

Strand Algebras for DNA Computing

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Abstract. We present a process algebra for DNA computing, discussing compilation of other formal systems into the algebra, and compilation of the algebra into DNA structures.

1 Introduction

DNA technology is reaching the point where one can envision automatically compiling high-level formalisms to DNA computational structures [18]. Examples so far include the ‘manual compilation’ of automata and Boolean networks, where some impressive demonstrations have been carried out [18],[15],[16]. Typically one considers sequential or functional computations, realized by massive numbers of molecules; we should strive, however, to take more direct advantage of massive concurrency at the molecular level. To that end it should be useful to consider *concurrent* high-level formalism, in addition to sequential ones. In this paper we describe three compilation processes for concurrent languages. First, we compile a low-level combinatorial algebra to a certain class of composable DNA structures [17]: this is intended to be a direct (but not quite trivial) mapping, which provides an algebraic notation for writing concurrent molecular programs. Second, we compile a higher-level expression-based algebra to the low-level combinatorial algebra, as a paradigm for compiling expressions of arbitrary complexity to ‘assembly language’ DNA combinators.

Third is our original motivation: translating heterogeneous collections of interacting automata [4] to molecular structures. How to do that was initially unclear, because one must choose some suitable ‘programmable matter’ (such as DNA) as a substrate, but must also come up with compositional protocols for interaction of the components that obey the high-level semantics of the language. We show a solution to this problem in Section 5, based on the combinatorial DNA algebra. The general issue there is how to realize the *external choice* primitive of interacting automata (also present in most process algebras and operating systems), for which there is currently no direct DNA implementation. In DNA we can instead implement a *join* primitive, based on [17]: this is a powerful operator, widely studied in concurrency theory [7],[13], which can indirectly provide an implementation of external choice. The DNA algebra supporting the translation is built around the join operator.

2 Strand Algebras

By a strand algebra we mean a process algebra [11] where the main components represent DNA strands, DNA gates, and their interactions. We begin with a nondeterministic

algebra, and we discuss a stochastic variant in Section 4. Our strand algebras may look very similar to either chemical reactions, or Petri nets, or multiset-rewriting systems. The difference is that the equivalent of, respectively, reactions, transitions, and rewrites, do not live *outside* the system, but rather are part of the system itself and are *consumed* by their own activity, reflecting their DNA implementation. A process algebra formulation is particularly appropriate for such an internal representation of active elements.

2.1 The Combinatorial Strand Algebra, \mathcal{P}

Our basic strand algebra has some atomic elements (*signals* and *gates*), and only two combinators: *parallel (concurrent) composition* $P \mid Q$, and *populations* P^* . An inexhaustible population P^* has the property that $P^* = P \mid P^*$; that is, there is always one more P that can be taken from the population. The set \mathcal{P} is formally the set of finite trees P generated by the syntax below; we freely use parentheses when representing these trees linearly as strings. Up to the algebraic equations described below, each P is a multiset, i.e., a solution. The *signals* x are taken from a countable set.

2.1.1 Syntax

$$P ::= x \mid [x_1, \dots, x_n]. [x'_1, \dots, x'_m] \mid 0 \mid P_1 \mid P_2 \mid P^* \quad n \geq 1, m \geq 0$$

A *gate* is an operator from signals to signals: $[x_1, \dots, x_n]. [x'_1, \dots, x'_m]$ is a gate that binds signals $x_1 \dots x_n$, produces signals x'_1, \dots, x'_m , and is consumed in the process. We say that this gate *joins* n signals and then *forks* m signals; see some special cases below. An inert component is indicated by 0 . Signals and gates can be combined into a ‘soup’ by parallel composition $P_1 \mid P_2$ (a commutative and associative operator, similar to chemical ‘+’), and can also be assembled into inexhaustible populations, P^* .

2.1.2 Explanation of the Syntax and Abbreviations

x		is a <i>signal</i>	0	is <i>inert</i>
$x_1.x_2$	$\stackrel{\text{def}}{=} [x_1].[x_2]$	is a <i>transducer gate</i>	$P_1 \mid P_2$	is <i>parallel composition</i>
$x.[x_1, \dots, x_m]$	$\stackrel{\text{def}}{=} [x].[x_1, \dots, x_m]$	is a <i>fork gate</i>	P^*	is <i>unbounded population</i>
$[x_1, \dots, x_n].x$	$\stackrel{\text{def}}{=} [x_1, \dots, x_n].[x]$	is a <i>join gate</i>		

The relation $\equiv \subseteq \mathcal{P}_X \mathcal{P}$, called *mixing*, is the smallest relation satisfying the following properties; it is a substitutive equivalence relation axiomatizing a well-mixed solution [2]:

2.1.3 Mixing

$P \equiv P$	equivalence	$P \equiv Q \Rightarrow P \mid R \equiv Q \mid R$	in context
$P \equiv Q \Rightarrow Q \equiv P$		$P \equiv Q \Rightarrow P^* \equiv Q^*$	
$P \equiv Q, Q \equiv R \Rightarrow P \equiv R$			
$P \mid 0 \equiv P$	diffusion	$P^* \equiv P^* \mid P$	population
$P \mid Q \equiv Q \mid P$		$0^* \equiv 0$	
$P \mid (Q \mid R) \equiv (P \mid Q) \mid R$		$(P \mid Q)^* \equiv P^* \mid Q^*$	
		$P^{**} \equiv P^*$	

The relation $\rightarrow \subseteq \mathcal{P} \times \mathcal{P}$, called *reaction*, is the smallest relations satisfying the following properties. In addition, \rightarrow^* , *reaction sequence*, is the symmetric and transitive closure of \rightarrow .

