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A DNA superstructure-based replicator without product inhibition

DAVID Y. ZHANG[1,*] and BERNARD YURKE[2]
[1]*Caltech M/C 136-93, California Institute of Technology, Pasadena, California, 91125, USA;* [2]*Bell Laboratories, 600 Mountain Ave., Murray Hill, NJ, 07974, USA*
*(*Author for correspondence, Fax: +1-626-584-0630 E-mail: dzhang@dna.caltech.edu)*

Abstract. A monomer structure based on a hairpin loop is described that can be linked via short oligonucleotide sequences (linkers) to form polymers. Independence of linked monomers allow for exponential complexity of the polymer structure. A method is described wherein the polymer structure can be replicated semi-conservatively with fidelity, given a source of monomer structures and linkers. Furthermore, the separation of the product from the parent allows for exponential amplification. These steps are achieved by secondary structure constraints and toehold-mediated strand displacement, and occur in the absence of enzymes. The parallel polymerization allows for replication to be achieved in O(log N) time, as opposed to O(N) from a processive process.

Key words: DNA based polymers, DNA motors, self-replication

1. Introduction

The ability to reproduce is one of the defining characteristics of life. This ability arises from a process by which DNA serves as its own template to make copies of itself (Alberts 2003). There is considerable interest in the construction of synthetic systems that are also capable of template-directed replication (Wintner et al. 1994). For our purposes synthetic systems will denote systems that do not take advantage of biologically derived and evolutionarily advanced enzymes, such as polymerases, to achieve replication of nucleic acids. Much of the interest in synthetic replication systems comes from the insights they may provide on how life originated or functions (Penrose 1959; Orgel 1995). There is interest also from the point of view of what template replication may have to offer for manufacturing. Replication by living organisms is an exponential growth process. In a manufacturing setting this kind of replication would allow for easy scale-up of

the volume of units produced. Another feature exhibited by living organisms is that the replication process is not perfect. This allows for Darwinian evolution. The power of directed evolution has been exploited in research and manufacturing settings (Bull and Wichman 2001). Error-prone synthetic replicators may also allow for the directed evolution of useful products.

A number of synthetic chemical systems have been constructed which exhibit template-directed replication (Johnston et al. 2001) or self-replication in oligonucleotide-based systems (von Kiedrowski 1986; Zielinski and Orgel 1987; von Kiedrowski et al. 1991; Achilles and von Kiedrowski 1993; Li and Nicolaou 1994; Sievers and von Kiedrowski 1994; Martin et al. 1997; Sievers and von Kiedrowski 1998; Schoneborn et al. 2001), peptide-based systems (Lee et al. 1996; Severin et al. 1997; Severin et al. 1998; Yao et al. 1998; Saghathelian et al. 2001), and other chemical systems (Tjivikua et al. 1990; Fang et al. 1992; Hong et al. 1992; Terfort and von Kiedrowski 1992; Pieters et al. 1994; Reinhoudt et al. 1996; Wang and Sutherland 1997). A characteristic problem of these systems is that the product remains bound to the template or competes with monomers for binding with the template. Such systems exhibit sublinear parabolic $O(\sqrt{N})$ growth rather than exponential growth. The replication process tends to stall as the concentration of product increases.

Exponential growth is a prerequisite for selection in the Darwinian sense (Szathmary and Gladkih 1989; Wills et al. 1998). The sub-exponential growth exhibited by these systems is thus nonconducive to Darwinian evolution. Recently a self-replicating system based on a ligase ribozyme has been constructed (Paul and Joyce 2002) that, at least, at early times exhibits exponential growth.

Recently exponential growth has also been demonstrated for a system employing a stepwise 'feeding' procedure and immobilization of the product on a support (Luther et al. 1998). In this system a template is immobilized on a solid support. Fragments of the product that bind to the template are introduced. The fragments are then ligated together to produce the product. Next, a denaturing step releases the product which is then immobilized on fresh solid support. The problem of the binding of a template with its product is thus overcome by immobilization.

Various DNA-based nanostructures (Chen and Seeman 1991; Seeman 1998; Winfree et al. 1998; Mao et al. 1999a; LaBean et al. 2000; Mao et al. 2000; Seeman 2003) and nanomachines (Mao et al. 1999b; Yurke et al. 2000; Simmel and Yurke 2001; Li and Tan 2002;

Simmel and Yurke 2002; Yan et al. 2002; Alberti and Mergny 2003; Feng et al. 2003) have been constructed. For a recent review see Seeman (2003). This suggests that DNA may be a suitable medium for the construction of synthetic replicators. Most of the DNA-based nanomachines that have been constructed (Yurke et al. 2000; Simmel and Yurke 2001; Li and Tan 2002; Simmel and Yurke 2002; Yan et al. 2002; Alberti and Mergny 2003; Feng et al. 2003) to date use the energy of hybridization to activate the machines. In addition, strand displacement through competitive binding mediated by toeholds is generally used to return the machine to its initial state. The operation of these machines involves stepwise feeding and, hence, are clocked in the sense that an external operator controls when the machine advances to its next state through the addition of the appropriate DNA strand to the solution containing the machines.

Here we present a design for a clocked replicator utilizing the energy of hybridization to pull the template-replicated product from the template, to allow for exponential growth. Toehold-mediated strand displacement is used to clear the spent replication machinery from the template and the product to prepare for the next round of template replication. The replication process proceeds in a clocked manner in which the replication process is sequenced through a series of steps via the addition of DNA strands in an appropriate sequence. In the discussion that follows, it will be assumed that the DNA strands are added in slight excess to facilitate the quick completion of reactions. The unreacted excess in each step does not influence the outcome of the procedure, since they are consumed by further excesses in the next stage.

