Structural DNA nanotechnology

a.k.a. DNA carpentry

a.k.a. DNA self-assembly

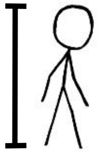
slides © 2021, David Doty

ECS 232: Theory of Molecular Computation, UC Davis

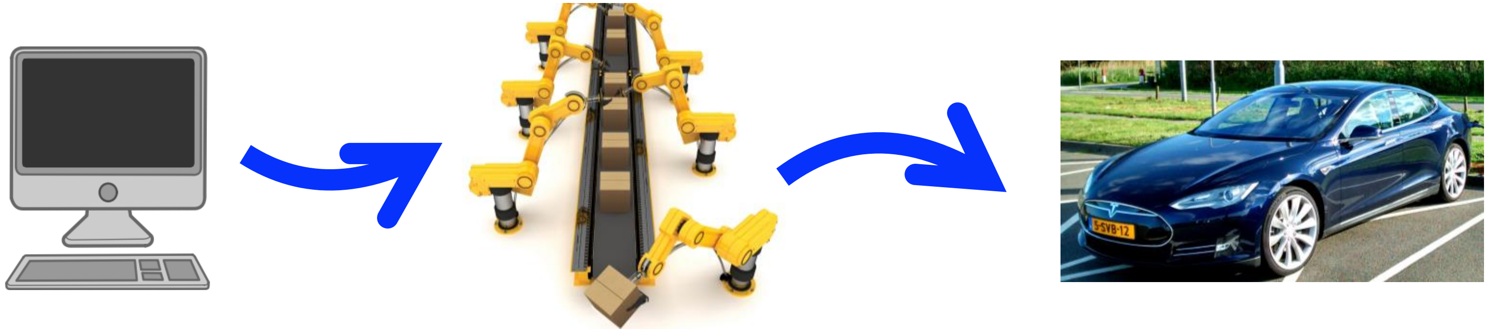
Ljubljana Marshes Wheel. 5k years old

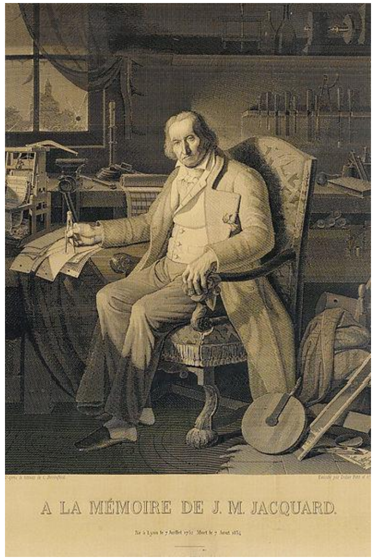
Building things

Newgrange, Ireland. 5.2k years old

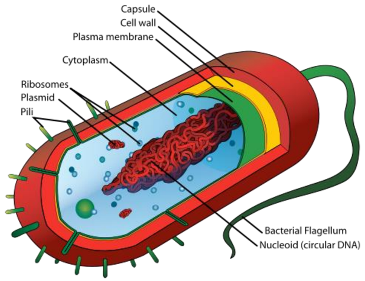
Building things by hand: use tools! Great for scale of $10^{\pm 2}$ × 

Building tools that build things: specify target object with a computer program





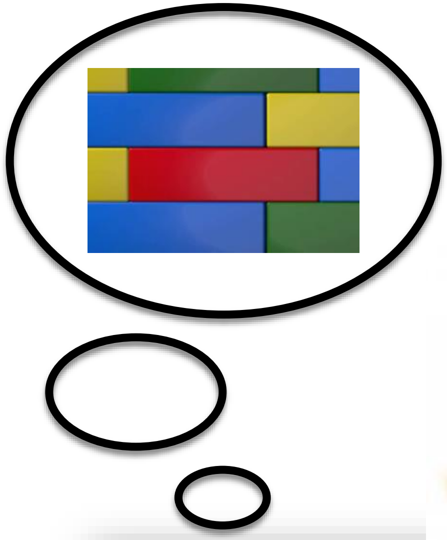
Programming **things to build themselves**: for building in small wet places where our hands or tools can't reach



Mariana Ruiz Villarreal

[slides credit: Damien Woods]

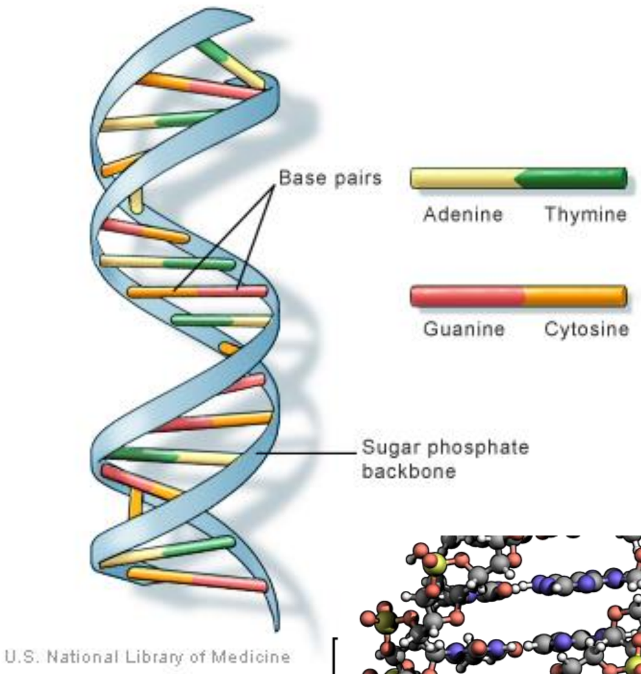
Things that build themselves

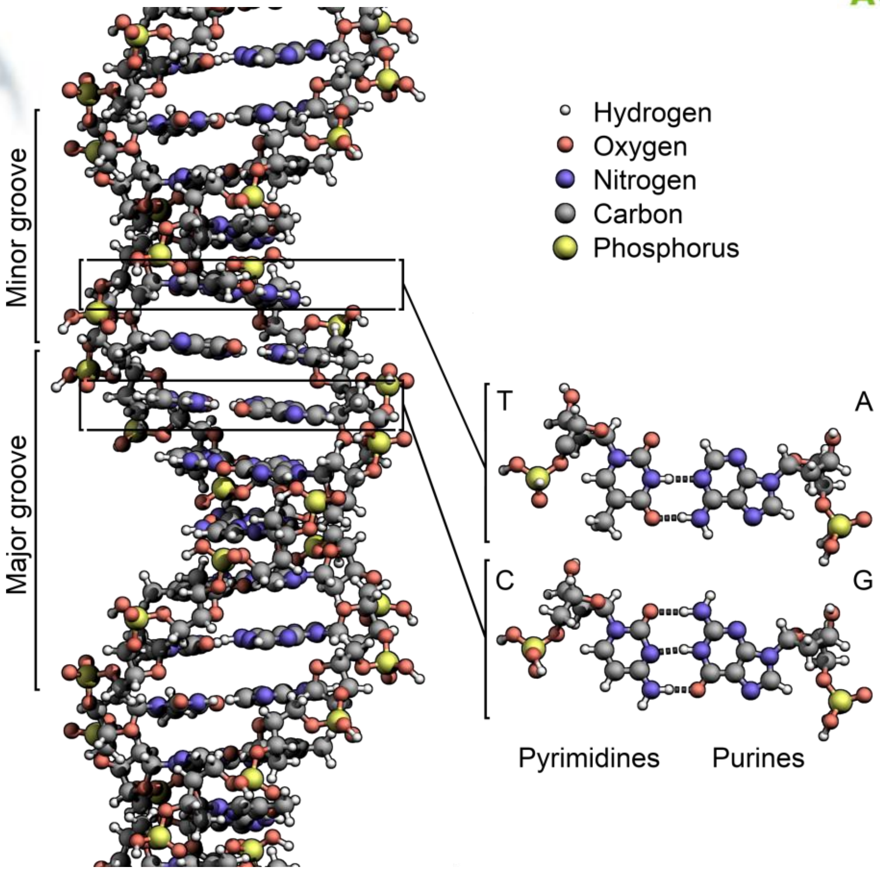


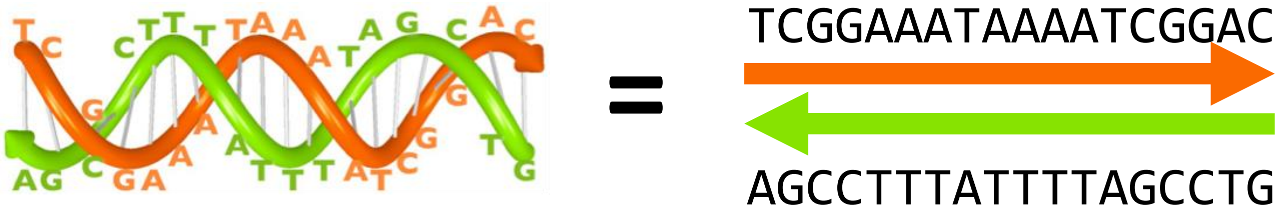
Our topic: self-assembling molecules that compute as they build themselves

[slides credit: Damien Woods]

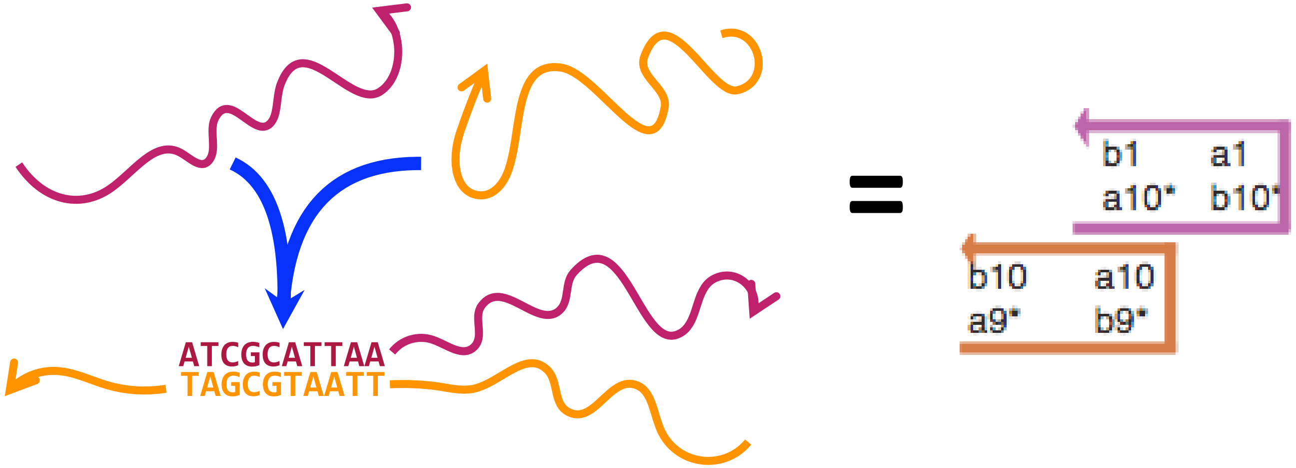
DNA as a building material



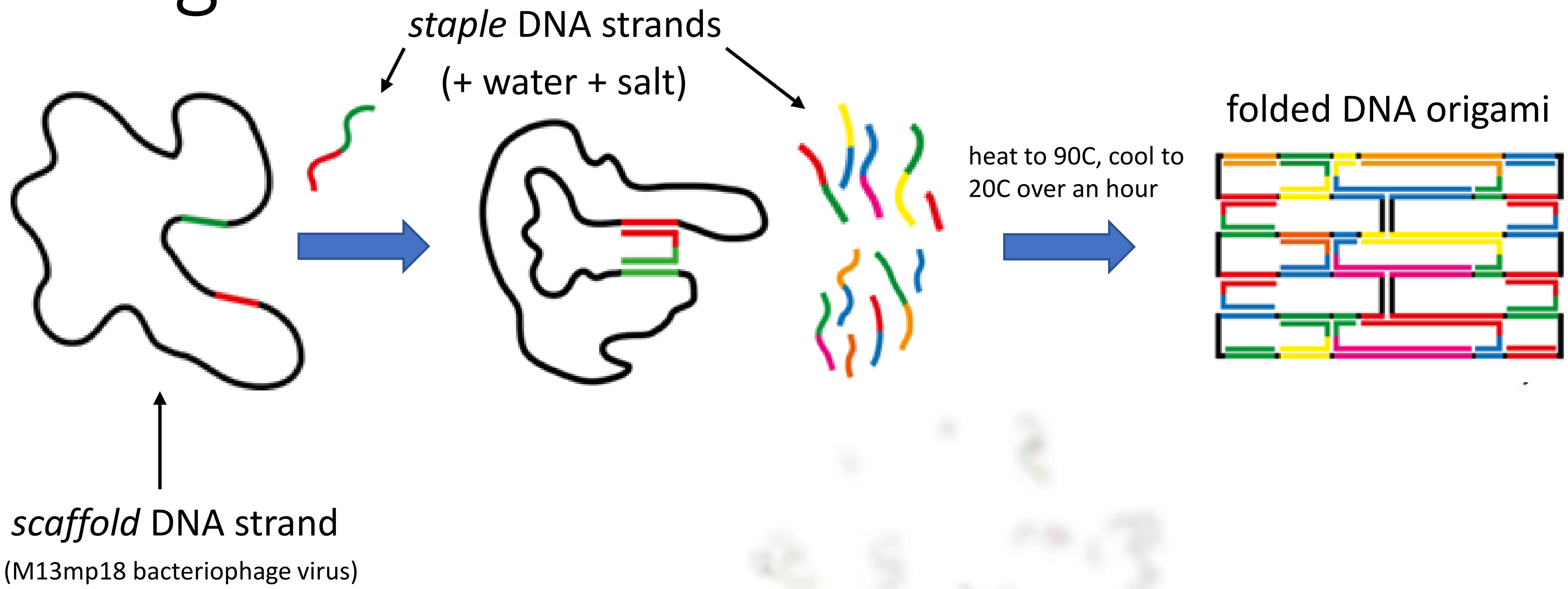




DNA strands bind even if only *part* of strands are complementary:



DNA origami



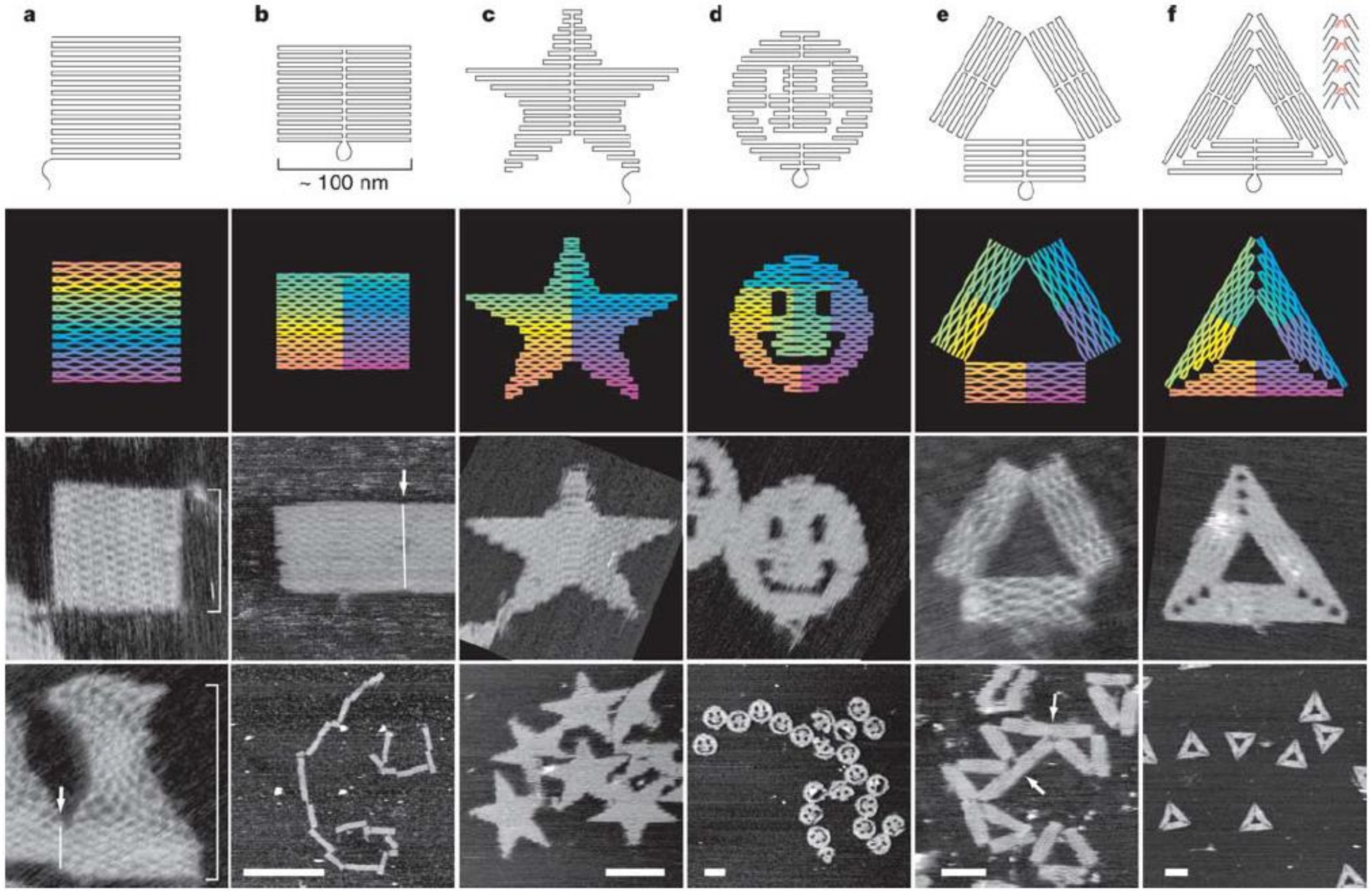
Paul Rothemund
Folding DNA to create nanoscale shapes and patterns
Nature 2006

© http://openwetware.org/wiki/Biomod/2014/Design

© Shawn Douglas

DNA origami

Paul Rothemund
Folding DNA to create nanoscale shapes and patterns
Nature 2006

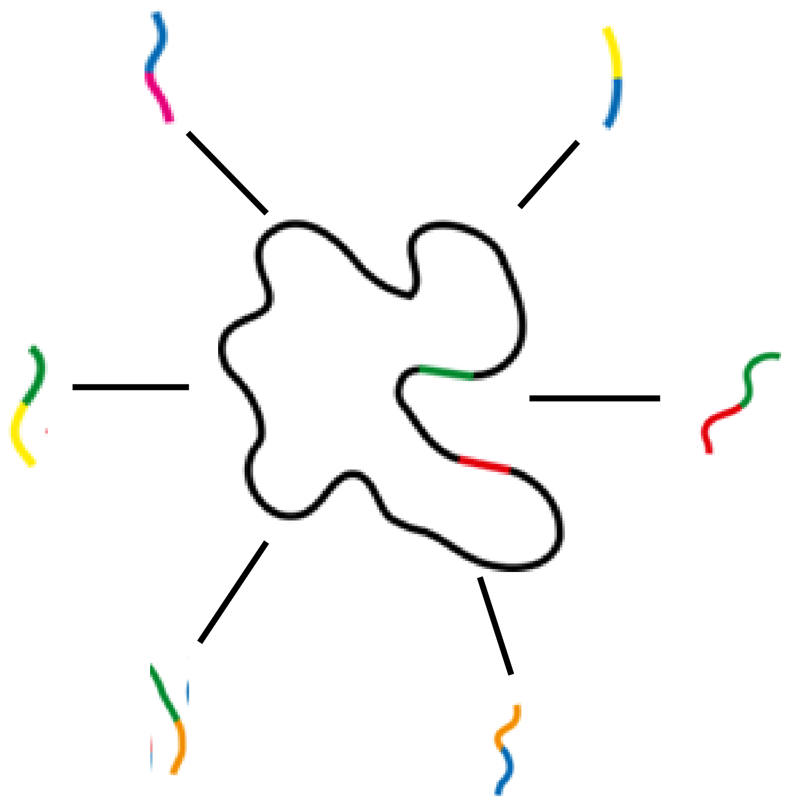


Atomic force microscope images

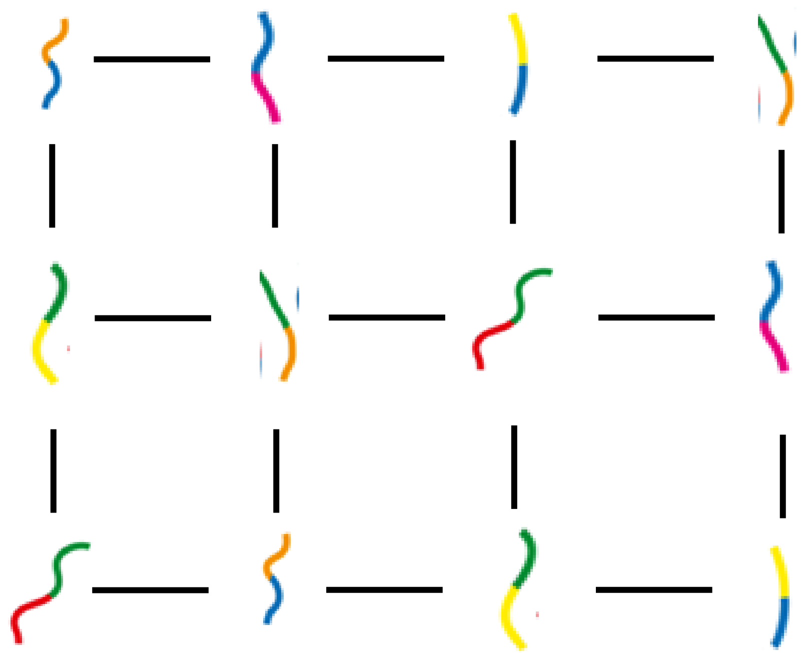
100 nm

Binding graphs

DNA origami: **star graph**
(all binding is between staples and scaffold)



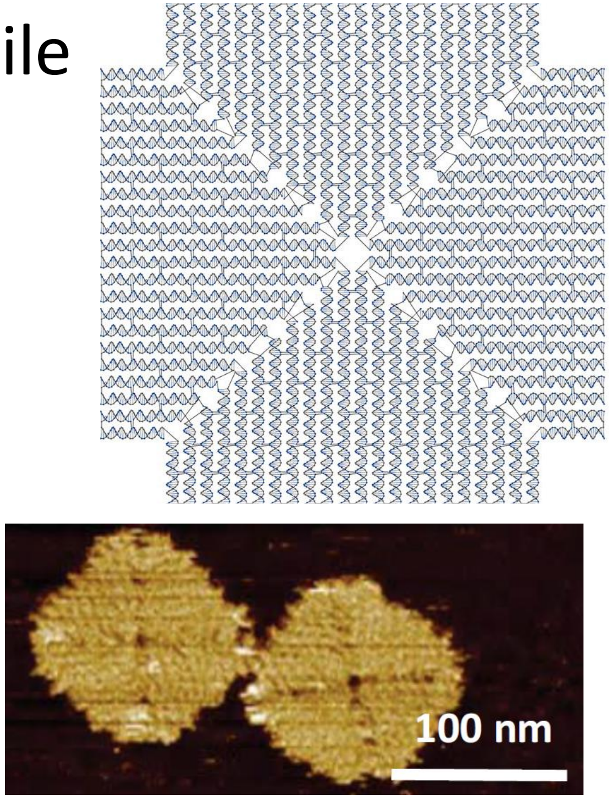
DNA tiles: **grid graph**
(tiles bind to each other, each has ≤ 4 neighbors)



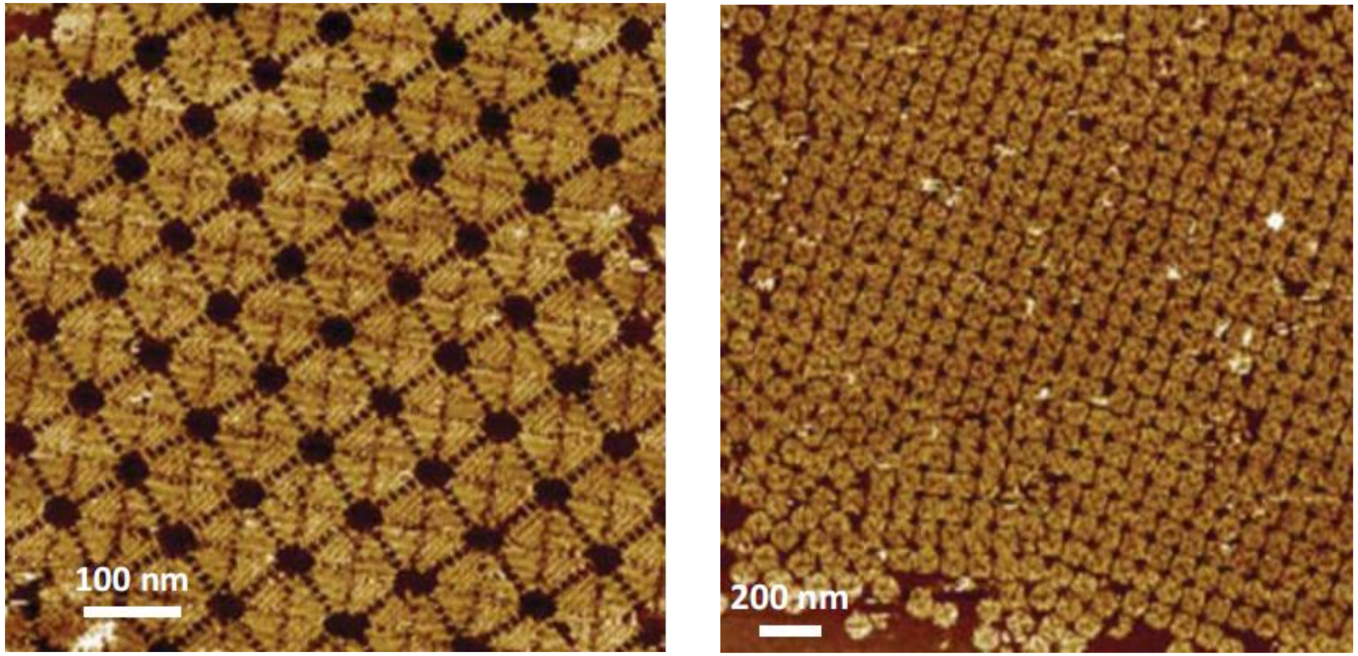
DNA tile self-assembly

monomers (“tiles” made from DNA) bind into a crystal lattice

tile



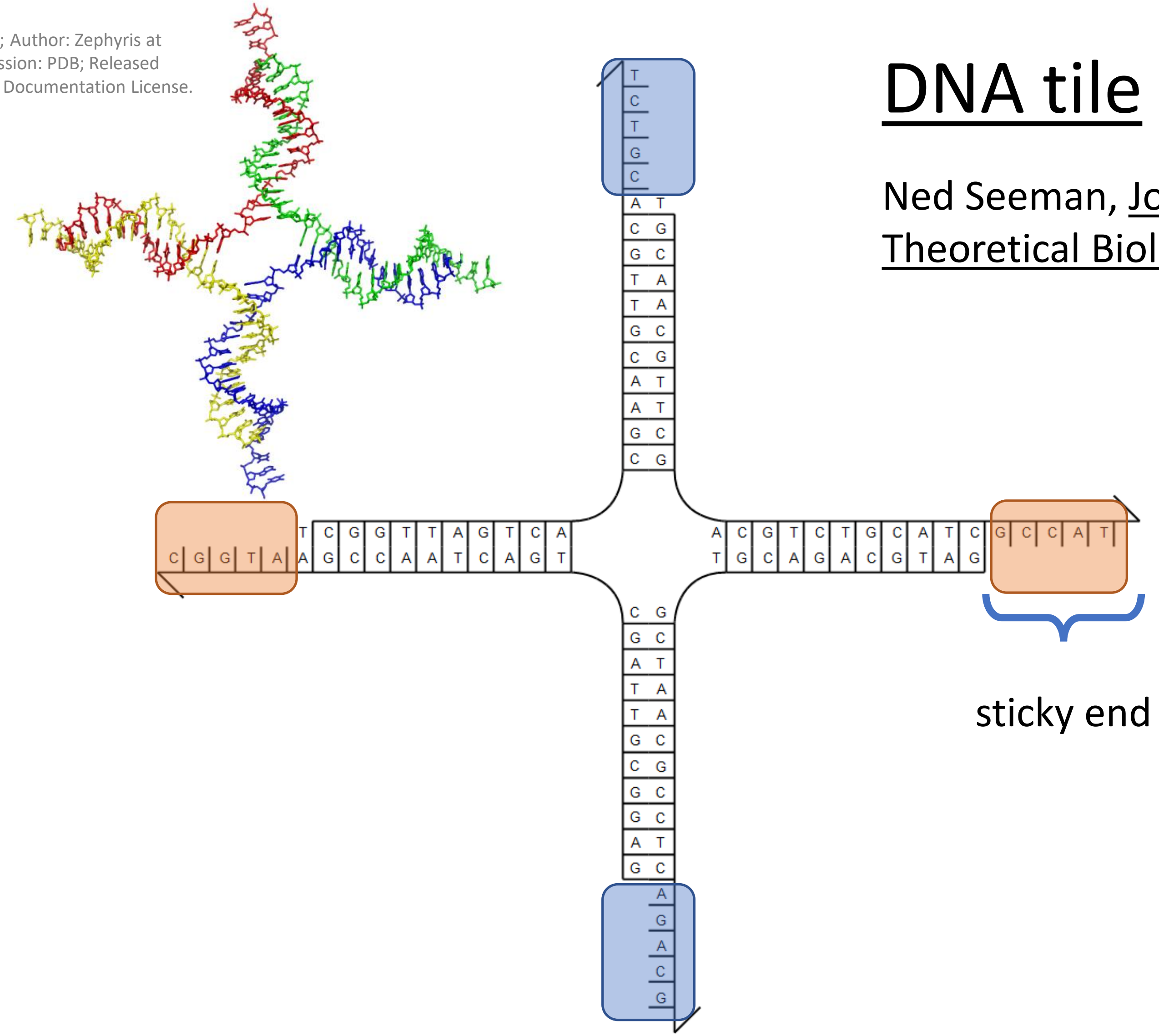
lattice



Source: *Programmable disorder in random DNA tilings*. Tikhomirov, Petersen, Qian, Nature Nanotechnology 2017

Practice of DNA tile self-assembly

Source:en.wikipedia; Author: Zephyris at en.wikipedia; Permission: PDB; Released under the GNU Free Documentation License.