2.1.4 Reaction

$x_1 \mid .. \mid x_n \mid [x_1, \dots, x_n]. [x'_1, \dots, x'_m] \rightarrow x'_1 \mid .. \mid x'_m$	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

The first reaction (gate) forms the core of the semantics: the other rules allow reactions to happen in context. Note that the special case of the gate rule for $m=0$ is $x_1 \mid .. \mid x_n \mid [x_1, \dots, x_n]. [] \rightarrow 0$. And, in particular, $x.[]$ annihilates an x signal. We can choose any association of operators in the formal gate rule: because of the associativity of parallel composition under \equiv the exact choice is not important. Since \rightarrow is a relation, reactions are in general nondeterministic. Some examples are:

- $x_1 \mid x_1.x_2 \rightarrow x_2$
- $x_1 \mid x_1.x_2 \mid x_2.x_3 \rightarrow^* x_3$
- $x_1 \mid x_2 \mid [x_1, x_2].x_3 \rightarrow x_3$
- $x_1 \mid x_1.x_2 \mid x_1.x_3 \rightarrow x_2 \mid x_1.x_3$ and $\rightarrow x_3 \mid x_1.x_2$
- $X \mid ([X, x_1]. [x_2, X])^*$ a catalytic system ready to transform multiple x_1 to x_2 , with catalyst X

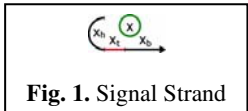


Fig. 1. Signal Strand

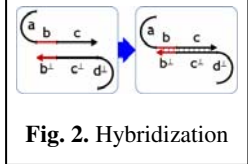


Fig. 2. Hybridization

There is a duality between signals and gates: signals can interact with gates but signals cannot interact with signals, nor gates with gates. As we shall see, in the DNA implementation the input part of a gate is the Watson-Crick dual of the corresponding signal strand. This duality need not be exposed in the syntax: it is implicit in the separation between signals and gates, so we use the same x_1 both for the ‘positive’ signal strand and for the complementary ‘negative’ gate input in a reaction like $x_1 \mid x_1.x_2 \rightarrow x_2$.

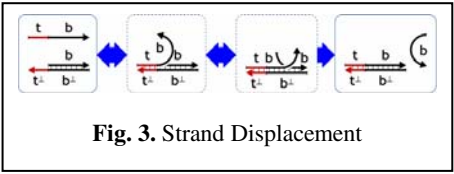


Fig. 3. Strand Displacement

3 DNA Semantics

In this section we provide a DNA implementation of the combinatorial strand algebra. Given a representation of signals and gates, it is then a simple matter to represent any strand algebra expression as a DNA system, since 0 , $P_1 \mid P_2$, and P^* are assemblies of signals and gates.

There are many possible ways of representing signals and gates as DNA structures. First one must choose an overall architecture, which is largely dictated by a representation of signals, and then one must implement the gates, which can take many forms with various qualitative and quantitative trade-offs.

We follow the general principles of [17], where DNA computation is based on strand displacement on loop-free structures. Other architectures are possible, like computation with hairpins [18], but have not been fully worked out. The four-segment signal structure in [17] yields a full implementation of the combinatorial strand algebra (not shown, but largely implied by that paper). Here we use a novel, simpler, signal structure.

We represent a signal x as a DNA *signal strand* with three segments x_h, x_t, x_b (Figure 1): $x_h = \text{history}$, $x_t = \text{toehold}$, $x_b = \text{binding}$. A toehold is a segment that can reversibly interact with a gate: the interaction can then propagate to the adjacent binding segment. The history is accumulated during previous interactions (it might even be hybridized) and is not part of signal identity. That is, x denotes the equivalence class of signal strands with any history, and a gate is a structure that operates uniformly on such equivalence classes. We generally use arbitrary letters to indicate DNA *segments* (which are single-stranded sequences of bases).

A strand like b, c, d has a *Watson-Crick complement* $(b, c, d)^\perp = d^\perp, c^\perp, b^\perp$ that, as in Figure 2, can partially hybridize with a, b, c along the complementary segments. For two signals x, y , if $x \neq y$ then neither x and y nor x and y^\perp are supposed to hybridize, and this is ensured by appropriate DNA coding of the segments [9],[10]. We assume that all signals are made of ‘positive’ strands, with ‘negative’ strands occurring only in gates, and in particular in their input segments; this separation enables the use of 3-letter codes, that helps design independent sequences [10],[20].

The basic computational step of *strand displacement* [17] is shown in Figure 3 for matching single and double strands. This reaction starts with the reversible hybridization of the toehold t with the complementary t^\perp of a

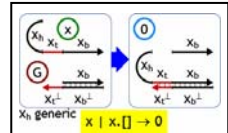


Fig. 4. Annihilator

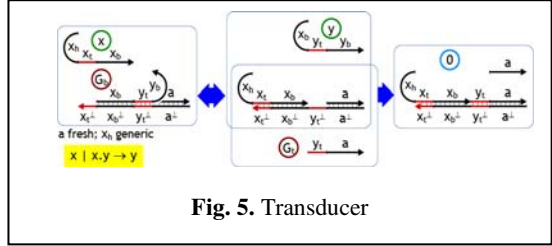


Fig. 5. Transducer

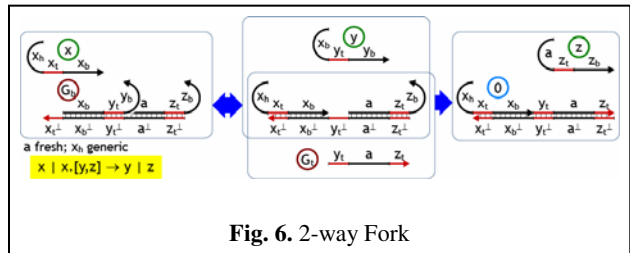


Fig. 6. 2-way Fork

structure that is otherwise double-stranded. The hybridization can then extend to the binding segment b by a neutral series of reactions between base pairs (*branch migration* [19]) each going randomly left or right through small exergy hills, and eventually ejecting the b strand when the branch migration randomly reaches the right end. The free b strand can in principle reattach to the double-stranded structure, but it has no toehold to do so easily, so the last step is considered irreversible. The simple-minded interpretation of strand displacement is then that the strand a,b is removed, and the strand b is released irreversibly. The double-stranded structure is consumed during this process, leaving an inert residual (defined as one containing no single-stranded toeholds).

