

Optimizing Tile Concentrations to Minimize Errors and Time for DNA Tile Self-assembly Systems

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Abstract. DNA tile self-assembly has emerged as a rich and promising primitive for nano-technology. This paper studies the problems of minimizing assembly time and error rate by changing the tile concentrations because changing the tile concentrations is easy to implement in actual lab experiments. We prove that setting the concentration of tile T_i proportional to the square root of N_i where N_i is the number of times T_i appears outside the seed structure in the final assembled shape minimizes the rate of growth errors for rectilinear tile systems. We also show that the same concentrations minimize the expected assembly time for a feasible class of tile systems. Moreover, for general tile systems, given tile concentrations, we can approximate the expected assembly time with high accuracy and probability by running only a polynomial number of simulations in the size of the target shape.

1 Introduction

Considerable modern research in science and engineering has aimed to control smaller and smaller systems in many fields, including computer science and material science. As the size of a system approaches the molecular scale, precise direct external control becomes prohibitively costly, if not impossible. As a result, bottom-up self-assembly has emerged as a rich and promising primitive for nano-technology. In particular, DNA has received much attention as a substrate for molecular self-assembly because its combinatorial nature enables the programming of molecular behaviors by choosing appropriate DNA sequences to encode information. In addition, lab techniques for the manipulation of DNA are already well developed. For these considerations, DNA self-assembly has been proposed for a variety of applications, e.g., as a means to perform computation [3, 22, 29], construct molecular patterns [9, 12, 18, 19, 24, 33], and build nano-scale machines [5, 10, 13, 23, 25, 32].

DNA tiles which self-assemble according to simple rules have been developed in lab [31] and mathematically analyzed based on the abstract tile assembly model (aTAM) proposed by Rothemund and Winfree [17]. Under this model, there is a set of square tiles with a *glue* on each of the four edges. Each glue has a certain affinity for itself called *strength*. The self-assembly process starts from a distinguished *seed structure*. Assembly proceeds as tiles attach to the

partially assembled structure (initially, just the seed structure) one by one when the combined strength of matched glues between a tile and the partial structure is at least the *temperature* of the tile system. Many interesting tile systems have been designed under aTAM, including systems that build counters [1, 8] and squares [11, 15, 17], perform Turing-universal computation [29], and produce arbitrary computable shapes [16, 27]. Unfortunately, in laboratory settings, several events that aTAM does not model have been frequently observed. These events are referred to as *errors* in the tile self-assembly process. A more realistic stochastic model called the kinetic tile assembly model (kTAM) was proposed by Winfree [29] to describe the rates of these errors. The kTAM model calculates the rates for various types of attachments and detachments of tiles based on thermodynamics.

In order to make DNA tile self-assembly practical, there are two important factors that need to be minimized, namely, the error rate and the time of the assembly process. One approach to reducing the error rate of a tile assembly system [6, 7, 14, 26, 30] is to convert an existing error-prone tile system to a more robust tile system that assembles into the same shape or pattern up to scaling. These error correcting techniques increase the number of tile types by a multiplicative factor and thus are hard to implement in practice. In contrast, it is easy to change the concentrations of tiles. Therefore, it is natural to consider reducing the error rate by changing the concentrations of tiles. This approach has been studied using computer simulations and lab experiments. However, no closed-form formulas or efficient algorithms for finding the optimal tile concentrations have been previously found. It is also natural to consider changing the tile concentrations in order to minimize the assembly time. Adleman et al. [2] designed an algorithm to find tile concentrations that approximate the minimum expected assembly time within an $O(\log n)$ factor. Cheng et al. [8] showed that for partial order systems, if all tiles have equal concentrations, then the expected assembly time is proportional to the longest length of a path in the assembly order of the target shape. Also, some studies employed computer simulations to characterize the trade-offs between the time and the error rate of an assembly process [6, 30].