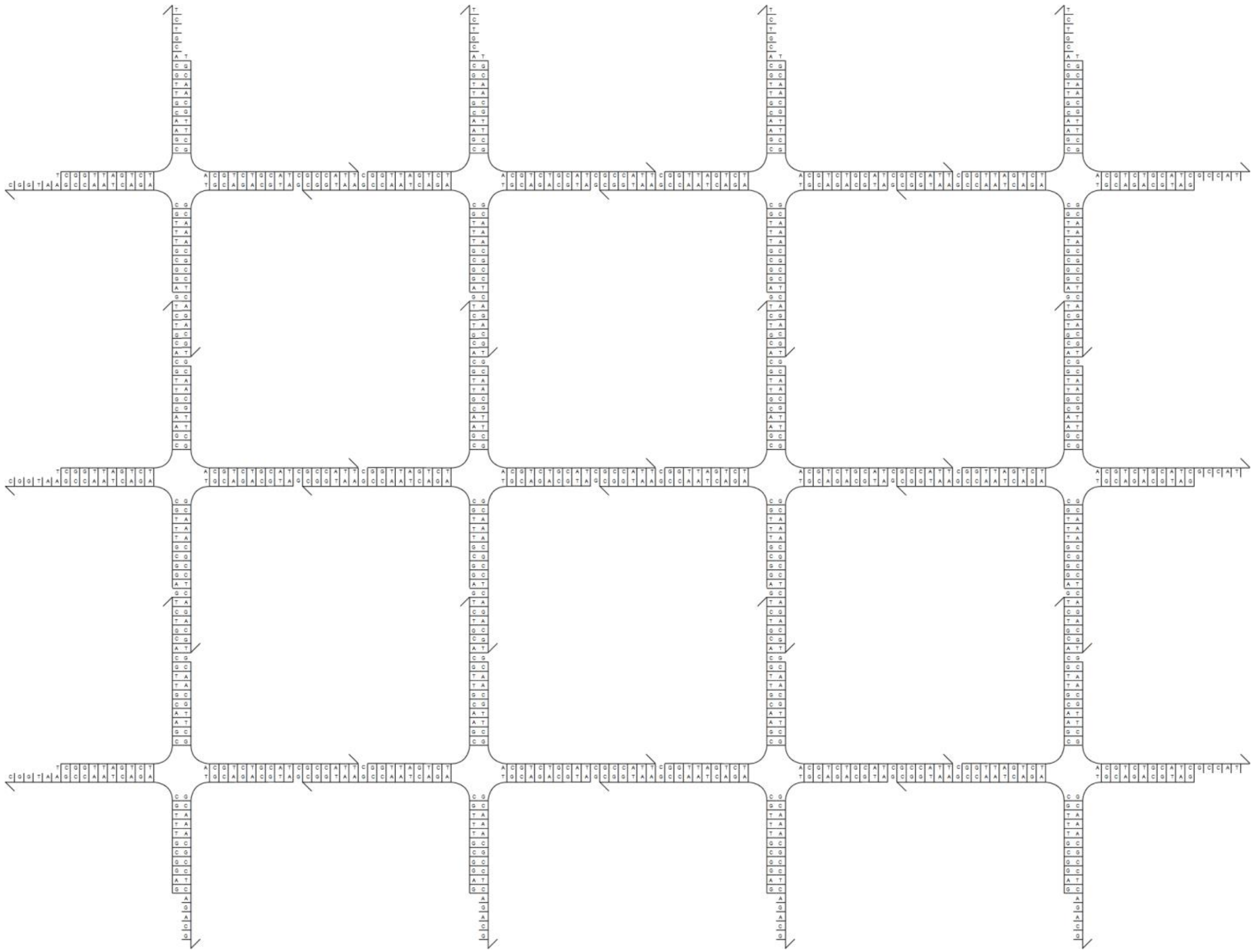
sticky end

DNA tile

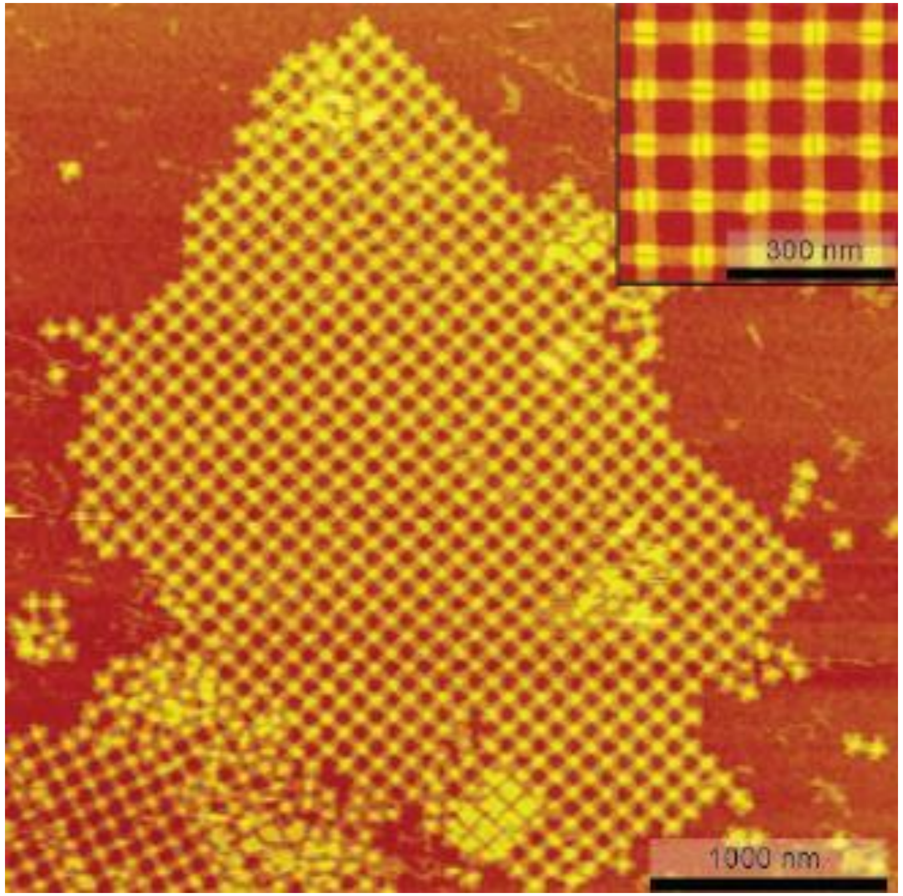
Ned Seeman, Journal of Theoretical Biology 1982

Practice of DNA tile self-assembly

Place many copies of DNA tile in solution…



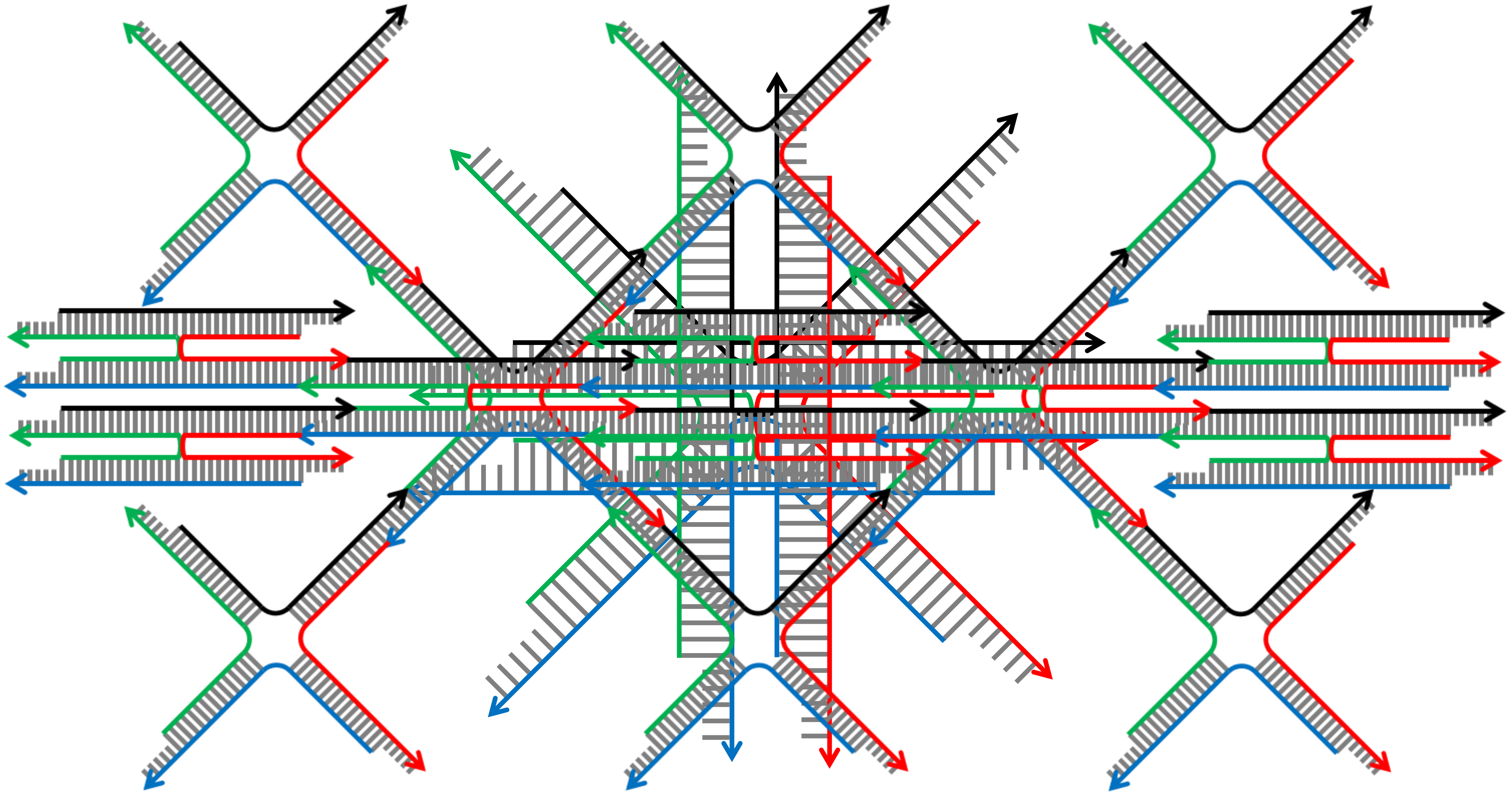
(not the same tile motif in this image)



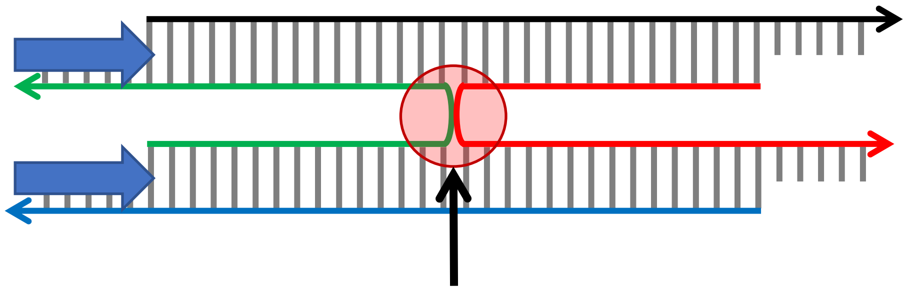
Liu, Zhong, Wang, Seeman, Angewandte Chemie 2011

Practice of DNA tile self-assembly

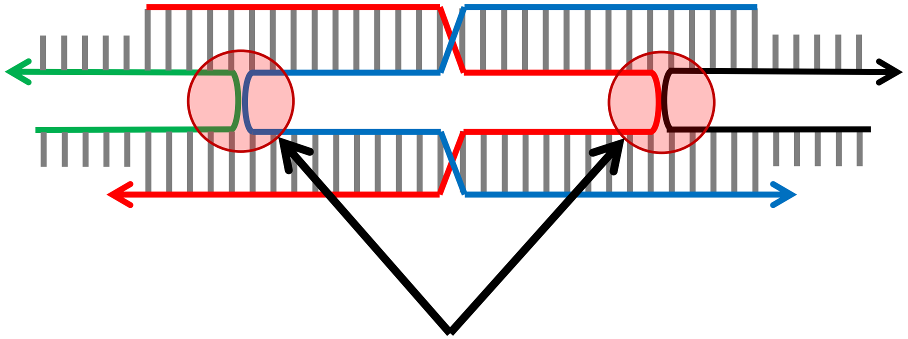
What really happens in practice to Holliday junction ("base stacking")



Practice of DNA tile self-assembly



single *crossover*



double crossover

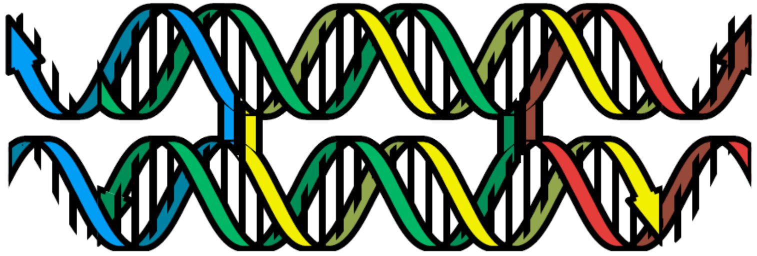
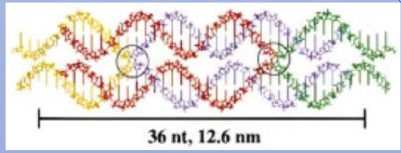
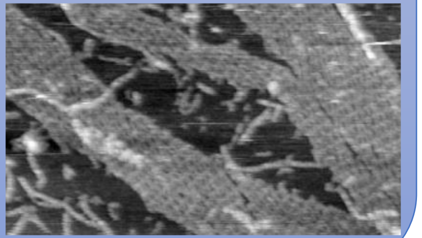


Figure from Schulman, Winfree, *PNAS* 2009

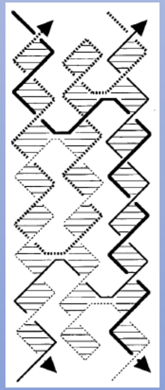
Practice of DNA tile self-assembly

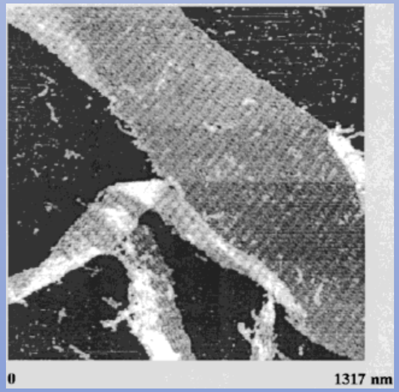
double-crossover tile (Winfree, Liu, Wenzler, Seeman, *Nature* 1998)



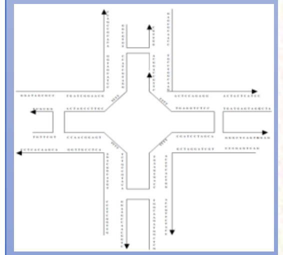


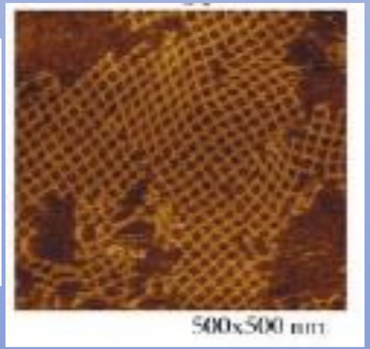
triple-crossover tile (LaBean, Yan, Kopatsch, Liu, Winfree, Reif, Seeman, *JACS* 2000)



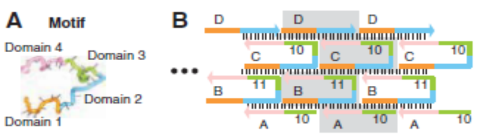


4x4 tile (Yan, Park, Finkelstein, Reif, LaBean, *Science* 2003)



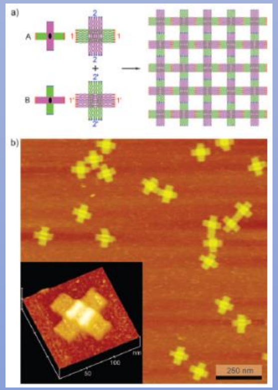


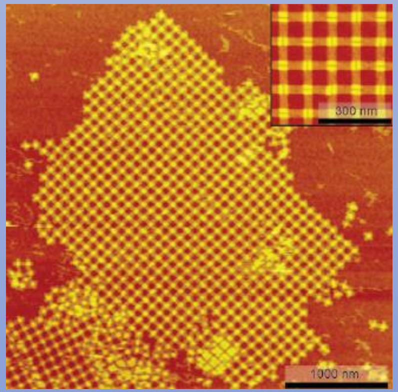
single-stranded tile (Yin, Hariadi, Sahu, Choi, Park, LaBean, Reif, *Science* 2008)



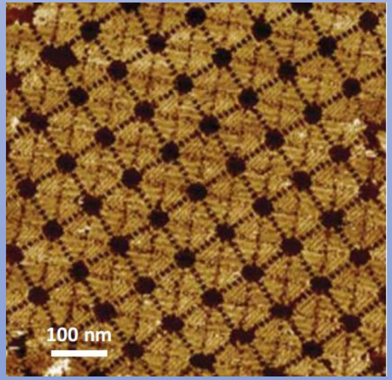
150 nm

DNA origami tile (Liu, Zhong, Wang, Seeman, *Angewandte Chemie* 2011)





Tikhomirov, Petersen, Qian, *Nature Nanotechnology* 2017



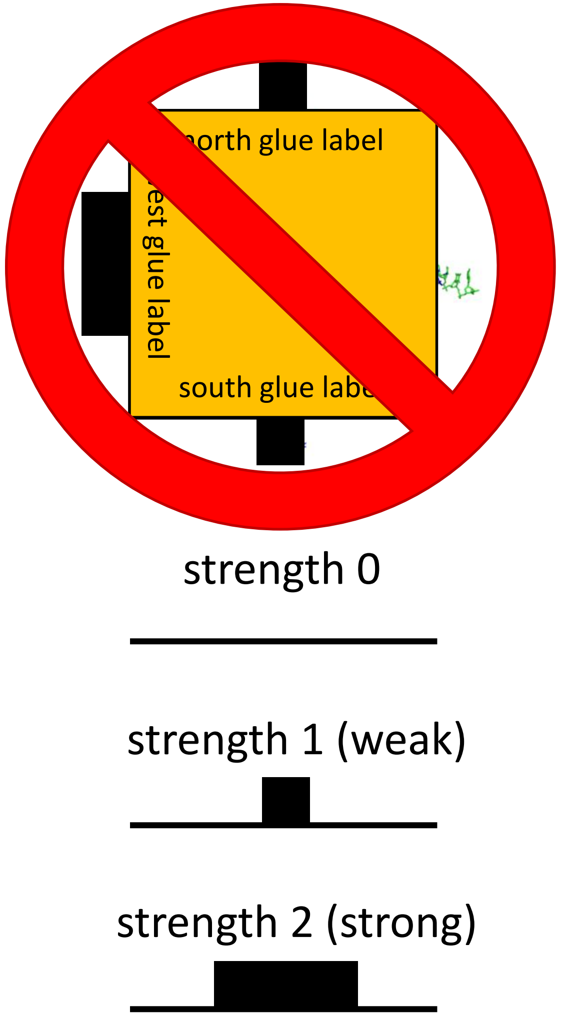
Theory of *algorithmic* self-assembly

What if…
… there is more than one tile type?
… some sticky ends are “weak”?

Erik Winfree

abstract Tile Assembly Model (aTAM)

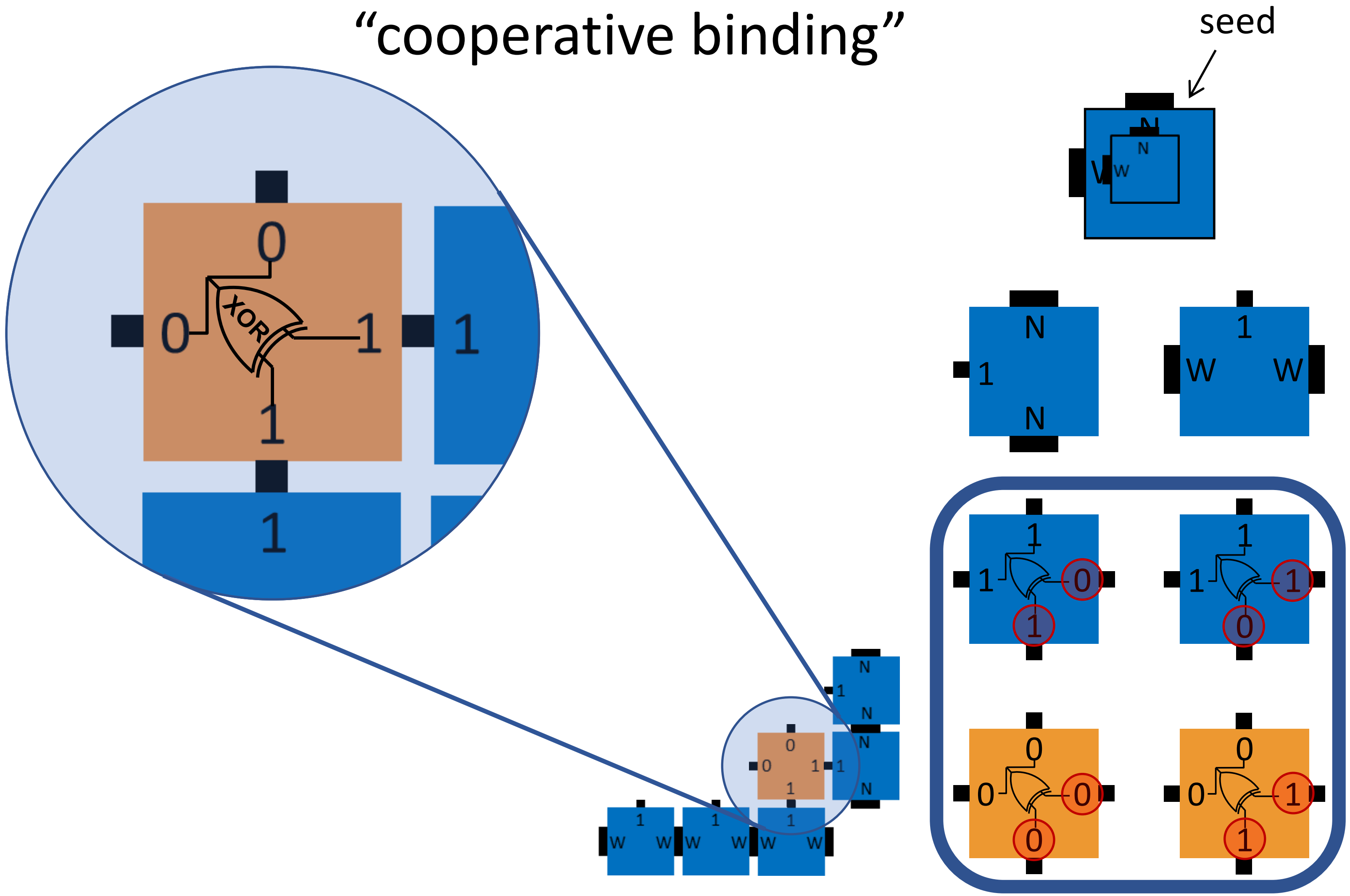
- **tile type** = unit square
- each side has a **glue** with a **label** and **strength** (0, 1, or 2)
- tiles cannot rotate

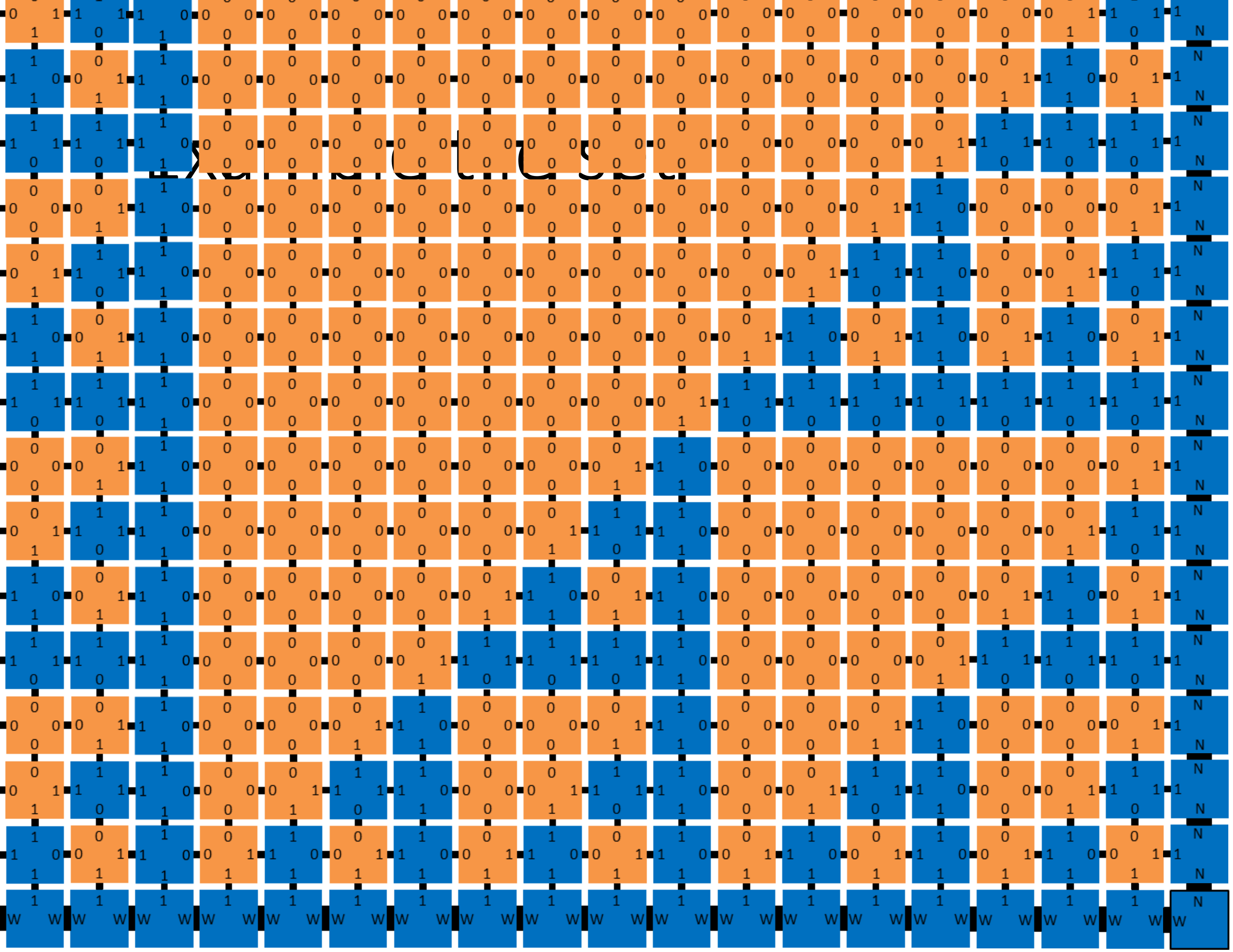


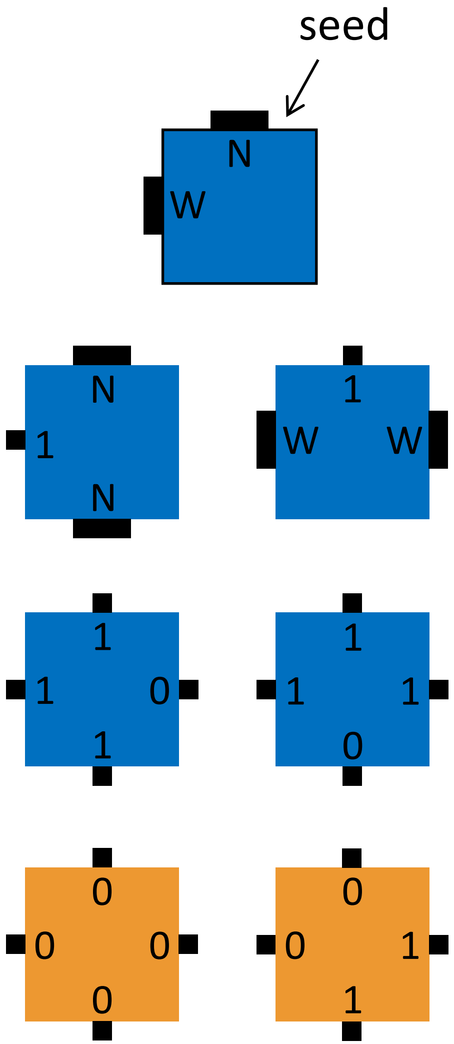
- finitely many tile **types**
- infinitely many **tiles**: copies of each type
- assembly starts as a single copy of a special **seed** tile
- tile can bind to the assembly if total binding strength ≥ 2 (two weak glues or one strong glue)

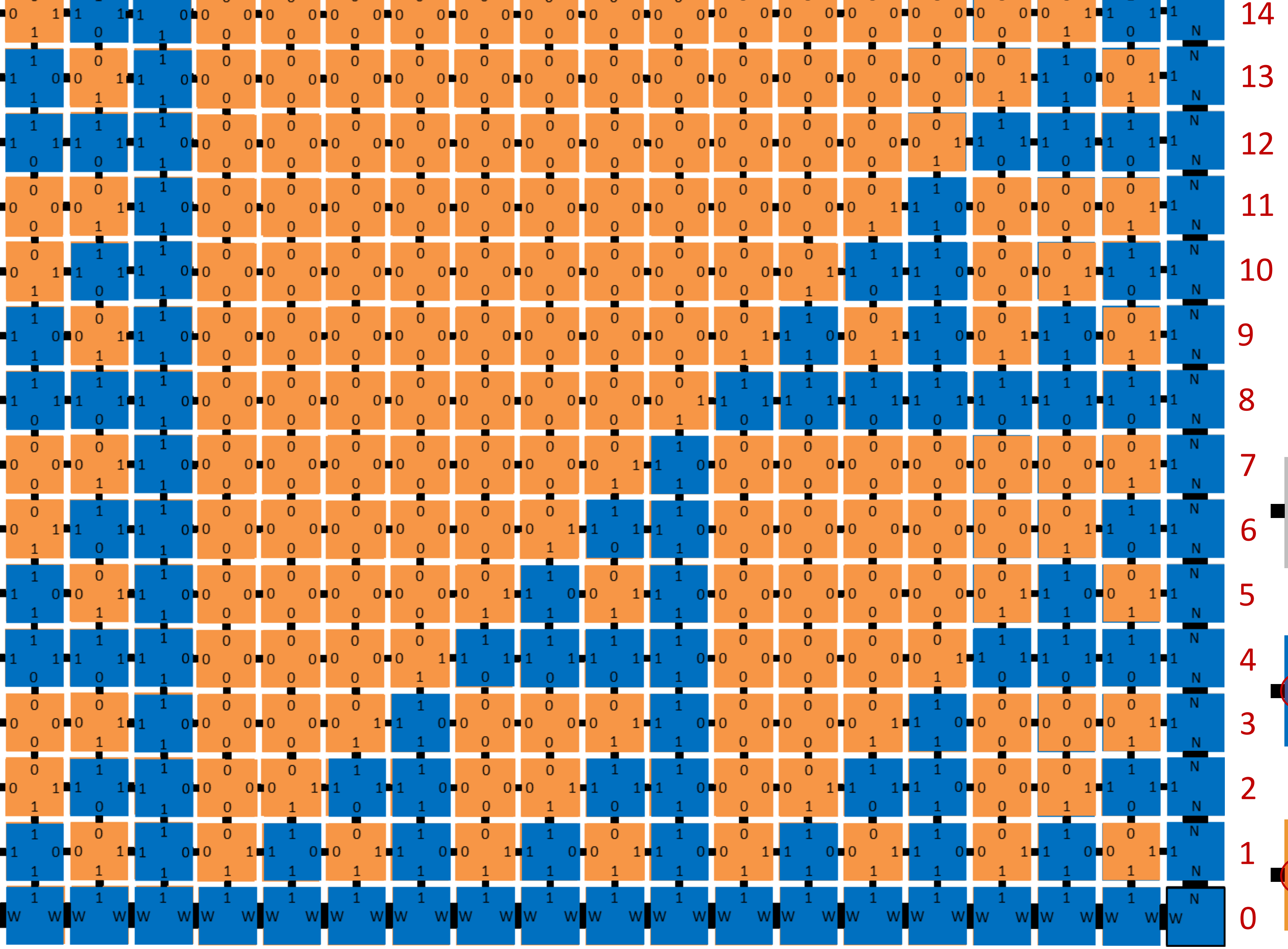
Erik Winfree, Ph.D. thesis, Caltech 1998

Example tile set

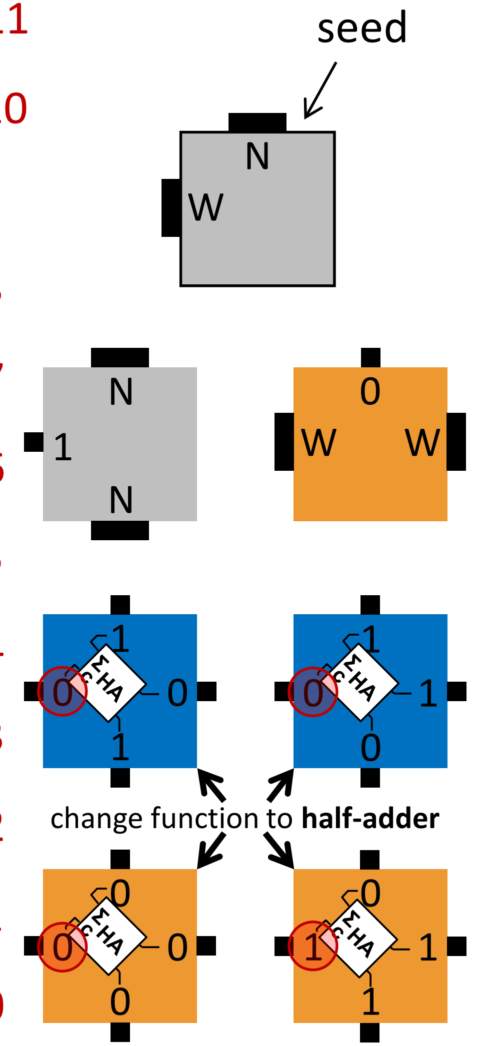





seed

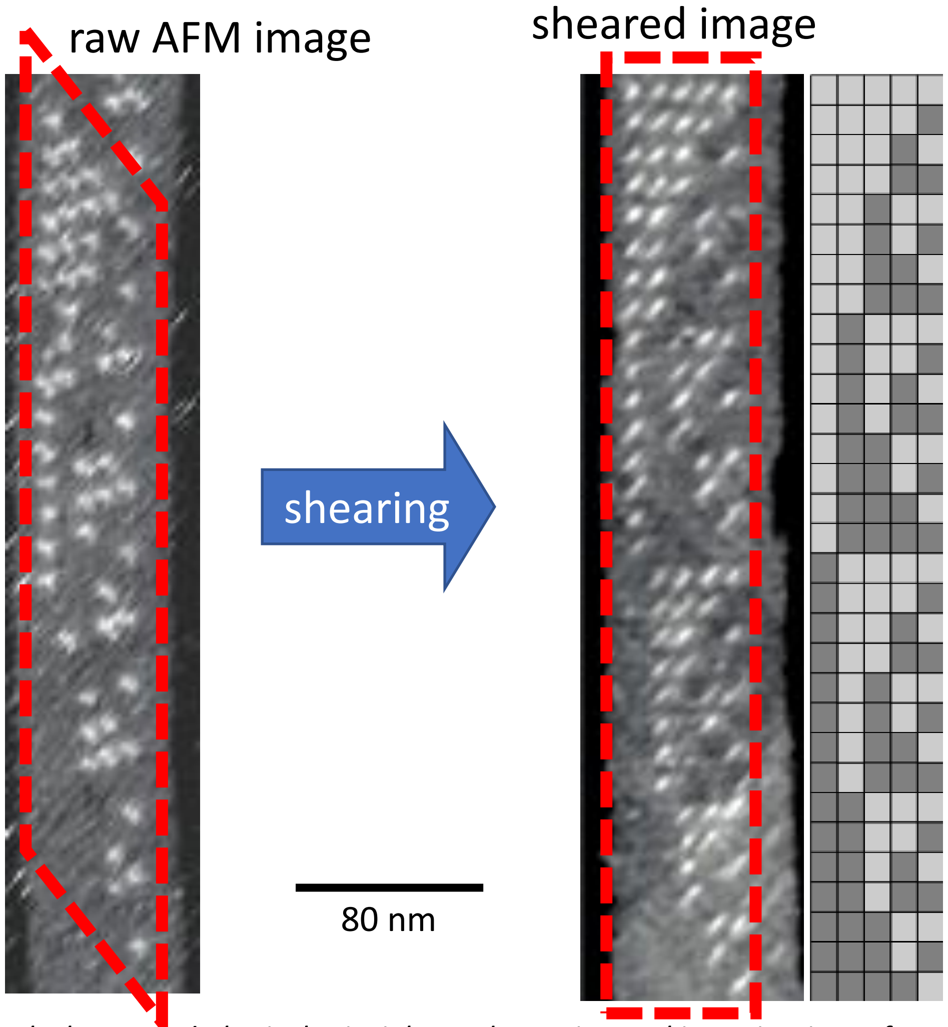


14
13
12
11
10
9
8
7
6
5
4
3
2
1
0



seed
N
W
N
1
N
0
W
W
change function to half-adder

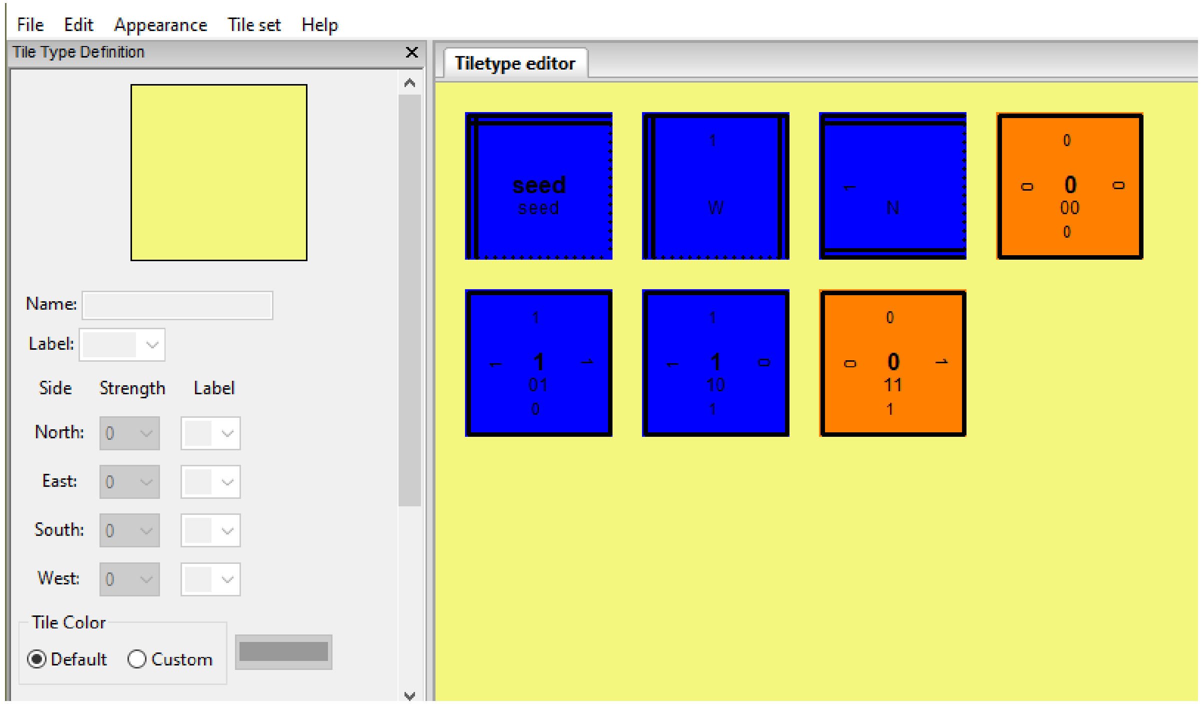
Algorithmic self-assembly in action

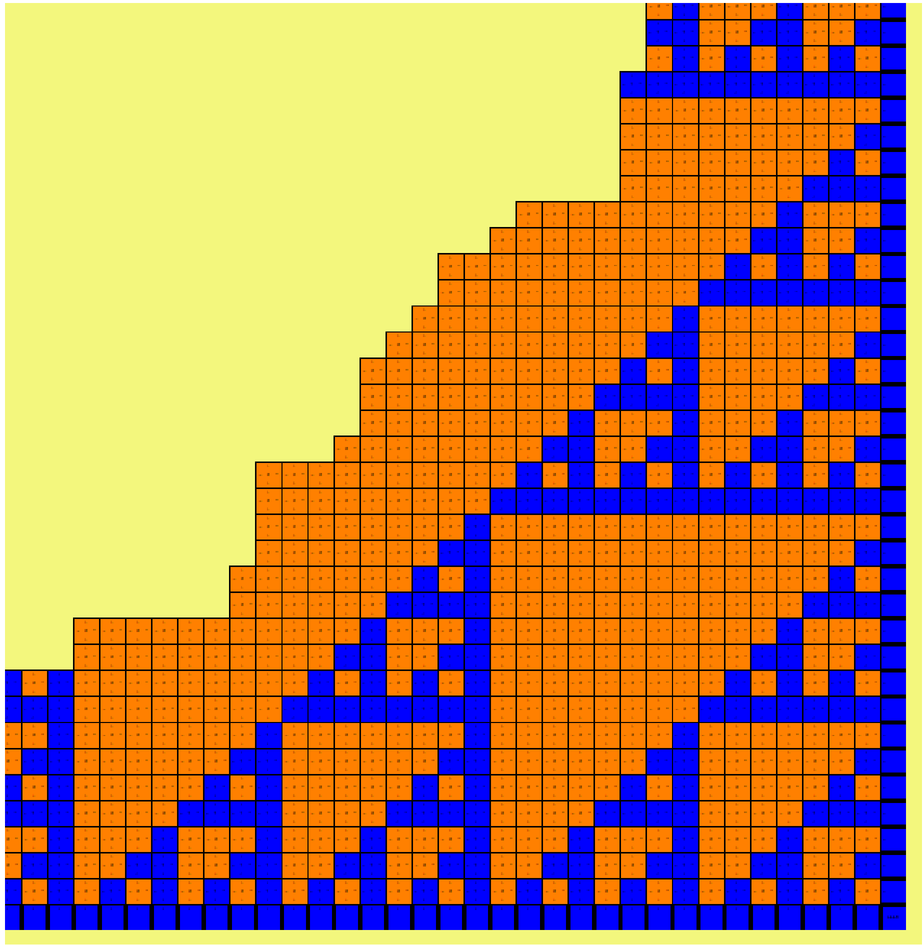


[*Crystals that count! Physical principles and experimental investigations of DNA tile self-assembly*, Constantine Evans, Ph.D. thesis, Caltech, 2014]

aTAM simulator (ISU TAS by Matt Patitz)

http://self-assembly.net/wiki/index.php?title=ISU_TAS
http://self-assembly.net/wiki/index.php?title=ISU_TAS_Tutorials
See also WebTAS by the same group:
http://self-assembly.net/software/WebTAS/WebTAS-latest/





