Polyomino-Safe DNA Self-assembly via Block Replacement

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Abstract. The standard abstract model for analyzing DNA self-assembly, aTAM, assumes that single tiles attach one by one to a larger structure. In practice, tiles may attach to each other forming structures called polyominoes and then attach to the assembly using bonds from multiple tiles. Such polyominoes may cause errors in systems designed with only aTAM in mind. In this paper, we first present a formal definition of when one tile system is a "block replacement" of another. Then we present a block replacement scheme for making any system that admits non-trivial block replacement polyomino-safe. In addition, we present a smaller block replacement scheme that makes the Chinese Remainder counter polyomino-safe and prove that the question of whether a system is polyomino-safe (or other similar properties) is undecidable. Finally, we show that applying our polyomino-safe system produces self-healing systems when applied to most self-healing systems.

1 Introduction

Nanotechnology presents obvious and enormous potential. Manipulating objects on that scale explicitly is infeasible though. As a result, the discipline of nano-scale self-assembly has arisen as a means to harness nanotechnology's promise. In a self-assembly model, small components attach to each other using simple local rules, producing large complicated shapes. DNA has two properties that make it a natural tool for self-assembly. First, strands of DNA naturally store strings of data that can be used to identify themselves. Second, for every strand of DNA there is a complementary strand that will attach. Thus, DNA provides a means to generate local rules in which two pieces will want to attach if they have complimentary strands of DNA. In addition, the lab techniques for manipulation of DNA are already well-developed because of their many other applications. As a result of these factors, DNA self-assembly has been used in many nanoscale applications including as a means to perform computation [1,2], to produce patterns [3,4], and to produce nano-scale machines [5,6,7,8,9,10].

One particularly well-studied type of DNA self-assembly is the tile model. Rectangular DNA molecules have been formed that have a piece of single-stranded DNA on each side [11]. An abstract version of their behavior, the

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asynchronous Tile Assembly Model (aTAM), was introduced by Rothemund and Winfree [12]. In this model, we think of each molecule as a *tile* with each of the strands as a *glue*. Each glue has an affinity for itself called its strength (which can be controlled in the lab by changing the length of the strand). In aTAM, assembly starts from a structure consisting of a single tile called the *seed*. One by one, tiles attach to the existing structure under the constraint that a tile may only attach to the system at a location if its glues that match the structure at that location exceed the *temperature*, a parameter of an aTAM system (corresponding to the actual temperature of the solution in which the assembly is taking place). Study of aTAM has led to many interesting tile systems such as counters [13,12,14,15] and systems capable of Turing-universal computation and producing arbitrary computable shapes [16,3,17].

While aTAM is a valuable tool for analyzing tile systems, it does not perfectly match behavior in the laboratory. For example, a tile may attach with a strength lower than the temperature. Such "insufficient attachments" will fall off much more quickly than attachments at the temperature but can persist if another nearby attachment locks them in. The experimental rate for such problems is somewhere between 1% and 10% [18], and a great deal of research has gone into schemes to minimize the effects of these errors [19,20,21,5,18,22,23]. Another problem that can occur is a large portion of an assembly may fall off in the middle of construction. This behavior can cause problems when an assembly intended to grow in one direction is not designed to grow uniquely from other directions. Systems resilient to this problem (called self-healing systems) have been developed for several interesting assembly problems [24,25].

Implicit in most of these error-reduction schemes is the concept of *block replacement*. In block replacement, we start with a tile system that forms some shape we want but has other undesirable properties such as susceptibility to the kinds of errors we described above. We then construct a new system by replacing each tile in the old system by a larger set of tiles. These tiles assemble into a rectangle that functions like the tile they are replacing in the new scheme, and at the same time they locally prevent the problems of the original system from occurring. For example, the block might halt its own formation when an insufficient attachment occurs giving the error time to fall off before it gets locked into the assembly [19,20] or be only able to grow in a desired subset of directions [25]. While the inuition is clear, a precise definition of what should be called a block replacement seems to be absent.