Our Results. On the problem of minimizing the error rate, we formulate the rate of growth errors in terms of tile concentrations based on the kinetic tile assembly model. Using our formulation, we show that setting the concentration of each tile T_i proportional to the square root of the number of times T_i appears outside the seed structure in the target shape minimizes the rate of growth errors. This result holds for all rectilinear tile systems (i.e., tile systems that have the same growth directions for all tiles fixed throughout the assembly process) as well as many other systems that have been implemented in lab [4, 21]. We also have simulation results showing that facet errors can significantly affect the accuracy of the optimal tile concentrations predicted by our mathematical analysis. On the problem of minimizing the assembly time, we prove that the above concentrations for minimizing the rate of growth errors also minimizes the expected assembly time for tile systems for which there is only one location for correct growth at any given time throughout the assembly process. Moreover, for general tile systems, given tile concentrations, we show that the average assembly time over a polynomial number of simulations in the size of the target shape can approximate the expected assembly time with high accuracy and probability.

The remainder of this paper is organized as follows. Section 2 describes the two tile assembly models that we use. Section 3 contains the theoretical results on minimizing the rate of growth errors. Section 4 contains the simulation results on growth errors and some discussion on facet errors. Section 5 contains the theoretical results on estimating and minimizing the expected assembly time. Section 6 concludes the paper with some open problems.

2 Two Tile Assembly Models

The Abstract Tile Assembly Model. The abstract tile assembly model was proposed by Rothmund and Winfree [17]. It extends the theoretical model of tiling by Wang [28] to include a mechanism for growth based on the physics of molecular self-assembly. Informally, a tile self-assembly system has a set of tiles, each of which is a square with glues of various types on each of the four edges. Two tiles will stick to each other if they have compatible glues. Below we present a succinct definition of this model with minor modifications for ease of explanation.

A *tile* is an oriented unit square with the *north*, *east*, *south* and *west* edges labeled from some alphabet Σ of *glues*. For each tile t , the glues of its four edges are denoted as $\sigma_N(t)$, $\sigma_E(t)$, $\sigma_S(t)$, and $\sigma_W(t)$. We describe a tile t as the quadruple $(\sigma_N(t), \sigma_E(t), \sigma_S(t), \sigma_W(t))$. Consider the triple $\langle T, g, \tau \rangle$ where T is a finite set of tiles, $\tau \in \mathbf{Z}_{>0}$ is the *temperature*, and g is the *glue strength* function from $\Sigma \times \Sigma$ to $\mathbf{Z}_{\geq 0}$. It is assumed that for all $x, y \in \Sigma$, the inequality $x \neq y$ implies $g(x, y) = 0$ and there is a glue $null \in \Sigma$, such that $g(x, null) = g(null, x) = 0$ for all $x \in \Sigma$. A *configuration* is a map from \mathbf{Z}^2 to $T \cup \{empty\}$, where *empty* is a special symbol indicating the absence of any tile.

A *tile system* is a quadruple $\mathbf{T} = \langle T, s, g, \tau \rangle$, where T, g, τ are as above and s is a special configuration called the *seed structure*. Let C and D be two configurations. Suppose that there exist some $t \in T$ and some $(x, y) \in \mathbf{Z}^2$ such that $D = C$ except that at (x, y) , $C(x, y) = null$ and $D(x, y) = t$. Let $f_{N,C,t}(x, y) = g(\sigma_N(t), \sigma_S(C(x, y + 1)))$. Informally, $f_{N,C,t}(x, y)$ is the strength of the bond on the north edge of t in configuration C . We define $f_{S,C,t}(x, y)$, $f_{E,C,t}(x, y)$ and $f_{W,C,t}(x, y)$ similarly. Then tile t is *attachable* to C at position (x, y) iff $f_{C,t}(x, y) \equiv f_{N,C,t}(x, y) + f_{S,C,t}(x, y) + f_{E,C,t}(x, y) + f_{W,C,t}(x, y) \geq \tau$. We write $C \rightarrow_{\mathbf{T}} D$ to denote the transition from C to D by attaching a tile to C at position (x, y) . Informally, $C \rightarrow_{\mathbf{T}} D$ iff D can be obtained from C by adding a tile t such that the total strength of interaction between t and C is at least τ . A *terminal assembly* is a configuration A such that there is no configuration B for which $A \rightarrow_{\mathbf{T}} B$.