VersaTile (by Eric Martinez and Cameron Chalk) https://github.com/ericmichael/polyomino
and xgrow (by Erik Winfree) https://www.dna.caltech.edu/Xgrow/

Tile complexity of squares

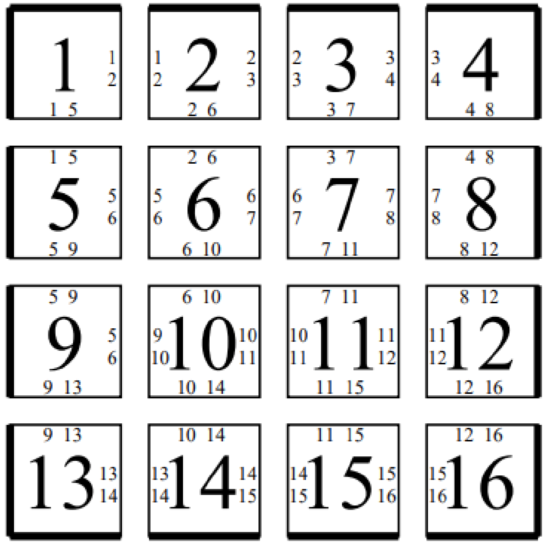
Tile complexity

- Resource bound to minimize, like time or memory with a traditional algorithm.
- Why minimize number of tile types?
  - Physically synthesizing new tile types is difficult.
  - Designing DNA sequences for new tile types is difficult. (DNA sequence design is tougher when more DNA sequences are present.)
  - But due to how modern synthesis technologies work, once a tile type is designed, making 50 quadrillion copies of the tile is as easy as making one copy.
- So, we ask: how many unique tile types to we need to self-assemble some shapes?
- We start with n x n squares as the "simplest" benchmark shape.
  - Why not a 1 x n line as an even simpler shape? What is its tile complexity?
- [*Note: we have not formally defined the aTAM yet… first let's build intuition.*]

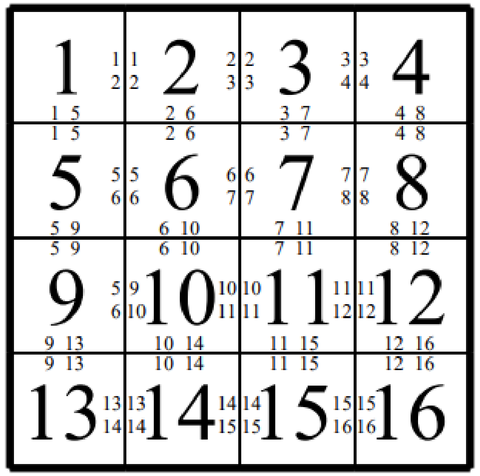
The program size complexity of self-assembled squares

Question: How many tile types do we need to self-assemble an *n* x *n* square?

Concretely: how to assemble a 4 x 4 square?



All glues are strength 2
(alternately: all are strength 1 and *temperature* τ = 1)



How many tile types does this construction need in general to assemble an *n* x *n* square?

n^2

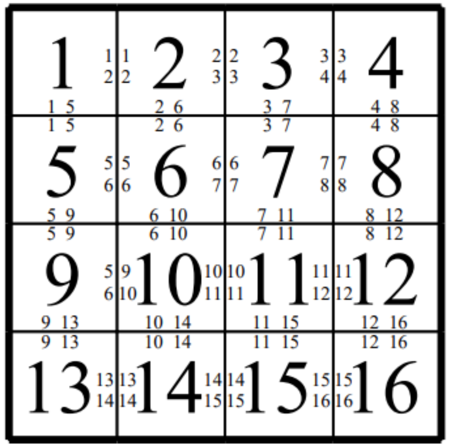
https://www.dna.caltech.edu/Papers/squares_STOC.pdf
This paper is directly responsible for convincing many theoretical computer scientists that DNA self-assembly is worth studying.

Tile complexity at temperature $\tau = 1$ (i.e., no cooperative binding allowed)

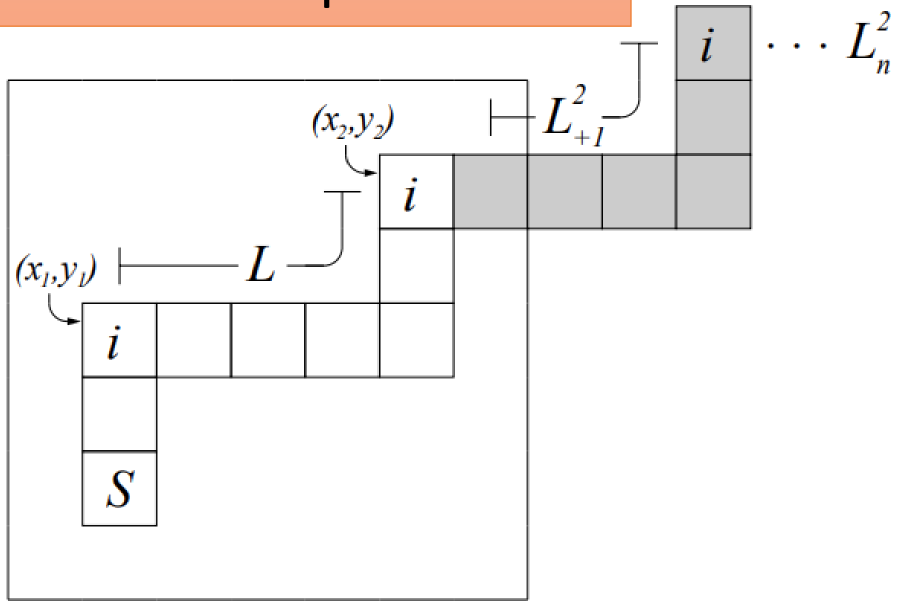
Is n^2 optimal?
Can we do better?

Theorem: At temperature $\tau = 1$, if all pairs of adjacent tiles bind with positive strength, then for every positive integer n, n^2 tile types are <u>necessary</u> to self-assemble an n x n square.

Note all pairs of adjacent tiles bind with positive strength:



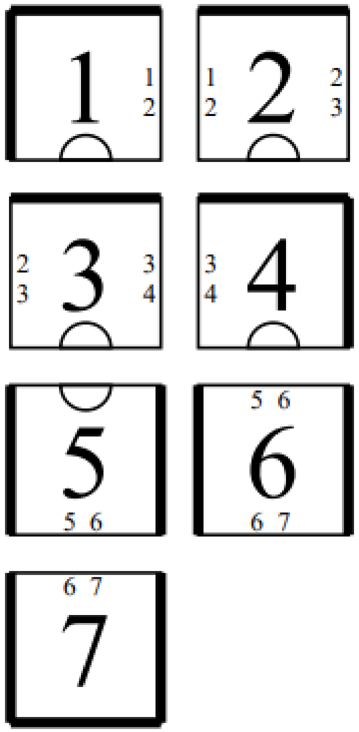
Proof: Suppose for contradiction we use the same tile type i at positions (x_1,y_1) and (x_2,y_2). Then they have a path L between them with all positive-strength glues, and this can happen instead:

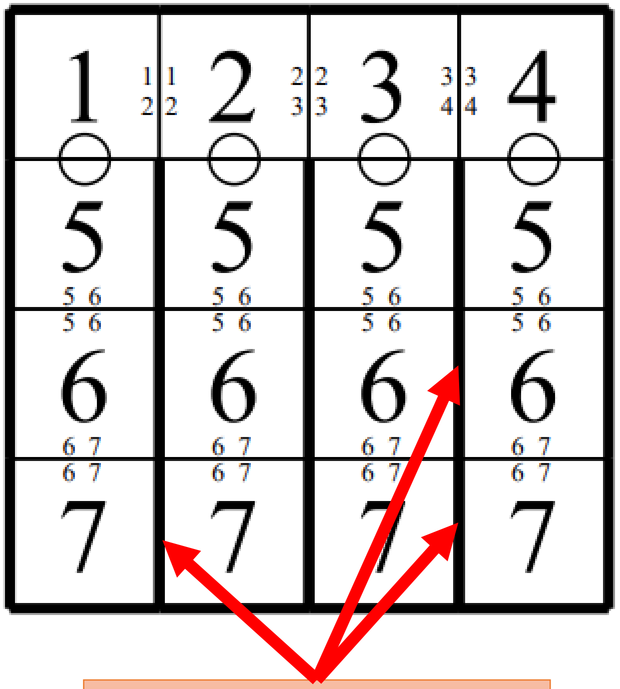


Tile complexity at temperature $\tau = 1$, where not all adjacent tiles are bound

Is n^2 still optimal?

No!





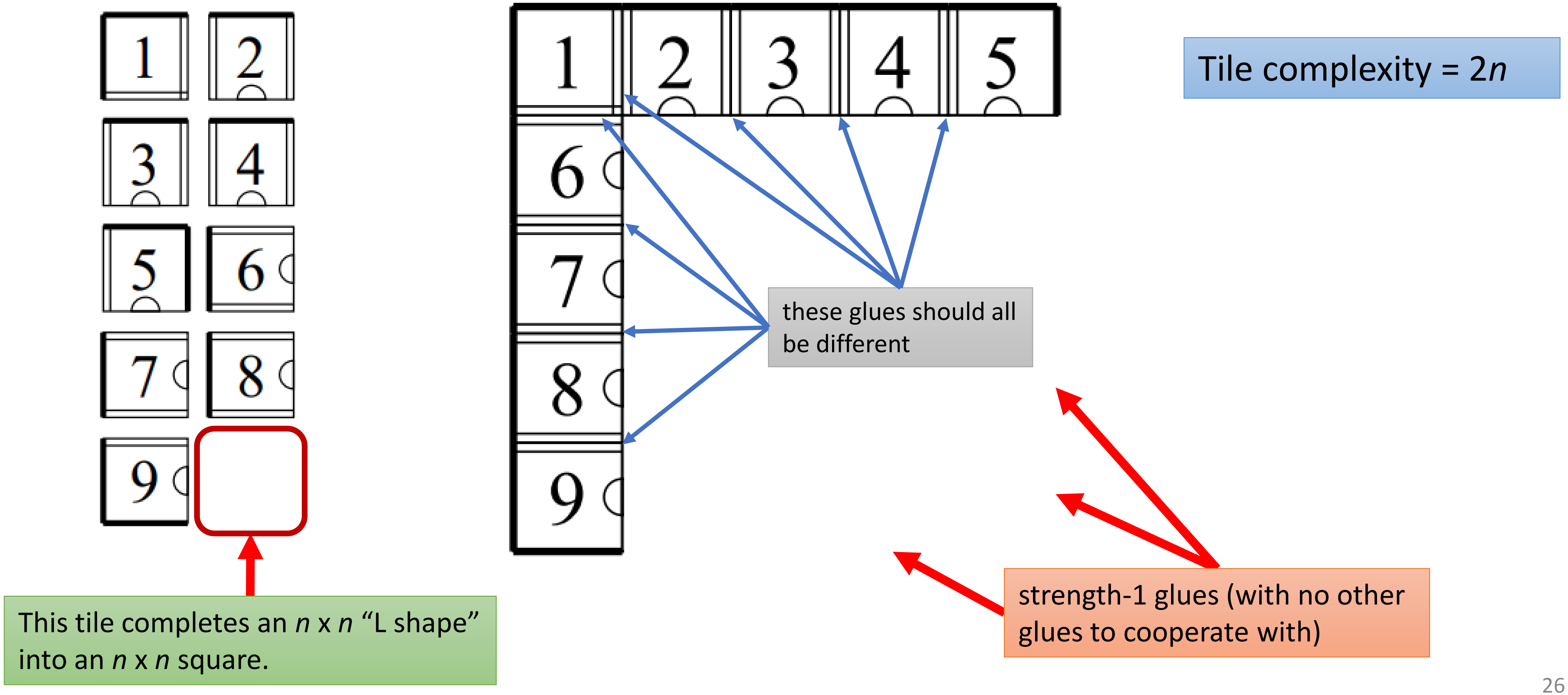
strength-0 glues

Tile complexity of this construction?

$2n - 1 = O(n)$

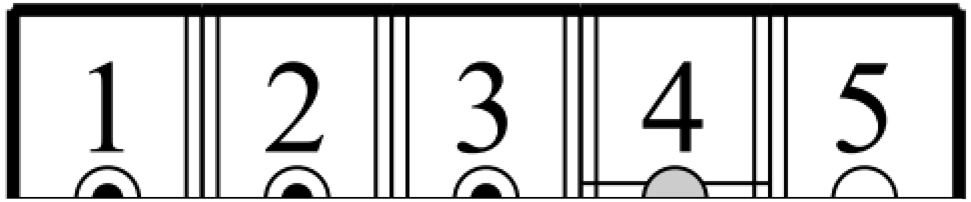
Conjecture: The temperature $\tau = 1$ tile complexity of an n x n square is $\Omega(n)$.
(most recent progress:
https://arxiv.org/abs/1902.02253
https://arxiv.org/abs/2002.04012)

Tile complexity at temperature $\tau = 2$ (i.e., cooperative binding allowed)

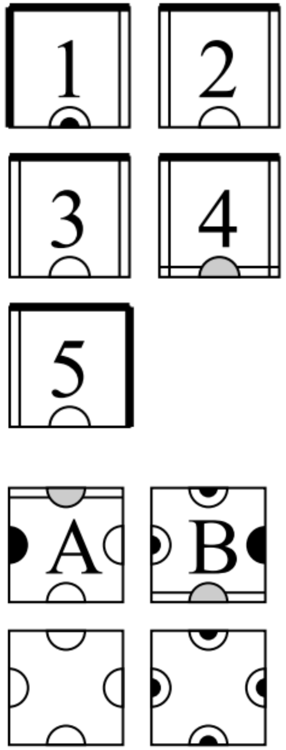


Tile complexity at temperature $\tau = 2$

Goal: complete a 1 x *n* line into an *n* x *n* square



Tile complexity = *n* + 4



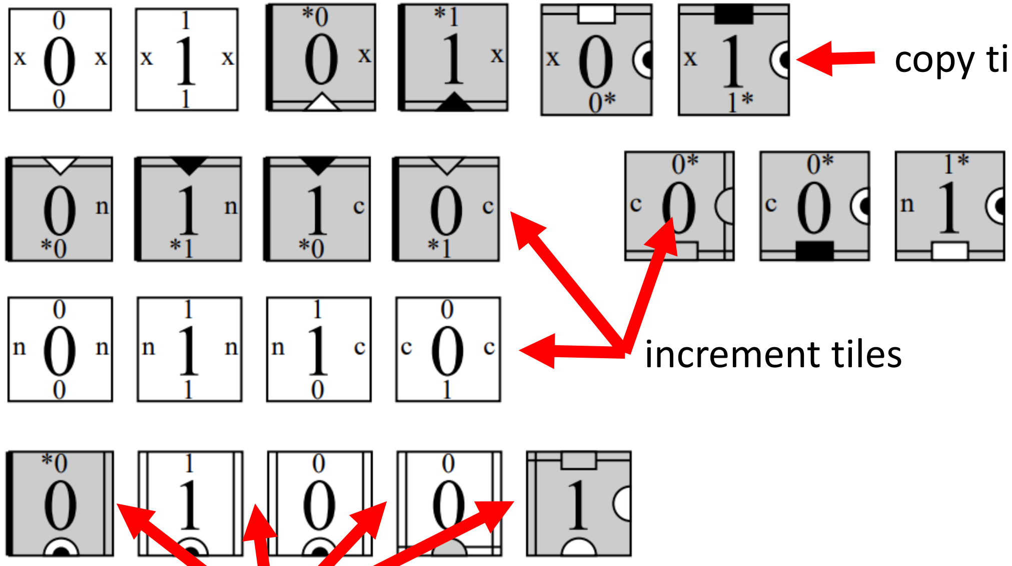
How to get *sublinear* tile complexity?

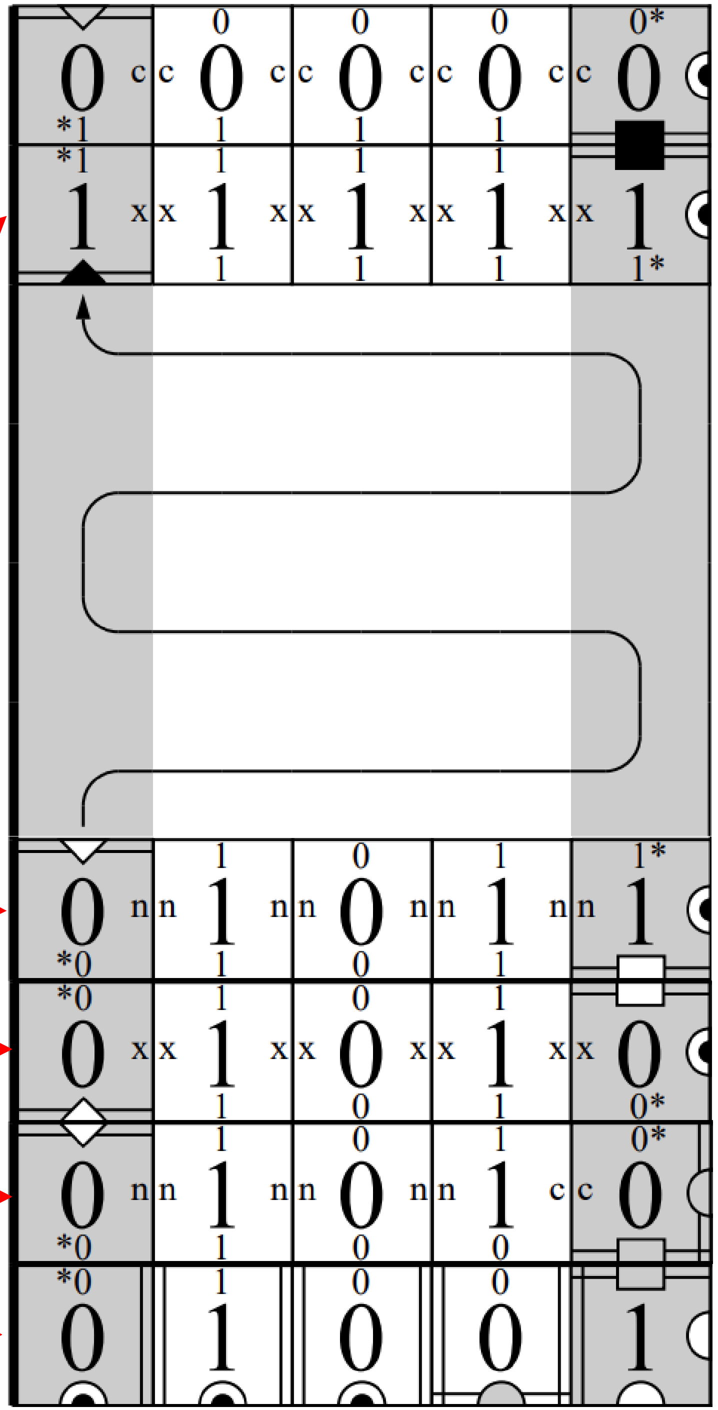
Logarithmic tile complexity at temperature $\tau = 2$

Goal: rectangle of height n using $O(\log n)$ tile types

for width of k bits, stops when it reaches what value?

“zig-zag counter”

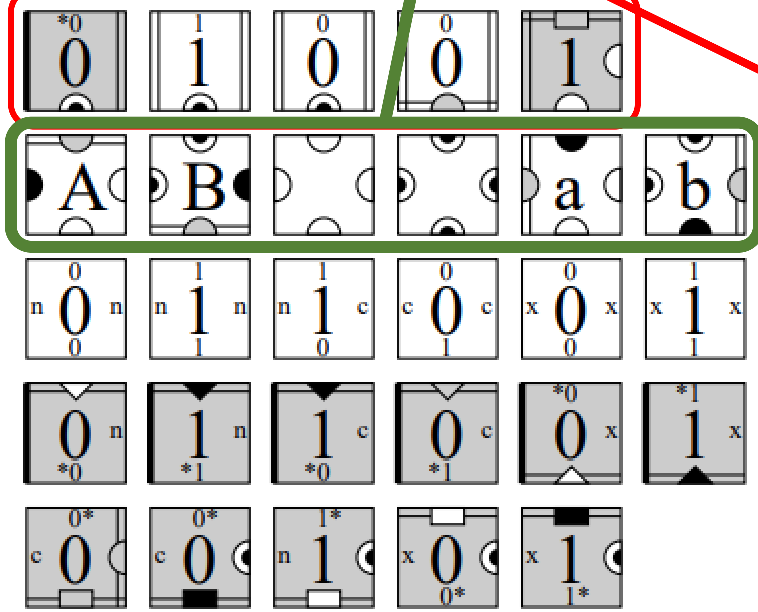


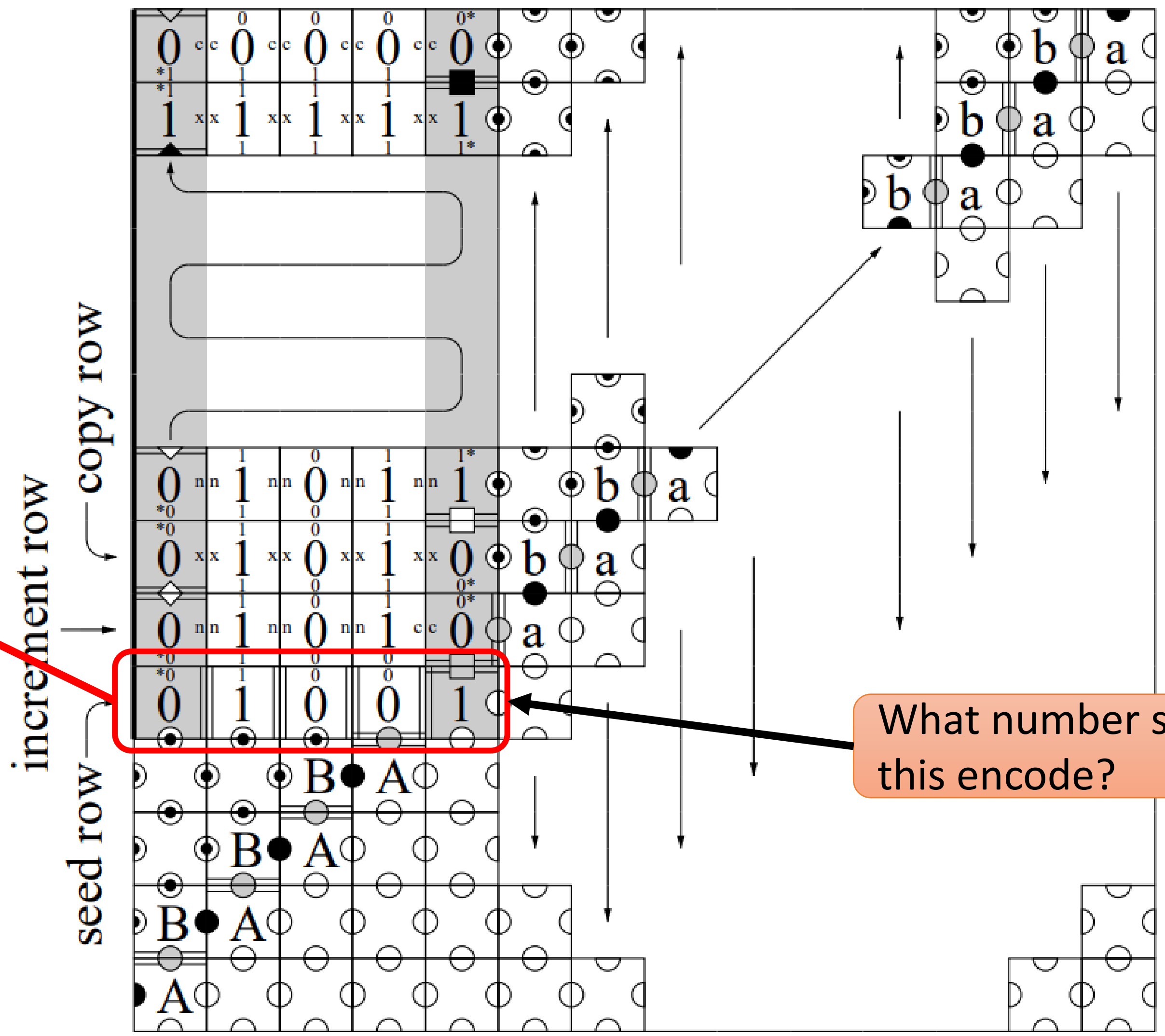


Logarithmic tile complexity at temperature $\tau = 2$

A few more "filler" tiles complete the ≈n x log n rectangle into an n x n square.

tile complexity = log n + 23





What number should this encode?

$\Omega(\log n / \log \log n)$ tile complexity lower bound for n x n squares

- What does $\Omega(\log n / \log \log n)$ tile complexity lower bound mean?
  - First let's think about what we already showed: what does $O(\log n)$ tile complexity upper bound mean? **For all *n***, $O(\log n)$ tile types is enough to self-assemble an n x n square.
  - A lower bound looks like: **For infinitely many *n***, $o(\log n / \log \log n)$ tile types is not enough to self-assemble an n x n square.
- How to prove? It's a counting argument:
  - Count number of (functionally distinct) tile systems with fewer than ¼ log p / log log p tile types.
    - We'll show that it's fewer than p.
  - There are p squares with width n between p+1 and 2p; each needs a different tile system.
  - By pigeonhole, some n x n square cannot be assembled with < ¼ log p / log log p tile types.
  - Since $p \leq n/2$, we have ¼ log p / log log p ≤ ¼ log n / log log n.
  - Since we can do this for every positive integer p, there are infinitely many n that require more than ¼ log n / log log n tile types (a stronger result holds: "most" values of n require that many)

How many tile systems with k tile types?

- **Goal**: show that there are fewer than p (“functionally distinct”) tile systems with $k = \frac{1}{4} \log p / \log \log p$ tile types.
- How many have exactly k tile types? Count each of the ways to define the tile system:
  a) How many different glues can we have? $4k$
  b) How many ways can we choose the 4 glues for one tile type? $a^4 = (4k)^4$
  c) How many ways to choose the glues for all k tile types? $b^k = (4k)^{4k}$
  d) How many ways to choose the seed tile? k
- How many tile systems? $c \cdot d = k(4k)^{4k}$

How many tile systems with k tile types?

- Number of tile systems with <u>exactly</u> k tile types: $\leq k(4k)^{4k}$
- Number of tile systems with <u>at most</u> k tile types: $\leq k^2(4k)^{4k}$
- Recall $k = ¼ \log p / \log \log p$; by algebra (see notes), $k^2(4k)^{4k} < p$.
- By pigeonhole principle, for some width n with $p < n \leq 2p$, the n x n square is not self-assembled by one of these $k^2(4k)^{4k}$ tile systems. Since those are all the tile systems with at most k tile types, the n x n square requires **more** than ¼ log p / log log p tile types to self-assemble. **QED**

"Descriptional Complexity" proof

Fact: "most" integers n require $\geq \log n$ bits to "describe".
(Though some require fewer: 1111111111111111111111 can be described by its length 22 in binary: 10110)

- Can be formalized with *Kolmogorov complexity*
  - https://en.wikipedia.org/wiki/Kolmogorov_complexity
- We can "describe" n with a tile system that self-assembles an n x n square.
- How many bits do we need to describe a tile system with k tile types?
  - $\log(4k)$ to describe one of the $4k$ glues, e.g., 8 glues: 000, 001, 010, 011, 100, 101, 110, 111
  - $4 \log(4k)$ to describe one tile type consisting of 4 glues, e.g., tile b = (010, 011, 111, 100)
  - $4k \log(4k)$ to describe all k tile types, plus $\log k$ to give index of the seed.
  - So $O(k \log k)$ bits total.
- For any n in the Fact, $\log n = O(k \log k)$, i.e., $k = \Omega(\log n / \log \log n)$.

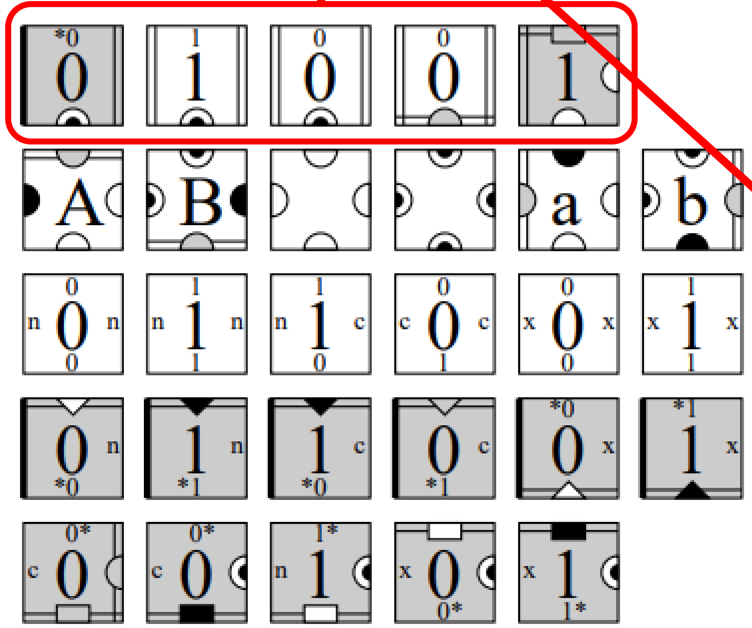
Note: we're ignoring glue strengths here; adds 2 bits per glue to describe at temperature 2.
(since there are 3 possible strengths 0, 1, 2);
see http://doi.org/10.1007/s00453-014-9879-3 for handling higher-temperature systems.

Which bound is tight?

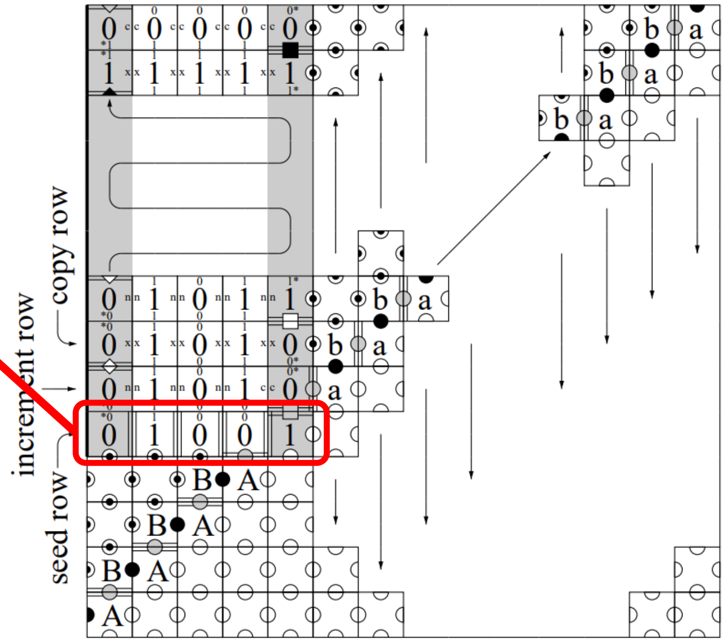
1. All n x n squares can be assembled with $O(\log n)$ tile types; can we get it down to $O(\log n / \log \log n)$?
2. Or do we need $\Omega(\log n)$ tile types to assemble infinitely many n x n squares?