It is argued that the replication scheme we propose is not stalled by product-template binding and can exhibit exponential growth in the presence of abundant monomer concentration. If the template-directed replication process is made a bit faulty this system could, in principle, be subjected to directed evolution.

2. The superstructure polymer

The superstructure polymer (*superduplex*) to be replicated is composed of two *superstrands* of polymers S_1 and S_2, much as duplex DNA is composed of two strands. Each superstrand in turn is composed of serially linked monomer *superbases* (see Figure 1). However, unlike DNA, the two superstrands are not identical.

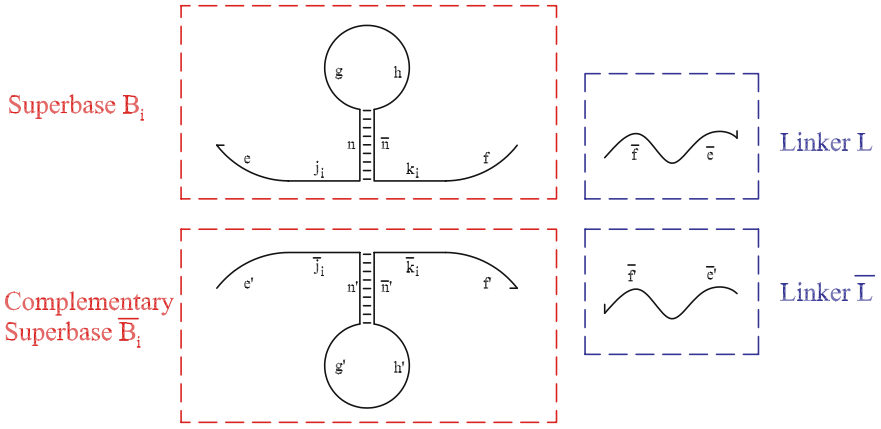

Figure 1. The monomer superbases and the linker strands.

Each different superbase B_i on superstrand S_1 is a single DNA oligonucleotide strand with a hairpin structure. The information-containing regions of the superbase B_i are the domains j_i and k_i. The complementary regions n and $\bar{n}$ form the stem of the hairpin that defines the structure of the free monomer superbase. Domains g and h form the loop of the hairpin, and are used for separating the two parental superstrands during replication. The dangling domains e and f serve to link to adjacent superbases to form the superstrand polymer (see Figure 2).

The i subscript of the superbase B_i refers to its identity, not its position in the superstrand. For example, B_1 could represent the superstructure analog of the DNA nucleotide base thymine, while B_2 represents cytosine.

Each superbase B_i on superstrand S_1 has a unique complementary superbase $\bar{B}_i$ on superstrand S_2 to which it binds perfectly. The complementary superbase $\bar{B}_i$ is very similar to B_i, possessing also a hairpin structure, two information domains (which are necessary complementary to the corresponding ones on B_i), and two linking domains.

The domains e, f, g, h, n, and $\bar{n}$ can be identical for all bases B_i, but are necessarily different for the two superstrands. Arbitrarily, we name the domains on the S_1 strand e, f, g, h, n, and $\bar{n}$, and the corresponding domains on the S_2 strand e', f', g', h', n', $\bar{n}'$. The n' and n domains (and other analogous pairs) are similar only in function and are completely unrelated in sequence. Specifically, they are not com-

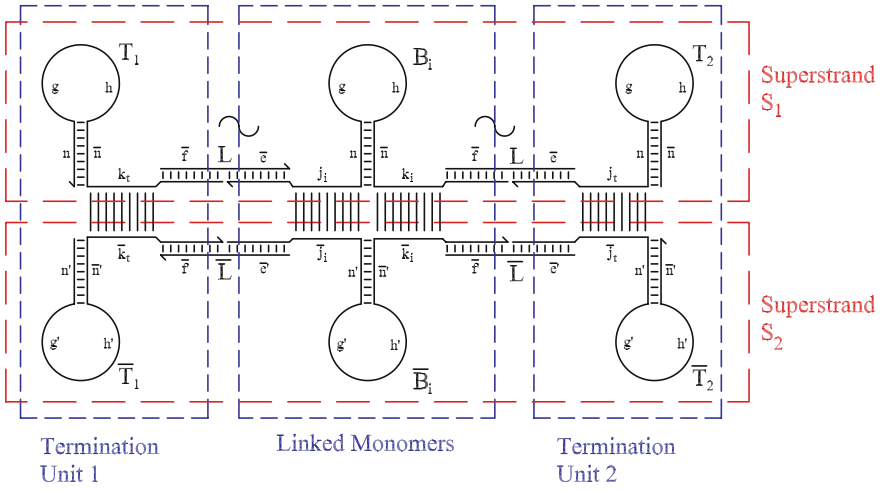

Figure 2. The formed superduplex, composed of two superstrands.

plements; the four-way junctions depicted in Figure 2 are stable. The complement of a domain p is denoted as $\bar{p}$.

The linker strands L and L' serve as the analog of the phosphate bonds which connect consecutive bases of nucleotides in DNA, connecting superbases to form superstrands. L is composed of the domains $\bar{e}$ and $\bar{f}$, complements to the similarly named domains on the superbases of S_1. Similarly, L' is composed of the domains $\bar{e}'$ and $\bar{f}'$. Connection of the superbases is effected by the simultaneous binding of the linker strands to two different superbases, as shown in Figure 2.