When a tile t attaches to configuration C at position (x, y) , the edges U of t with $f_{U,C,t}(x, y) > 0$ are called the *input* edges; all other edges are called the *output* edges. A tile system is *rectilinear* if there is a unique terminal assembly that can be reached starting from the seed structure, each tile t has the same input and output edges every time it attaches, and all tiles have the same input and output edges.

The Kinetic Tile Assembly Model. According to the abstract tile assembly model, a tile t attaches at a position (x, y) in a configuration C iff the total strength $f_{C,t}(x, y)$ of the matched glues between C and t is at least τ , and any tiles that attached never fall off. In practice, tiles may attach with a weaker binding strength, and tiles that already attached may fall off. These events can

cause the tile system to behave differently from the abstract tile assembly model. We treat these deviations as errors and try to minimize the probability of these events. In this paper, we use the kinetic tile assembly model proposed by Winfree [29] to model the *forward* and *reverse* rates, which are the rates at which a tile attaches to and falls off from a specific position, respectively. This model computes these rates as functions of thermodynamic parameters as follows:

1. The concentrations of the tiles are held constant throughout the self-assembly process.
2. The only two reactions allowed are single tiles attaching to and dissociating from a configuration.
3. The forward rate for tile T_i is $k_f c_i$, where k_f is a constant and c_i is the concentration of tile T_i . This notation is used throughout this paper.
4. The reverse rate for a tile t attached to configuration C at position (x, y) to fall off is $k_f e^{-bG_{se}}$, where k_f and G_{se} are constants and $b = f_{C,t}(x, y)$ is the total strength of the matched glues between t and C .

Here, the parameters k_f and k_f give the time scale of the self-assembly. The value of G_{se} is determined by the binding strength of the sticky ends of DNA tiles. We use c_{\max} and c_{\min} to denote the maximum and minimum concentrations allowed in the tile system. If one wants the tile system to assemble according to the abstract tile assembly model most of the time, then the following two conditions need to hold. First, if the total binding strength between a tile and the original configuration it just attached to is less than τ , then the tile must fall off quickly, i.e.,

$$k_f e^{-(\tau-1)G_{se}} \gg k_f c_{\max}.$$

Second, if a tile t is attachable to a position in C , then the forward rate at which it attaches should be greater than the reverse rate at which it falls off, i.e.,

$$k_f c_{\min} > k_f e^{-\tau G_{se}}.$$

In practice, since each tile may have a slightly different value for the parameter k_f and the strength of each glue may vary, one often needs to set k_f and G_{se} (by changing an experiment's temperature) such that

$$k_f c_{\min} \gg k_f e^{-\tau G_{se}}.$$

For the remainder of the paper, we assume

$$k_f e^{-(\tau-1)G_{se}} \gg k_f c_{\max} > k_f c_{\min} \gg k_f e^{-\tau G_{se}}.$$

We also assume that our seed structure is made by some other processes (e.g., DNA origami [18]) and its tiles never fall off.

3 Minimizing the Error Rate

In this section, we consider the problem of changing the concentrations of tiles to minimize the failure probability (i.e., error rate) for a rectilinear tile system. There are three types of errors in tile self-assembly. A *growth error* refers to an incorrect tile attaching at a position instead of the correct tile [30]. A *facet error*

refers to an incorrect tile attaching at a position where no tile is supposed to attach [6]. A *nucleation error* refers to single tiles attaching to each other to form a lattice without the seed structure [20]. In this section, we only consider minimizing growth errors.