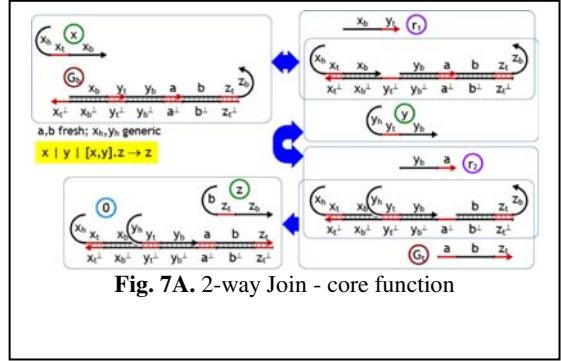


Fig. 7A. 2-way Join - core function

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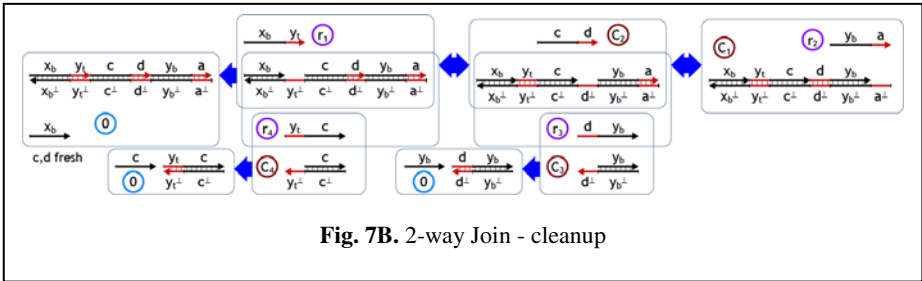


Fig. 7B. 2-way Join - cleanup

Figure 4 shows the same structure, but seen as a gate G absorbing a signal x and producing nothing (0). The annotation 'x_h generic' means that the gate works for all input histories x_h, as it should. In Figure 5 we implement a gate x.y that transduces a signal x into a signal y. The gate is made of two separate structures G_b (gate backbone) and G_t (gate trigger). The forward G_b reaction can cause y to detach because the binding of a toehold (y_i) is reversible. That whole G_b reaction is reversible via strand displacement from right to left, but the G_t reaction eventually 'locks' the gate in the state where x is consumed and y is produced. The annotation 'a fresh' means that the segment 'a' is not shared by any other gate in the system to prevent interference (while of course the gate is implemented as a population of identical copies that share that segment). In general,

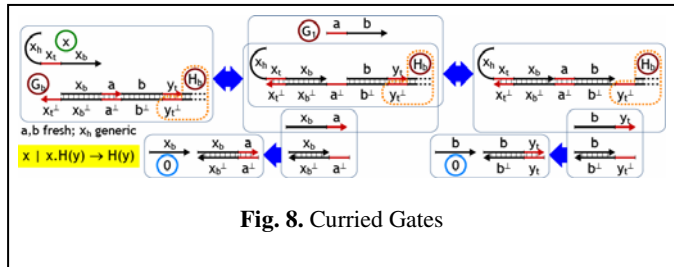


Fig. 8. Curried Gates

In Figure 5 we implement a gate x.y that transduces a signal x into a signal y. The gate is made of two separate structures G_b (gate backbone) and G_t (gate trigger). The forward G_b reaction can cause y to detach because the binding of a toehold (y_i) is reversible. That whole G_b reaction is reversible via strand displacement from right to left, but the G_t reaction eventually 'locks' the gate in the state where x is consumed and y is produced. The annotation 'a fresh' means that the segment 'a' is not shared by any other gate in the system to prevent interference (while of course the gate is implemented as a population of identical copies that share that segment). In general,

we take all gate segments to be fresh unless they are non-history segments of input or output signals. Abstractly, an x to y transduction is seen as a single step but the implementation of $x.y$ takes at least two steps, and hence has a different kinetics. This is a common issue in DNA encodings, but its impact can be minimized [17], e.g. in this case by using a large G_t population. In Figure 6 (cf. Figure 2 in [17]), we generalize the transducer to a 2-way fork gate, $x.[y,z]$, producing two output signals; this can be extended to n -way fork, via longer trigger strands.

Many designs have been investigated for join gates [5]. The solution shown in Figure 7 admits the coexistence of joins with the same inputs, $[x,y].z \mid [x,y].z'$, without disruptive crosstalk or preprocessing of the system (not all join gates have this property). It is crucial for join to fire when both its inputs are available, but not to absorb a first input while waiting for the second input, because the second input may never come, and the first input may be needed by another gate (e.g., another join with a third input). The solution is to *reversibly* bind the first input, taking advantage of chemical reversibility. Given two inputs x,y , a ‘reversible-AND’ G_b backbone releases two strands r_1,r_2 , with r_1 providing reversibility while waiting for y (cf. Figure 3 in [17]); the trigger G_t finally irreversibly releases the output z (or outputs). In a cleanup phase (Figure 7B), off the critical path, we use a similar reversible-AND C_1 structure (working from right to left) to remove r_1 and r_2 from the system, so that they do not accumulate to slow down further join operations. This phase is initiated by the release of r_2 , so we know by construction that both r_1 and r_2 are available. Therefore, the r_3 and r_4 reversibility strands released by C_1 can be cleaned up immediately by C_3,C_4 , ending a possible infinite regression of reversible-ANDs. (Note that without the extra c,d segments, a strand $y_t,y_b = y$ would be released.) This gate structure can be easily generalized to n -way join gates by cascading more inputs on the G_b backbone. Alternatively, we can implement a 3-way join from 2-way joins and an extra signal x_0 , but this encoding ‘costs’ a population: $[x_1,x_2,x_3].x_4 \stackrel{\text{def}}{=} ([x_1,x_2].x_0 \mid x_0.[x_1,x_2])^* \mid [x_0,x_3].x_4$.