Another assumption aTAM makes is that tiles attach to the existing structure one by one. In practice, there are large numbers of each tile floating around in solution and if two tiles have enough attraction between them to attach independent of the existing structure they will do so. This new supertile or *polyomino* can use the glues from both tiles and may be able to attach to the super-structure in places where neither tile could attach individually. Such a model of assembly was first discussed by Aggarwal et al. [15]. In that paper, they propose what they call the q-tile assembly model, which permits supertiles consisting of q or fewer tiles. In that paper, polyominoes are seen as a tool to potentially produce more efficient tile systems. Similarly, Demaine et al. proposed doing DNA self-assembly in stages [26]; different sets of tiles would be allowed to assemble in different test tubes, and then those test tubes would be mixed so that resultant polyominoes could attach to each other. By doing so, they produced tile systems that could theoretically produce shapes more efficiently than those in single-stage self-assembly. Polyominoes are not a strictly positive effect though. aTAM assumes single tiles attach one by one, but polyominoes may attach using their shared glues in places none of the individual tiles could attach by themselves. As a result, the intended assembly may be derailed. Tile systems not prone to such problems are called *polyomino-safe* and were first discussed by Winfree [24]. In his paper, he proposes a 5×5 block replacement scheme that would make a class of tile systems he calls *transformable* polyomino-safe. The primary requirement for a system to be transformable is that each side of a tile is always either used to attach that tile to the existing assembly or always used as an attachment for future tiles. While many natural tile systems have this property, not all do. In particular, any system that wants to be able to regenerate from more than a single location cannot have this property.

Polyomino tile attachments are not only a possibility, they are frequent enough that some experiments have depended on them [21]. Thus, we need a way to produce polyomino-safety in as much generality as possible.

1.1 Our Results

We begin our paper by presenting the definitions of aTAM, its extension for polyominoes, and block replacement. While there is an intuitive understanding of what a block replacement scheme should do in the literature, a formal expression of this intuition is subtle, and we know of no paper giving a rigorous definition.

Then we develop a 6×6 (slightly larger than Winfree's scheme for transformable systems) block replacement scheme that guarantees polyomino-safety. Our system will work for a class of tile sets we call *block admissible*. This restriction is rather minor as any system failing this requirement not only cannot have a polyomino-safe block replacement scheme but can have no non-trivial block replacement scheme whatsoever. We then show that the Chinese remainder counter is not polyomino-safe and present a 3×1 polyomino-safe block replacement scheme for it. We also show that determining whether a given tile system is polyomino-safe is undecidable. The proof is more generally applicable and can be applied to other important properties of a tile system (such as whether a system is self-healing). Finally, we show that our polyomino-safe block replacement scheme preserves self-healing for any block admissible self-healing tile system.

2 Definitions

The tile assembly model was originally developed by Rothemund and Winfree [12]. Informally, a tile is a square with glues on each side. When the glues of two tiles on corresponding sides match the tiles will want to attach. Here, we present a slightly modified version from the standard.

Formally, let Σ be a set of glues containing a distinguished glue *null*. Let δ denote the set of four directions $\{N, S, E, W\}$, with the inverse of a direction defined naturally. Associate each direction with a unit vector $v_N = (0, 1)$, $v_S = (0, -1)$, $v_E = (1, 0)$, and $v_W = (-1, 0)$ respectively. A tile t is defined by its four glues, one for each direction in δ, denoted $\sigma_i(t)$ for each i in δ, drawn from Σ. We define a *tile system* as a tuple $< T, s, g, \tau >$. Here, T is a set of tiles, s is a distinguished seed tile, g is the *glue function* from $\Sigma \times \Sigma$ to the non-negative integers, and τ is the *temperature*, a positive integer. We assume $g(x, y) = 0$ for $x \neq y$ (glues only attach to themselves) and that $g(null, null) = 0$ (*null* is inert). The standard aTAM model has s in T, but in this paper we will not include s in T. This modification may correspond to the seed being much rarer than the rest of the tiles or the seed being generated by some special unique process. We will use this assumption to preclude two large polyominoes both of which contain the seed from interacting with each other.