Figure 2 also show four special monomers, T_1, $\bar{T}_1$, T_2 and $\bar{T}_2$, which serve as chain terminators. They are similar to the standard superbase B_i, except they have only one linking domain (e or f), and one information domain (j or k). These special terminators are necessary to prevent the random saltation of monomers onto the ends of the parental superstrands during the replication process.

With the given structure of the superbases and the linkers, it is worthwhile to point out that monomers may cyclize as in Figure 3. This feature of the system will actually be useful during the replication process, in inactivating excess monomers.

Binding of the two superstrands S_1 and S_2 is specific, due to the recognition domains j, k, $\bar{j}$, and $\bar{k}$. However, just as with DNA, two superstrands that are mostly complementary can associate despite the presence of a few mismatches. Also, just as with DNA, the binding of a single superbase with its complement should not be irreversibly

strong. Thus, information domains j and k should be short, on the order of five bases.

3. The replication process

An overview flowchart of the replication process is shown in Figure 4. As can be seen, the process can be compartmentalized into five distinct steps, each triggered by the manual addition of one set of DNA strands. For the purposes of this section, we will only consider what happens in the proper function of the replication process, under perfect stochiometric conditions. Considerations for excess reagents will be made in the Discussions section.

Replication involves the use of a "motor" apparatus, the components of which are depicted in Figure 5. There are seven different oligonucleotide strands involved, labeled X, X', Y, Y', Z, Z', and M. The strands X and X' associate with the double-superstranded polymer that is to be replicated first, and then the two parental strands are separated physically with the use of effector strands M. Strands Y, Y', Z, and Z' serve to detach the X and X' strands after the replication process is complete so that a new round of replication may begin. At the end of a replication cycle, each instance of X is bound to Y, Z, and M, and the resulting $XYZM$ complex is a fully doubled-stranded inert waste product. Similarly, $X'Y'Z'M$ is also formed, and also inert.

The hybridization energy of the m and $\bar{m}$ domains on the motor strands provide the driving force that serves to pull the two parental

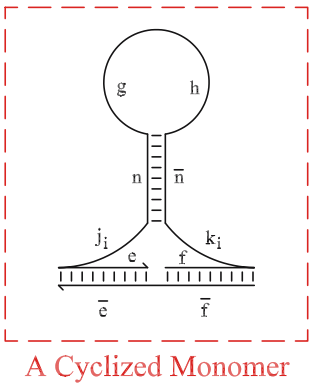

Figure 3. A cyclized monomer.

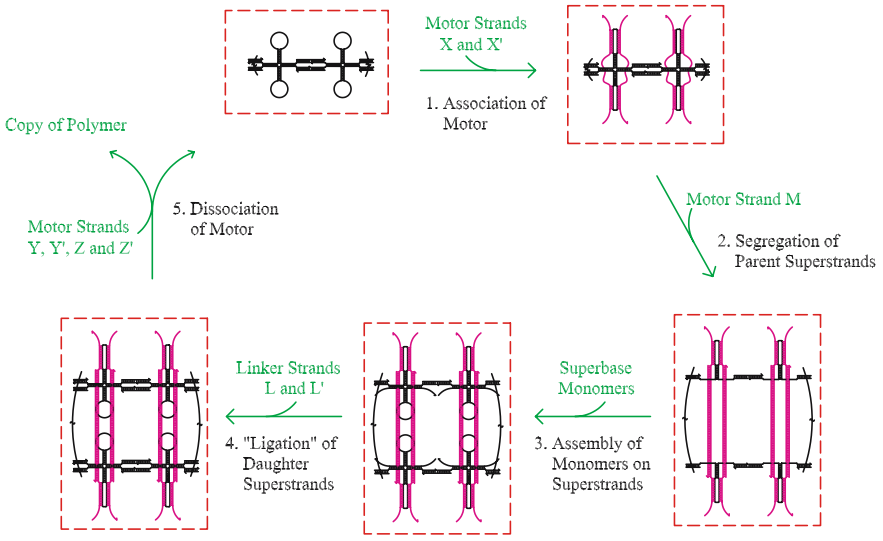

Figure 4. Flowchart of the replication process.

strands apart, and necessarily must be long, at very minimum longer than the sum of the lengths of the j and k information domains of the superbases.

3.1. *Step 1: association of the motor apparatus*

The first step, the association of the motor apparatus, is triggered by the external addition of the X and X' strands. They associate with the superduplex as in Figure 6.

The hybridization of the X and X' domains to their respective complements on the loop region are relatively straightforward. The loop region itself is geometrically constrained, but both X and X' are single-stranded, and can wind around the loop to form the double-helix of the g, g', h, and h' domains.

This step of the replication cycle is the one most prone to error, since each motor strand X (or X') must simultaneously bind two different domains relatively far from each other. Figure 6 shows the correct, and only one of many possible, ways for the X and X' strands to associate with the superstrands.