Improved upper bound: self-assembling an n x n square with $O(\log n / \log \log n)$ tile types

tile complexity = $O(\log n)$ + 23



Recall:



Idea:

1) Use same 23 tiles that turn the seed row encoding a binary integer n' (related to n) into an n x n square.

2) Create the binary seed row from only $\log n / \log \log n$ tiles.

Creating a row of log n glues with arbitrary bit string $s \in \{0,1\}^{\log n}$ using O(log n / log log n) tile types

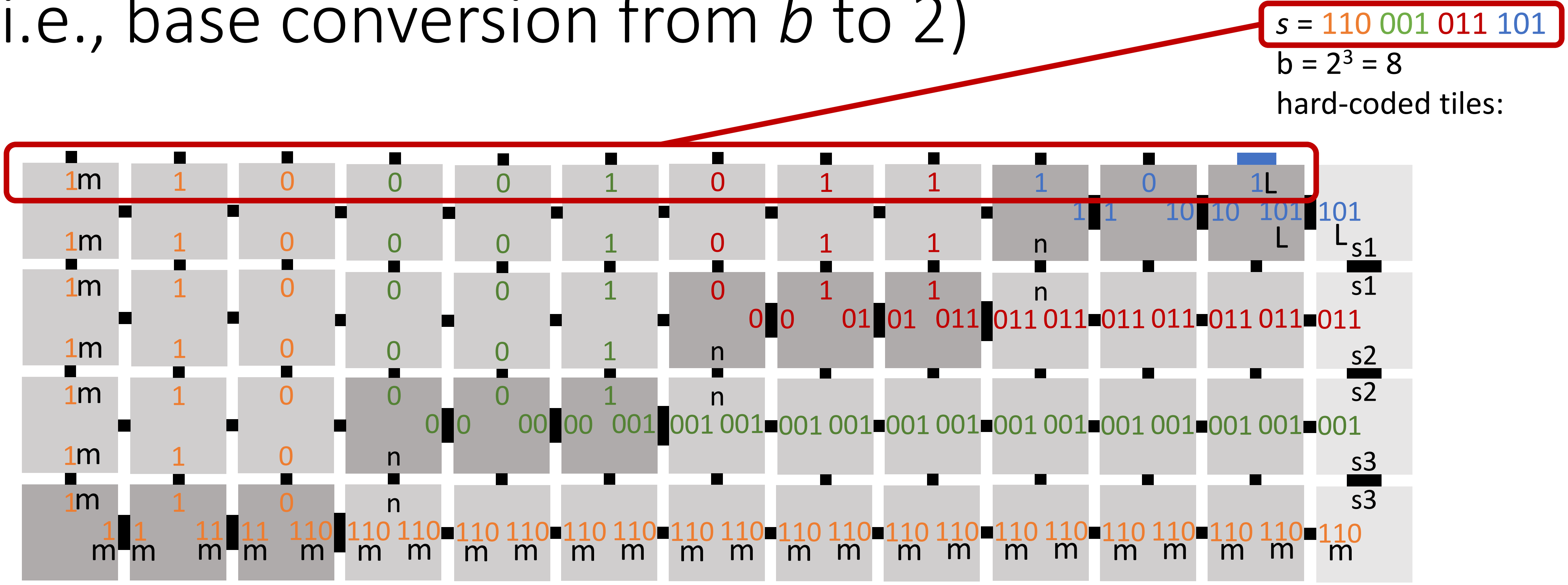
- Key idea: choose larger power-of-two base $b = 2^k$, with $b \approx \log n / \log \log n$, and convert from base b to base 2.
- How many base-b digits needed to represent a log(n)-bit integer?
- Each base-b digit is k bits
    - e.g., if $b=2^3=8$, then 0=000 1=001 2=010 3=011 4=100 5=101 6=110 7=111
    - e.g., the octal number 7125_8 in binary is 111001010101_2
    - need $\log(n) / k = \log(n) / \log(\log n / \log \log n) = \log(n) / (\log \log n - \log \log \log n) \approx \log(n) / \log \log n$ base-b digits.

Creating a row of log n glues with arbitrary bit string $s \in \{0,1\}^*$ using log n / log log n tile types (i.e., base conversion from b to 2)

s = 110 001 011 101

$b = 2^3 = 8$

hard-coded tiles:



"almost" works… what's missing?

mark glues of most and least significant bit

Formal definition of aTAM

abstract Tile Assembly Model (aTAM), formal definition

- Fix a finite alphabet Σ. A **glue** is a pair $g = (\ell,s) \in \Sigma^* \times \mathbb{N}$, with **label** ℓ and **strength** s.
- A **tile type** is a 4-tuple of glues $t \in (\Sigma^* \times \mathbb{N})^4$, with each glue listed in order north, east, south, west.
  - Define unit vectors N = (0,1), S = (0,–1), E = (1,0), W = (–1,0)
  - For $d \in$ {N, E, S, W}, let d^* denote the **opposite direction** of d, i.e., N* = S, S* = N, E* = W, W* = E.
  - Let t[N], t[E], t[S], t[W] be the glues of t in order.
  - T denotes the set of tile types.
- An **assembly** is a partial function $\alpha: \mathbb{Z}^2 \dashrightarrow T$, such that dom α (set of points where α is defined) is connected.
  - a partial function indicating, for each $(x,y) \in \mathbb{Z}^2$, which tile is at (x,y), with $\alpha(x,y)$ undefined if no tile appears there.
- Let S_α = dom α denote the **shape** of α. Let $|\alpha| = |S_\alpha|$.
- Given $p,q \in S_\alpha$, two tiles $t_p = \alpha(p)$ and $t_q = \alpha(q)$ **interact** (a.k.a. **bind**) if:
  - $\|p - q\|_2 = 1$ (*positions* $p \in \mathbb{Z}^2$ *and* $q \in \mathbb{Z}^2$ *are adjacent*)
  - letting $d = q - p$ (*the direction pointing from p to q*), $t_p[d] = t_q[d^*]$ (*the glues match where* t_p *and* t_q *touch*)
  - $t_p[d]$ has positive strength (*the glues are not zero-strength*)
- Let $B_\alpha = (V,E)$ denote the **binding graph** of α, where
  - $V = S_\alpha$
  - E = { (p,q) | $\alpha(p)$ and $\alpha(q)$ interact }
  - B_α is a *weighted*, *undirected* graph: Each edge's weight is the strength of the glue it represents.
- Given $\tau \in \mathbb{N}^+$, α is **τ-stable** if the minimum weight cut of B_α is at least τ.
  - i.e., to separate α into two pieces requires breaking bonds of strength at least τ.

abstract Tile Assembly Model (aTAM), formal definition

- Given assemblies $\alpha,\beta: \mathbb{Z}^2 \dashrightarrow T$, we say α is a **subassembly** of β, written $\alpha \sqsubseteq \beta$ if
  - $S_\alpha \subseteq S_\beta$ (*α is contained in* β), and
  - for all $p \in S_\alpha$, $\alpha(p) = \beta(p)$ (α *and* β *agree on tile types wherever they share a position*)

Question: If $\alpha \sqsubseteq \beta$, can α grow into β?

- We say $\Theta = (T,\sigma,\tau)$ is a **tile system**, where T is a finite set of tile types, $\tau \in \mathbb{N}^+$ is the **temperature**, and $\sigma: \mathbb{Z}^2 \dashrightarrow T$ is the finite, τ-stable **seed assembly**.
- We say **α produces β in one step**, denoted $\alpha \to_1 \beta$, to denote that $\alpha \sqsubseteq \beta$, $|S_\beta \setminus S_\alpha| = 1$, and letting $\{p\} = S_\beta \setminus S_\alpha$ be the point in β but not α, the cut $(\{p\},S_\alpha)$ of the binding graph B_β has weight $\geq \tau$.
  - (*one new tile* $\beta(p)$ *attaches to* α *with strength at least* τ *to create* β)
  - If the tile type added is t, write $\beta = \alpha + (p \mapsto t)$.
- The **frontier** of α is denoted $\partial\alpha = \bigcup_{\alpha \to_1 \beta} (S_\beta \setminus S_\alpha)$ (*empty locations adjacent to α where a tile can stably attach to α.*)
- A sequence of $k \in \mathbb{N}\cup\{\infty\}$ assemblies $\alpha_0, \alpha_1, \ldots$ is an **assembly sequence** if for all $0 \leq i < k$, $\alpha_i \to_1 \alpha_{i+1}$.
- We say that **α produces β** (in 0 or more steps), denoted $\alpha \to \beta$, if there is an assembly sequence $\alpha_0, \alpha_1, \ldots$ of length $k \in \mathbb{N}\cup\{\infty\}$ such that
  - $\alpha = \alpha_0$
  - for all $0 \leq i < k$, $\alpha_i \sqsubseteq \beta$, and
  - $S_\beta = \bigcup_i S_{\alpha i}$

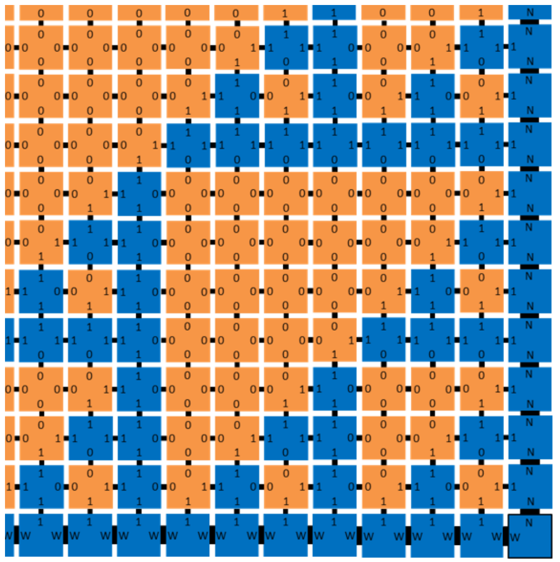
Why can't we just say $\to$ is the reflexive, transitive closure $\to_1^*$ of $\to_1$?

Sometimes we write $\alpha \to^\Theta \beta$ to emphasize this is with respect to a particular tile system Θ.

- We say β is the **result** of the assembly sequence.
- If k is finite, it is routine to verify that $\beta = \alpha_k$, and $\to$ <u>is</u> the reflexive, transitive closure $\to_1^*$ of $\to_1$.

abstract Tile Assembly Model (aTAM), formal definition

- Given tile system $\Theta = (T,\sigma,\tau)$, we say α is **producible** if $\sigma \rightarrow \alpha$.
  - Write $A[\Theta]$ to denote the set of all producible assemblies.
- We say α is **terminal** if α is stable and $\partial\alpha = \emptyset$. (*no tile can stably attach to it*)
  - Write $A_{\square}[\Theta] \subseteq A[\Theta]$ to denote the set of all producible, terminal assemblies.
- We say Θ is **directed** (a.k.a., **deterministic**) if
  - $|A_{\square}[\Theta]| = 1$. (*this is what we want it to mean: only one terminal producible assembly*)
  - equivalently, the partially ordered set $(A[\Theta], \rightarrow)$ is *directed*: for each $\alpha,\beta \in A[\Theta]$, there exists $\gamma \in A[\Theta]$ such that $\alpha \rightarrow \gamma$ and $\beta \rightarrow \gamma$.
  - equivalently, for all $\alpha,\beta \in A[\Theta]$ and all $p \in S_\alpha \cap S_\beta$, $\alpha(p) = \beta(p)$.
- Let X be a **shape**, a connected subset of $\mathbb{Z}^2$. Θ **strictly self-assembles** X if, for all $\alpha \in A_{\square}[\Theta]$, $S_\alpha = X$. (*every terminal producible assembly has shape X*)
  - Note X can be infinite.
  - Example: strict self-assembly of entire second quadrant $X = \{ (x,y) \in \mathbb{Z}^2 \mid x \geq 0 \text{ and } y \leq 0 \}$
  - Example of tile system Θ that does not strictly self-assemble any shape?
- Let $X \subseteq \mathbb{Z}^2$. Θ **weakly self-assembles** X if there is a subset $B \subseteq T$ (the "blue tiles") such that, for all $\alpha \in A_{\square}[\Theta]$, $X = \alpha^{-1}(B)$. (*every terminal producible assembly puts blue tiles exactly on X*.)
  - example: weak self-assembly of the discrete Sierpinski triangle.



Basic stability result

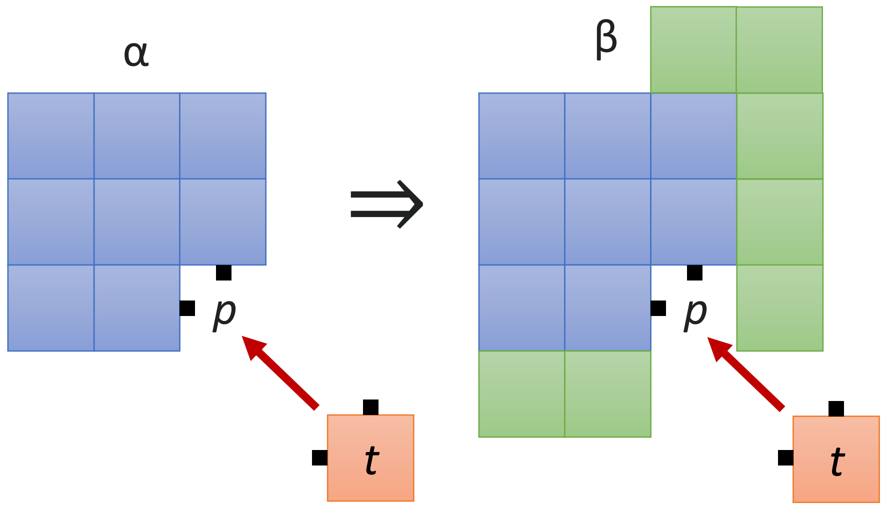
Observation: Let $\alpha \sqsubseteq \beta$ be stable assemblies and $p \in \mathbb{Z}^2 \setminus S_\beta$ such that $\alpha + (p \mapsto t)$ is stable. Then $\beta + (p \mapsto t)$ is also stable.

Intuition: if a tile can attach to α, it can attach in the presence of extra tiles on α.

Proof:

1. Since β is stable and glue strengths are nonnegative, the only *potentially* unstable cut is $(\{p\}, S_\beta)$.
2. But:
    1. $\alpha \sqsubseteq \beta$,
    2. $\alpha + (p \mapsto t)$ is stable,
    3. compared to α, β only has extra tiles on the other side of the cut (t, S_β).
    4. so the cut (t, S_β) is also stable. **QED**

example:



Basic reachability result

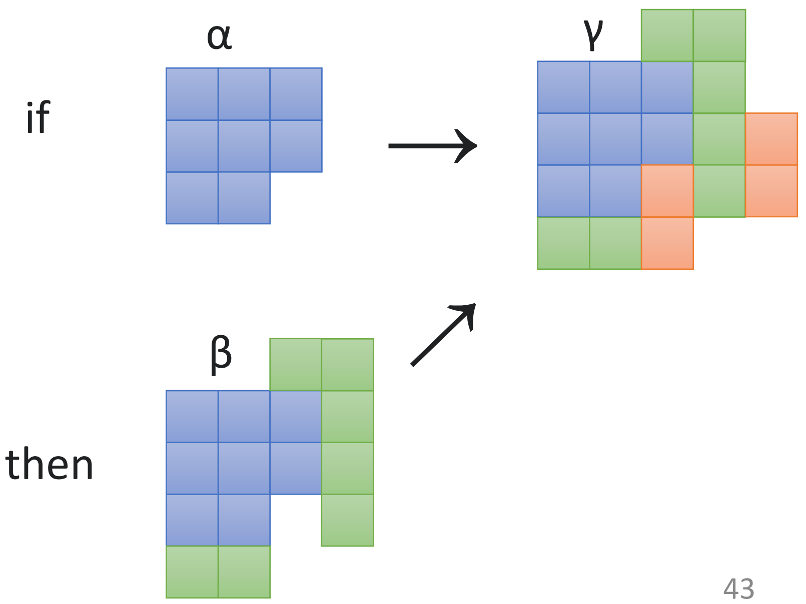
Rothemund's Lemma: Let $\alpha \sqsubseteq \beta \sqsubseteq \gamma$ be stable assemblies such that $\alpha \to \gamma$. Then $\beta \to \gamma$.

Intuition: if α can grow into γ, then if some of what will attach is already present (β), the remaining tiles can still attach.

Proof:

1. Let $\alpha=\alpha_0, \alpha_1, \ldots$ be an assembly sequence with result γ.
2. For each i, let $p_i = S_{\alpha i+1} \setminus S_{\alpha i}$ (*i'th attachment position*) and t_i the *i*'th tile added.
3. Let $i(0) < i(1) < \ldots$ such that $S_\gamma \setminus S_\beta = \{i(0), i(1), \ldots\}$ (*subsequence of indices of tile attached outside of* β).
4. Define assembly sequence $\beta=\beta_0,\beta_1,\ldots$ by $\beta_{j+1} = \beta_j+(p_{i(j)} \mapsto t_{i(j)})$. (*adding tiles to* $S_\gamma \setminus S_\beta$ *in order they were added to* α*, skipping tiles already in* S_β.)
5. Then for each j, $\alpha_{i(j)} \sqsubseteq \beta_j$, so previous Observation implies that $\beta_j + (p_{i(j)} \mapsto t_{i(j)})$ is stable.
6. Thus the assembly sequence is valid (each tile attachment is stable), showing $\beta \to \gamma$. **QED**

example:



example of usefulness of Rothemund's Lemma

- Recall two alternate characterizations of deterministic tile systems:
  (a) $|A_{\square}[\Theta]| = 1$.
  (b) for all $\alpha,\beta \in A[\Theta]$ and all $p \in S_\alpha \cap S_\beta$, $\alpha(p) = \beta(p)$.
- Rothemund's Lemma can be used to show that (b) implies (a)
  - will skip in lecture (optional problem on homework 1)

Fair assembly sequences

Definition: Let $\alpha_0, \alpha_1, \ldots$ be an assembly sequence. We say it is **fair** if, for all $i \in \mathbb{N}$ and all $p \in \partial\alpha_i$, there exists $j > i$ such that $p \in S_{\alpha j}$.

Intuition: Every frontier location eventually gets a tile; none are "starved"

Lemma: Let $\alpha_0, \alpha_1, \ldots$ be a fair assembly sequence. Then its result γ is terminal.

Corollary: For every assembly α, there is a terminal assembly γ such that $\alpha \to \gamma$.

Proof:

1. Suppose for the sake of contradiction that γ is not terminal, i.e., it has frontier location $p \in \partial\gamma$; note in particular $p \notin S_\gamma$.
2. Simpler if assembly sequence is finite:
   1. in this case, $\gamma = \alpha_{k-1}$, so p never receives a tile.
   2. Thus the assembly sequence is not fair. (*there is no $j > k-1$ such that $p \in S_{\alpha j}$*)
3. Now assume assembly sequence is infinite. (*actually, rest of proof works in finite case*)
4. Since $p \in \partial\gamma$, there are positions adjacent to p with enough strength to bind a tile t. Let N be the set of these positions. Note N is finite since p has at most four neighbors.
5. Since $S_\gamma = \bigcup_i S_{\alpha i}$, there exists i such that $N \subseteq \partial\alpha_i$ (*after some finite number of tile attachments, all of the positions in N are on the frontier of the current assembly*)
6. Thus $p \in \partial\alpha_i$. (*the tile t can attach to α_i, reached after only i steps*)
7. By fairness, there exists j such that $p \in S_{\alpha j} \subseteq S_\gamma$ (*eventually p gets a tile*), which contradicts the claim that $p \notin S_\gamma$. **QED**

Proof: Pick any fair assembly sequence $\alpha=\alpha_0, \alpha_1, \ldots$; its result γ is terminal and $\alpha \to \gamma$. **QED**

Concrete example of simulation algorithm creating a fair assembly sequence?

How computationally powerful are self-assembling tiles?

Turing machines

state ≈ line of code

initial state = s

current symbol — next symbol

current state — next state — next move

s,0: q,0,→

q,0: t,1,←

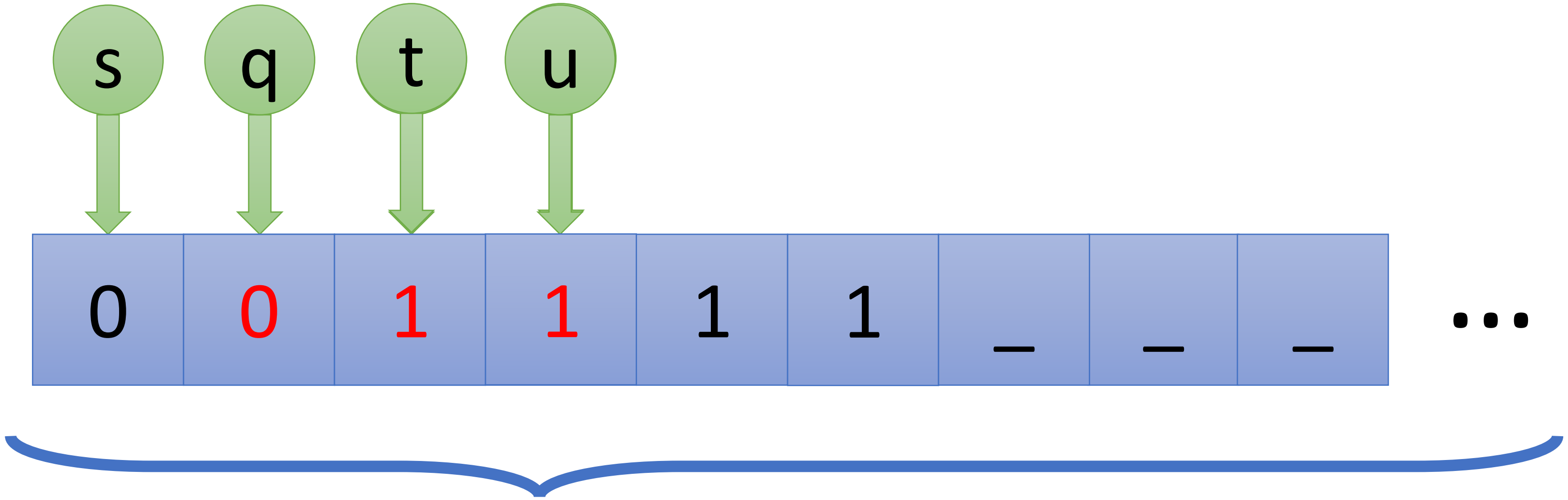
q,1: s,0,→

t,0: u,1,→

u,1: HALT

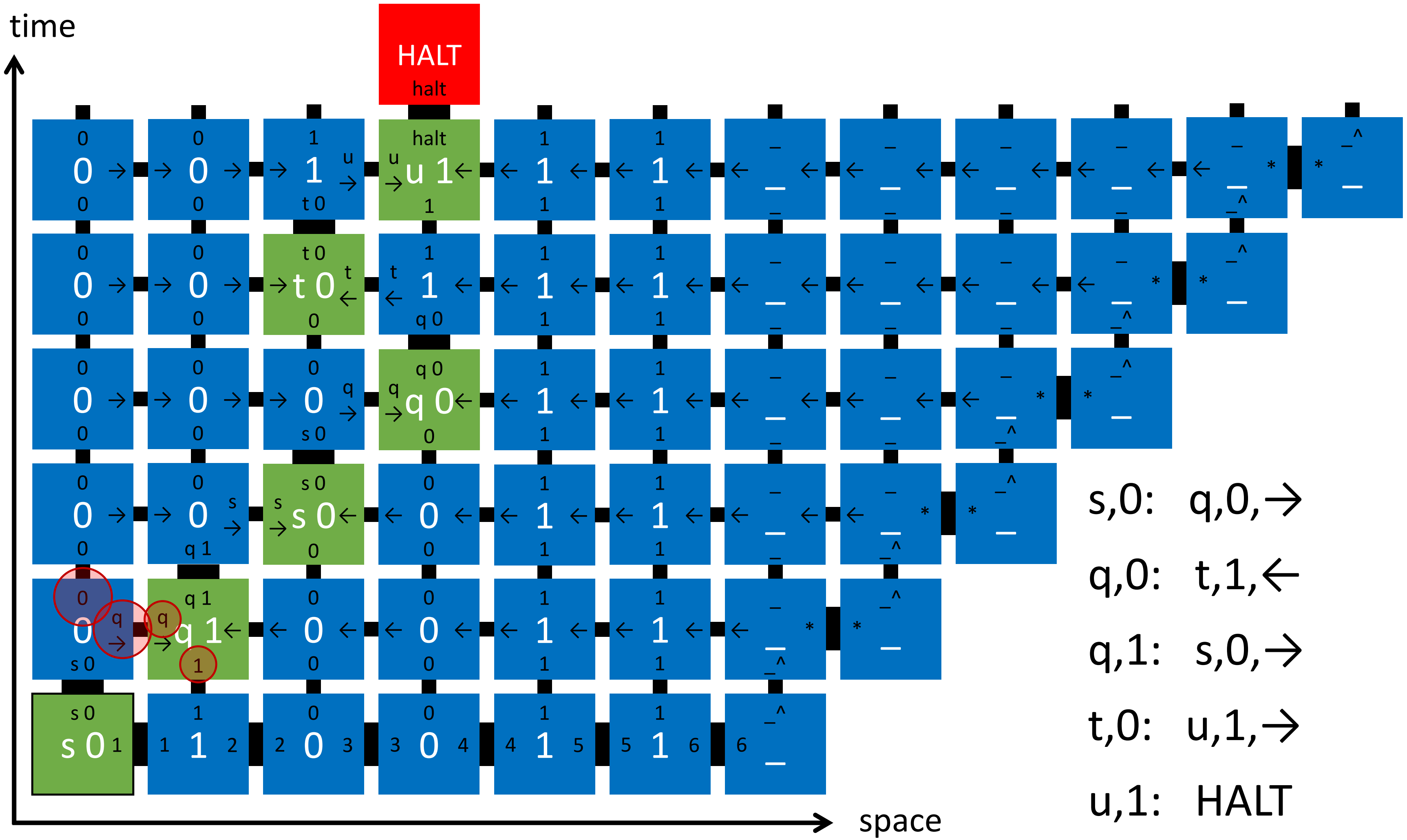
transitions

(instructions)



tape ≈ memory

Tile assembly is Turing-universal



s,0: q,0,→

q,0: t,1,←

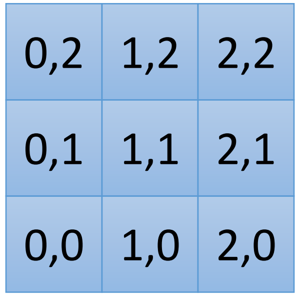
q,1: s,0,→

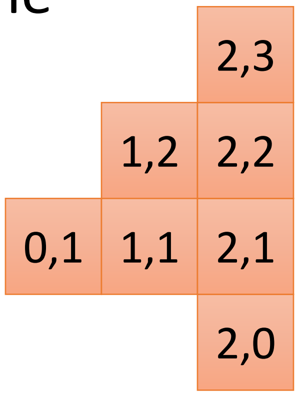
t,0: u,1,→

u,1: HALT

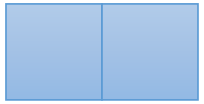
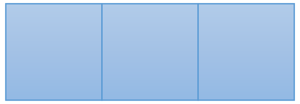
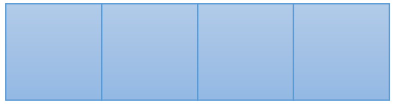
Complexity of self-assembled shapes

- We've seen how use algorithmic tiles to:
  - self-assemble n x n squares with "few" tile types $O(\log n / \log \log n)$
  - simulate a Turing machine that grows a "wedge" describing its space-time configuration history
- What other shapes can be self-assembled?
  - Define a shape to be a finite, connected subset of $\mathbb{N}^2$.
  - Any shape with n points can be self-assembled with <u>at most</u> how many tile types? n



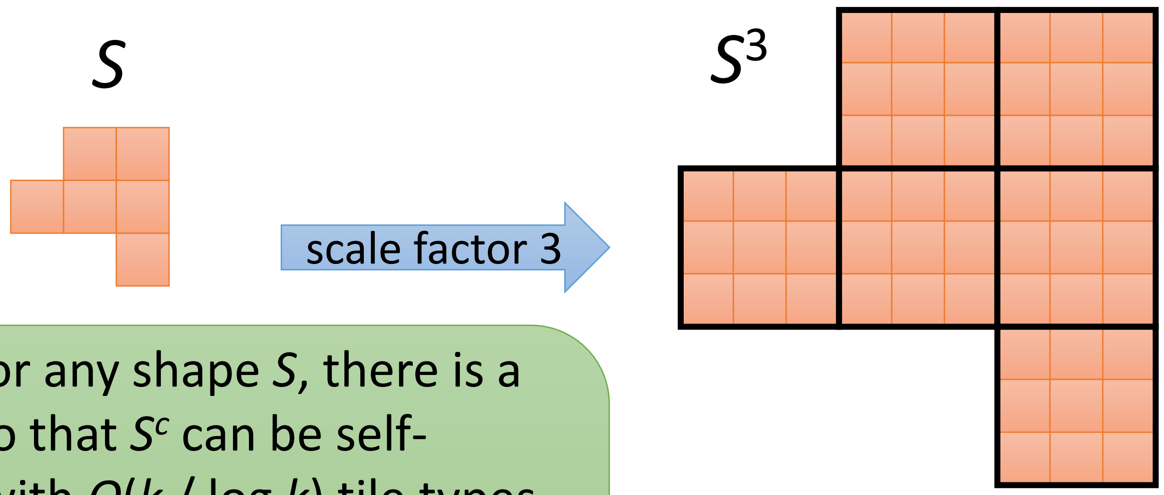


- Is there an infinite family of shapes $S_1, S_2, \ldots$, with $|S_n| = n$, such that each S_n requires <u>at least</u> n tile types to self-assemble?

$S_1 =$  $S_2 =$  $S_3 =$  $S_4 =$  …

Complexity of self-assembled shapes

Suppose we are content to create a scaled up version of the shape:



Theorem: For any shape *S*, there is a constant *c* so that S^c can be self-assembled with $O(k / \log k)$ tile types, where *k* is the length in bits of the shortest program (input to a universal Turing machine) that, on input (x,y), indicates whether $(x,y) \in S$.