A *configuration* for a tile system is a map from $\mathbb{Z} \times \mathbb{Z}$ to $T \cup \{s\} \cup \{empty\}$. Let C and D be two configurations such that C matches D except at (x, y) where C is *empty* and D is some tile $t \in T$. t is *attachable* to C at (x, y) if the sum of its glue functions with the surrounding tiles is at least the temperature: $\sum_{d \in \delta} g(\sigma_d(t), \sigma_{d^{-1}} C((x, y) + v_d)) \geq \tau$. If this is the case we write $C \rightarrow D$. Define a sequence (possibly infinite) of configurations $\{C_i\}$ to be an *assembly sequence* if $C_i \rightarrow C_{i+1}$. We say D is *derivable* from C (denoted $C \rightsquigarrow D$) if there is an assembly sequence beginning at C whose limit is D. The set of *reachable* configurations is the set of configurations derivable from the configuration that is s at $(0, 0)$ and *empty* elsewhere.

We now define the *polyomino Tile Assembly Model* (pTAM) to reflect the possibility of polyominoes interacting during assembly. As in aTAM a tile configuration is a mapping from $\mathbb{Z} \times \mathbb{Z}$ to $T \cup \{s\} \cup \{empty\}$. We define the set of *reachable* configurations in pTAM recursively as follows. All configurations that are a tile from T in a single coordinate or s at $(0, 0)$ and *empty* elsewhere are reachable. Two configurations C and D are *compatible* if at least one of them is *empty* at each coordinate. For two compatible configurations the *composition* is the configuration that takes on C or D's value wherever one of them is non-*empty* and is *empty* elsewhere. Given two reachable, compatible configurations their composition is reachable if

$$\sum_{(x,y)} \sum_{d \in \delta} g(\sigma_d C(x, y), \sigma_{d^{-1}}(D(x, y) + v_d) \geq \tau.$$

In other words, two polyominoes can attach if they overlap nowhere and the sum of the matching glue strengths everywhere they are adjacent exceeds τ. Since all single tile configurations are reachable and the attachment function for pTAM agrees with aTAM in that case, the reachable configurations under aTAM are a subset of the reachable configurations under pTAM. We say that a tile system is *polyomino-safe* if the reachable configurations under aTAM are exactly the reachable configurations under pTAM containing s. That is, we allow arbitrarily complicated polyominoes to form as long as their formation does not alter what configurations are reachable from the seed.

Many papers add a desired property (for example self-healing or reliable stochastic assembly) to a tile system by replacing single tiles with blocks of tiles. The intuition for what such systems should do is very natural, but we know of no paper that writes out a formal definition of what such a construction should achieve. We propose a definition of what it means for a system to be a *block replacement* of another system here.

For two tile systems $X =< T, s, g, \tau >$ and $Y =< T', s', g', \tau' >$ a (m, n)-*blowup function* ϕ is a function from $T \cup \{s\}$ to $(T' \cup \{s'\})^{m \times n}$. Let Φ map a configuration C of X to a configuration $\Phi(C)$ of Y produced by saying that the $m \times n$ block of tiles starting at $(mx + a, ny + b)$ (for some fixed offset (a, b)) is $\phi(C(x, y))$. We say Y is an (m, n)-*block replacement* of X under ϕ if:

1. The image of all reachable configurations in X under Φ are reachable in Y.
2. For any reachable configuration D of Y there are configurations D' in Y and C reachable in X such that $D \rightsquigarrow D'$, $D' = \Phi(C)$, and there is at least one non-*empty* square in D in every block corresponding to a non-*empty* square of C.