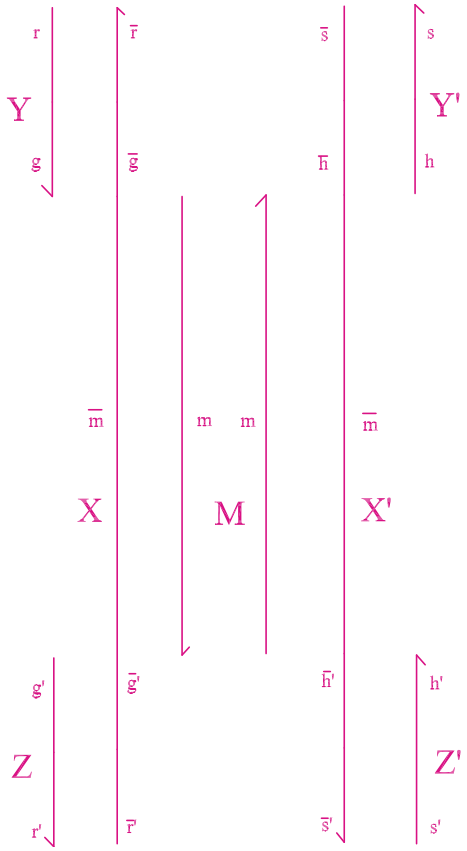

Figure 5. The motor apparatus that effects the separation of the two parent superstrands.

One possibility of error is that an X strand with its 3′ end bound to the $\bar{g}$ of B_i might bind to $\bar{g}'$ of $\bar{B}_j$, rather than the corresponding domain on $\bar{B}_i$. This type of error can be arbitrarily disfavored by adjusting the relative lengths of the m, e, and f domains.

Another possibility of error is that of dimerization and aggregation. This occurs when an X strand simultaneously binds to both the g domain of an S_1 superstrand and the g' domain of an S_2 superstrand on a different superduplex. If this occurs, then the two superduplexes would be tethered together, causing unwanted reactions in later steps. We propose no universal solution to this problem, but note that this is unlikely to happen when the concentration of the superduplexes is low. As the concentration of the superduplex

increases through repeated rounds of replication, this effect may set the upper limit on production.

The loop formed by the single-stranded *m* domain can be either in front of or behind the linker duplex. The two configurations are energetically equal, and thus approximately half of the loops will be behind the duplex. The position of the *m* loops does not matter for the replication process.

3.2. *Step 2: segregation of the parent superstrands*

Upon the addition of the *M* strands, the *m* domains bind to the $\bar{m}$ domains on *X* and *X′*. The first few base pairs form normally. However, since duplex DNA adopts a double-stranded structure with substantial persistence length (on the order of 40nm, or 120 base pairs),

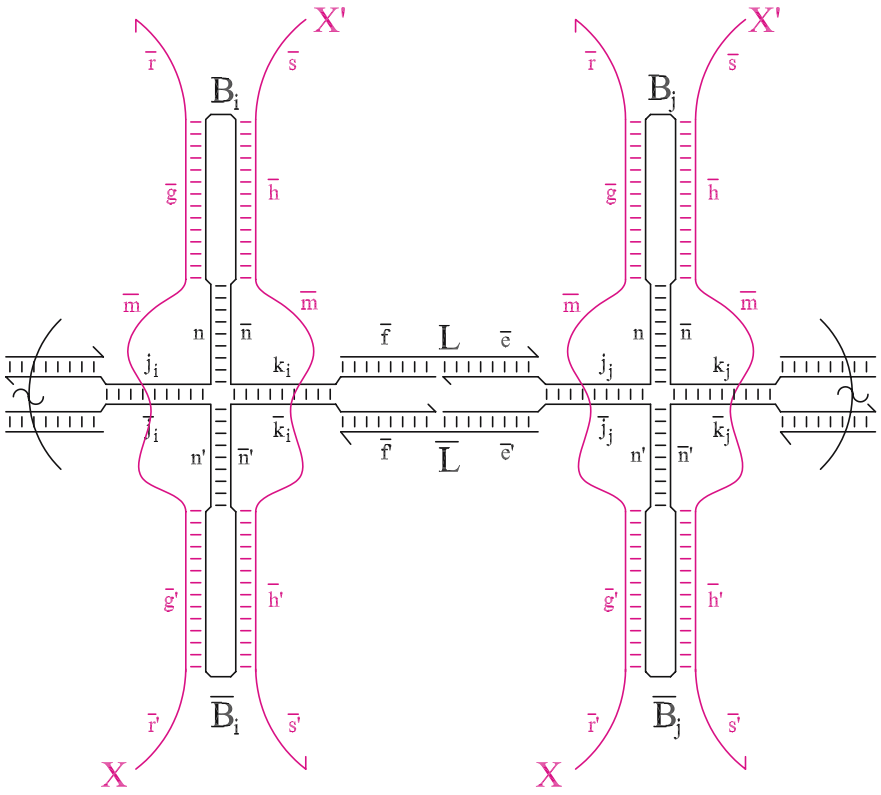

Figure 6. The superduplex after the addition of the motor strands *X* and *X′*.

as more base pairs form along the m domain, superstrands S_1 and S_2 are forced apart.

The free energy gained by the hybridization of the base pairs of m to $\bar{m}$ favor the segregation of the parent strands, while the already formed base pairs of the information domains j and k oppose this. Due to the geometry of the system, every base pair formed in the m domain by X and X' will break one base pair of either j or k domains. Thus, this stage is an unbiased random walk, just as normal branch migration is.

The segregation of the parent superstrands is favored by making the m domain much longer than the j and k domains, so that j and k are kept physically far away from $\bar{j}$ and $\bar{k}$, and no reverse reaction is possible. As mentioned previously, j and k should be on the order of five bases. The length of domain m is recommended to be on the order of 30 bases; this choice is in consideration of making the critical Euler buckling force larger than the force required to pull a base pair apart, so that separation is favored over the motor domain $m\bar{m}$ developing a kinked structure.