This completes the implementation of strand algebra in DNA. For the purposes of the next section, however, it is useful to consider also *curried gates* (gates that produce gates). Figure 8 shows a gate $x.H(y)$ that accepts a signal x and activates the backbone H_b of a gate $H(y)$, where $H(y)$ can be any gate with initial toehold y_t^\perp , including another curried gate. For example, if $H(y)$ is a transducer $y.z$ as in Figure 5, we obtain a curried gate $x.y.z$ such that $x \mid x.y.z \rightarrow y.z$. (The extra a,b segments prevent the release of a strand x_b,y_t that would interfere with r_1 of $[x,y].z$; see Figure 7A.) This implies that there is an extension of strand algebra with gates of the form $G ::= [x_1,\dots,x_n].[x'_1,\dots,x'_m] \vdash [x_1,\dots,x_n].G$; this extension can be translated back to the basic strand algebra, e.g. by setting $x.y.z = x.w \mid [w,y].z$ for a fresh w , but a direct implementation of curried gates is also available.

4 Stochastic Strand Algebra

Stochastic strand algebra is obtained by assigning stochastic rates to gates, and by dropping the unbounded populations, P^* . Since the binding strengths of toeholds of the same length are comparable [18], we assume that all gates with the same number n of

inputs have the same stochastic rate g_n , collapsing all the gate parameters into a single effective parameter. Although gate rates are fixed, we can vary population sizes in order to achieve desired macroscopic rates. Moreover, as we describe below, it is possible to maintain stable population sizes, and hence to achieve desired stable rate ratios.

In this section $[x_1, \dots, x_n]. [y_1, \dots, y_m]$ is a stochastic gate of rate g_n , and we write P^k for k parallel copies of P . In a global system state P , the *propensity* of a gate reaction is $(P \text{ choose } (x_1 \mid \dots \mid x_n \mid [x_1, \dots, x_n]. [y_1, \dots, y_m])) \times g_n$; that is, the gate rate g_n multiplied by the number of ways of choosing out of P a multiset consisting of a gate and its n inputs. For example, if $P = x^n \mid y^m \mid ([x, y]. z)^p$ with $x \neq y$, then the propensity of the first reaction in P is $n \times m \times p \times g_2$. A *global transition* from a global state P to a next global state, labeled with its propensity, has then the following form, where \setminus is multiset difference:

$$P \rightarrow^{(P \text{ choose } (x_1 \mid \dots \mid x_n \mid [x_1, \dots, x_n]. [y_1, \dots, y_m])) \times g_n} P \setminus (x_1 \mid \dots \mid x_n \mid [x_1, \dots, x_n]. [y_1, \dots, y_m]) \mid y_1 \mid \dots \mid y_m$$

The collection of all global transitions from P and from its successive global states forms a labeled transition graph, from which one can extract the Continuous Time Markov Chain of the system [4]. We shall soon use also a curried gate of the form $x.G$, whose DNA structure is discussed in Section 3, and whose global transitions are:

$$P \rightarrow^{(P \text{ choose } (x \mid x.G)) \times g_1} P \setminus (x \mid x.G) \mid G$$

In a stochastic system, an unbounded population like P^* has little meaning because its rates are unbounded as well. In stochastic strand algebra we simply drop the P^* construct. In doing so, however, we eliminate the main mechanism for iteration and recursion, and we need to find an alternative mechanism. Rather than P^* , we should instead consider finite populations P^k exerting a stochastic pressure given by the size k . It is also interesting to consider finite populations that *remain* at constant size k : let's indicate them by $P^{=k}$. In particular, $P^{=1}$ represents a single catalyst molecule.

We now show that we can model populations of constant size k by using a bigger buffer population to keep a smaller population at a constant level. Take, e.g., $P = [x, y]. z$, and define:

$$P^{=k} \stackrel{\text{def}}{=} ([x, y]. [z, X])^k \mid (X. [x, y]. [z, X])^{f(k)} \quad \text{for a fresh (otherwise unused) signal } X$$

Here $f(k)$ is the size of a large-enough buffer population. A global transition of $P^{=k}$ in context Q (with Q not containing other copies of those gates) is $(Q \mid P^{=k}) \rightarrow^{((Q \mid P^{=k}) \text{ choose } (x|y|[x, y]. [z, X])) \times g_2} (Q \setminus (x \mid y) \mid ([x, y]. [z, X])^{k-1} \mid z \mid X \mid (X. [x, y]. [z, X])^{f(k)})$. For a large enough $f(k)$, the propensity of a next reaction on gate $X. [x, y]. [z, X]$ can be made arbitrarily large, so that the two global transitions combined approximate $(Q \mid P^{=k}) \rightarrow^{((Q \mid P^{=k}) \text{ choose } (x|y|[x, y]. [z, X])) \times g_2} (Q \setminus (x \mid y) \mid ([x, y]. [z, X])^k \mid z \mid (X. [x, y]. [z, X])^{f(k)-1})$, where the gate population is restored at level k , and the buffer population decreases by 1. We have shown that the reaction propensity in $(Q \mid P^{=k})$ can be made arbitrarily close to the reaction propensity in $(Q \mid P^k)$, but with the gate population being restored to size k . Moreover, it is possible to periodically replenish the buffer by external intervention *without disturbing the system* (except for the arbitrarily fast reaction speed on X). This provides a practical way of implementing recursion and unbounded computation,

by ‘topping-up’ the buffer populations, without a notion of unbounded population. The construction of a stable population $([x,y].z)^=k$ can be carried out also without curried gates, but it then requires balancing the rate of a ternary gate against the desired rate of a binary gate.