Here, the first constraint says that each reachable configuration of X maps to a reachable configuration of Y. The second constraint is in some sense an inverse of the first. It would be too strong a requirement for every reachable configuration of Y to be the image of a reachable configuration of X. Tiles attach one by one in Y, but every tile in X corresponds to multiple tiles in Y. Thus, there must be intermediate configurations that do not correspond perfectly to any configuration of X. Hence, we allow ourselves to grow a configuration of Y until it agrees with something in X. Letting Y grow until it could reach any configuration that matches a configuration of X would be too weak a constraint though. In the extreme case, Y could grow in some arbitrary fashion so long as its terminal configurations match those of X. This case would not match our intuition that Y should have essentially the same growth dynamics as X but with each tile being replaced by several. We would not want to say one system emulated another if the second grows in some completely different direction, and the two systems's assemblies only converged much later. Thus, our definition restricts Y to grow to match X only by finishing blocks it had started.

There may be room for variation in the above definition, but our definition fits with all examples of block replacement we know of in the literature. With the above definition, it may be the case that two systems work the same way when starting from the seed but have divergent behavior when starting from different beginnings. A stronger concept would be a block replacement where if both systems start out in analagous positions they continue analgously regardless of whether or not the original positions were reachable from the seed. We define Y to be a *strong block replacement* of X if:

1. The image of all reachable configurations in X are reachable in Y, and for all configurations C in X, the image of all configurations derivable from C under Φ are derivable from $\Phi(C)$ in Y.
2. For all configurations C in X, for any configuration D such that $\Phi(C) \rightsquigarrow D$ there are C' in X and D' in Y such that $C \rightsquigarrow C'$, $D \rightsquigarrow D'$, $\Phi(C') = D'$, and there is at least one non-empty square in D in every block corresponding to a non-empty square in C'.

3 Universal Block Replacement for Polyomino Safety

In this section we present a strong $(6, 6)$-block replacement scheme for polyomino safety at temperature 2. There are two fundamental barriers to producing such a scheme that cannot be directly overcome. The first problem is the seed. Regardless of what scheme we use, the whole system must be able to form from the seed. Thus, any sub-assembly of the system must be a potential polyomino, so if two sub-assemblies attaching to each other is a potential problem in the original system there is little we can do to fix it. Our approach to this problem is to treat the seed as a special tile that only starts assembly and does not appear in the solution as stated in the definitions. The second problem is that some tile systems can never have a non-trivial block replacement.

3.1 Block Admissibility

There are essentially two reasons a tile system cannot have a non-trivial (larger than $(1, 1)$) block replacement scheme. First, a system can never require a tile to attach using glues on opposite sides (i.e. north and south, or east and west). If such an attachment were required no non-trivial block replacement scheme would be possible. Consider a situation in the original tile system where a tile will attach using its north and south glues. In any block replacement longer than 1 in this dimension, there is no single tile where there is enough information to determine if this tile should attach: the first tile that attaches in this block must attach using either only the north or only the south face, which would be an error if the other side is not present.

The second problem is when two different tiles might be able to attach at the same location but using glues from different sides (e.g one tile could attach using its north and east glues while another tile could attach using its north and west glues). In the original system either one tile or the other would attach first, locking the other tile out. In a block replacement, this process would not be atomic. The first tile for one of the blocks can start attaching on one side or corner while tiles for the other block start attaching somewhere else. The result is that neither of the blocks can form completely, breaking block replacement.

Because no system having either of these two properties can have a meaningful block replacement we call systems where tiles never attach using opposite glues and never allow two different tiles to simultaneously be able to attach at the same location *block admissible*.

Definition 1. *A tile system is block admissible if:*

1. *No tile can ever attach in a way that requires both its north and south glues or its east and west glues.*
2. *It is never possible for two tiles to attach at the same location using glues from different directions.*

In fact, block admissibility is a sufficient condition for polyomino-safe block replacement.