The actual hybridization of the M strand to the X and X' strands is a simple DNA hybridization process that is unlikely to encounter errors, assuming that the X and X' strands had associated with the superduplex correctly in the previous step.

3.3. *Step 3: assembly of monomers on parental superstrands*

Following the segregation of the two parent superstrands, superbase monomers of both B and $\bar{B}$ types are added. These will seek out their complements on the separated parent superstrands, and bind transiently by the information domains j and k, as shown in Figure 8.

The chance of error on this step is low, because the two domains by which the monomers bind (j and k) are both weak. The large loop entropy of bridging over a distance to bind two different superbases will destabilize the thermodynamics enough to cause the monomer superbase to spontaneously dissociate from its erroneous binding.

3.4. *Step 4: "ligation" of daughter superstrands*

Since the appropriate sequence of monomers has already been assembled on both parental superstrands, all that remains in finishing the

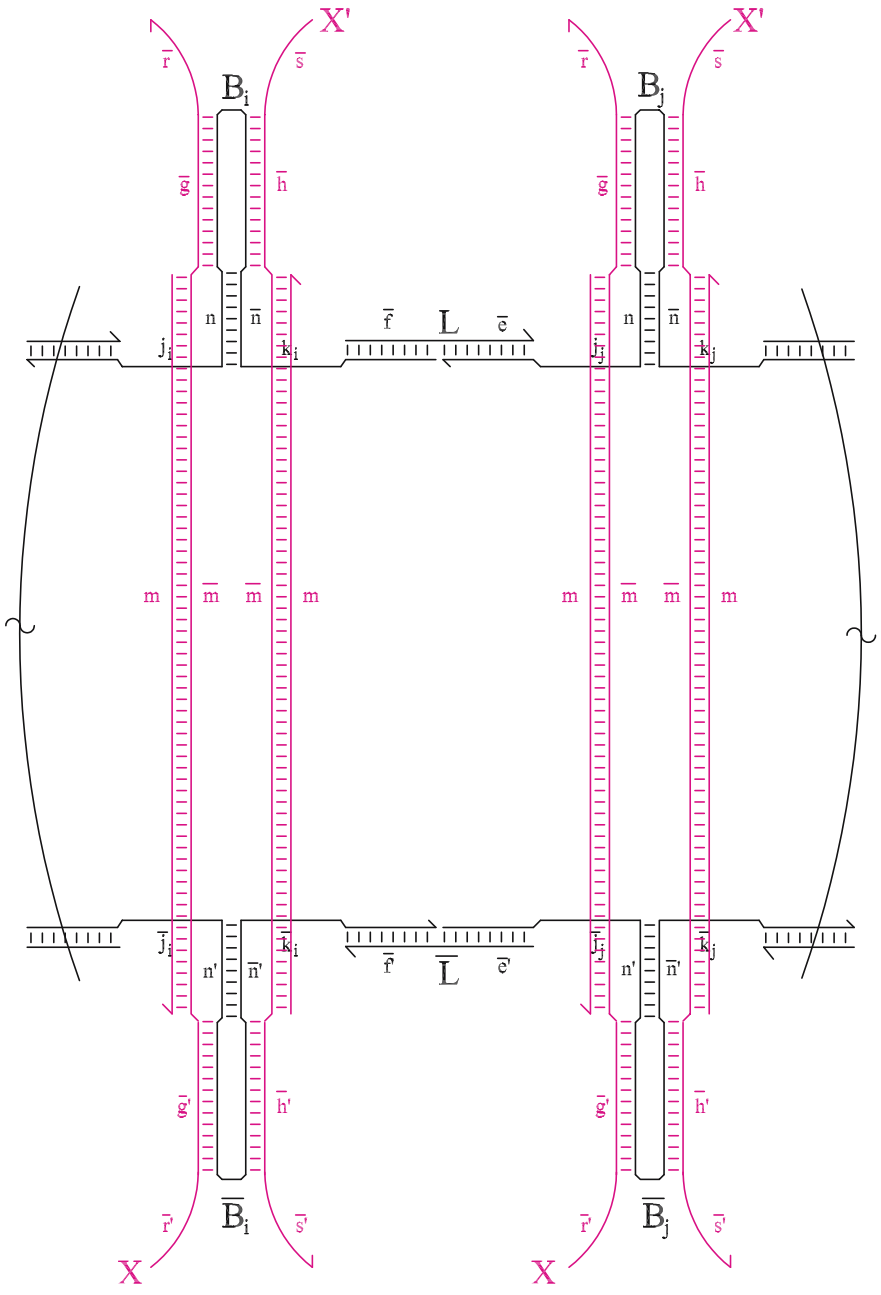

Figure 7. Pulling apart the two superstrands.