Theorem (that we won't prove): This is optimal! No smaller tile system could self-assemble any scaling of *S*. If one existed, we could turn it into a program with < *k* bits "describing" *S* in this way. (*Why?*)

[*Complexity of Self-Assembled Shapes*. Soloveichik and Winfree, SIAM Journal on Computing 2007]

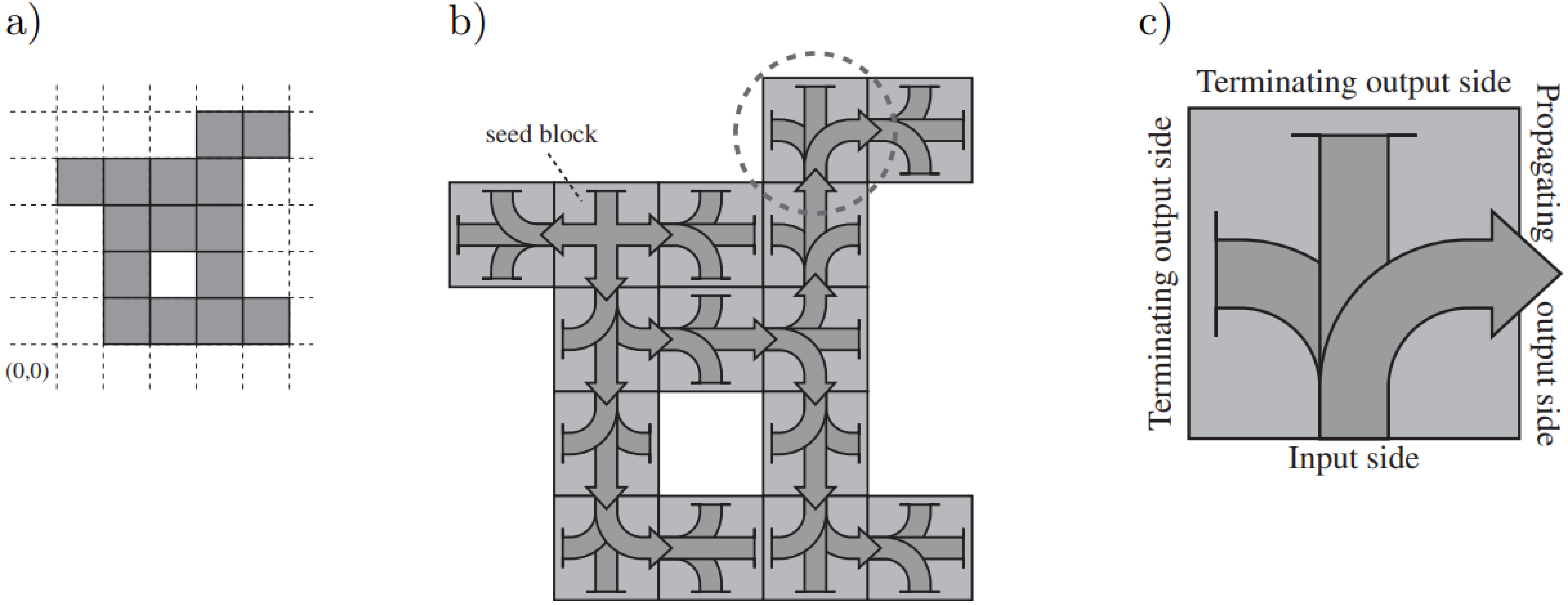
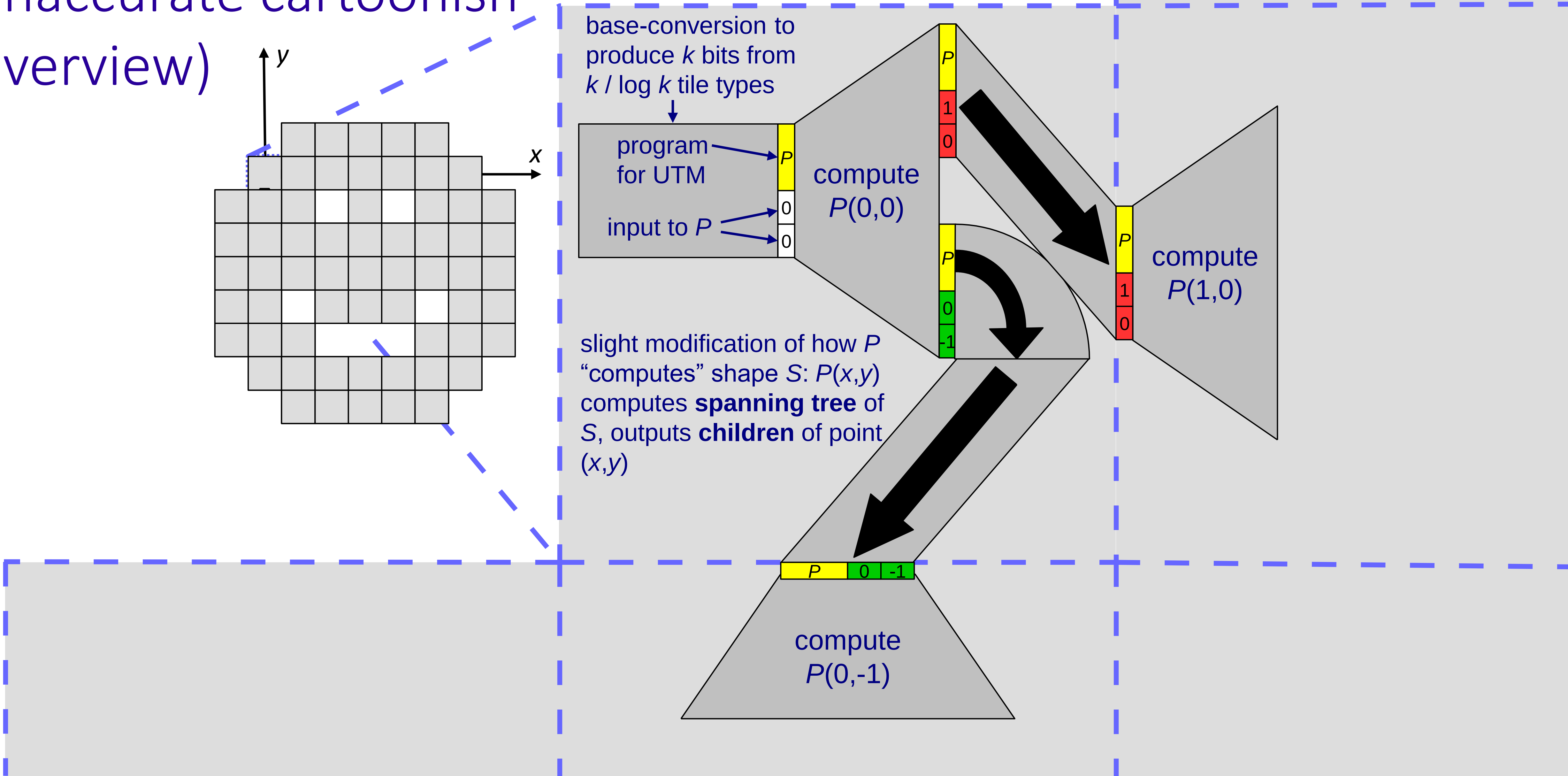


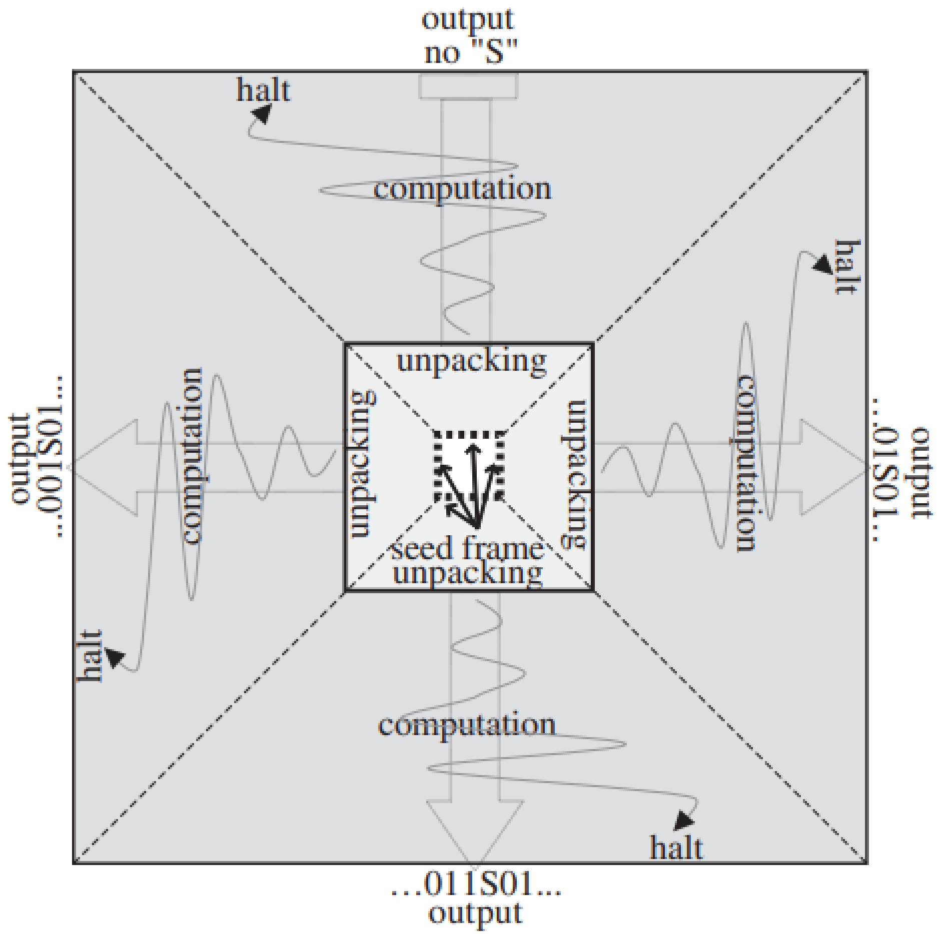
FIG. 5.1. *Forming a shape out of blocks:* (a) *A coordinated shape S.* (b) *An assembly composed of $c \times c$ blocks that grow according to transmitted instructions such that the shape of the final assembly is $\tilde{S}$ (not drawn to scale). Arrows indicate information flow and order of assembly. The seed block and the circled growth block are schematically expanded in Figure 5.2.* (c) *The nomenclature describing the types of block sides.*

Programming a shape (inaccurate cartoonish overview)

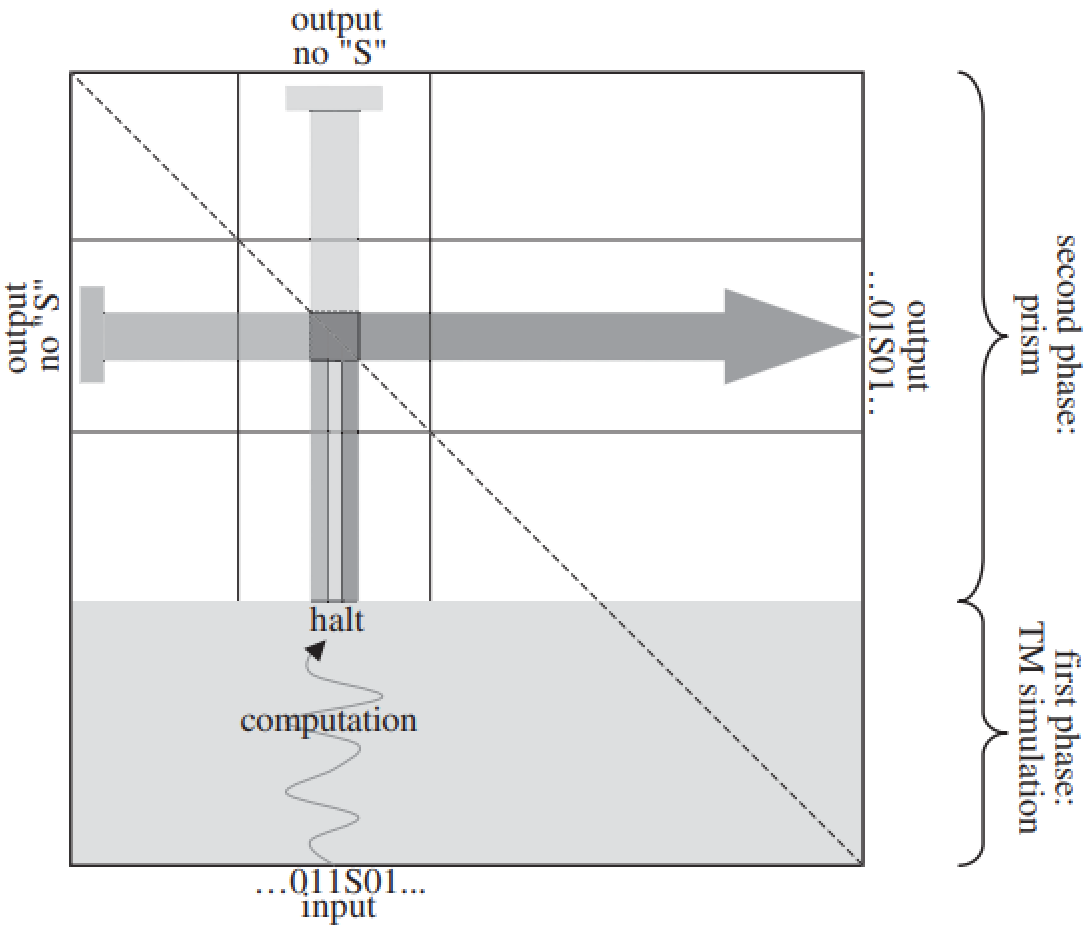


More accurate detailed overview

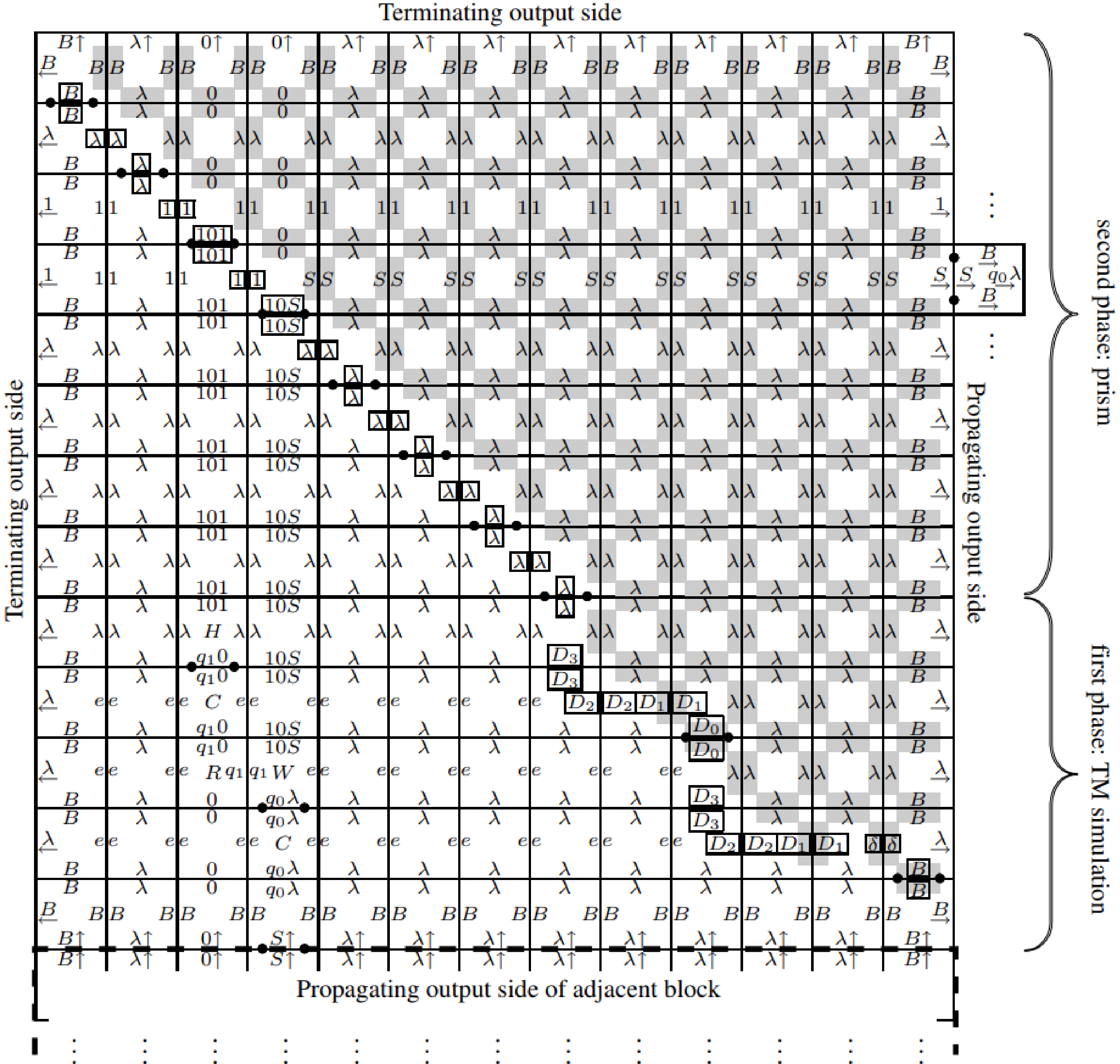
seed block



growth block



fully-detailed example of growth block



Two interpretations

as stated for single seed tile:

Theorem: For any shape S, there is a constant c so that S^c can be self-assembled with <u>$O(k$ / log $k)$ tile types</u>, where k is the length in bits of the shortest program (input to a universal Turing machine) that, on input (x,y), indicates whether $(x,y) \in S$.

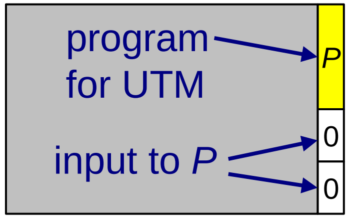
most of the tile complexity is encoding the binary string representing the program P that encodes shape S, and <u>$O(1)$ tile types</u> can read that string and self-assemble S^c from it.

i.e., T is a **universal** set of tile types that can self-assemble any shape, by giving it the right seed.

alternative statement for larger seed:

Theorem: There is a <u>single</u> set T of tile types (<u>$O(1)$ tile types</u>), so that, for any finite shape S, there a constant c and a seed assembly σ_S "encoding" S, so that T self-assembles S^c from σ_S.

σ_S =



Strict and weak self-assembly

Computability-theoretic questions about self-assembly

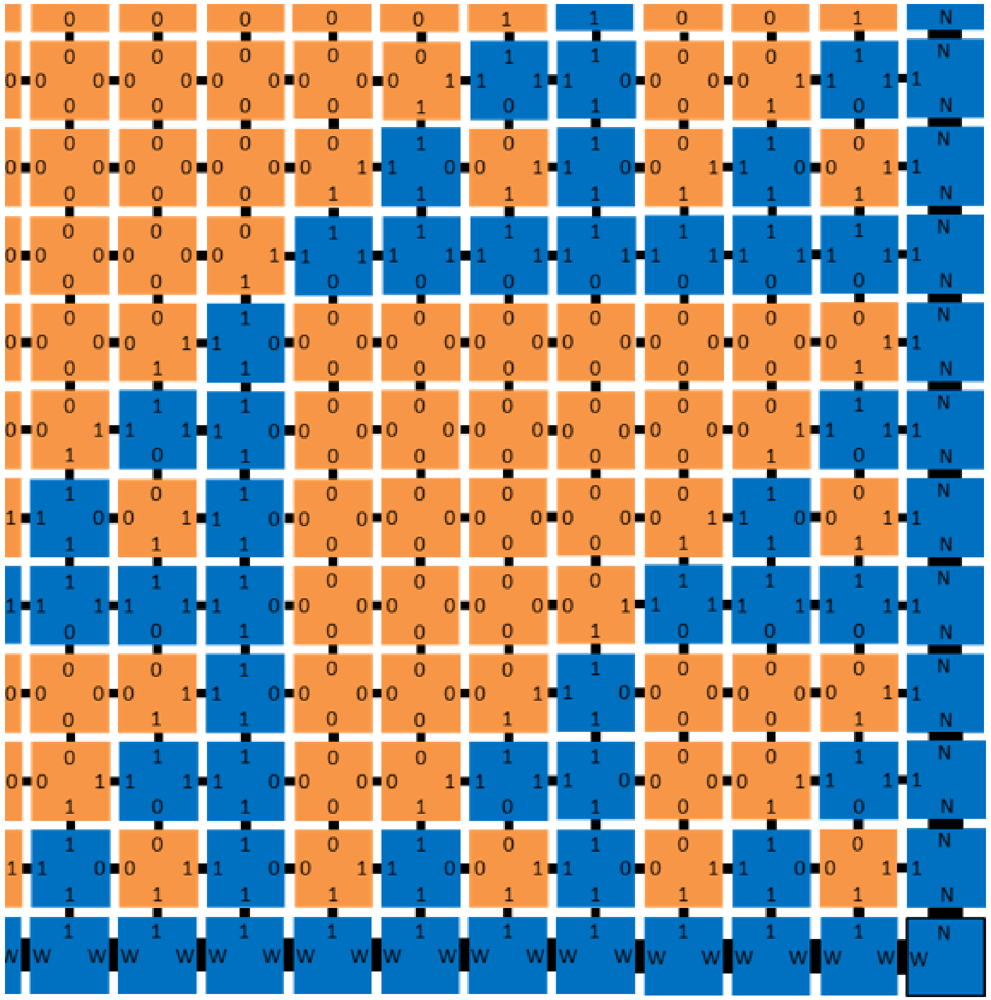
Strict and weak self-assembly

Recall:

Let $X \subseteq \mathbb{Z}^2$ be a **shape**, a connected subset of $\mathbb{Z}^2$. Θ **strictly self-assembles** X if, for all $\alpha \in A_{\Box}[\Theta]$, $S_\alpha = X$.
(*every terminal producible assembly has shape X*)

Let $X \subseteq \mathbb{Z}^2$. Θ **weakly self-assembles** X if there is a subset $B \subseteq T$ (the "blue tiles") such that, for all $\alpha \in A_{\Box}[\Theta]$, $X = \alpha^{-1}(B)$.
(*every terminal producible assembly puts blue tiles exactly on X.*)

Tile system on right strictly self-assembles the whole second quadrant, and it weakly self-assembles the discrete Sierpinski triangle.



Strict self-assembly

Observation: There is an infinite shape $S \subseteq \mathbb{Z}^2$ that cannot be strictly self-assembled by any tile system.

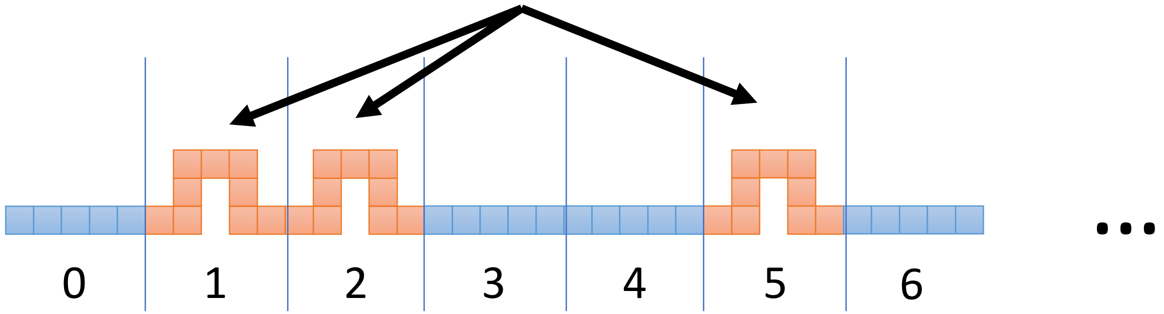
Proof:
There are uncountably many shapes but only countably many tile systems.

Observation is *non-constructive*: Doesn't tell us what is the shape *S*. Can we devise a concrete example of a shape that cannot be strictly self-assembled?

Homework problem: you will show that any shape $S \subseteq \mathbb{Z}^2$ that can be strictly self-assembled is also computably enumerable.

Use that fact now to define an explicit shape that cannot be strictly self-assembled.

path in block *n* has a "turnout" if and only if *n*'th Turing machine halts on empty input

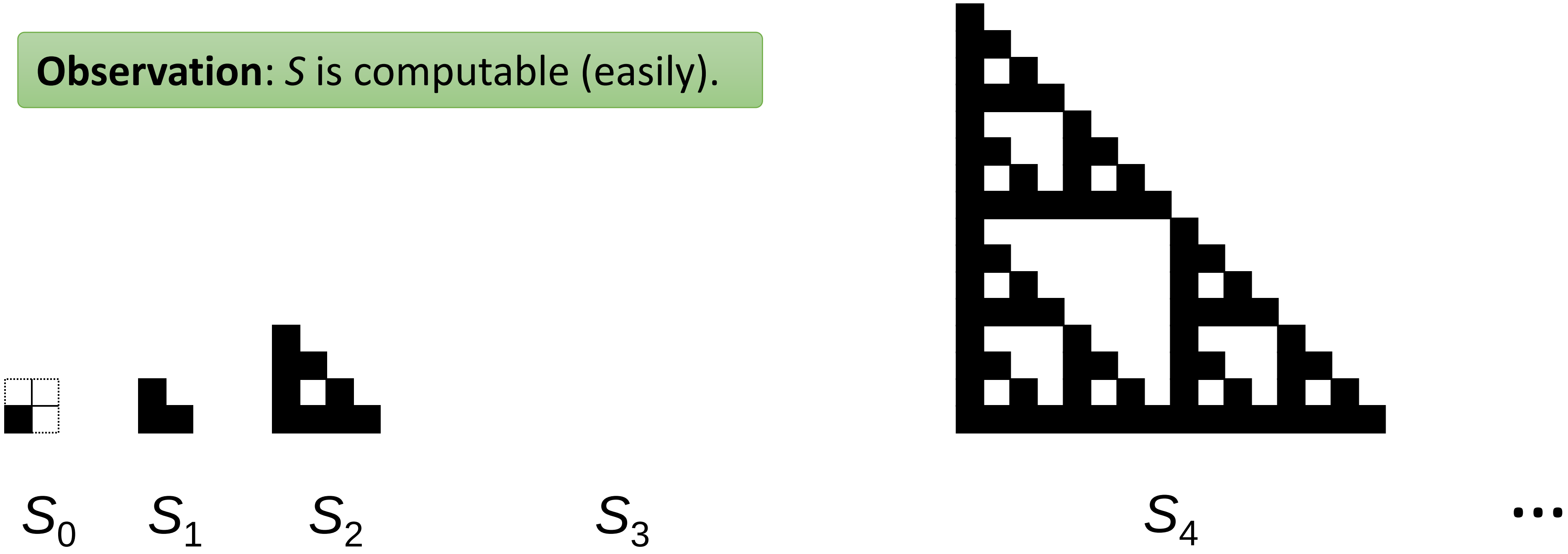


Question: Is there a computable shape $S \subseteq \mathbb{Z}^2$ that cannot be strictly self-assembled?

A famous fractal

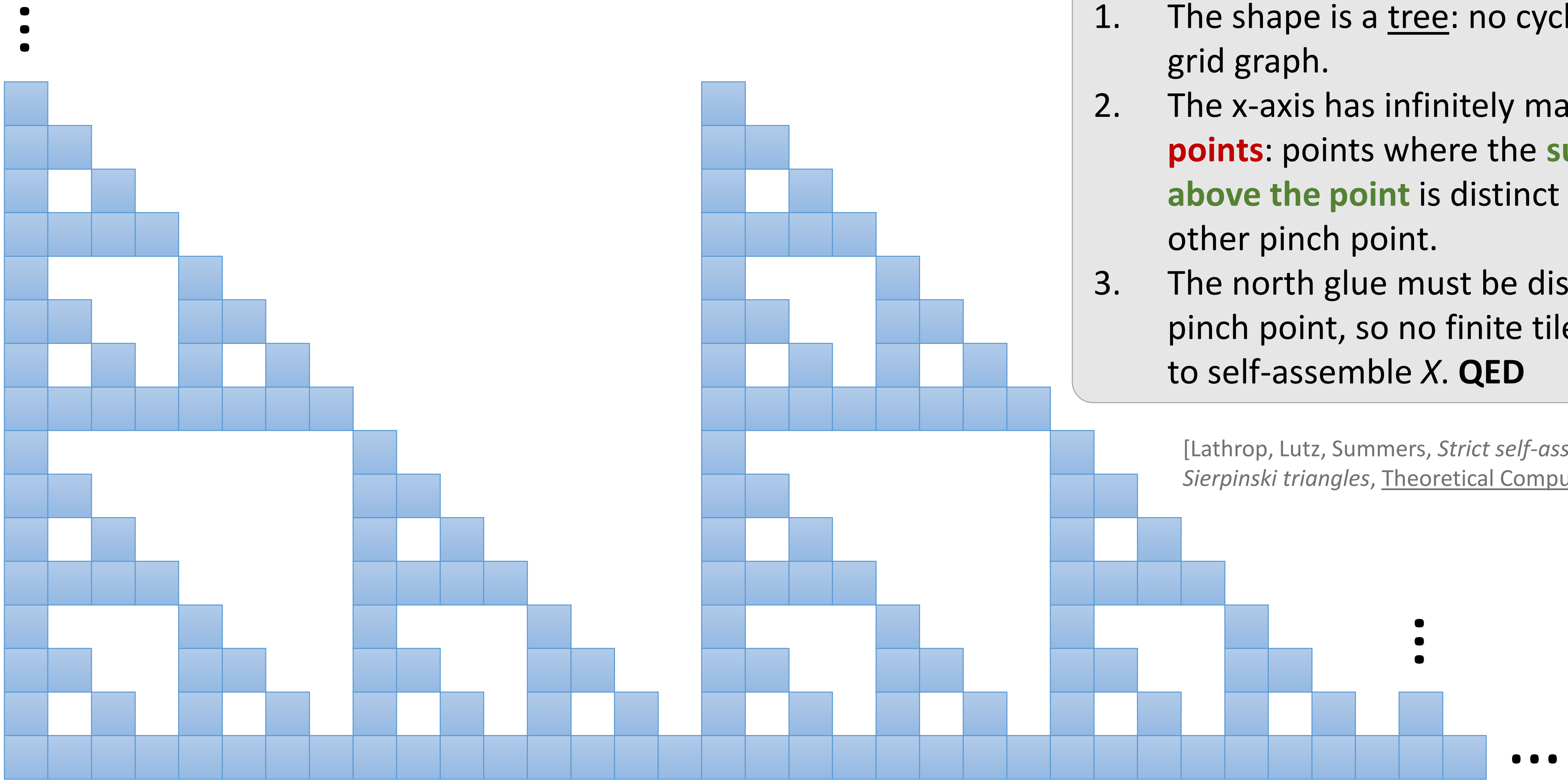
- Let S_0 = { (0,0) }
- Let V = { (0,0), (0,1), (1,0) } be three vectors for “recursive translation”.
- *S* is known as the *discrete Sierpinski triangle*…

Observation: *S* is computable (easily).



[slide credit:
Scott Summers]

The discrete Sierpinkski triangle cannot be strictly self-assembled



Proof:

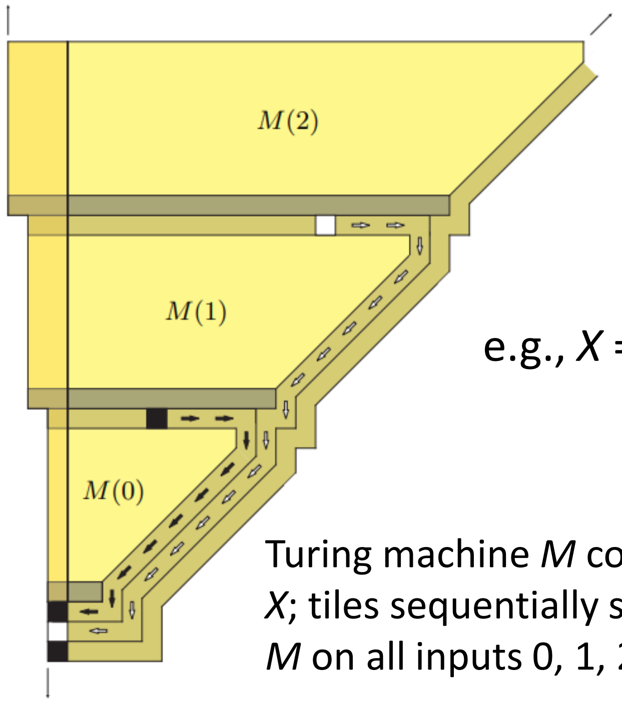
1. The shape is a tree: no cycles in the grid graph.
2. The x-axis has infinitely many **pinch points**: points where the **subtree above the point** is distinct from any other pinch point.
3. The north glue must be distinct at each pinch point, so no finite tile set suffices to self-assemble *X*. **QED**

[Lathrop, Lutz, Summers, *Strict self-assembly of discrete Sierpinski triangles*, Theoretical Computer Science 2009.]

Weak self-assembly

Theorem: Some computable sets $X \subseteq \mathbb{Z}^2$ cannot be weakly self-assembled.

Theorem: Every computable set $X \subseteq \mathbb{N}$, "embedded straightforwardly" in $\mathbb{Z}^2$, can be weakly self-assembled.

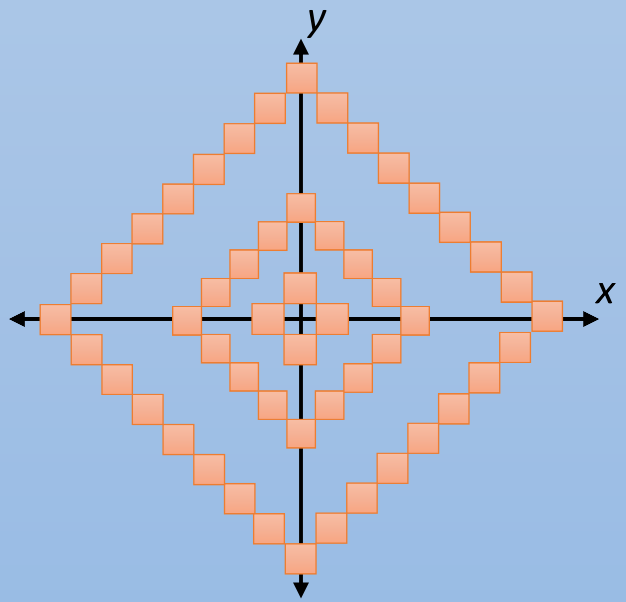


e.g., $X = \{0, 2, \ldots\}$

Turing machine M computes X; tiles sequentially simulate M on all inputs 0, 1, 2, …,

Proof:

1. The Time Hierarchy Theorem says there is a computable set $A \subseteq \{1\}^*$ not computable in $O(n^4)$ time.
2. Let $R = \{|x| : x \in A\}$ be the set of lengths of strings in A.
3. Define $X \subseteq \mathbb{Z}^2$ to be the set of "concentric diamonds" whose L_1 radii are in R, e.g., if $R = \{1, 4, 8, \ldots\}$



4. Suppose X could be weakly self-assembled. Then simulating self-assembly for $(2n)^2$ steps necessarily places a tile at some point at L_1 radius n from the origin; the tile's color tells us whether $n \in R \Leftrightarrow 1^n \in A$.
5. This can be done in time $O(n^4)$ time (why?), a contradiction. **QED**

[Patitz, Summers, *Self-assembly of decidable sets*, UCNC 2008.]

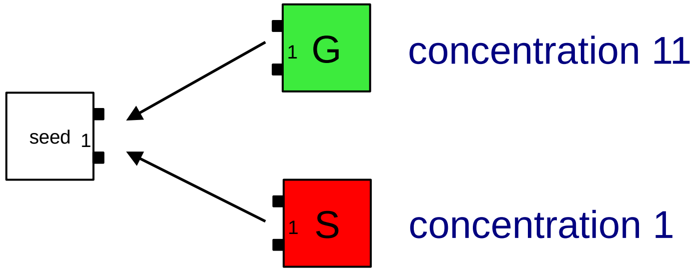
[Lathrop, Lutz, Patitz, Summers, *Computability and Complexity in Self-Assembly*, CiE 2008.]