3.2 The Polyomino-Safe Block Replacement Scheme

The workhorse of our construction is the 6×6 block presented in figure 1(a). All glues are unique in the interior of a block. On a face of a block, the glues match the glues on the face of another block if and only if those two faces had the same glue in the original system. If the glue in the original system was strength 1 all glues on the face are strength 1. If it was strength 2, we also make the glue on the third tile strength 2. If the tile was inert we make all the glues strength 0. The block has two useful properties. First, the whole block can form from any complete (non-inert) face and a single tile attached to that face. Second, it is easy to check that the system has no polyominoes larger than size 2 (this even applies for the polyominoes that cross blocks using the strength 2 glues on faces between blocks), and none of these polyominoes have two faces on the exterior of the block. Because the seed block will have no face to grow from, we must use a different construction for the block corresponding to the seed, which we show in figure 1(b). The full block can assemble if the seed tile s is present, but no polyomino of size larger than 2 can assemble otherwise. We handle the glues on the faces as we did previously.

Theorem 1. *The system described above is a polyomino-safe strong* $(6, 6)$*-block replacement scheme for any block admissable tile system.*

Proof. Call the original system X and the system produced by our transformation Y. We first verify that Y is a strong block replacement scheme for X. Given only the seed tile of our block replacement scheme the whole seed block can form, so the image of the seed tile is reachable. Thus, we may start with a configuration of X and its image in Y, and proceed by induction on the length of the assembly sequence. Consider an assembly sequence in X, and assume the image of the kth configuration is derivable. Consider the $(k + 1)$th tile attachment and the image of the location where it would attach in Y. The entire faces corresponding to whatever tiles it used to attach are present. It either attached using a single strength 2 glue or two strength 1 glues. If it used a strength 2 glue in X the face it used has a strength 2 glue in Y, so a first tile of the block can attach and the rest of the block can attach using that face. Similarly, if two strength 1 glues were used in X then a first tile in that block can attach at the corner between the two faces and either face is sufficient for the rest of the

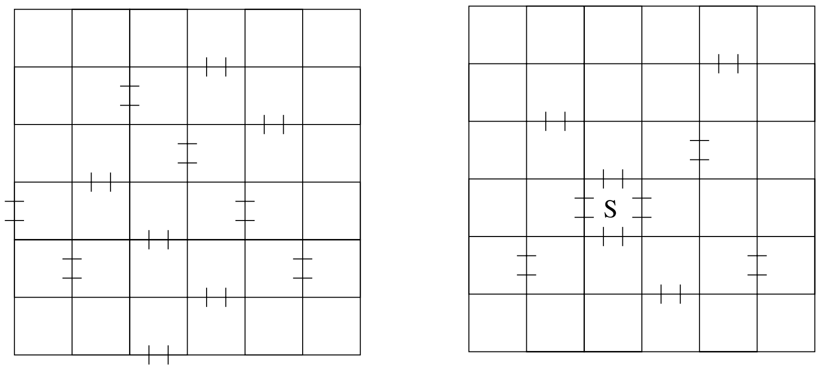

Fig. 1. (a) The basic structure for the polyomino-safe block replacement scheme where the original block had strength 2 glues in the south and west and strength 1 glues in the north and west. (b) The block corresponding to the seed in our replacement scheme with the seed of the new system labelled s here. Two lines indicate strength 2 glues, and all other glues are strength 1.

block to attach. Thus, the images of all configurations derivable from a configuration in X are derivable from its image in Y, and the images of all reachable configurations are reachable.

The second part of the block replacement definition can be broken into two pieces; first, we show that no erroneous tile (a tile that precludes the assembly from being extended to the image of some derivable configuration) can ever attach, and then we show that we can complete any assembly to be the image of a derivable configuration without introducing new blocks. For the first, consider the first time an erroneous tile attaches. All glues internal to blocks are unique in the assembly, so the error must occur on the border of some block. All tiles currently in the configuration are correct, so the error tile must attach using only the faces of valid blocks. But then the tile must either use a strength 2 glue from a face corresponding to a strength 2 tile in X or two strength 1 glues from faces corresponding to strength 1 glues. In either case, the tile must be part of a block corresponding to a tile that could have attached in that location in X. Also, since there is only one place for the first tile of a block to attach given the sides it attaches from, this tile cannot be erroneous because it does not match tiles that have already attached in the block. For the second part, a tile can only attach if a tile in its block is already present or using glues from other blocks whose preimage tiles would allow its preimage tile to attach. Thus, any assembly sequence in Y induces an assembly sequence in X by adding a tile in the original system the first time a tile from its block attaches. We can then extend our configuration by completing blocks one by one in this assembly sequence's order. The result is the image of the final configuration in the assembly sequence of the original system, and no tiles from outside blocks that already had a tile were needed.

