of presenting the protocols using DNA strand algebra is capable of clarifying the reasoning being used to develop the DNA cryptographic framework.

5. Conclusion

In this paper we have exploited the power of DNA strand displacement and flexibility of DNA strand algebra which is essentially derived from process algebra. It demonstrates the algebraic study of the concurrent communicating process which provides the high-level description to formal reasoning for controlling and analyzing the equivalences between processes. We have projected that this formal modelling tool has a huge real-life applications in the domain of reasoning and theorem proving. We have a plan to extend the merit of DNA strand algebra and process calculus in the promising area of formal modelling of DNA cryptography protocols. The implementation of DNA strand graph in DNA cryptographical methodologies is required for authentication of security, logic and reasoning of the proposed protocol.

References

1. Adleman, L. (1994) ‘Molecular computation of solutions to combinatorial problems’, Science, Vol. 266, No. 5187, pp. 1021–1024.
2. Baeten J.C.M. (2004). A brief history of process algebra. Rapport CSR 04-02 (Vakgroep Informatica, Technische Universiteit Eindhoven).
3. Benenson Y., Paz-Elizur T., Adar R., Keinan E., Livneh Z., and Shapiro E., (2001) ‘Programmable and autonomous computing machine made of biomolecules’, Nature, Vol. 414, No. 22, pp. 430–434.
4. Berry, G. and Boudol, G. (1989). The Chemical Abstract Machine. Proc. 17th POPL, ACM, pp. 81-94.
5. Cardelli L. (2009). Strand Algebras for DNA Computing. DNA Computing and Molecular Programming: 15th International Conference, DNA 15, Fayetteville, AR, USA, June 8-11, 2009, Revised Selected Papers, Springer-Verlag, Berlin, Heidelberg, 2009.
6. Cardelli L. (2013). Two-domain DNA strand displacement. Mathematical Structures in Computer Science 23(2), pp. 247-27.
7. Chang, C. L. and Lee, R. C. T. (1997). Symbolic logic and mechanical theorem proving. Academic Press, Inc. Orlando, FL, USA, ISBN:0121703509.

8. Green C. and Tibbetts C. (1981) ‘Reassociation rate limited displacement of DNA strands by branch migration’, Nucleic Acids Res., Vol. 9, No. 8, pp.1905–1918.

9. Green S.J., Lubrich D., Turberfield A.J., (2006) ‘DNA hairpins: fuel for autonomous DNA devices’, Biophysical Journal, Vol. 91, No. 8, pp. 2966–2975.

10. Lee, I. H., Park, J. Y., Jang, H. M., Chai, Y. G. and Zhang B. T. (2002). DNA Implementation of Theorem Proving with Resolution Refutation in Propositional Logic. Revised Papers from the 8th International Workshop on DNA Based Computers: DNA Computing (DNA8), Masami Hagiya and Azuma Ohuchi (Eds.). Springer-Verlag, London, UK, 156-167.

11. Mondal, M. and Ray, K.S. (2017), “Syllogistic Reasoning by strand algebra”, International Journal of Bio-inspired Computation, Vol. 1, No. 1, pp. 56-66.

12. Petersen, R. L., Lakin, M. R. and Phillips, A. (2016). A strand graph semantics for DNA-based computation. Theoretical Computer Science, Vol. 632, pp. 43-73.

13. Ray, K. S. and Mondal, M. (2016), “Logical Inference by DNA Strand Algebra”, New Mathematics and Natural Computation, Vol. 12, No. 1, pp. 29-44.

14. Ray, K. S. and Mondal, M. (2012), "Reasoning with Disposition using DNA Tweezers", International Journal of Bio-inspired Computation, Vol. 4, No. 5, pp. 302-318.

15. Winfree E., Liu F., Wenzler L.A., and Seeman N.C., (1998) ‘Design and self assembly of two dimensional DNA crystals’, Nature, Vol. 394, No. 6693, pp. 539–544.

16. Yurke, B., Turberfield, A.J., Mills, A. P. Jr, Simmel, F.C. and Neumann, J. L. (2000). A DNA-fuelled molecular machine made of DNA. Nature, Vol. 406, No. 6796, pp.605-608.

17. Zhang D.Y. and Winfree E., (2009) ‘Control of DNA strand displacement kinetics using toehold exchange’, Journal of American Chemical Society, Vol. 131, No. 47, pp.17303–17314.