We should note that the stochastic strand algebra is a convenient abstraction, but the correspondence with the DNA semantics of Section 3 is not direct. More precisely, it is possible to formulate a formal translation from the stochastic strand algebra to a chemical algebra, by following the figures of Section 3 (considering strand displacement as a single reaction). Such a chemical semantics does not exactly match the global transition semantics given above, because for example a single reaction $x \mid x.y \rightarrow y$ is modeled by two chemical reactions. It is possible to define a chemical semantics that approximates the global transition semantics, by using the techniques discussed in [17], but this topic requires more attention that we can provide here.

5 Compiling to Strand Algebra

We give examples of translating other formal languages to strand algebra, in particular translating interacting automata. The interesting point is that by these translations we can map all those formal languages to DNA, by the methods in Section 3.

Finite Stochastic Reaction Networks

We summarize the idea of [17], which shows how to encode with approximate dynamics a stochastic chemical system as a set of DNA signals and gates. A unary reaction $A \rightarrow C_1 + \dots + C_n$ is represented as $(A.[C_1, \dots, C_n])^*$. A binary reaction $A+B \rightarrow C_1 + \dots + C_n$ is represented as $([A,B].[C_1, \dots, C_n])^*$. The initial solution, e.g. $A+A+B$, is represented as $A \mid A \mid B$ and composed with the populations representing the reactions. For stochastic chemistry, one must replace the unbounded populations with large but finite populations whose sizes and rates are calibrated to provide the desired chemical rates. Because of technical constraints on realizing the rates, one may have to preprocess the system of reactions [17].

Petri Nets

Consider a place-transition Petri Net [13] with places x_i ; then, a transition with incoming arcs from places $x_1 \dots x_n$ and outgoing arcs to places $x'_1 \dots x'_m$ is represented as $([x_1, \dots, x_n].[x'_1 \dots x'_m])^*$. The initial marking $\{x_1, \dots, x_k\}$ is represented as $x_1 \mid \dots \mid x_k$. The idea is similar to the translation of chemical networks: those can be represented as (stochastic) Petri nets. Conversely (thanks to Cosimo Laneve for pointing this out), a signal can be represented as a marked place in a Petri net, and a gate $[x_1, \dots, x_n].[x'_1 \dots x'_m]$ as a transition with an additional marked ‘trigger’ place on the input that makes it fire only once; then, P^* can be represented by connecting the transitions of P to refresh the trigger places. Therefore, strand algebra is equivalent to Petri nets. Still, the algebra provides a compositional language for describing such nets, where the gates/transitions are consumed resources.

Finite State Automata

We assume a single copy of the FSA and of the input string. An FSA state is represented as a signal X . The transition matrix is represented as a set of terms $([X,x].[X',\tau])^*$ in parallel, where X is the current state, x is from the input alphabet, X' is the next state, and τ is a signal used to synchronize with the input. For non-deterministic transitions there will be multiple occurrences of the same X and x . The initial state $X_0 \mid \tau$ is placed in parallel with those terms. An input string x_1, x_2, x_3, \dots is encoded as $\tau.[x_1, y_1] \mid [y_1, \tau].[x_2, y_2] \mid [y_2, \tau].[x_3, y_3] \mid \dots$ for fresh y_1, y_2, y_3, \dots .

Interacting Automata

Interacting automata [4] (a stochastic subset of CCS [11]) are finite state automata that interact with each other over synchronous stochastic channels. An interaction can happen when two automata choose the same channel c_r , with rate r , one as input ($?c_r$) and the other as output ($!c_r$). Intuitively, these automata ‘collide’ pairwise on complementary exposed surfaces (channels) and change states as a result of the collision. Figure 9 shows two such automata, where each diagram represents a population of identical automata interacting with each other and with other populations (see [3] for many examples). Interacting automata can be faithfully emulated in stochastic strand algebra by generating a binary join gate for each possible collision, and by choosing stable population sizes that produce the prescribed rates. The translation can cause an n^2 expansion of the representation [4].

A system of interacting automata is given by a system E of equations of the form $X = M$, where X is a species (an automaton state) and M is a molecule of the form $\pi_1; P_1 \oplus \dots \oplus \pi_n; P_n$, where \oplus is stochastic choice among possible interactions, P_i are multisets of resulting species, and π_i are either delays τ_r , inputs $?c_r$, or outputs $!c_r$ on a channel c at rate r . For example, in an E_1 population, an automaton in state A_1 can collide by $!a_r$ with an automaton in state B_1 by $?a_r$, resulting in two automata in state A_1 :