We finally are ready to establish polyomino safety. By inspection, there are no polyominoes larger than two tiles that do not contain the seed. Thus, it is sufficient to show none of these dominoes can attach to the assembly in an erroneous location. Consider the first error generated by a polyomino attachment. Since all glues internal to a block are unique a polyomino must still attach at the appropriate coordinates in a block. The error cannot attach using glues from any tiles in the same block because all previous tiles are correct, and if one tile in a block is correct completing the rest of the block must also be correct. Thus, the only way a first error could occur is if a polyomino is using glues on the boundary of two blocks. But none of our dominoes has more than one face on a boundary, so a single tile could attach in those places any time a polyomino could. Thus, there can be no first polyomino error completing the proof.

3.3 Higher Temperatures

Our construction above can easily be extended to higher temperatures. Regardless of the temperature, there are only two ways a tile can attach in a block admissible system: using a glue with strength equal to the temperature from a single tile or using the combination of two glues that share a corner. In the first case, we can put the first attachment in the middle of a face of our block replacement. In the second case, the block must start assembling at the corner. Given a tile t in a system of temperature τ we can provide a $(6,6)$-block replacement as follows:

1. For all directions with glue strength at least τ place a strength τ glue on the outer face of the third tile on that face.
2. For all directions with glue strength s less than τ place a strength s glue on the first and sixth tiles of that face.
3. Place a strength τ glue everywhere the temperature 2 polyomino-safe block replacement scheme had a strength 2 glue in the interior of the block.
4. Place a strength $\lceil \frac{\tau}{2} \rceil$ everywhere the temperature 2 polyomino-safe block replacement scheme had a strength 1 glue.

Theorem 2. *The system described above is a strong polyomino-safe block replacement scheme.*

Proof. The proof proceeds as above, using the facts that any block can form completely given one of its tiles and a face, the first tile in a block will only attach if the preimage of its block could attach in the original system, there are no polyominoes without the seed of size larger than 2, and none of the polyominoes has more than one face on a boundary between blocks.

4 Complexity Properties

Ideally, we would like an algorithm to verify if a tile system is polyomino-safe. Unfortunately the problem is undecidable.

Theorem 3. *Determining if a given tile assembly system is polyomino-safe undecidable.*

Proof. aTAM is strong enough to emulate a Turing machine by producing the entire tape after each step [3]. Take a polyomino-safe implementation of a universal Turing machine, and add a structure that is not polyomino-safe that only attaches to a specific state tile. Determining whether a Turing machine will reach this state is undecidable, so determining if a polyomino-safety violation can occur is undeciable as well.

The problem is still undecidable even given a finite final structure because the potential problem can be produced by a Turing machine that is not part of the normal assembly and assembles as a polyomino. Note that there is nothing special about polyomino-safety in the above proof: it would apply to any property of an assembly system that is only present if a certain tile attaches. In particular:

Theorem 4. *Deterimining if a given tile assembly system is self-healing from a given configuration is undecidable.*

5 Polyomino Safety in Existing Systems

Many existing systems are already polyomino-safe. For example, consider rectilinear systems (like the Sierpinski tile system [3]) as shown in figure 2 in which tiles form an L using strength 2 glues and fill in the L with strength one glues. Arbitrarily long polyominoes can form from either of the leg tiles. There is never any place for them to attach inside the system though, so all rectilinear systems are polyomino-safe. Similarly, a basic binary counter as described in Adleman et al. [13] can easily be verified as polyomino-safe. Polyomino-safety does not always come for free though.