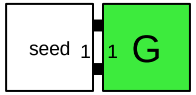
Randomized self-assembly

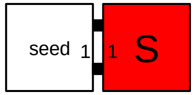
Tile complexity of universal shape construction

- Recall: if we can have a seed structure encoding a shape *S* (in a binary string $x \in \{0,1\}^*$, in glues on one side), we can self-assemble some scaling S^c of S with $O(1)$ additional tile types that read and interpret *x*.
- $\Theta(K(x) / \log K(x))$ tile types are necessary and sufficient to create *x* from a single seed tile in the aTAM. ($K(x)$ = length in bits of shortest program for universal Turing machine that prints *x*)
- We'll see how to get this down to $O(1)$ with high probability by *concentration programming*.
    - i.e., move the effort from designing new tile types to (*the plausibly simpler lab step of*) altering concentrations of existing tile types

Nondeterministic binding

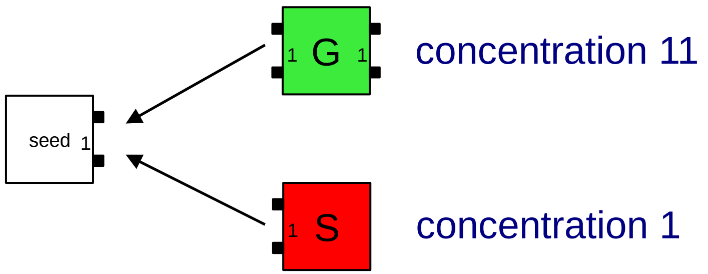


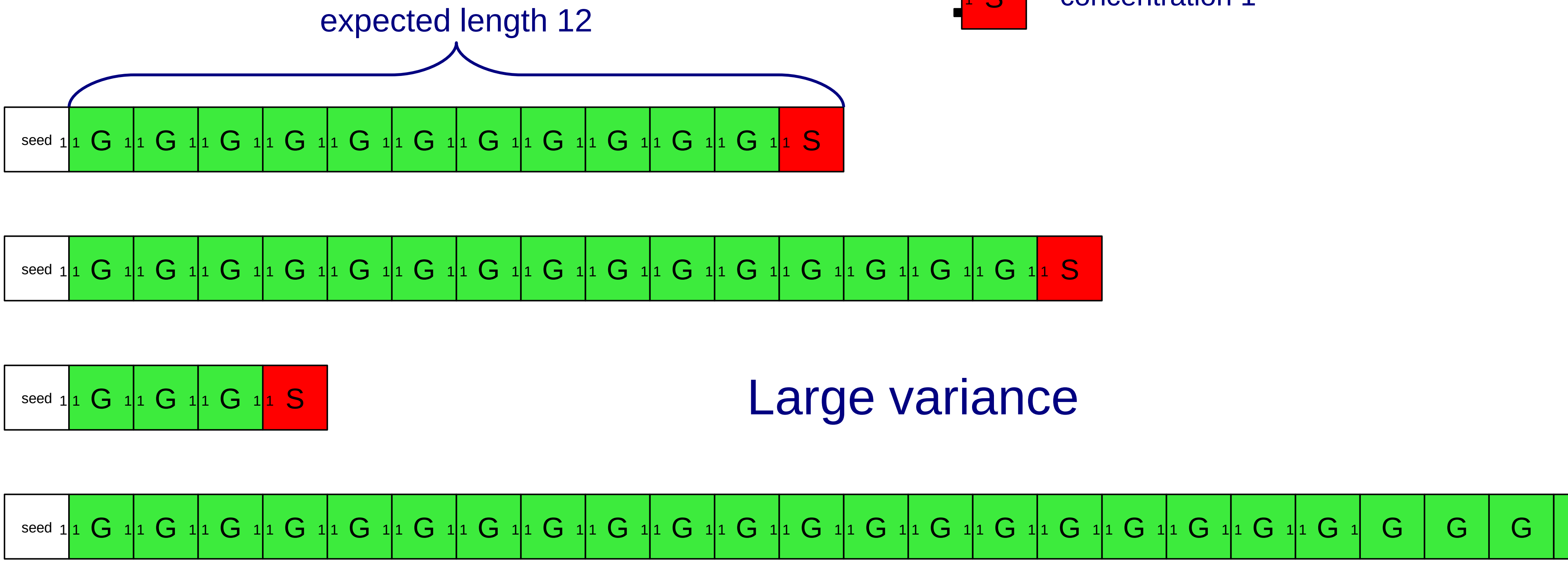
Pr[] = 11/12

Pr[] = 1/12

Programming polymer length with concentrations

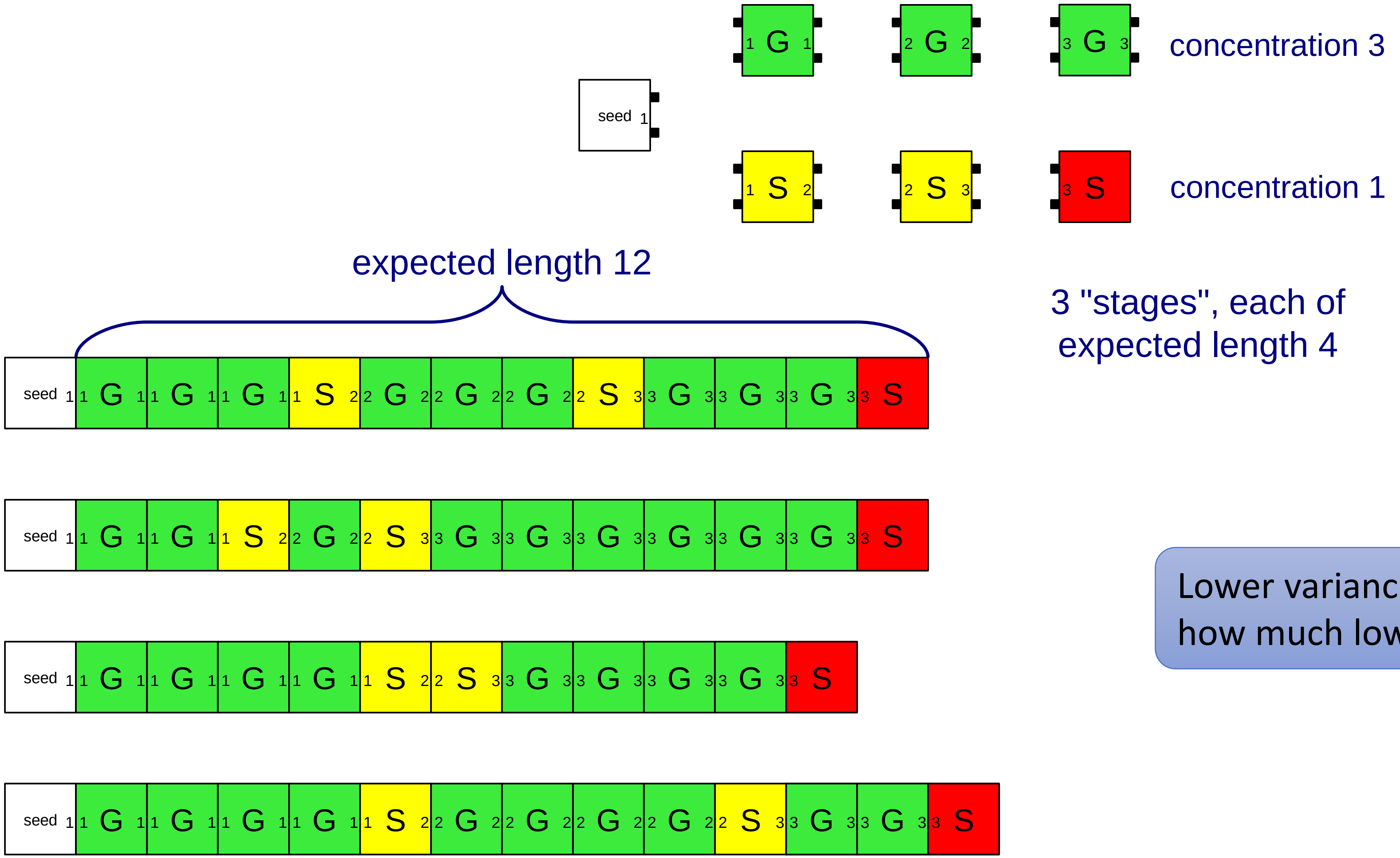
[Becker, Rapaport, Rémila, *FSTTCS* 2006]





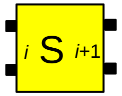
Large variance

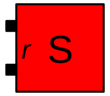
Programming polymer length (improved)



Lower variance…
how much lower?

Bounding the probability the length deviates much from its mean

- r total stages, each with Pr[next tile 

increments stage] = p.
- Let $\mathbf{L}(r,p)$ = total length; number of tile attachments until attaching 

- Expected total length $E[\mathbf{L}(r,p)] = r / p$.
- <u>Recall</u>: a binomial random variable $\mathbf{B}(n,p)$ = number of heads when flipping a coin n times, with Pr[heads] = p. $E[\mathbf{B}(n,p)] = np$.
- for any n,r,p: $\Pr[\mathbf{L}(r,p) \le n] = \Pr[\mathbf{B}(n,p) \ge r]$

flipping a coin until the r'th heads requires $\le n$ flips $\Leftrightarrow$ flipping a coin n times results in $\ge r$ heads

- similarly, $\Pr[\mathbf{L}(r,p) \ge n] = \Pr[\mathbf{B}(n,p) \le r]$

Chernoff bound

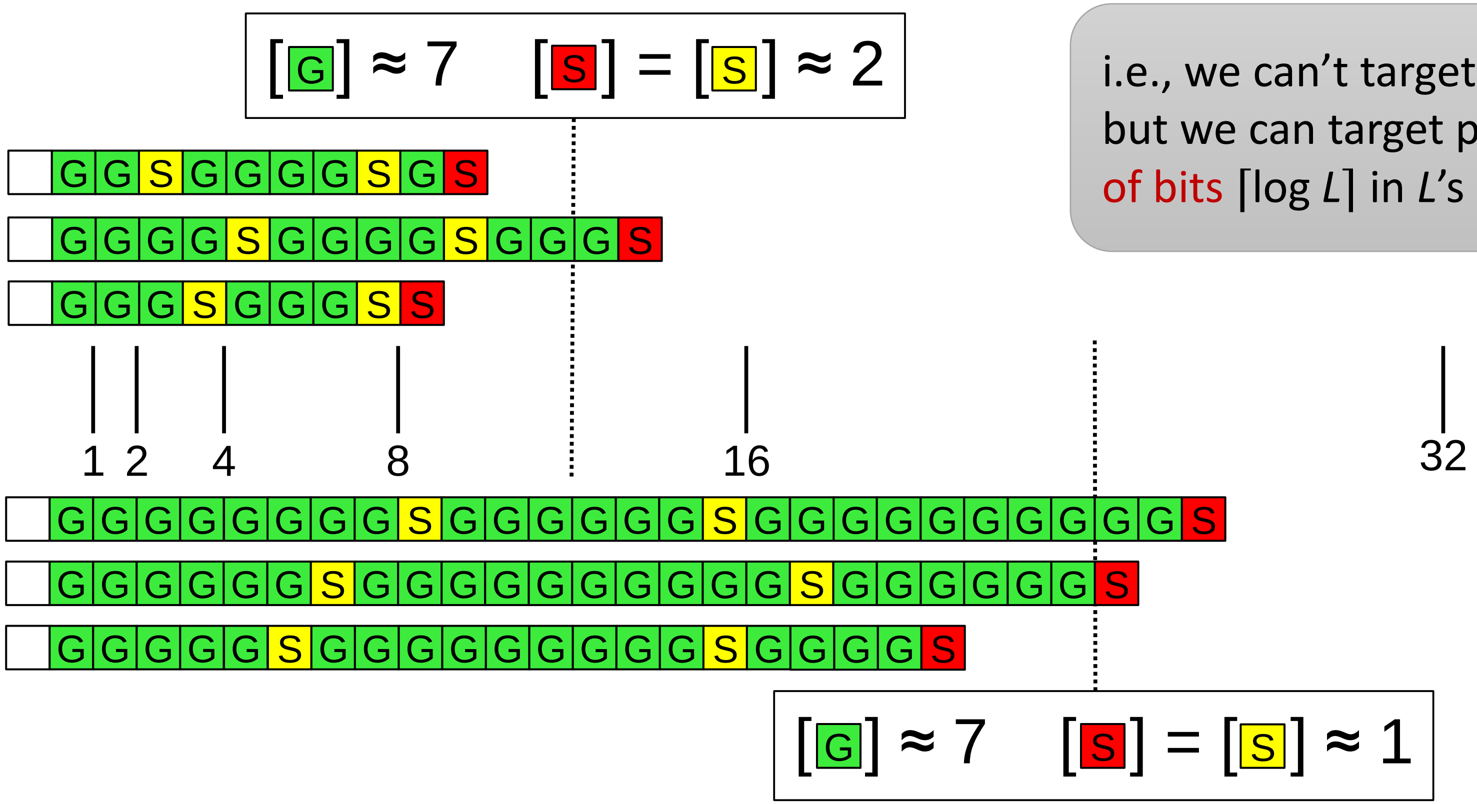
Chernoff bound: For a binomial random variable $\mathbf{B}(n,p)$ (recall $E[\mathbf{B}(n,p)] = np$), and for any $0 < \delta < 1$,
$\Pr[\mathbf{B}(n,p) > (1+\delta)np] < \exp(-\delta^2 np/3)$
$\Pr[\mathbf{B}(n,p) < (1-\delta)np] < \exp(-\delta^2 np/2)$

Let $\delta \approx 0.27$ and set p such that $r/p(1-\delta) = 2^k$.
Let $\delta' \approx 0.44$: then $r/p(1+\delta') \approx 2^{k-1}$.
Applying this to our setting gives
$\Pr[\mathbf{L}(r,p)$ is not between 2^{k-1} and $2^k] < 2 \cdot 0.9421^r$

Programming polymer length (improved)

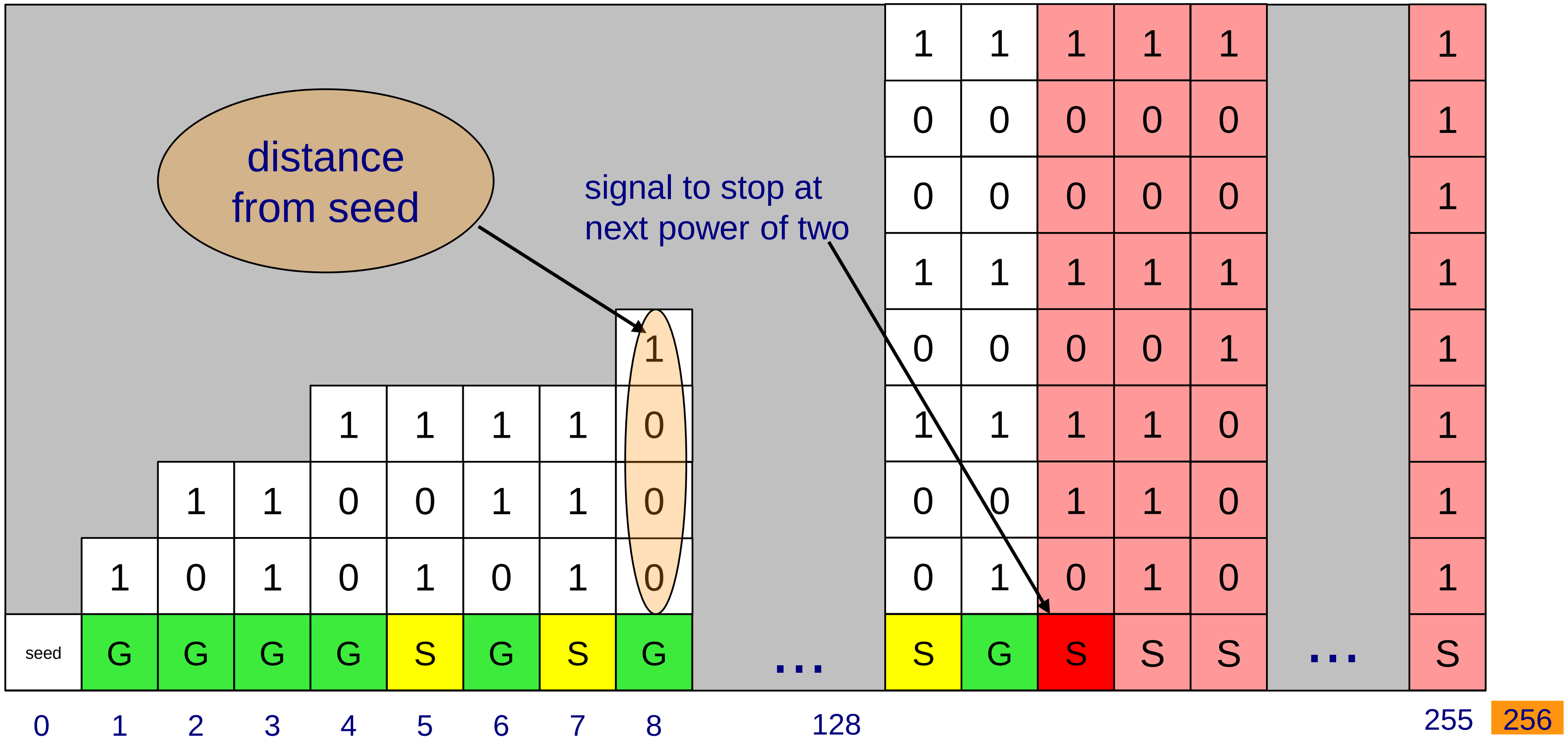
if r = 90 stages, expected length midway in $[2^{k-1}, 2^k)$

→ with probability > 99%, **actual** length in $[2^{k-1}, 2^k)$

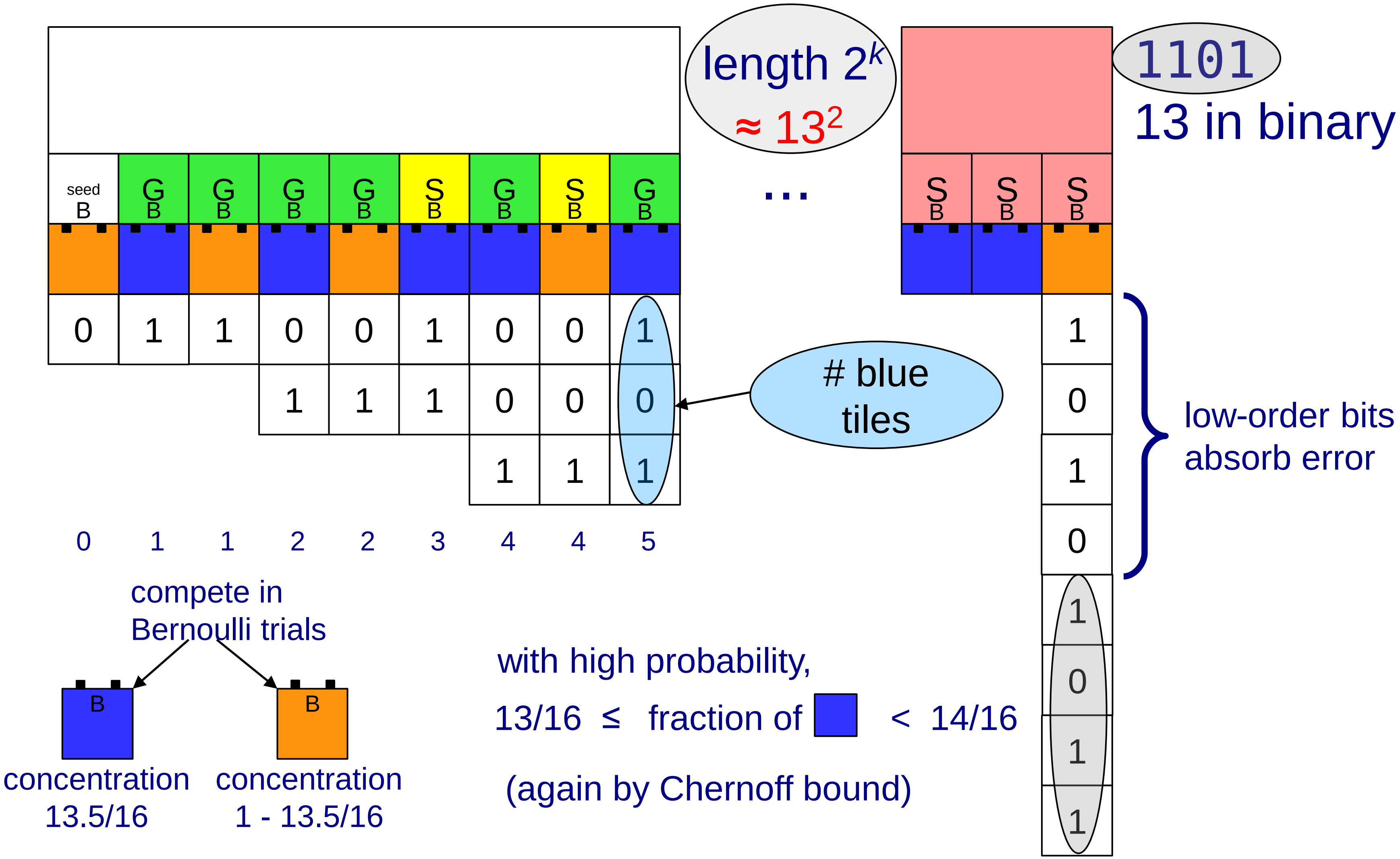


i.e., we can’t target a precise length *L*, but we can target precisely the number of bits ⌈log *L*⌉ in *L*’s binary expansion.

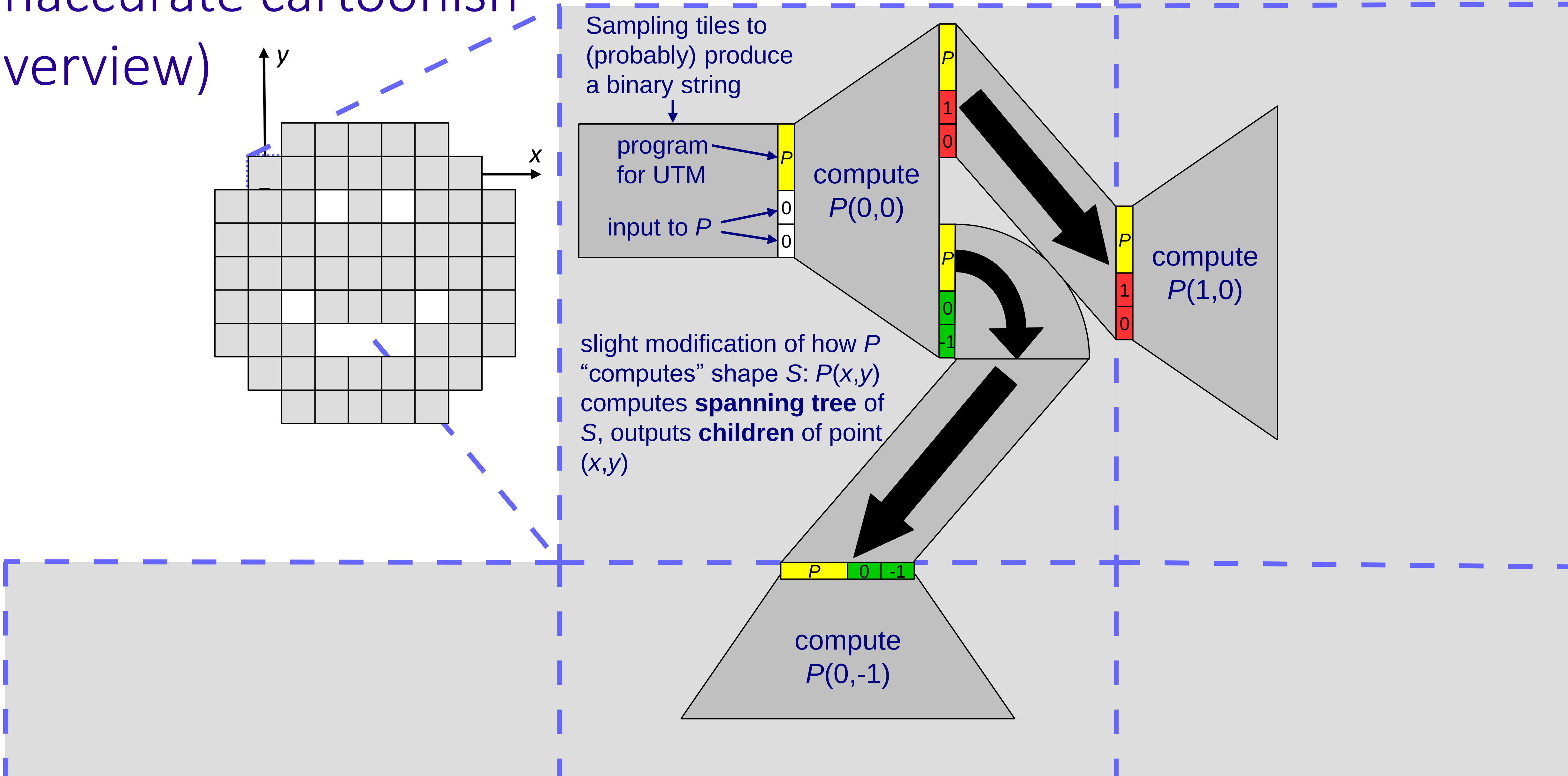
Programming polymer length 2^k precisely



Programming a binary string

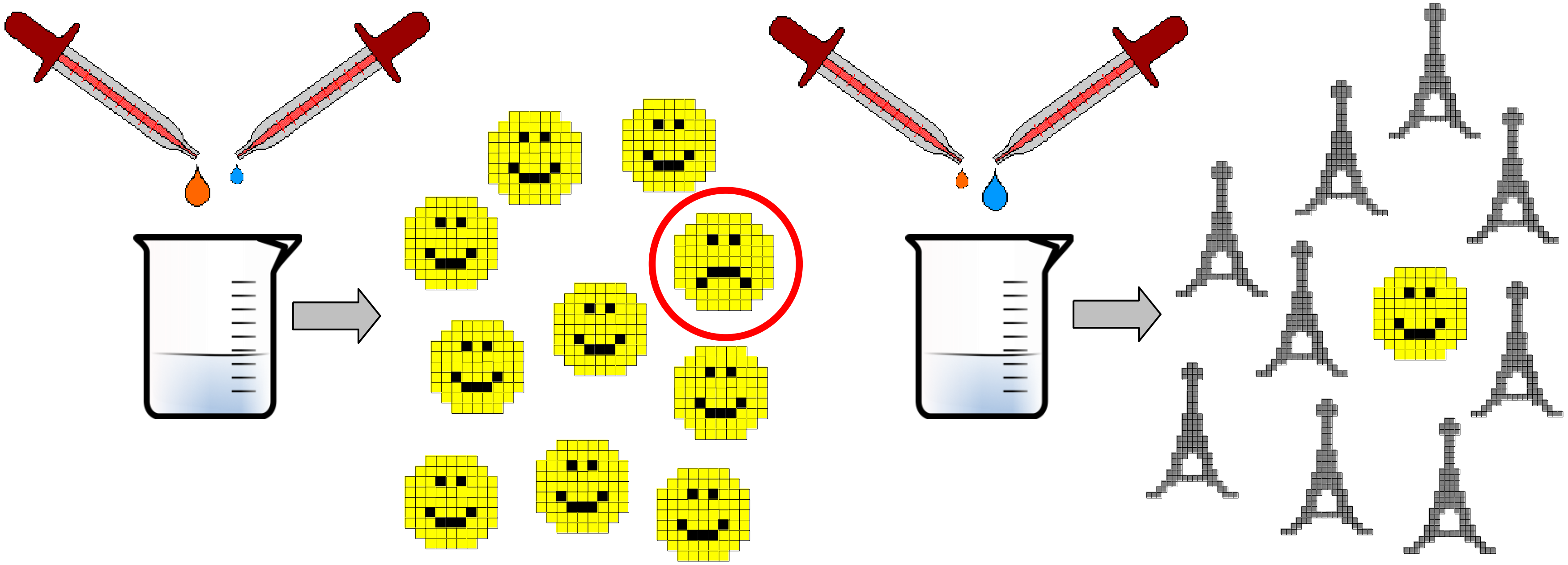


Programming a shape (inaccurate cartoonish overview)



Universal self-assembling molecules

A **fixed** set of tile types can assemble *any* finite (scaled) shape (with high probability) by mixing them in the right concentrations.



[Doty, *Randomized self-assembly for exact shapes*, SICOMP 2010, FOCS 2009]

Other plausible modifications of aTAM model that can reduce tile complexity

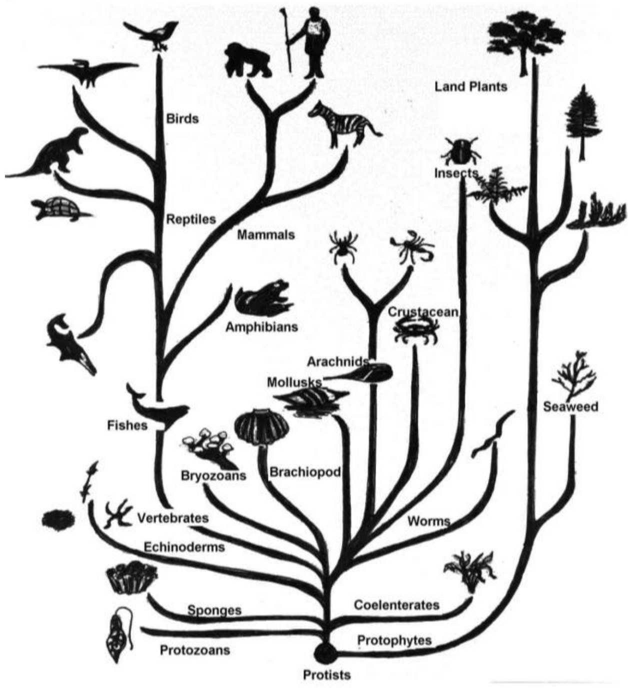
- staged self-assembly:
  - https://doi.org/10.1007/s11047-008-9073-0
- temperature programming:
  - https://dl.acm.org/doi/10.5555/1109557.1109620

The power of nondeterminism in self-assembly

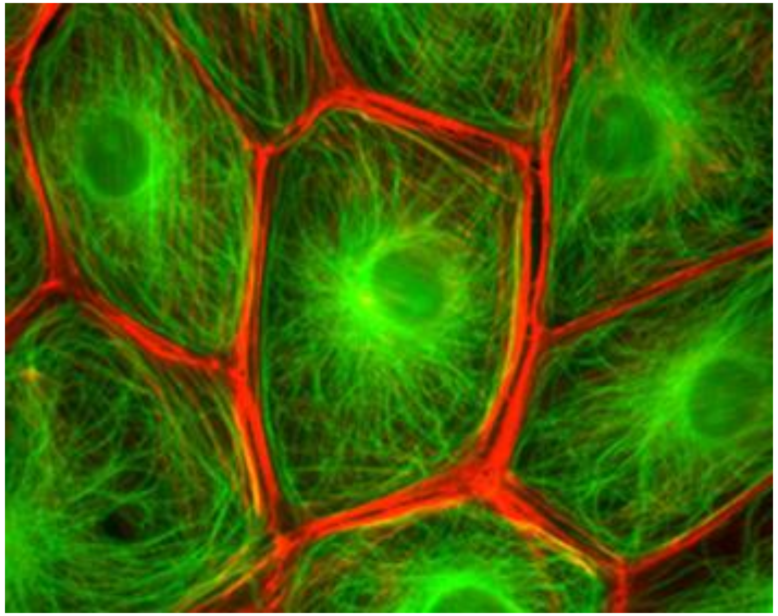
Can nondeterminism help to self-assemble shapes?

Nondeterminism in Biology

Genetic mutation



Cytoskeleton formation



Nondeterminism can allow complex structures to be created from a compact encoding.

Nondeterminism in Computer Science

Algorithm types:

Nondeterministic:
flips coins; magical

Randomized:
flips coins; realistic

Trivially nondeterministic (“pseudodeterministic”):
flips coins, but *final output* independent of flip results

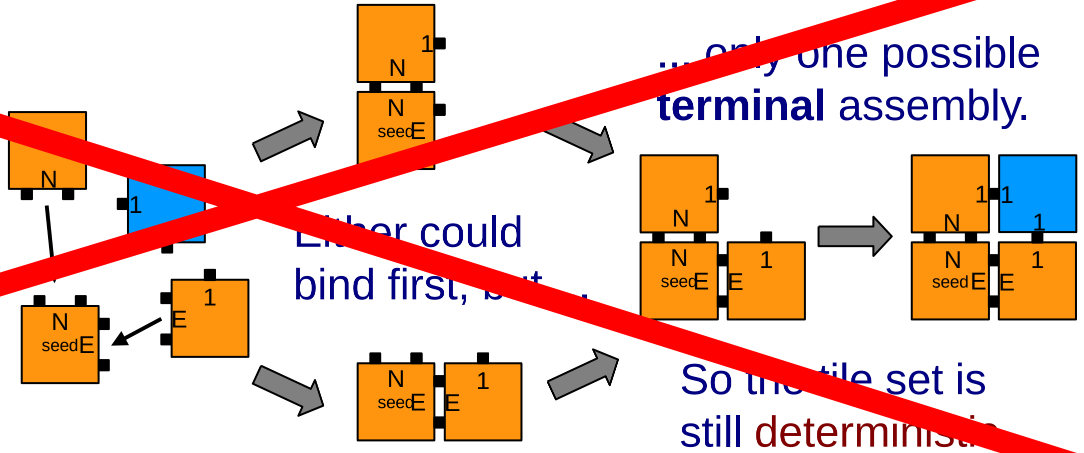
Deterministic: entire computation uniquely determined by input

Power

Nondeterminism in Self-Assembly

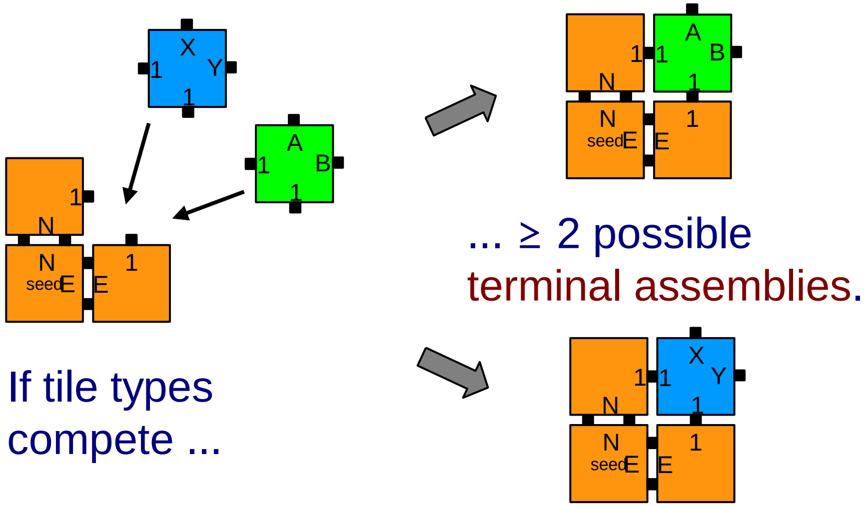
Perhaps:

≥ 2 potential binding sites



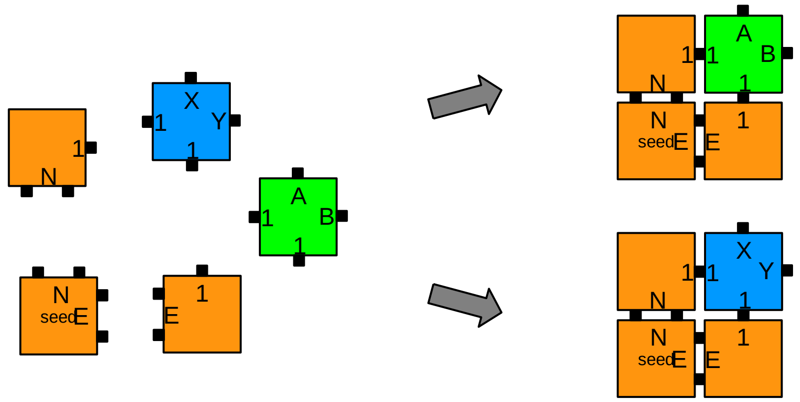
More meaningful:

at a *single* binding site, ≥ 2 tile types attachable



Nondeterminism in Self-Assembly

- A tile set is **deterministic** if it has only one terminal assembly (map of tile types to points).
- This tile set has multiple terminal assemblies, *but* they all have the same shape.

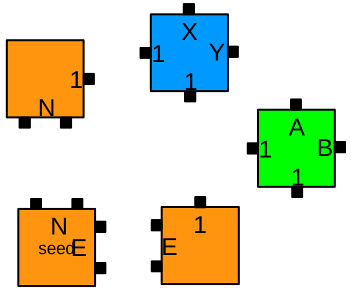


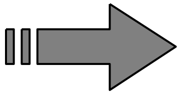
- The tile set **self-assembles** a 2 x 2 square.

Power of Nondeterminism

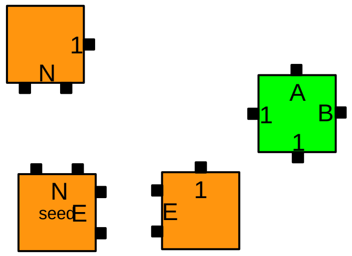
Question: Let *S* be a finite shape self-assembled by some nondeterministic tile set. Does some deterministic tile set also self-assemble *S*?

In this example, we can convert this nondeterministic tile set that self-assembles a 2 x 2 square ...





... to this deterministic tile set that self-assembles the same shape.



In general???