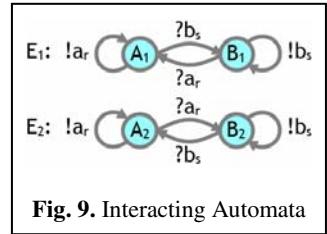


Fig. 9. Interacting Automata

$$E_1: A_1 = !a_r.A_1 \oplus ?b_s.B_1 \quad E_2: A_2 = !a_r.A_2 \oplus ?a_r.B_2$$

$$B_1 = !b_s.B_1 \oplus ?a_r.A_1 \quad B_2 = !b_s.B_2 \oplus ?b_s.A_2$$

With initial conditions $A_1^n \mid B_1^m$ (that is, n automata in state A_1 and m in state B_1), the Continuous Time Markov Chain semantics of [4] prescribes the propensities of the interactions. On channel a_r , in E_1 the propensity is $n \times m \times r$, while in E_2 , with two symmetric $?/!$ ways for A_2 to collide with A_2 , the propensity is $2 \times (n \text{ choose } 2) \times r = n \times (n-1) \times r$:

$$A_1^n | B_1^m: (a_r) A_1^n | B_1^m \rightarrow^{n \times m \times r} A_1^{n+1} | B_1^{m-1} \quad A_2^n | B_2^m: (a_r) A_2^n | B_2^m \rightarrow^{n \times (n-1) \times r} A_2^{n-1} | B_2^{m+1}$$

$$(b_s) A_1^n | B_1^m \rightarrow^{n \times m \times s} A_1^{n-1} | B_1^{m+1} \quad (b_s) A_2^n | B_2^m \rightarrow^{m \times (m-1) \times s} A_2^{n+1} | B_2^{m-1}$$

Subsequent transitions are computed in the same way. One can also mix E_1, E_2 populations.

The translation of interacting automata to strand algebra is as follows. $E.X.i$ denotes the i -th summand of the molecule associated to X in E ; $\langle\langle \dots \rangle\rangle$ and \cup denote multisets and multiset union to correctly account for multiplicity of interactions; and $Parallel(S)$ is the parallel composition of the elements of multiset S . $Strand(E)$ is then the translation of a system of equations E , using the stable buffered populations $P^{=k}$ described in Section 4, where g_i are the gate rates of i -ary gates (we assume for simplicity that the round-off errors in r/g_i are not significant and that $r/g_i \geq 1$; otherwise one should appropriately scale the rates r of the original system):

$$Strand(E) = Parallel((X.[P])^{=r/g_1} \text{ s.t. } \exists i. E.X.i = \tau_i; P \rangle \cup \\ \langle\langle ([X,Y].[P,Q])^{=r/g_2} \text{ s.t. } X \neq Y \text{ and } \exists i,j,c. E.X.i = ?c_i; P \text{ and } E.Y.j = !c_i; Q \rangle\rangle \cup \\ \langle\langle ([X,X].[P,Q])^{=2r/g_2} \text{ s.t. } \exists i,j,c. E.X.i = ?c_i; P \text{ and } E.X.j = !c_i; Q \rangle\rangle)$$

The E_1, E_2 examples above, in particular, translate as follows:

$$P_1 = Strand(E_1) = ([B_1, A_1].[A_1, A_1])^{=r/g_2} \mid ([A_1, B_1].[B_1, B_1])^{=s/g_2} \mid P_1 \quad P_2 = Strand(E_2) = ([A_2, A_2].[B_2, A_2])^{=2r/g_2} \mid ([B_2, B_2].[A_2, B_2])^{=2s/g_2} \mid P_2$$

Initial automata states are translated identically into initial signals and placed in parallel. As described in Section 4, a strand algebra transition from global state $A^n \mid B^m \mid ([A,B].[C,D])^{=p}$ has propensity $n \times m \times p \times g_2$, and from $A^n \mid ([A,A].[C,D])^{=p}$ has propensity $(n \text{ choose } 2) \times p \times g_2$. From the same initial conditions $A^n \mid B^m$ as in the automata, we then obtain the global strand algebra transitions:

$$A_1^n \mid B_1^m \mid P_1 \rightarrow^{n \times m \times r/g_2 \times g_2} A_1^{n+1} \mid B_1^{m-1} \mid P'_1 \quad A_2^n \mid B_2^m \mid P_2 \rightarrow^{(n \times (n-1))/2 \times 2r/g_2 \times g_2} A_2^{n-1} \mid B_2^{m+1} \mid P''_2 \\ A_1^n \mid B_1^m \mid P_1 \rightarrow^{n \times m \times s/g_2 \times g_2} A_1^{n-1} \mid B_1^{m+1} \mid P''_1 \quad A_2^n \mid B_2^m \mid P_2 \rightarrow^{(m \times (m-1))/2 \times 2s/g_2 \times g_2} A_2^{n+1} \mid B_2^{m-1} \mid P''_2$$

which have the same propensities as the interacting automata transitions. Here P'_i, P''_i are systems where a buffer has lost one element, but where the active gate populations that drive the transitions remain at the same level as in P_i . We have shown that the stochastic behavior of interacting automata is preserved by their translation to strand algebra, assuming that the buffers are not depleted.

Figure 10 shows another example: a 3-state automaton and a Gillespie simulation of 1500 such automata with $r=1.0$. The equation system and its translation to strand algebra are (take, e.g., $r=g_2=1.0$):

$$A = !a_r.A \oplus ?b_r.B \quad ([A,B].[B,B])^{=r/g_2} \mid \\ B = !b_r.B \oplus ?c_r.C \quad ([B,C].[C,C])^{=r/g_2} \mid \\ C = !c_r.C \oplus ?a_r.A \quad ([C,A].[A,A])^{=r/g_2} \mid \\ A^{900} \mid B^{500} \mid C^{100} \quad A^{900} \mid B^{500} \mid C^{100}$$

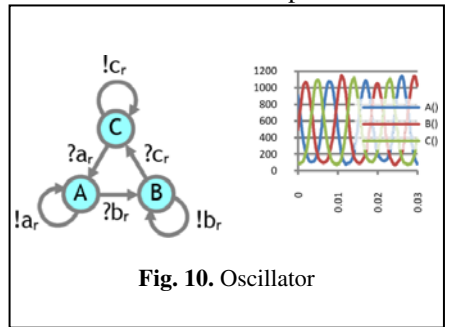


Fig. 10. Oscillator

6 Nested Strand Algebra

The purpose of this section is to allow nesting of join/fork operators in strand algebra, so that natural compound expressions can be written. We provide a uniform translation of

this extended language back to \mathcal{P} , as a paradigm for the compilation of high(er) level languages to DNA strands. Consider a simple cascade of operations, $?x_1.!x_2.?x_3$, with the meaning of first taking an input ('?') x_1 , then producing an output ('!') x_2 , and then taking an input x_3 . This can be encoded as follows:

$$?x_1.!x_2.?x_3 \stackrel{\text{def}}{=} x_1.[x_2,x_0] \mid [x_0,x_3].[]$$

where the right hand side is a set of \mathcal{P} combinators, and where x_0 can be chosen fresh so that it does not interfere with other structures (although it will be used by all copies of $?x_1.!x_2.?x_3$).