We want to compute the probability that a tile T_j causes a growth error by attaching at a position (x, y) where only T_i can attach with total binding strength at least τ . First, T_i can attach at that position at rate $k_f c_i$. Once T_i has attached, the probability of it falling off is negligible since $k_f c_{\min} \gg k_f e^{-\tau G_{se}}$. Second, T_j can attach at that position at rate $k_f c_j$. Once T_j has attached, it can fall off at rate $k_f e^{-(\tau-m)G_{se}}$, where m is the total strength of the mismatched glues between T_i and T_j on their input edges. T_j can also get locked in place and cause an error due to the attachment of one or more adjacent tiles. The rate r at which T_j gets locked in place may vary with the features in the partially assembled shape near position (x, y) such as long facets. In this paper, we assume that r is the same for all positions (x, y) and tiles t . The allowable reactions related to T_i and T_j are summarized in Figure 1. From the above description of reaction rates, we know that at a given position (x, y) where tile T_i is supposed to attach, the probability of having a growth error caused by T_j is $\frac{c_j}{c_i} \epsilon_{ij}$. Here, $\epsilon_{ij} = \frac{r}{r + k_f e^{-(\tau-m)G_{se}}}$, where m is the total number of mismatches between the input sides of tiles T_i and T_j . The value of ϵ_{ij} is roughly at the order of $e^{-mG_{se}}$ since $r \leq 2k_f c_{\max}$. Therefore, at position (x, y) , the total probability of a growth error is

$$\frac{\sum_{j \neq i} \epsilon_{ij} c_j}{c_i}.$$

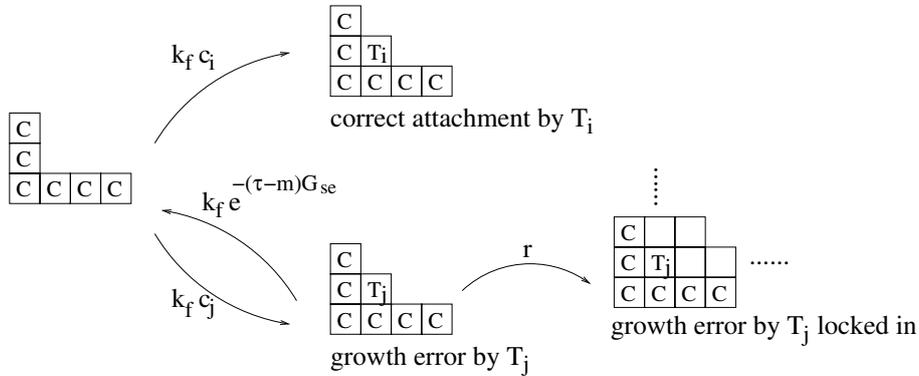


Fig. 1. A Markov chain describing attachments of T_i and T_j , where C indicates a correct tile

For a self-assembly process, the error rates at different positions depend on each other. However, if one wants to have a high probability of success, one almost always needs to set the experimental condition such that the error rate at each position is much smaller than $1/n$, where n is the total number of tiles

in the desired terminal assembly. In this case, minimizing the sum of error rates over all positions is a good approximation of minimizing the actual overall error rate of the tile assembly system. Thus, in the remainder of this section, we will minimize

$$\sum_i N_i \left(\frac{\sum_{j \neq i} \epsilon_{ij} c_j}{c_i} \right), \quad (1)$$

where N_i is the number of positions outside the seed structure to which T_i is supposed to attach.

Theorem 1. *For a rectilinear tile system with a unique terminal assembly, the error rate (i.e., probability of failure) is minimized when the concentration of each tile T_i is proportional to $\sqrt{N_i}$, where N_i is the number of times tile T_i appears outside the seed structure in the correct terminal assembly of the tile system.*

Proof. From Equation 1, we can scale the tile concentrations c_i without loss of generality such that $\sum_i c_i = 1$, and we need to solve the following minimization problem:

$$\begin{aligned} & \text{Minimize } \sum_i N_i \left(\frac{\sum_{j \neq i} \epsilon_{ij} c_j}{c_i} \right), \\ & \text{subject to } \sum_i c_i = 1. \end{aligned}$$