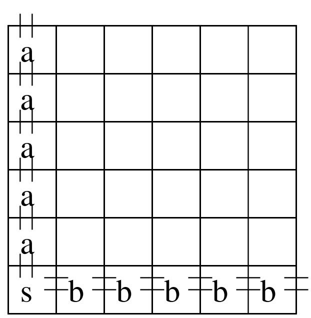

Fig. 2. The basic rectilinear system in which long strings of the same tile are formed on the west and east edges from the seed *s*. The interior is then filled in with strength 1 glues.

5.1 The Chinese Remainder Counter

Consider the Chinese remainder counter system, described as follows. Let p_1, $\ldots p_n$ be distinct primes. Column i of the counter consists of tiles $a_1^i \ldots a_{p_i}^i$ such that there is a strength 3 glue between the north face of a_k^i and the south face of a_{k+1}^i for k from 0 to $p_i - 1$ and a strength 2 glue from the north of $a_{p_i}^i$ to a_1^i as shown in figure 3. The east and west glues of each tile are strength 1 matching with the west and east glues on all tiles in the adjacent columns. We take the row of tiles $a_1^1 \ldots a_1^n$ as our "seed" (a minor modification of the system can allow for a single-tile seed [25]). At temperature 3 each column can count from 1 to p_i by itself, stalling at transitions from p_i to 1. If the column on either side has a tile in the next row though, it can use the additional strength 1 glue to roll over from p_i to 1 again. Thus, this system will grow until all columns are simultaneously on the p_i to 1 transition, which happens at row $\prod p_i$. The Chinese remainder counter is not polyomino-safe. Single-width columns of tiles up to size p_i can form by themselves. As all glues between adjacent columns are the same, such polyominoes of length 3 or greater may attach at any point to which an adjacent column has progressed, whether or not that string of tiles is appropriate. Thus, the Chinese remainder system is unpredictable in the presence of polyominoes.

We could of course use the 6×6 construction to make the system polyomino-safe. However, in this particular case we can do much better, using a $(1, 3)$-block replacement scheme where we reduce the temperature to 2 and replace each tile with three tiles as illustrated in figure 4. For tiles between 1 and $p_i - 1$ the middle north and south glues have strength 2, and the glue from p_i to 1 has strength 1. We can think of this construction as adding an additional buffer tile on the left and right of each of the old blocks and then lowering the temperature of the system to 2 (making north/south glues 2 normally and 1 on the rollover from p_i to 1). The block replacement still permits long chains of tiles to form in the center of each column. However, these chains can no longer cause problems.

Theorem 5. *The tile system described above is a strong polyomino-safe* $(1, 3)$-*block replacement scheme.*

Proof. The proof for strong block replacement is very similar to the one in Theorem 1, and we omit it here. For polyomino-safety, we see by inspection that the only polyominoes that can form without the seed are chains of middle blocks such that there are no p_i to 1 attachments. Consider a first polyomino

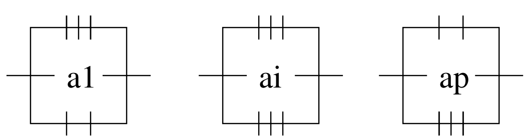

Fig. 3. The first, ith ($1 < i < p$), and pth, tiles in a column corresponding to the prime p. The east and west glues of each tile match the west and east glues of the adjacent columns.

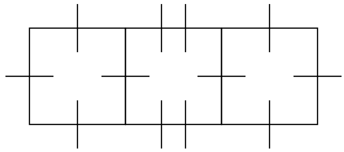

Fig. 4. The polyomino-safe (1,3)-block replacement scheme for the Chinese remainder counter. The middle north (south) glue is strength 1 instead for the step from p_i to 1.

error in some assembly sequence. Every tile uniquely determines what the tile above it and below it is if there is such a tile. In fact, since there are no p_i to 1 attachments in these polyominoes we know that if one tile in a polyomino belongs in the location it attached all the other tiles must also belong where they attached. But the east and west glues of a middle tile are unique to the block they are part of, so any attachment using one must put that tile in its correct place. Similarly, any time a north or south strength 2 glue is used that tile must also be correct because those glues are sufficient to determine if a tile should attach in the original system. All that remains is the strength one north or south glues. However, using the block replacement property if there were a tile for the north glue to attach to then all blocks below it must have already started forming, and the polyomino would be correct. Finally, a strength 1 glue from the south is not sufficient for the polyomino to attach, and the system is polyomino-safe.