Power of Nondeterminism

Question: Let *S* be a finite shape self-assembled by some nondeterministic tile set. Does some deterministic tile set als

Answer: T

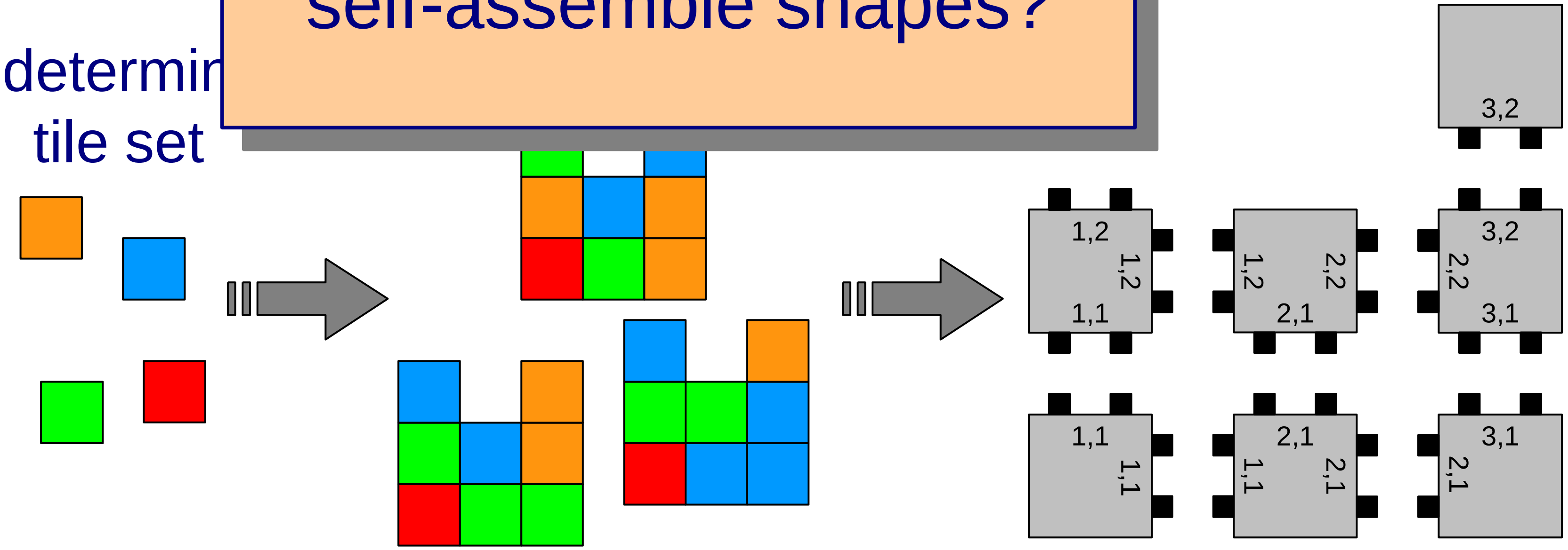
rministic tile set

d-coding *S*)

nondetermi

tile set

Is there some way that nondeterminism helps to self-assemble shapes?



Power of Nondeterminism

Question 1: Let *S* be an <u>infinite</u> shape strictly self-assembled by some nondeterministic tile system. Does some deterministic tile set also self-assemble *S*?
Is *tile computability* unaffected by nondeterminism?
Answer: **No**

There is an infinite shape *S* strictly self-assembled by <u>only</u> nondeterministic tile systems.

Remainder of talk

Question 2: Let *S* be a <u>finite</u> shape strictly self-assembled by some nondeterministic tile system <u>with *k* tile types</u>. Does some deterministic tile system <u>with at most *k* tile types</u> also self-assemble *S*?
Is *tile complexity* unaffected by nondeterminism?
Answer: **No**

There is a finite shape *S* strictly self-assembled with at most *k* tile types by <u>only</u> nondeterministic tile systems.

Optimization Problems

MinTileSet

Given: finite shape *S*

Find: size of smallest tile system that self-assembles *S*

MinDetTileSet

Given: finite shape *S*

Find: size of smallest **deterministic** tile system that self-assembles *S*

False statement: Nondeterminism does not affect tile complexity:
for every nondeterministic tile set of size *k* that self-assembles a shape *S*,
there is a deterministic tile set of size at most *k* that self-assembles *S*.

if true, would imply MinDetTileSet = MinTileSet

Main Result

- We show: MinTileSet is $\mathbf{NP}^{\mathbf{NP}}$-complete.

  a.k.a., Σ_2^P

- MinDetTileSet is **NP**-complete. (Adleman, Cheng, Goel, Huang, Kempe, Moisset de Espanés, Rothemund, *STOC* 2002)

- $\mathbf{NP} \neq \mathbf{NP}^{\mathbf{NP}} \Rightarrow$ MinTileSet $\neq$ MinDetTileSet

Nondeterminism in Algorithms and Self-Assembly

Algorithm that flips coins but always produces same output

- coin flips **useless**

Tile set that flips coins but always produces same shape

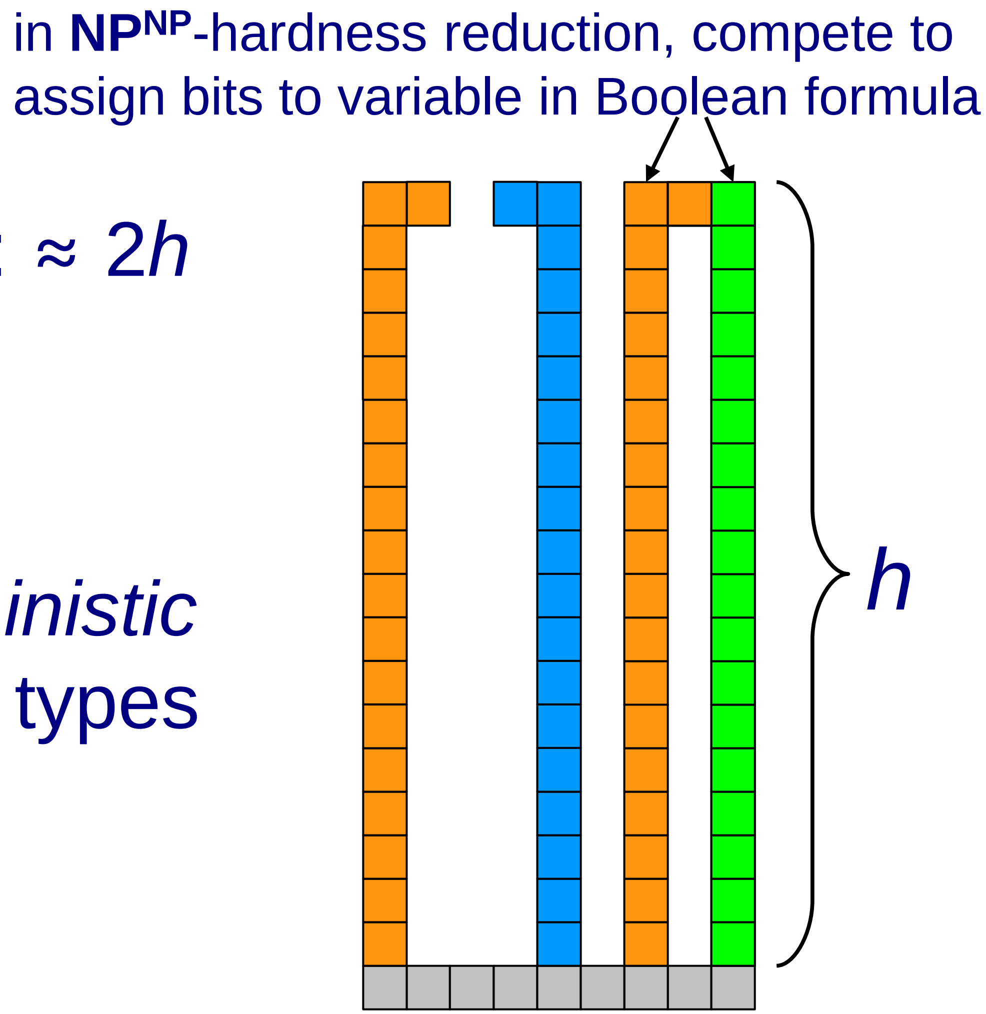
- coin flips **useful**

But … finding smallest tile set is harder if it flips coins.

A Finite Shape for which Nondeterminism Affects Tile Complexity

- Smallest tile set: ≈ 2*h* tile types

- Smallest *deterministic* tile set: ≈ 3*h* tile types



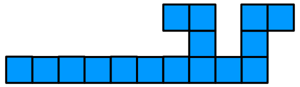
NP^{NP}-hardness Reduction

- **NP^{NP}**-complete problem (Stockmeyer,Wrathall 1976): ∃∀CNF-UNSAT
  - Given: CNF Boolean formula Φ with $k+n$ input bits $x=x_1 \ldots x_k$ and $y=y_1 \ldots y_n$
  - Question: is $(\exists x)(\forall y)\neg\Phi(x,y)$ true?
- **Reduction goal:** Given Φ, output shape S and integer c such that $(\exists x)(\forall y)\neg\Phi(x,y)$ holds if and only if some tile set of size at most c self-assembles S.

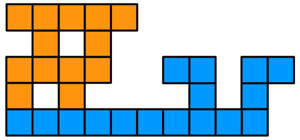
$\mathbf{NP}^{\mathbf{NP}}$-hardness Reduction

<u>Main idea</u> (due to Adleman et al. *STOC* 2002):

- Given a tree shape (no simple cycles), it is possible to compute its minimum tile set in polynomial time.
- Create a tree shape ϒ that "encodes" Φ.


ϒ

- Compute ϒ's minimal tile set *T*. (*c*=*T*)
- Create shape *S* ⊃ ϒ such that


S

  - If $(\exists x)(\forall y)\neg\Phi(x,y)$, tiles from *T* can be altered to assemble *S*.
  - Otherwise, tiles from *T* cannot be altered to assemble *S*.
  - "Since ϒ ⊆ *S*," every tile set that assembles *S* contains *T*, so if tiles from *T* cannot be altered to assemble *S* then additional tiles are needed; i.e., *S* requires more than $c = |T|$ tile types.

Evaluation of Formula

- Order variables $w = w_1 \dots w_n$ (both ∃ and ∀ variables) and clauses $C_1 \dots C_m$ arbitrarily.
- Fix an assignment to variables.
- For each clause C_j and variable w_i, let a_{ij} be the pair (U/S, T/F) representing whether C_j is satisfied by w_k for $k \le i$, and whether w_k is true or false.
- The matrix $A = (a_{ij})$ looks like

$w = 0011$

$\Phi = (w_1 \lor w_3) \land (w_1 \lor w_2 \lor w_4) \land (\neg w_1 \lor w_2)$

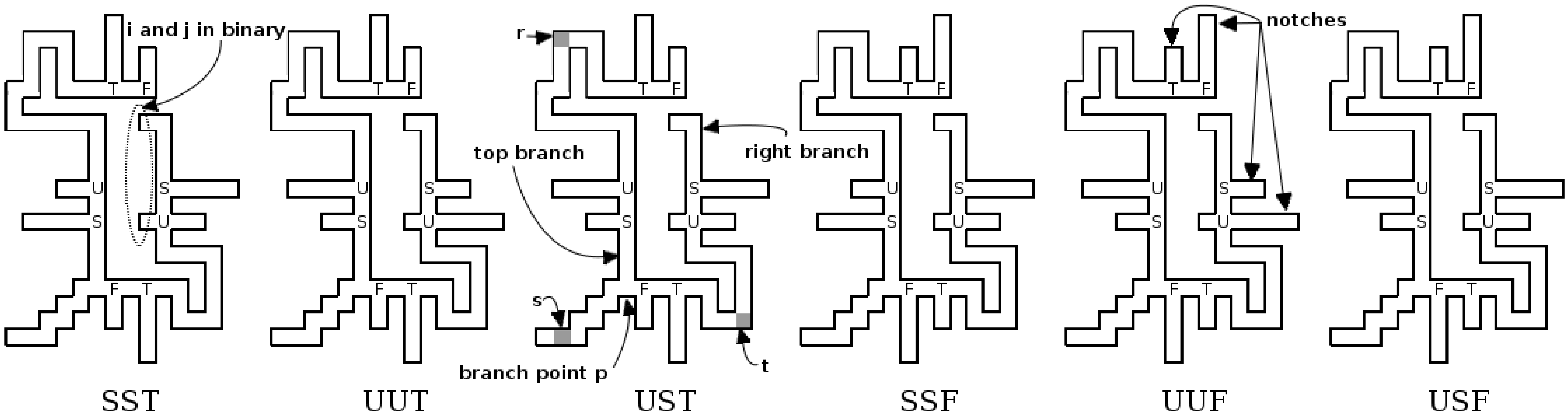
C_3	SF	SF	ST	ST
C_2	UF	UF	UT	ST
C_1	UF	UF	ST	ST
	w_1	w_2	w_3	w_4

→

highlighting when C_j goes from unsatisfied (U) to satisfied (S)

C_3	USF	SSF	SST	SST
C_2	UUF	UUF	UUT	UST
C_1	UUF	UUF	UST	SST
	w_1	w_2	w_3	w_4

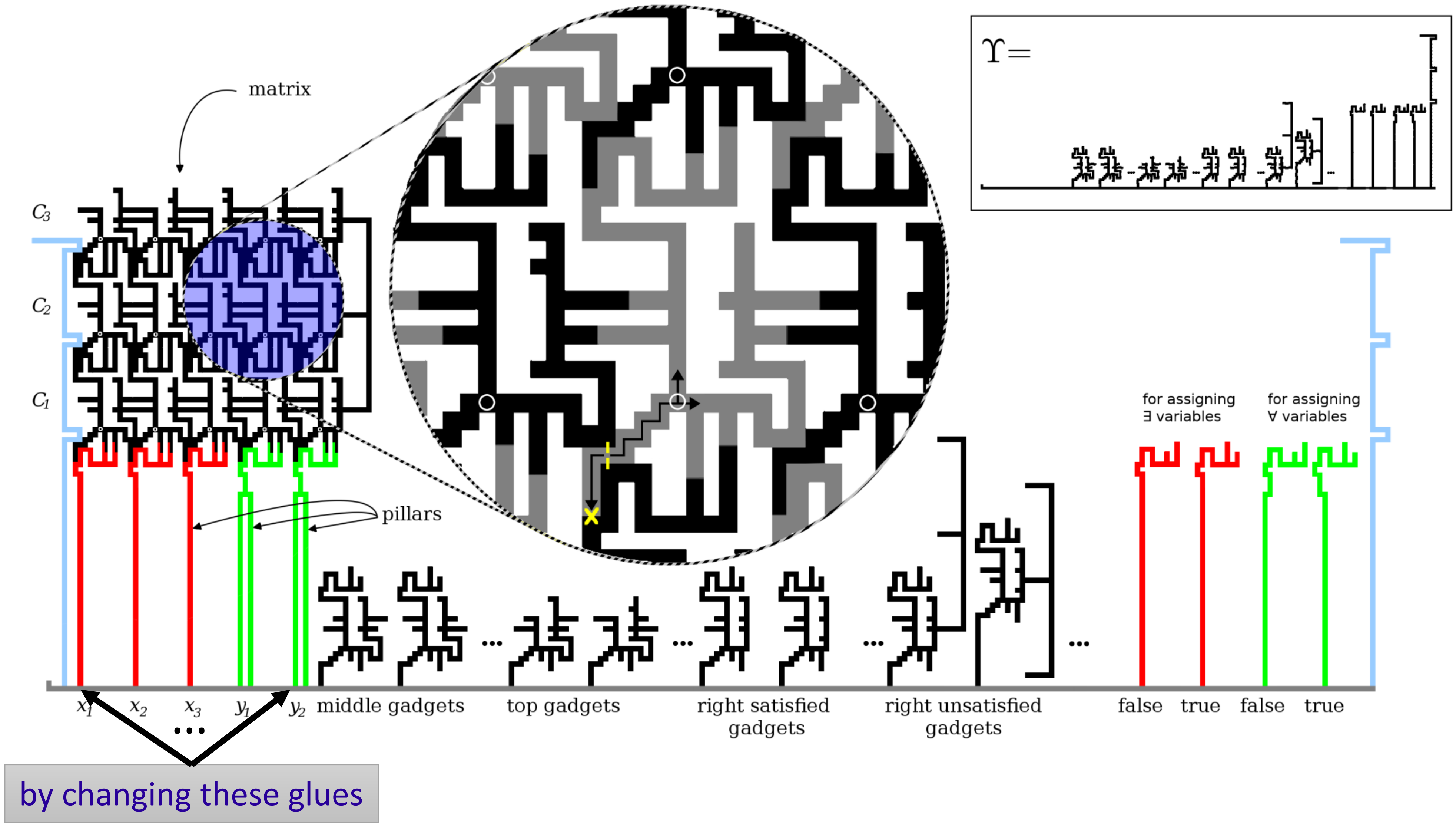
Gadgets (Adleman et al. 2002)



For each variable w_i and clause C_j, value of w_i = T/F and

SS_{ij} – C_j satisfied by a previous variable (w_k for $k < i$)
US_{ij} – C_j unsatisfied by previous variables but is satisfied by w_i
UU_{ij} – C_j unsatisfied by previous variables and by w_i

Shape S



T_Υ = tile types to self-assemble ϒ; size $c = |T_\Upsilon|$

$(\exists x)(\forall y)\neg\Phi(x,y)$ is true ⇔ tiles in T_Υ can be modified to self-assemble S

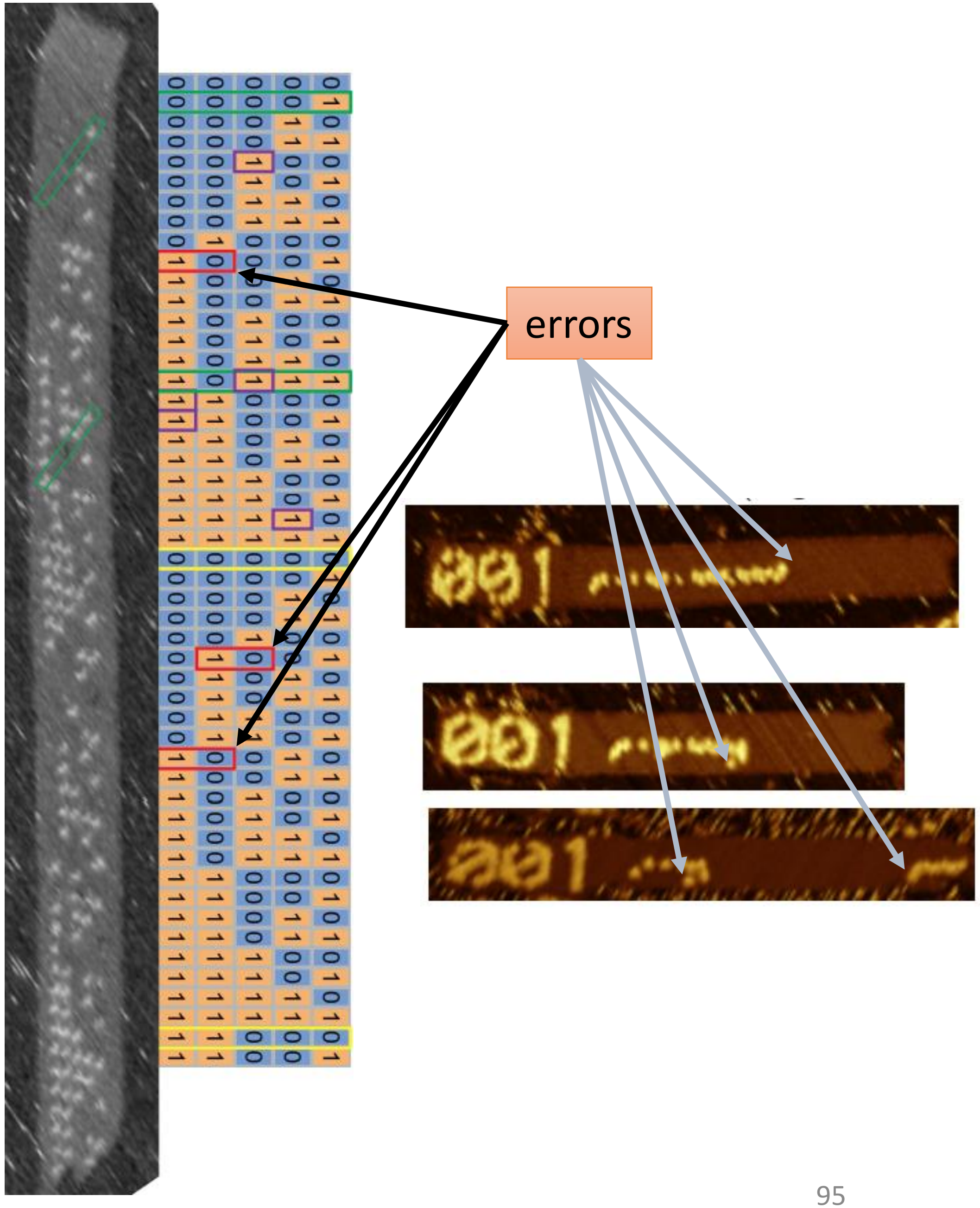
Open Questions

- How large is the gap between deterministic tile complexity and unrestricted tile complexity? our example has ratio 3/2; Schweller (unpublished) improved to quadratic gap: https://faculty.utrgv.edu/robert.schweller/papers/TheGap.pdf
- Hardness of approximation of minimum tile set problem
- Minimum tile set problem when shape is a square
  - deterministic case in **P**; likely not **NP**-hard by Mahaney's theorem (no sparse set is **NP**-hard unless **P**=**NP**)
- *Weak self-assembly* (pattern painting): paint some tile types "black", and say "pattern assembled" is set of points with a black tile
  - *Minimum tile set problem:* uncomputable! (**NP**-complete with some restrictions: https://arxiv.org/abs/1404.0967)
  - *Power of nondeterminism:* is it possible to uniquely paint a pattern, but only by assembling more than one shape on which the pattern is painted?

Errors in algorithmic self-assembly

Errors in self-assembly

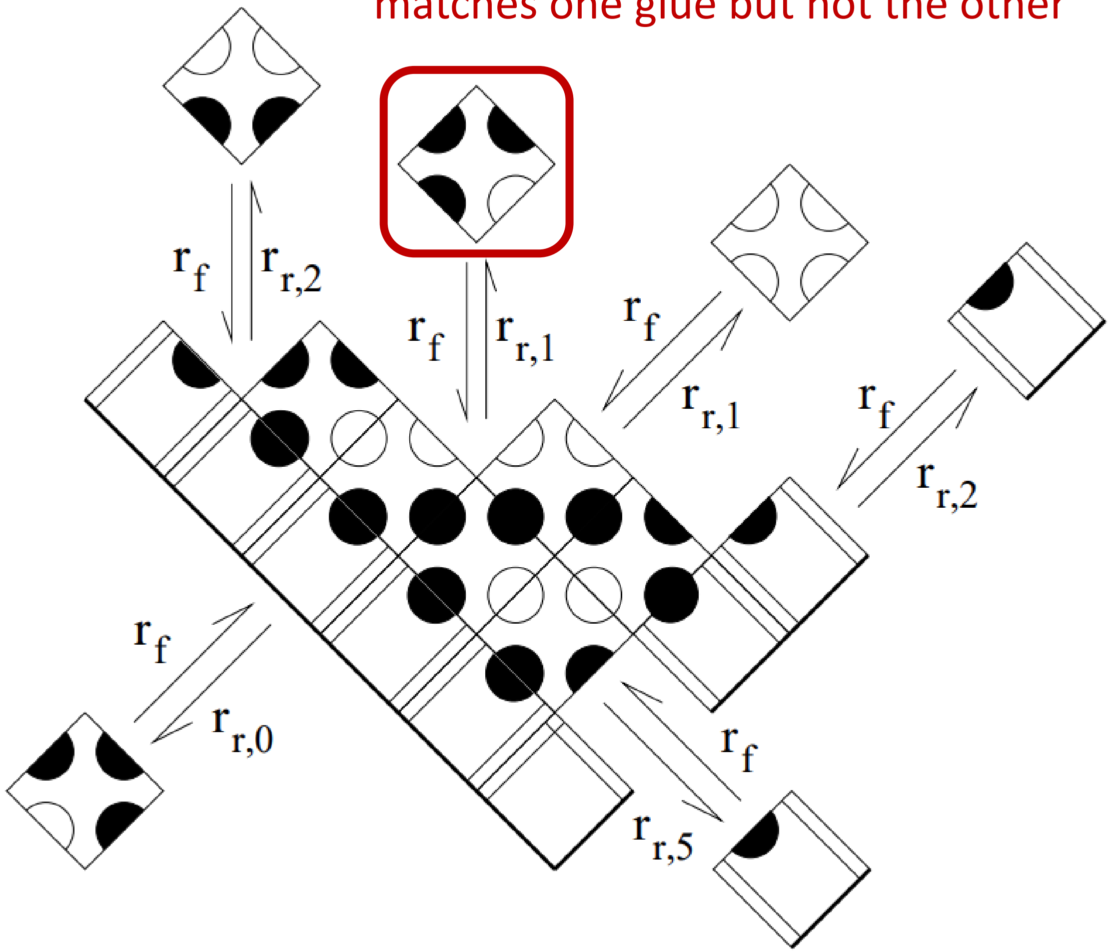
- abstract Tile Assembly Model (aTAM, the model we've used so far):
  - tiles attach but never detach
  - tiles bind only with strength 2 or higher
- unrealistic… what's a better model?
- kinetic Tile Assembly Model (kTAM); essential differences with aTAM:
  - tiles can detach
  - tiles can bind with strength 1



Modeling errors: kinetic Tile Assembly Model

- All tiles attach with rate r_f (no matter how many glues match)
- Tiles detach with rate $r_{r,b}$, if they are attached by total glue strength *b*
- "rate" = time until it occurs is exponential random variable with that rate; expected time 1/rate
  - a.k.a., continuous time Markov process
- Take home message: tiles bound with fewer glues (potential errors) fall off faster, but could get locked in by subsequent neighboring attachment

main cause of algorithmic errors: tile matches one glue but not the other



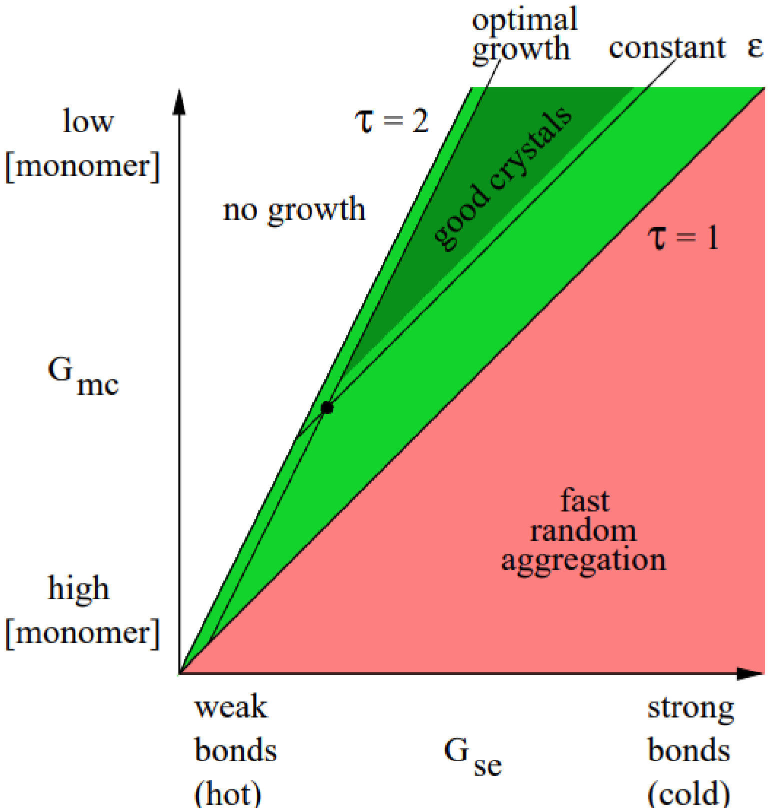
kTAM simulators

- ISU TAS (developed by Matt Patitz) also does kTAM simulation:
  - http://self-assembly.net/wiki/index.php?title=ISU_TAS
  - http://self-assembly.net/wiki/index.php?title=ISU_TAS_Tutorials
- xgrow (developed by Erik Winfree)
  - https://www.dna.caltech.edu/Xgrow/
  - older and a bit less intuitive

Tradeoff between assembly speed and errors

- attach rate r_f can be controlled through concentrations
  - "energy" of attachment is called G_{mc} (<u>m</u>onomer <u>c</u>oncentration): $r_f \propto e^{-G_{mc}}$
- detach rate $r_{r,b}$ can be controlled through temperature
  - "energy" of detachment is called G_{se} (<u>s</u>ticky <u>e</u>nd): $r_{r,b} \propto e^{-b \cdot G_{se}}$
- Intuitively, setting $r_f \approx r_{r,2}$ is like "temperature $\tau = 2$" assembly
  - … but with net zero growth rate
  - make r_f a little larger, and growth is faster, but error rates go up

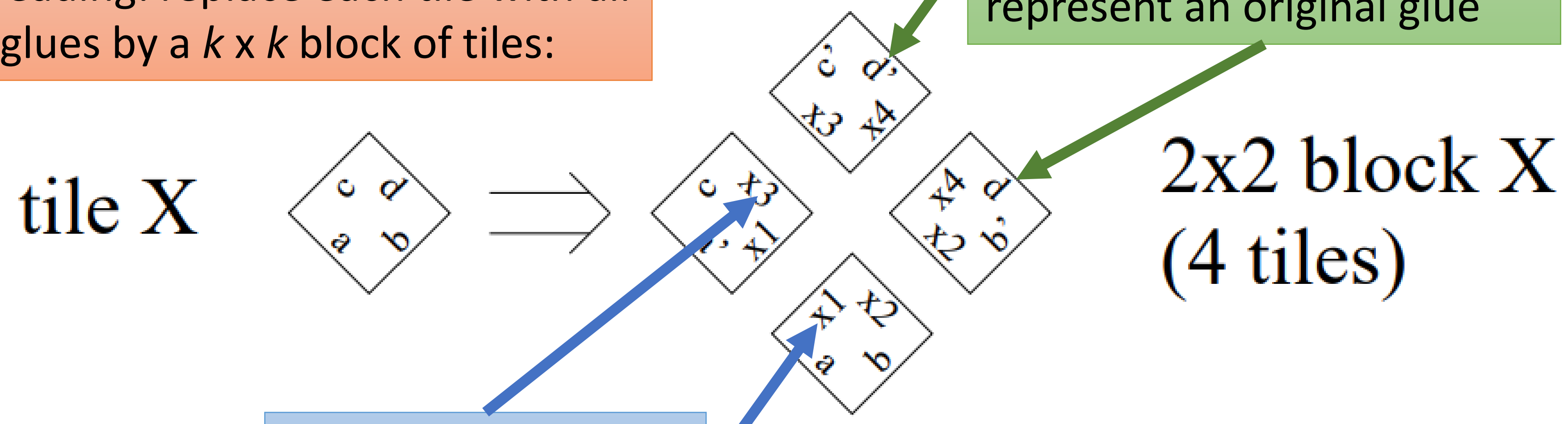
Theorem [Winfree, 1998]: To have total error rate ε, for fastest assembly speed, set $G_{se} = \ln(4/\varepsilon)$ and $G_{mc} = \ln(8/\varepsilon^2)$, i.e., $G_{mc} = 2G_{se} - \ln 2$, i.e., $r_f/r_{r,2} = 2$



Proofreading: Algorithmic error correction

k x *k* proofreading: replace each tile with all strength-1 glues by a *k* x *k* block of tiles:

glues external to the block come in *k* versions that each represent an original glue



glues internal to the block all unique

Proposition: No tiling of the *k* x *k* region with "consistent external glues" (all represent the same glue in original tile set) has *m* mismatches, where $0 < m < k$, i.e., if any mismatch occurs, then at least *k* mismatches occur before the *k* x *k* block can be completed to represent the wrong external glue.

Theorem(ish): If the error rate of the original tile system is ε, the error rate of the *k* x *k* proofreading tile system is $O(\varepsilon^k)$, e.g., if $\varepsilon = 0.01$, then 2 x 2 proofreading gets error rate about $\varepsilon^2 = 0.0001$.

Experimental algorithmic self-assembly

Crystals that think
about how they’re growing

joint work with Damien Woods, Erik Winfree, Cameron Myhrvold, Joy Hui, Felix Zhou, Peng Yin

slides for ECS 232: Theory of Molecular Computation

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(co-first author)

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co-authors

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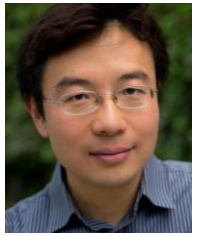
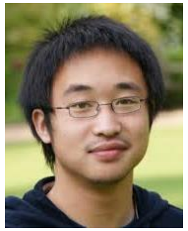
Peng Yin



Felix Zhou



Joy Hui

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Bryan Wei
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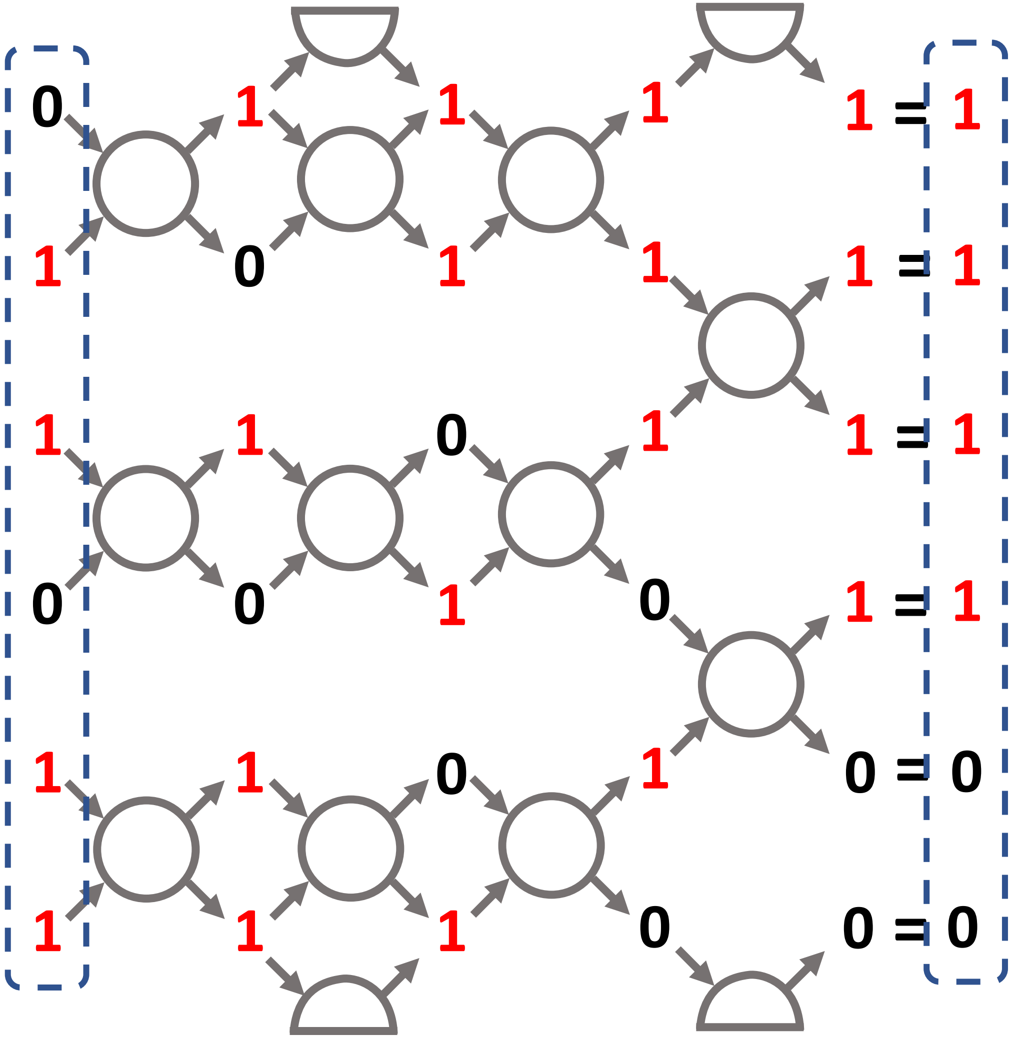
Ashwin Gopinath

Diverse and robust molecular algorithms using reprogrammable DNA self-assembly.
Damien Woods†, David Doty†, Cameron Myhrvold, Joy Hui, Felix Zhou, Peng Yin, Erik Winfree.
Nature 2019. †*These authors contributed equally*.