The Lagrange multiplier for this minimization problem is

$$\Lambda = \sum_i N_i \left(\frac{\sum_{j \neq i} \epsilon_{ij} c_j}{c_i} \right) + \lambda \left(\sum_i c_i - 1 \right).$$

We need to solve

$$\frac{\partial \Lambda}{\partial c_i} = -N_i \left(\frac{\sum_{j \neq i} \epsilon_{ij} c_j}{c_i^2} \right) + \sum_{j \neq i} N_j \frac{\epsilon_{ij}}{c_j} + \lambda = 0 \quad \text{for all } i \quad (2)$$

and

$$\sum_i c_i = 1.$$

Simplifying Equation 2, we obtain

$$\sum_{j \neq i} \left(-N_i \frac{\epsilon_{ij} c_j}{c_i^2} + N_j \frac{\epsilon_{ij}}{c_j} \right) + \lambda = 0 \quad \text{for all } i,$$

and consequently the error rate is minimized when

$$c_i = \frac{\sqrt{N_i}}{\sum_j \sqrt{N_j}}.$$

Two points about the proof of Theorem 1 are worth noticing. First, the error rate only depends on the ratio between the tile concentrations. Specifically, the error rate is minimized when the concentration of T_i is proportional to $\sqrt{N_i}$ even when we vary each c_i between c_{\max} and c_{\min} . Second, the same proof can apply

to all tile systems that satisfy $\epsilon_{ij} = \epsilon_{ji}$ for all i, j . Hence Theorem 1 is valid for other systems already implemented in lab such as zig-zag ribbons [21] and counters seeded by origami [4].

4 Simulation Results for Theorem 1

We used a software called xgrow developed in Erik Winfree’s lab to simulate four tile systems to determine their error rates under different tile concentrations. To obtain a good estimate of the error rate of a tile system, we would choose our parameters such that errors can be frequently observed. However, in most tile systems, if we use such parameters, we will reach some configuration very different from the terminal assembly predicted by the abstract tile assembly model. Since our prediction of the optimal tile concentrations depends on the terminal assembly, we made a design decision to perform simulations on tile systems for which each error only affects one position of the terminal assembly.

We simulated four tile systems named as A_1 , A_2 , B_1 , and B_2 . Each of the four systems operates at $\tau = 2$ and only has two tiles X and Y shown in Figure 2(a) beside the seed structure. The only difference between the four systems is their seed structures. The seed structures of tile systems A_1 and A_2 are shown in Figure 2(b). The lengths of their seed structures are adjusted such that $N_X : N_Y = 25 : 1$ and $64 : 1$ for A_1 and A_2 , respectively, where N_X and N_Y are the numbers of positions X and Y appear in the terminal assembly. The seed structures of tile systems B_1 and B_2 are shown in Figure 2(c). The lengths of their seed structures are also adjusted such that $N_X : N_Y = 25 : 1$ and $64 : 1$ for B_1 and B_2 , respectively. These systems are rectilinear with all tiles having their input edges on the south and east edges. Since tiles X and Y have the same output edges, when an error happens, the error only affects the position where the erroneous tile is attached. The unique terminal assemblies and example configurations generated by simulations of tile systems A_1 and B_1 are shown in Figures 3 and 4, respectively. Theorem 1 predicts that the rate of growth errors is minimized at $c_X : c_Y = 5 : 1$ for systems A_1 and B_1 , and at $c_X : c_Y = 8 : 1$ for systems A_2 and B_2 .