The nested algebra $n\mathcal{P}$ admits such nesting of operators in general. The main change from the combinatorial \mathcal{P} algebra consists in allowing syntactic nesting after an input or output prefix. This has the consequence that populations can now be nested as well, as in $?x.(P^*)$. The new syntax is:

$$P ::= x \mid ?[x_1,\dots,x_n].P \mid ![x_1,\dots,x_n].P \mid 0 \mid P_1 \mid P_2 \mid P^* \quad n \geq 1$$

Here $![x_1,\dots,x_n].P$ spontaneously releases x_1,\dots,x_n into the solution and continues as P , while $?[x_1,\dots,x_n].P$ extracts x_1,\dots,x_n from the solution (if they are all available) and continues as P . The mixing relation is the same as in \mathcal{P} . The reaction relation is modified only in the gate rule:

$$\begin{array}{ll} ?[x_1,\dots,x_n].P \mid x_1 \mid \dots \mid x_n \rightarrow P & \text{input gate} \quad (\text{e.g.: } ?x.0 \mid x \rightarrow 0) \\ ![x_1,\dots,x_n].P \rightarrow x_1 \mid \dots \mid x_n \mid P & \text{output gate} \quad (\text{e.g.: } !x.0 \rightarrow x \mid 0) \end{array}$$

We now show how to compile $n\mathcal{P}$ to \mathcal{P} . Let \mathcal{X} be an infinite lists of distinct signals, and \mathfrak{X} be the set of such \mathcal{X} 's. Let \mathcal{X}_i be the i -th signal in the list, $\mathcal{X}_{\geq i}$ be the list starting at the i -th position of \mathcal{X} , $evn(\mathcal{X})$ be the even elements of \mathcal{X} , and $odd(\mathcal{X})$ be the odd elements. Let \mathfrak{X}_P be the set of those $\mathcal{X} \in \mathfrak{X}$ that do not contain any signal that occurs in P . The unnest algorithm $U(P)\mathcal{X}$, for $P \in n\mathcal{P}$ and $\mathcal{X} \in \mathfrak{X}_P$, is shown in Table 6.1–5. The inner loop $U(X,P)\mathcal{X}$ uses X as the trigger for the translation of P .

6.1.1 Unnest Algorithm

$U(P)\mathcal{X}$	$\stackrel{\text{def}}{=} \mathcal{X}_0 \mid U(\mathcal{X}_0,P)\mathcal{X}_{\geq 1}$
$U(X, x)\mathcal{X}$	$\stackrel{\text{def}}{=} X.x$
$U(X, ?[x_1,\dots,x_n].P)\mathcal{X}$	$\stackrel{\text{def}}{=} [X,x_1,\dots,x_n].\mathcal{X}_0 \mid U(\mathcal{X}_0,P)\mathcal{X}_{\geq 1}$
$U(X, ![x_1,\dots,x_n].P)\mathcal{X}$	$\stackrel{\text{def}}{=} X.[x_1,\dots,x_n,\mathcal{X}_0] \mid U(\mathcal{X}_0,P)\mathcal{X}_{\geq 1}$
$U(X, 0)\mathcal{X}$	$\stackrel{\text{def}}{=} X.[]$
$U(X, P' \mid P'')\mathcal{X}$	$\stackrel{\text{def}}{=} X.[\mathcal{X}_0,\mathcal{X}_1] \mid U(\mathcal{X}_0,P')_{evn}(\mathcal{X}_{\geq 2}) \mid U(\mathcal{X}_1,P'')_{odd}(\mathcal{X}_{\geq 2})$
$U(X, P^*)\mathcal{X}$	$\stackrel{\text{def}}{=} (X.[\mathcal{X}_0,X] \mid U(\mathcal{X}_0,P)\mathcal{X}_{\geq 1})^*$

For example, the translations for $?x_1.[x_2,x_3].?x_4.0$ and $?x_1.(x_2^*)$ are:

$$\begin{aligned} U(?x_1.[x_2,x_3].?x_4.0)\mathcal{X} &= {}_0 \mid [\mathcal{X}_0,x_1].\mathcal{X}_1 \mid \mathcal{X}_1.[x_2,x_3,\mathcal{X}_2] \mid [\mathcal{X}_2,x_4].\mathcal{X}_3 \mid \mathcal{X}_3.[] \\ U(?x_1.(x_2^*))\mathcal{X} &= \mathcal{X}_0 \mid [\mathcal{X}_0,x_1].\mathcal{X}_1 \mid (\mathcal{X}_1.[x_2,\mathcal{X}_1] \mid \mathcal{X}_2.x_2)^* \end{aligned}$$

In $?x_1.(x_2^*)$, activating x_1 once causes a linear production of copies of x_2 . For an exponential growth of the population one should change $U(X,P^*)\mathcal{X}$ to produce $(X.[\mathcal{X}_0,X,X] \mid U(\mathcal{X}_0,P^*)\mathcal{X}_{\geq 1})^*$. In the nested algebra we can also easily solve systems of recursive definitions; for example: ‘ $X = (?x_1.X \mid !x_2.Y)$ and $Y = ?x_3.(X \mid Y)$ ’ can be written as: ‘ $(?X.(?x_1.X \mid !x_2.Y))^* \mid (?Y.?x_3.(X \mid Y))^*$ ’.