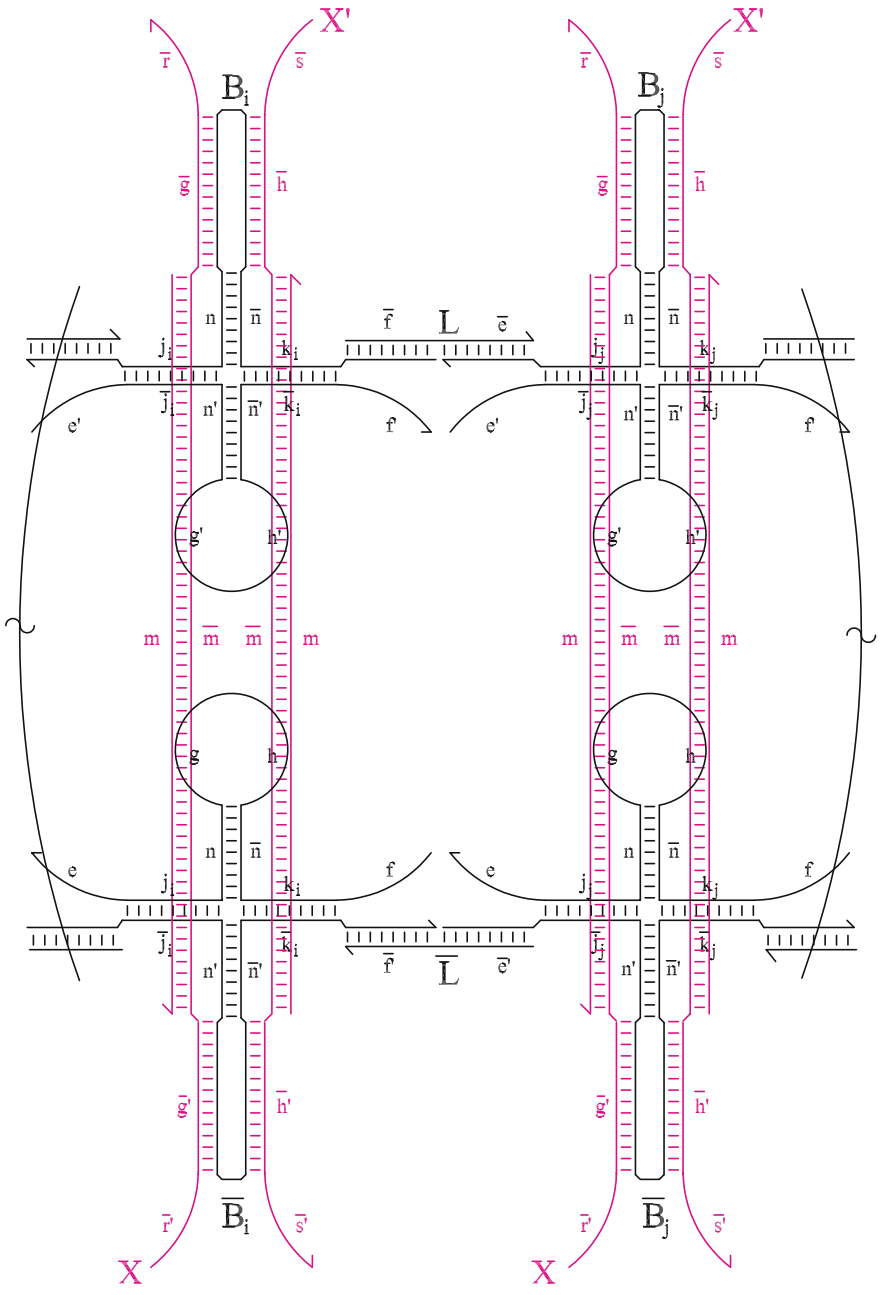

Figure 8. Parental superstrands direct the binding of the appropriate monomers for forming daughter superstrands.