The simulation results are shown in Figure 5. In systems A_1 and A_2 , the optimal tile concentration ratios are $2.5 : 1$ and $3 : 1$, respectively. In systems B_1 and B_2 , the optimal tile concentration ratios are roughly $7.5 : 1$ and $15 : 1$, respectively. The major reason causing these simulation results to deviate from the predictions made by Theorem 1 appears to be the facet errors. Since tiles X and Y both have glue 0 on the south edge, having a long horizontal facet may introduce a large number of facet errors. For systems A_1 and A_2 , notice that long horizontal facets are generated because tile Y (colored yellow) has lower concentrations and grows slower than X . An example configuration for system A_1 that demonstrates these horizontal facets is shown in Figure 3. Such undesirable facets become longer and more when we increase the ratio between c_X and c_Y . Therefore, the actual optimal tile concentrations are biased towards having more Y than predicted by Theorem 1. For systems B_1 and B_2 , each terminal assembly is separated into a left portion and a right portion by the seed structure, as shown in Figure 4. Horizontal facets can only be generated in the left portion, where all tiles should be X . Hence, we can reduce facet errors by decreasing the concentration of tile Y , and thus the actual optimal tile concentrations are biased towards having fewer Y than predicted by Theorem 1.

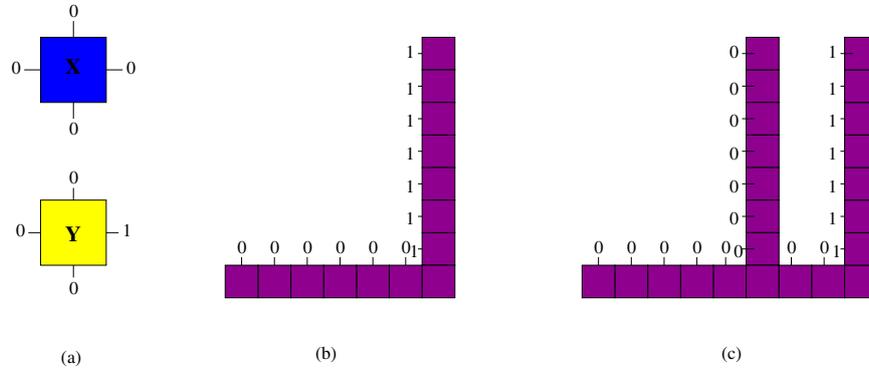


Fig. 2. (a) Tiles X and Y , where all glues have strength 1. (b) An L-shaped seed structure for systems A_1 and A_2 . (c) A seed structure with two vertical facets and one horizontal facet for systems B_1 and B_2 .

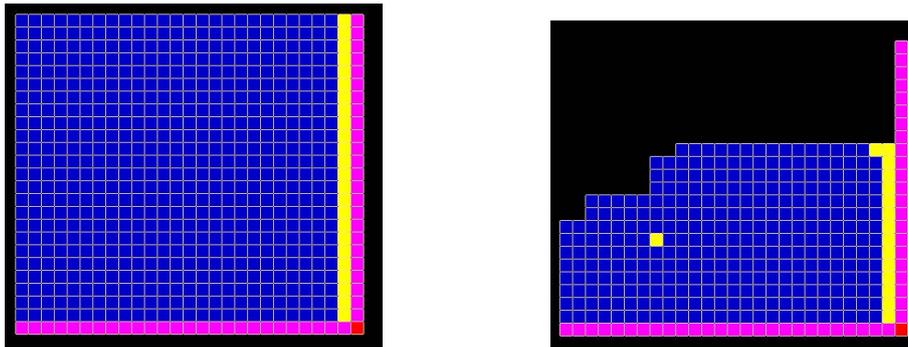


Fig. 3. The left figure is the unique target terminal assembly for system A_1 . The right figure is an example configuration for system A_1 generated by an xgrow simulation.