Note that our system reduces the temperature to 2, a desirable property. Normally, a $(1, 2)$-block replacement is used to lower the Chinese Remainder counter's temperature, so our polyomino-safe system represents only a 50% increase in size over that basis.

6 Self-healing and Block Replacement

Occasionally, a large portion of an assembly can get knocked out of a tile system. A system is self-healing if it can rebuild itself correctly and completely after such an event provided one of a set of relatively small pieces is intact. Essentially, there are two aspects of a system being self-healing. For two configurations C and D, $C \preceq D$ if C is *empty* everywhere D is *empty*, and $C(x, y) = D(x, y)$ whenever $C(x, y)$ is not empty. A tile system is *immutable* if for all reachable configurations D, $C \preceq D$ and $C \rightsquigarrow E$ imply $D(x, y) = E(x, y)$ when $D(x, y)$ and $E(x, y)$ are both not *empty*. Thus, a system is immutable if whenever a tile attaches no other tile can take its place if it falls off. A tile system is *progressive* for a configuration B if for all reachable D, when $B \preceq C \preceq D$ there is E such that $C \rightsquigarrow E$ and E is not *empty* wherever D is not empty. Thus, a system is progressive from B if any tiles that fall off can be recovered as long as B remains. A system is progressive from a set of configurations $\mathcal{B}$ if it is progressive from all $B \in \mathcal{B}$. A system is *self-healing* from $\mathcal{B}$ if it is immutable and progressive from $\mathcal{B}$. We now prove that a strong block replacement of a self-healing system is self-healing provided all tiles in a block have unique internal glues.

Note that an immutable system can never allow two different tiles to be able to attach in the same location. Thus, a self-healing system is block admissible if it never uses glues on opposite sides of a tile to attach. Block admissibility is sufficient to turn a system that is self-healing into a system that is self-healing *and* polyomino-safe.

Theorem 6. *A strong block replacement of a tile system that is block admissible and self-healing from $\mathcal{B}$ is self-healing from $\Phi\mathcal{B}$ (the image of $\mathcal{B}$ under the block replacement) if the tiles within a block all have unique glues.*

Proof. Let X be the old system and Y be the new system. Progressiveness from $\Phi\mathcal{B}$ follows immediately from the ability to imitate any assembly sequence in X with a sequence in Y. For immutability consider some reachable configuration D and $C \preceq D$. Consider the first attachment of a tile t to C that does not match D. This attachment can use no glues within its block because all glues are unique, and only the one correct tile can use them at any location. If the attachment uses only glues from outside its block the preimage of t's block in X must have been able to attach in that location in X. Then since X is immutable, and any assembly sequence in Y induces a sequence in X, t must come from the same block that was present there in D. Since each tile in a block can only attach at one location in that block t must match the tile in D, and Y is immutable.

In particular, our $(6,6)$-block replacement scheme meets the requirements of the theorem, allowing us to make block admissible self-healing systems polyomino-safe as well.

7 Open Problems

One potential improvement to our results would be a smaller polyomino-safe block replacement scheme. It is clear that a 2×2 block replacement is too small, but we have no proof that a 3×3 scheme cannot exist. The primary challenge to creating polyomino-safe block replacements is spreading out the necessary strength 2 glues, so that they do not allow polyominoes that are too big to form. A 6×6 scheme allows every strength 2 glue to be isolated from every other, bounding the polyomino size by 2. It is possible that a smaller polyomino-safe block replacement exists that allows larger polyominoes to form. Another worthwhile question is how to address systems that are neither polyomino-safe nor block admissible.

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