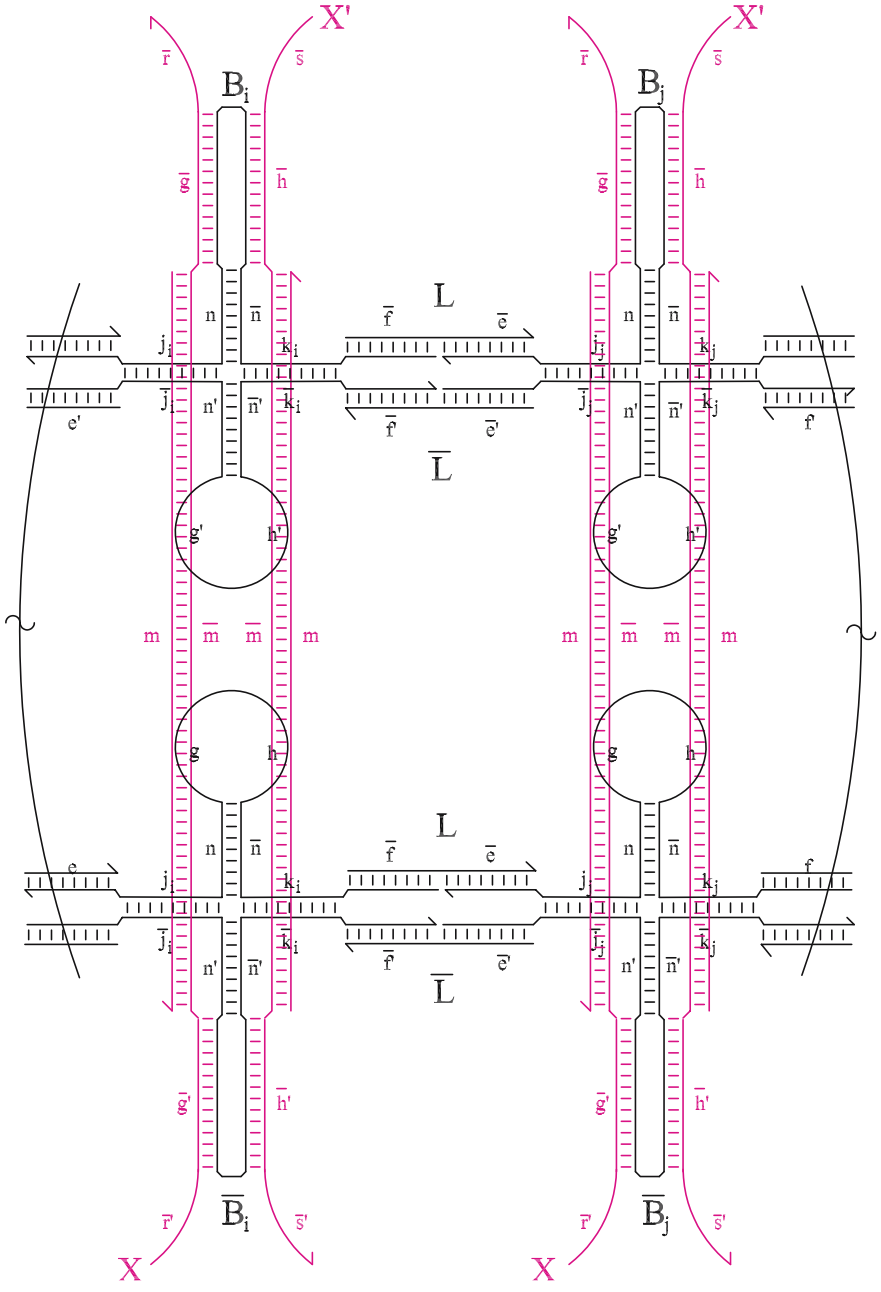

Figure 9. Addition of L and L' linker strands ligate the assembled monomers bound to the two parental superstrands, forming daughter superstrands.

replication step is to ligate them into a new superstrand. Ligation, as used in this paper, does not refer to the formation of covalent bonds using the biologically derived enzyme ligase. Rather, we use the linker strands L and L' to act as permanent splints, which join connected superbases. See Figure 9.

We do not wish for the ligated superstrands to dissociate spontaneously within the lifetime of the reaction; therefore the linking domains e and f should be reasonably long, on the order of 20 base pairs each.

The process of "ligating" the monomers is a straight-forward hybridization reaction. The f and e domains of adjacent monomers are held to fairly close proximity, so the chance of incorrect binding by the linker strands is low.

3.5. *Step 5: dissociation of the motor apparatus*

The process of replication is complete by this point; we started with two parental superstrands, and we now have two additional daughter superstrands. Just as DNA, replication was semi-conservative; each of the superduplexes contain one parental strand and one daughter strand.

All that remains to be done in this step is to remove the motor apparatus and separate the two superduplexes to allow another round of replication. This is achieved with the addition of the four motor removal strands Y, Y', Z, and Z'. All four function similarly, so only the process for Y will be described.

First, a molecule Y binds to every instance X via the toehold domain r. This allows the Y strand to be localized near the X strand, greatly increasing the effective concentration. A simple branch migration process occurs, until Y is bound to X by the entirety of the g domain as well, at which point strand X is no longer constrained to be near the loop region of B_i, and no reverse reaction is possible.

Upon the completion of this step, the system is restored to its original state, shown in Figure 10. There are a number of inert $XYZM$ and $X'Y'Z'M$ duplexes, and twice the number of superduplex polymers as from the beginning of the replication cycle.

Toehold-mediated branch-migration used in this step is well characterized and extensively tested in the laboratory; thus it is not likely for an error to occur.