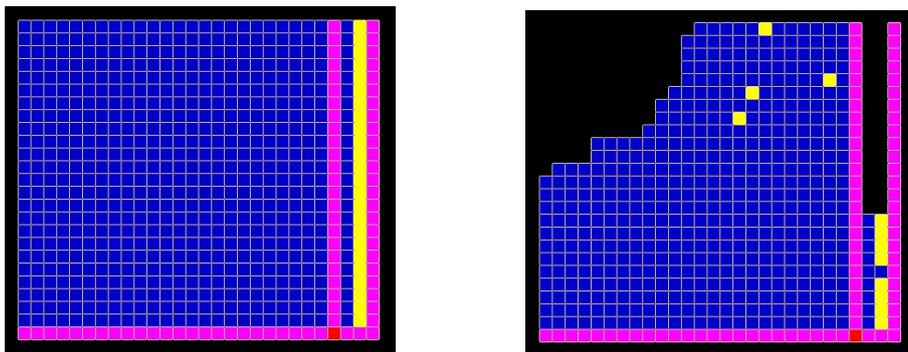


Fig. 4. The left figure is the unique target terminal assembly for system B_1 . The right figure is an example configuration for system B_1 generated by an xgrow simulation.

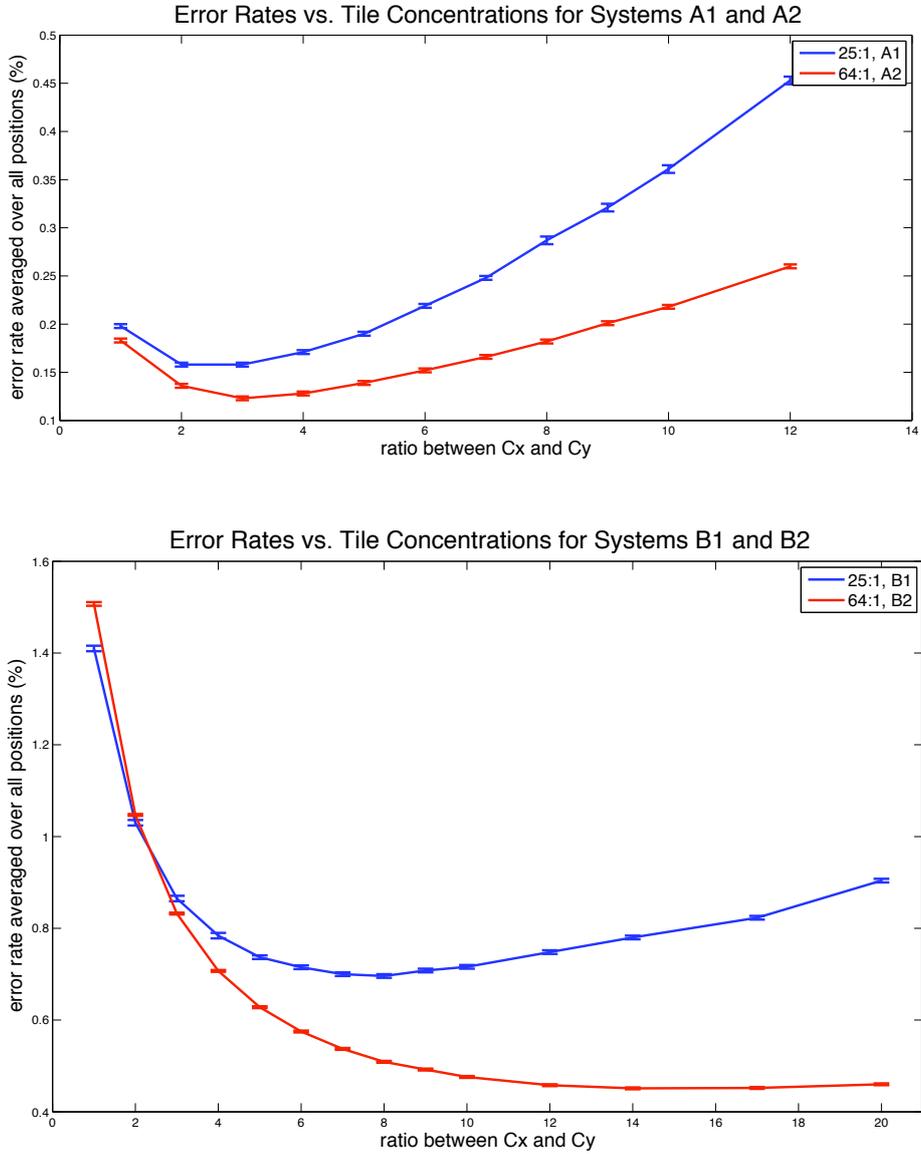


Fig. 5. Plots of error rates vs. the ratios between tile concentrations. Each data point represents $m = 20,000$ simulations. The simulations use $G_{se} = 9$ for systems A_1 and A_2 , $G_{se} = 11$ for systems B_1 and B_2 , $c_X + c_Y = e^{-16}$. Error bars show two standard deviations of the errors, computed using $\sigma = \sigma_{\text{simulation}}/\sqrt{m}$.

5 Minimizing the Expected Assembly Time

This section assumes that only the correct tiles can attach and any tile that has already attached never falls off. We minimize the expected assembly time by varying the tile concentrations.

Theorem 2. *Consider any tile system with the four properties that*

1. *at any given time, only one location can have a tile attach correctly,*
2. *only the correct tiles can attach,*
3. *any tile that has already attached never falls off, and*
4. *there is a unique terminal assembly.*

Assume that the total tile concentration is $\sum_i c_i = 1$. Setting $c_i = \frac{\sqrt{N_i}}{\sum_j \sqrt{N_j}}$ minimizes the expected assembly time of the tile system.

Proof. Omitted due to space constraints.

In settings that are more general than Theorem 2 assumes, the optimal tile concentrations to minimize the expected assembly time may significantly deviate from the c_i 's determined in Theorem 1.

For general tile assembly systems, we do not know how to analytically find the optimal tile concentrations to minimize the expected assembly time. However, we show in Theorem 3 below that given a set of tile concentrations, only a polynomial number of simulations is required in order to approximate the expected assembly time with high accuracy and probability.

Lemma 1. *Consider any tile system for which Properties 2 through 4 in Theorem 2 hold but there is no assumption on whether tiles can attach only one by one or in parallel. If the assembly process of the tile system takes expected time S , then for any $\epsilon > 0$, the average of the assembly times over $48S^2 \frac{1}{\epsilon}$ simulations of the assembly process will be between $S - \epsilon$ and $S + \epsilon$ with probability at least $3/4$.*