As an example, consider a coffee vending machine controller, $Vend$, that accepts two coins for coffee. An ok is given after the first coin and then either a second coin (for coffee) or an abort (for refund) is accepted:

$$\begin{aligned} Vend &= ?coin. ![ok,mutex]. (Coffee \mid Refund) \\ Coffee &= ?[mutex,coin]. !coffee. (Coffee \mid Vend) \\ Refund &= ?[mutex,abort]. !refund. (Refund \mid Vend) \end{aligned}$$

Each $Vend$ iteration spawns two branches, $Coffee$ and $Refund$, waiting for either coin or abort. The branch not taken in the mutual exclusion is left behind; this could skew the system towards one population of branches. Therefore, when the $Coffee$ branch is chosen and the system is reset to $Vend$, we also spawn another $Coffee$ branch to dynamically balance the $Refund$ branch that was not chosen; conversely for $Refund$.

7 Contributions and Conclusions

We have introduced strand algebra, a formal language based on a simple relational semantics that is equivalent to place-transition Petri nets (in the current formulation), but allows for compositional descriptions where each component maps directly to DNA structures. Strand algebra connects a simple but powerful class of DNA system to a rich set of techniques from process algebra for studying concurrent systems. Within this framework, it is easy to add operators for new DNA structures, or to map existing operators to alternative DNA implementations. We show how to use strand algebra as an intermediate compilation language, by giving a translation from a more convenient syntax. We also describe a stochastic variant, and a technique for maintaining stable buffered populations to support indefinite and unperturbed computation.

Using strand algebra as a stepping stone, we describe a DNA implementation of interacting automata that preserves stochastic behavior. Interacting automata are one of the simplest process algebras in the literature. Hopefully, more advanced process algebra operators will eventually be implemented as DNA structures, and conversely more complex DNA structures will be captured at the algebraic level, leading to more expressive concurrent languages for programming molecular systems.

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References

1. Benenson, Y., Paz-Elizur, T., Adar, R., Keinan, E., Livneh, Z., Shapiro, E.: Programmable and Autonomous Computing Machine made of Biomolecules. *Nature* 414(22) (November 2001)
2. Berry, G., Boudol, G.: The Chemical Abstract Machine. In: Proc. 17th POPL, pp. 81–94. ACM, New York (1989)
3. Cardelli, L.: Artificial Biochemistry. In: Condon, A., Harel, D., Kok, J.N., Salomaa, A., Winfree, E. (eds.) *Algorithmic Bioprocesses*. Springer, Heidelberg (2009)
4. Cardelli, L.: On Process Rate Semantics. *Theoretical Computer Science* 391(3), 190–215 (2008)
5. Cardelli, L., Qian, L., Soloveichik, D., Winfree, E.: Personal communications
6. Danos, V., Laneve, C.: Formal molecular biology. *Theoretical Computer Science* 325(1), 69–110 (2004)
7. Fournet, C., Gonthier, G.: The Join Calculus: a Language for Distributed Mobile Programming. In: Barthe, G., Dybjer, P., Pinto, L., Saraiva, J. (eds.) *APPSEM 2000*. LNCS, vol. 2395, p. 268. Springer, Heidelberg (2002)
8. Hagiya, M.: Towards Molecular Programming. In: Ciobanu, G., Rozenberg, G. (eds.) *Modelling in Molecular Biology*. Springer, Heidelberg (2004)
9. Kari, L., Konstantinidis, S., Sosf, P.: On Properties of Bond-free DNA Languages. *Theoretical Computer Science* 334(1-3), 131–159 (2005)
10. Marathe, A., Condon, A.E., Corn, R.M.: On Combinatorial DNA Word Design. *J. Comp. Biology* 8(3), 201–219 (2001)
11. Milner, R.: *Communicating and Mobile Systems: The π -Calculus*. Cambridge University Press, Cambridge (1999)
12. Qian, L., Winfree, E.: A Simple DNA Gate Motif for Synthesizing Large-scale Circuits. In: Proc. 14th International Meeting on DNA Computing (2008)
13. Reisig, W.: *Petri Nets: An Introduction*. Springer, Heidelberg (1985)
14. Regev, A., Panina, E.M., Silverman, W., Cardelli, L., Shapiro, E.: BioAmbients: An Abstraction for Biological Compartments. *Theoretical Computer Science* 325(1), 141–167 (2004)
15. Sakamoto, K., Kiga, D., Komiya, K., Gouzu, H., Yokoyama, S., Ikeda, S., Sugiyama, H., Hagiya, M.: State Transitions by Molecules. *Biosystems* 52, 81–91 (1999)
16. Seelig, G., Soloveichik, D., Zhang, D.Y., Winfree, E.: Enzyme-Free Nucleic Acid Logic Circuits. *Science* 314(8) (2006)
17. Soloveichik, D., Seelig, G., Winfree, E.: DNA as a Universal Substrate for Chemical Kinetics. *DNA14*
18. Yin, P., Choi, H.M.T., Calvert, C.R., Pierce, N.A.: Programming Biomolecular Self-assembly Pathways. *Nature* 451, 318–322 (2008)
19. Yurke, B., Mills Jr., A.P.: Using DNA to Power Nanostructures. *Genetic Programming and Evolvable Machines* archive 4(2), 111–122 (2003)
20. Zhang, D.Y., Turberfield, A.J., Yurke, B., Winfree, E.: Engineering Entropy-driven Reactions and Networks Catalyzed by DNA. *Science* 318, 1121–1125 (2007)