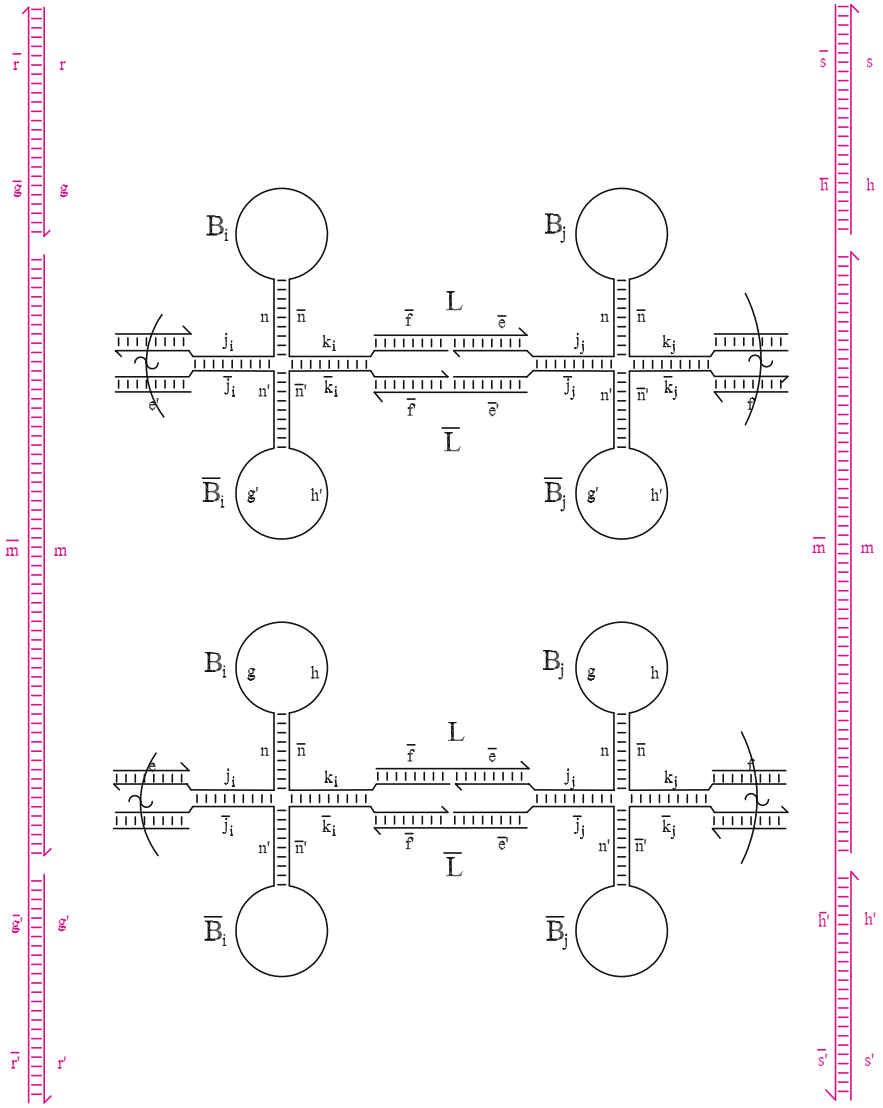

Figure 10. Addition of Z and Z' strands cause the motor to detach from the superstructure, releasing two identical daughter superduplexes.

3.6. *Excess clean-up*

Optionally, an excess clean-up step can be inserted before starting another replication cycle. Though probably not necessary for short procedures, it may be needed if the number of cycles is large since the

accumulation of excess strands may substantially alter the kinetics and fidelity of the replication. See the Discussion section for details.

4. Discussion

4.1. *Stochiometric issues*

Addition of reagents at every step of the replication process should be in slight excess. This is necessary for two purposes: First, experimentally it is not possible to achieve perfect stoichiometry. Second, perfect 1:1 stoichiometry would cause most reactions to possess second-order kinetics, rather than first-order kinetics in the case of excesses. Excesses serve to speed up the replication process considerably.

We consider the effects of having excess DNA strands in solution during each of the steps:

Step 1: the strands being added are X and X'. Excess X and X' will float in solution, since no other binding sites for them are available.

Step 2: the strand being added is M. Excess M will bind to the excess X and X' from Step 1, and form XM and $X'M$, with some leftover M.

Step 3: the strands being added are superbase monomers B and $\bar{B}$. XM and $X'M$ formed in excess reactions of Step 2 may bind to either the assembling or the excess monomers on the loop domains g, g', h, or h'. This will have no substantial effect other than possible slowing of the kinetics of the ligation of Step 4 due to steric hindrance. Excess B and M are inert.

Step 4: the strands being added are L and L'. Excess L and L' will cause excess monomers B and $\bar{B}$ from Step 3 to cyclize (see Figure 3), inactivating them from further reaction.

Step 5: the strands being added are Y, Y', Z, and Z'. Excess of Y, Y', Z, and Z' will displace the improperly bound XM and $X'M$ on the daughter strands, from Step 3, and form the inert $XYZM$ and $X'Y'Z'M$.

At the end of a replication cycle, the excesses that remain are M, Y, Y', Z, Z', L, L', cyclic B, and cyclic B'.

Cyclic B and cyclic B', as mentioned before, are inert. L and L' will inactivate some of the B and B' monomers by cyclizing them in Step 3 of the next cycle before they assemble on the superstrands, but is otherwise harmless to the replication process.

Excess Y, Y', Z, and Z' will bind to and deactivate the X and X' strands during Step 2 of the next cycle. If only one end of X or X' is deactivated while the other end binds to a superbase, then addition of motor strand M will fail to segregate the parent superstrands at that base, causing non-disjunction. Excess M will bind to X and X' prematurely in Step 1, and favor the dimerization and aggregation described in Section 3.1.

Thus, we must clean up excesses of Y, Y', Z, Z', and M before the next cycle of replication. This can be done by adding excesses of the $\bar{Y}, \bar{Y}', \bar{Z}, \bar{Z}'$, and $\bar{m}$ strands (not shown), which are the full complements of the respective strands. Excesses of $\bar{Y}$, $\bar{Y}'$, $\bar{Z}$, $\bar{Z}'$, and $\bar{m}$ will do nothing except inactivate some of their respective complements in the next cycle.

4.2. *Parallel assembly*

The assembly of monomer superbases onto the parent superstrands is parallel, rather than serial. Polymerization is not processive – the failure of a monomer to bind at a position will lead to two truncated fragments, rather than one. There is no clear indication of whether the system is ready to proceed onto the next step of replication, so fragmentation rate will be higher than that of a system which waits for each base to be assembled before continuing.

The parallel nature of the replication process, however, also allows for faster kinetics. Whereas any serial (processive) replication process requires O(N) time, where N is the number of superbases, parallel assembly decreases the asymptotic time complexity of one replication cycle to O(log N). In the presence of excess monomers, the kinetics of assembly approaches first-order.

This allows for the fast replication of very long sequences of superduplexes.

5. Conclusions

We have described a DNA superstructure-based polymer capable of information storage and its associated mechanism for replication. It resembles DNA in that it is double-superstranded and that its replication is semi-conservative, but it does not require any enzymes for replication. Our replication design possesses a mechanism for parental superstrand segregation so that product inhibition is not a problem.

Thus the system should exhibit amplification exponential in the number of cycles performed. Due to the parallel nature of the assembly process, each cycle of our replication process should take O(log N) time, which is superior to the processive biological methods that take O(N) time.

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