Proof. Omitted due to space constraints.

Theorem 3. *Consider any tile system for which Properties 2 through 4 in Theorem 2 hold but there is no assumption on whether tiles can attach only one by one or in parallel. Let n be the number of positions outside the seed structure in the terminal assembly. If the assembly process of the tile system takes expected time S , then for any $\epsilon > 0$, the average of the assembly times over $O(n^4 \frac{1}{\epsilon c_{\min}^2})$ simulations of the assembly process will be between $S - \epsilon$ and $S + \epsilon$ with probability at least $3/4$.*

Proof. Omitted due to space constraints.

6 Further Research

In Section 3, we gave closed-form formulas to minimize the growth errors by varying the concentration of each tile. In Section 4, we found in simulations that facet errors are also an important factor that needs to be considered in order

to minimize the error rate in lab implementations. At the theoretical level, it is open to find closed-form formulas or efficient algorithms to minimize the facet errors by varying the tile concentrations.

In Section 5, we gave closed-form formulas to minimize the expected assembly time for a feasible class of tile systems by varying the tile concentrations. For general tile systems, the best known algorithm can compute an $O(\log n)$ -approximation of the minimum expected assembly time [2]. It is of interest to determine whether one can compute the precise minimum expected assembly time or an estimate with a better approximation factor than $O(\log n)$. Given tile concentrations, we showed that simulations can accurately predict the expected assembly time with high probability. The computing time it takes to run the required simulations is polynomial in the size of the terminal assembly, not the tile system itself. Since the size of a tile system is normally smaller than that of its terminal assembly, it would be useful if one can approximate the expected assembly time just by analyzing the tile system and some succinct features of the terminal assembly (e.g., the number of times each tile appears outside the seed structure in the terminal assembly) in time polynomial in the size of the tile system.

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