Hierarchy of abstractions

Bits:	**Boolean circuits compute**
Tiles:	Tile growth implements circuits
DNA:	DNA strands implement tiles

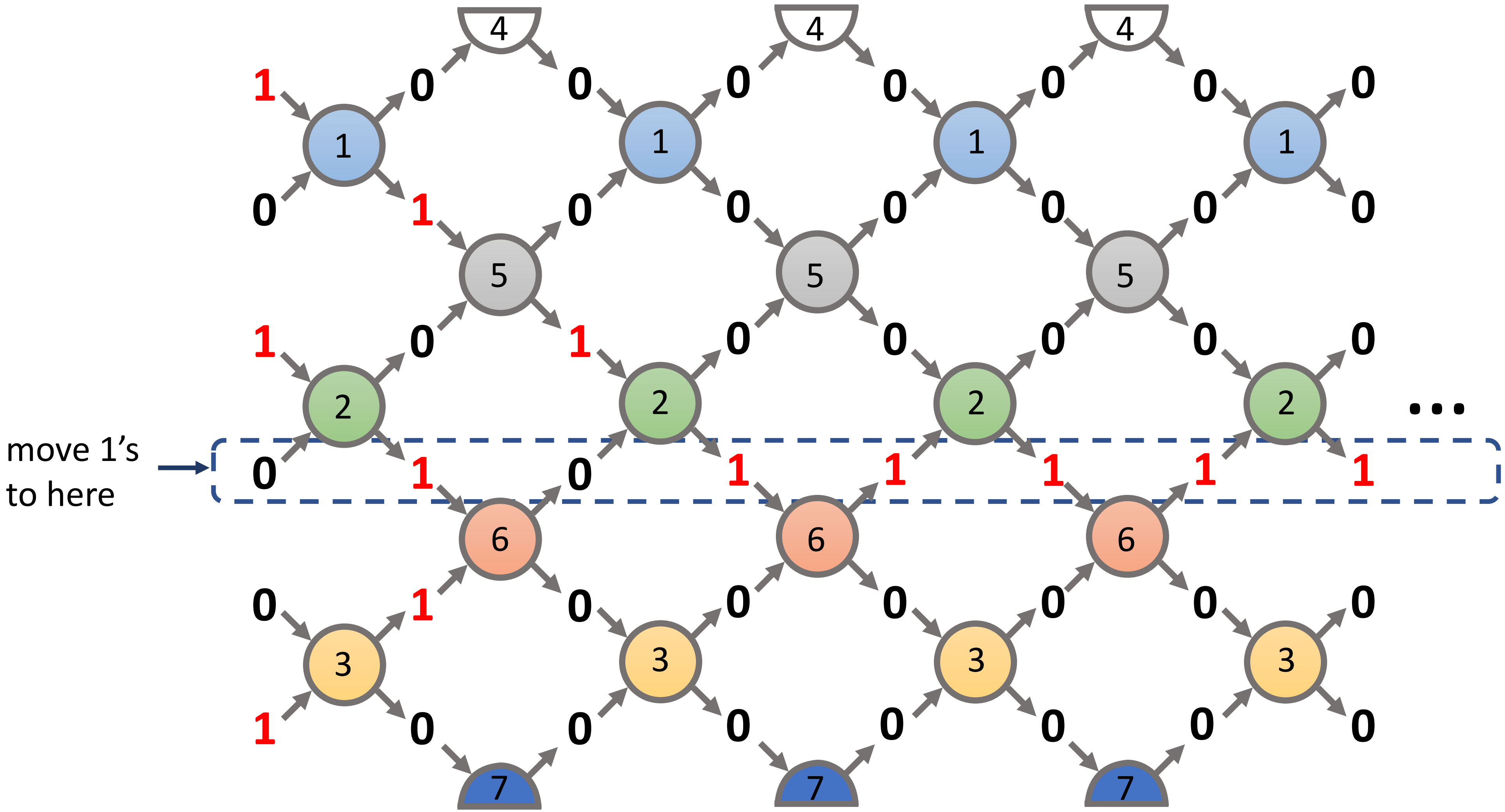
Harmonious arrangement



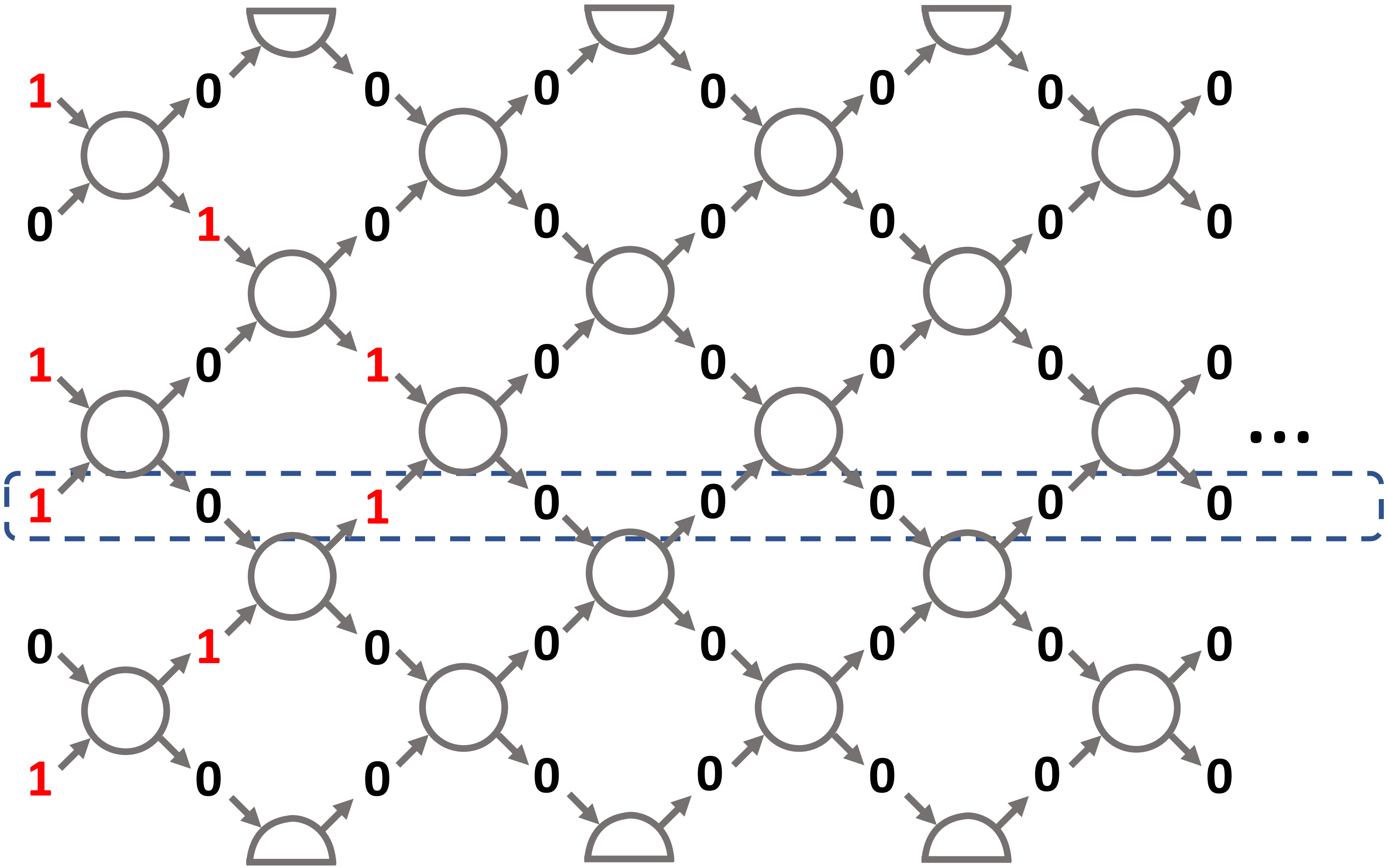
a.k.a. sorting

Odd bits

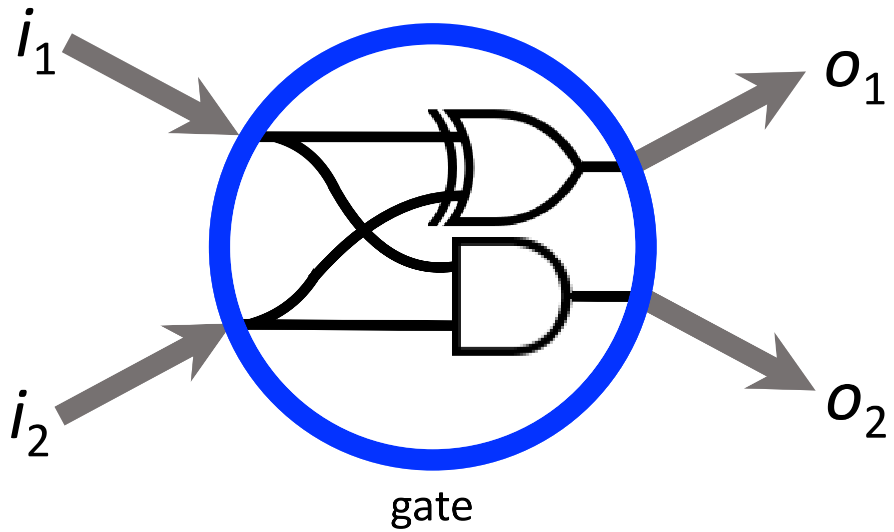
a.k.a. parity



Parity



Circuit model

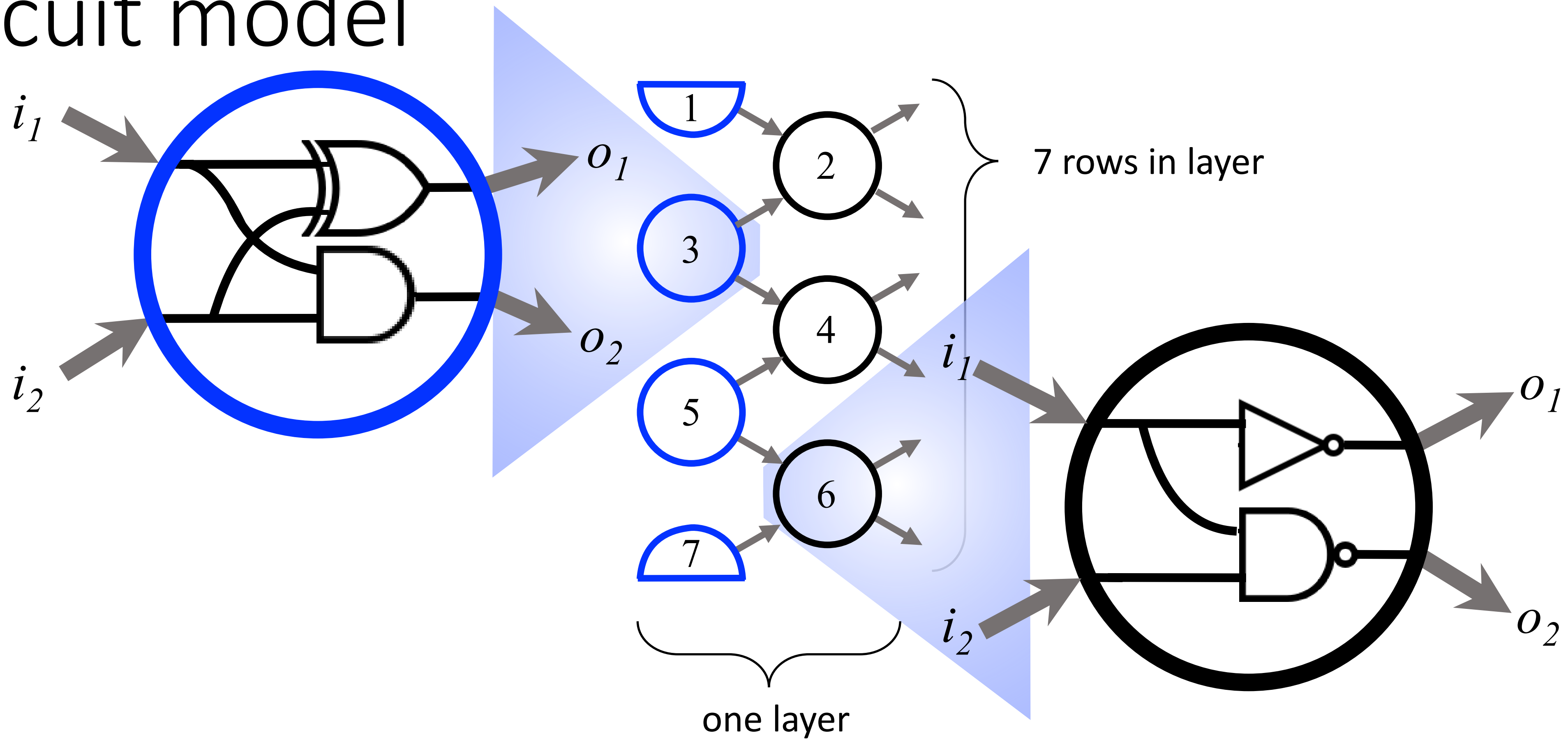


truth table

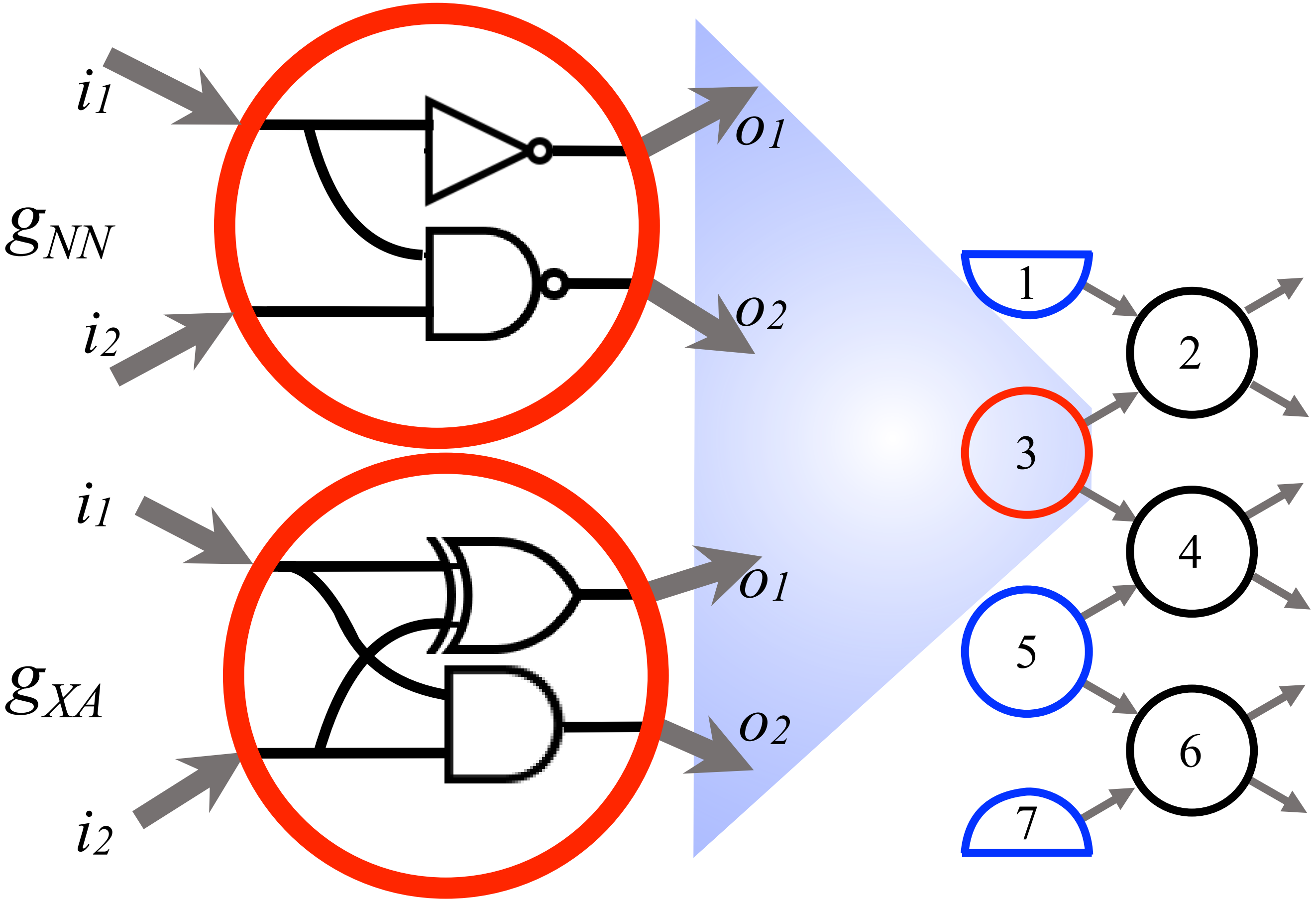
i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	0	1

gate: function with two input bits i_1,i_2
and two output bits o_1,o_2

Circuit model



Circuit model

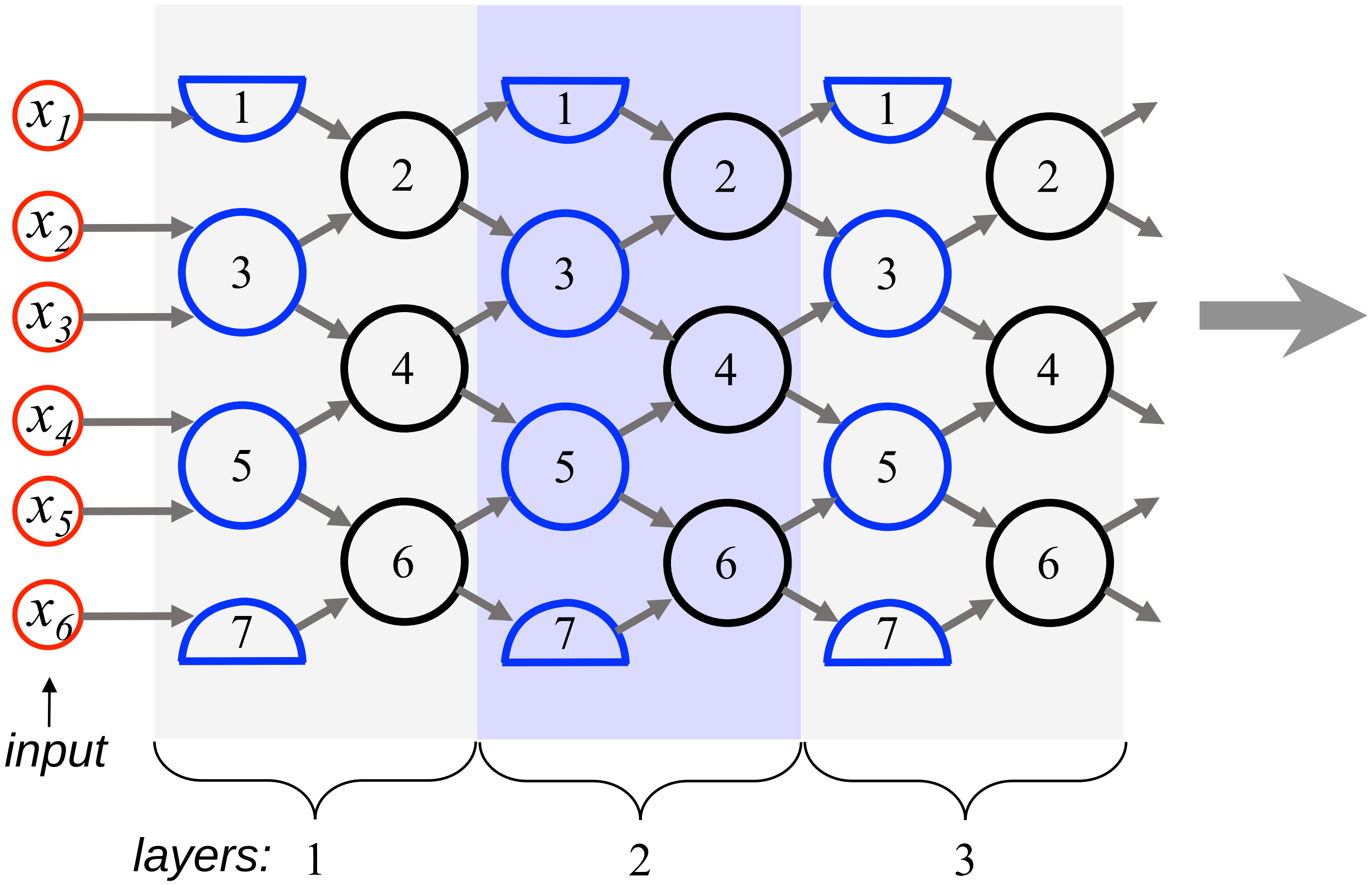


Randomization: Each row may be assigned ≥ 2 gates, with associated probabilities, e.g., $\Pr[g_{NN}] = \Pr[g_{XA}] = ½$

Circuit model

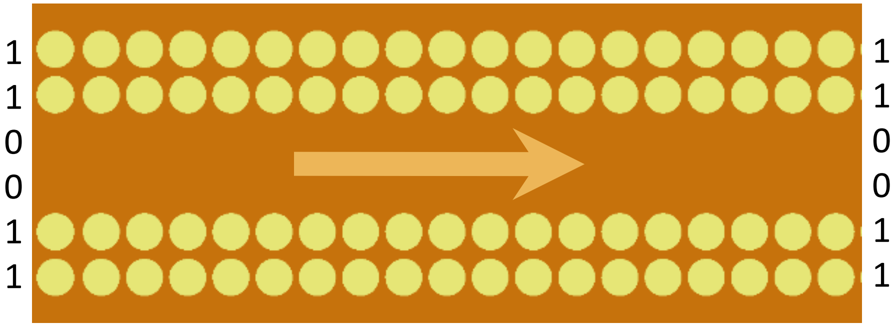
Programmer specifies layer: gates to go in each row

User gives n input bits

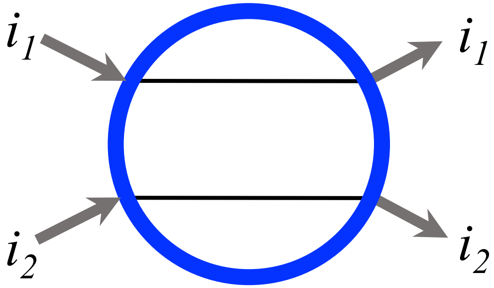


Example circuits with same gate in every row

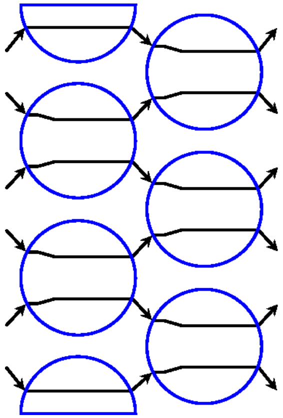
COPY



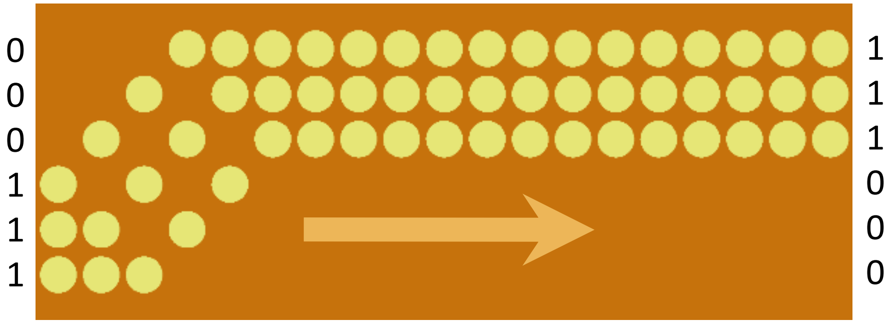
COPY gates



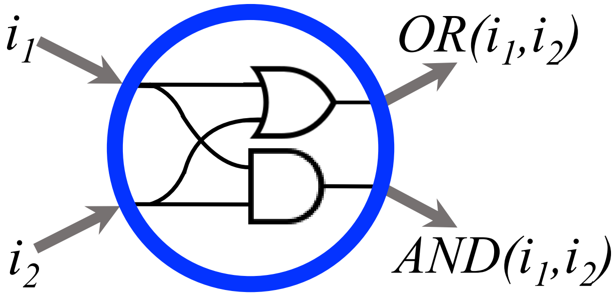
i_1	i_2	o_1	o_2
0	0	0	0
0	1	0	1
1	0	1	0
1	1	1	1



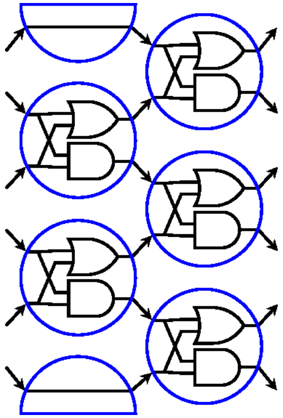
SORTING



SORTING gates

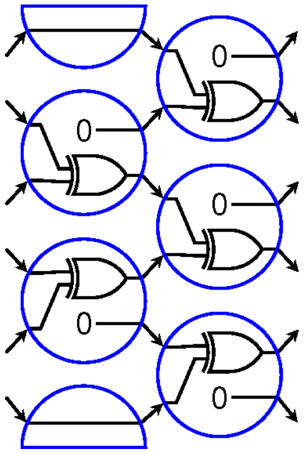


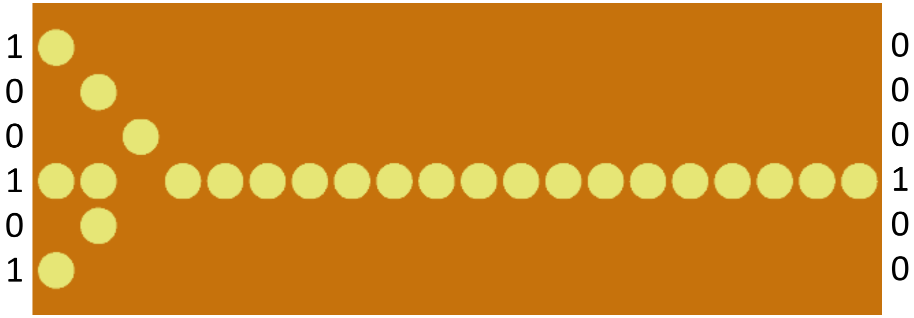
i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	1	1



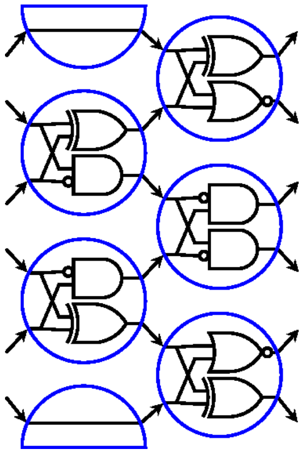
Example circuits with different gates in each row

PARITY

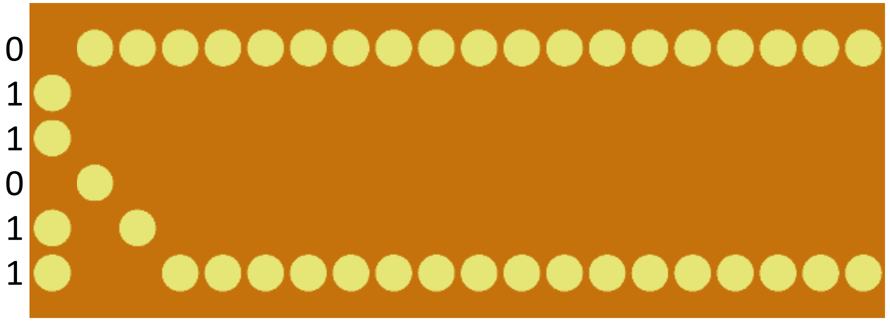




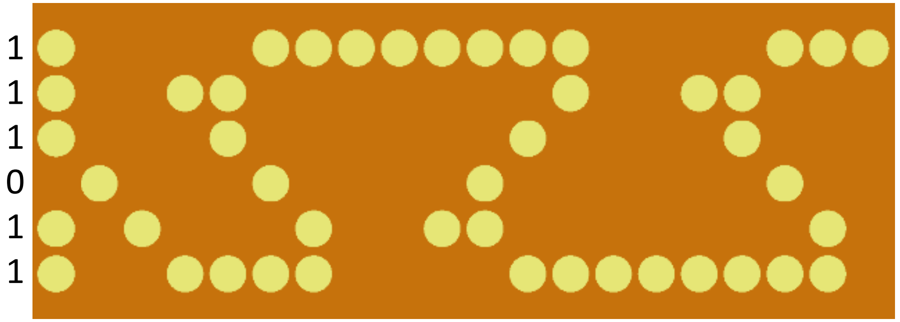
MULTIPLEOF3



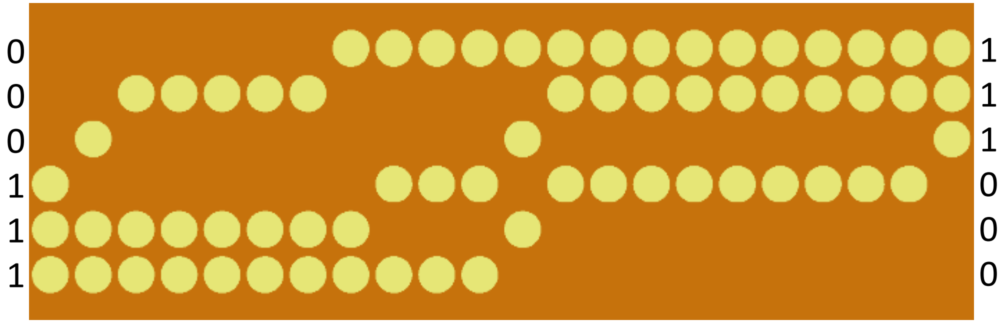
$011011_2 = 27_{10} = 3 \cdot 9$



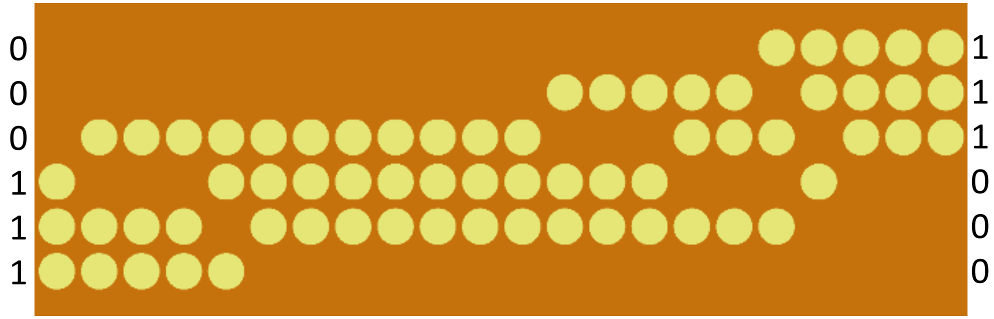
$111011_2 = 59_{10} = 3 \cdot 19 + 2$

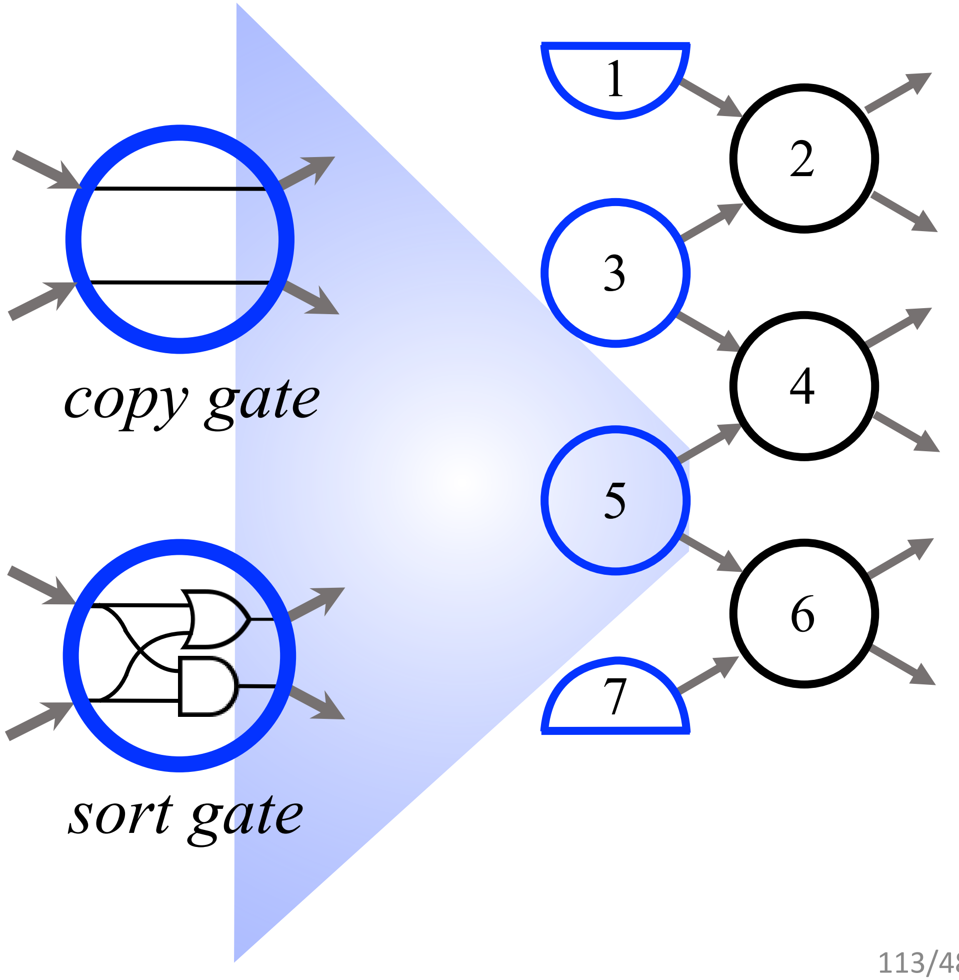


Randomization: "Lazy" sorting



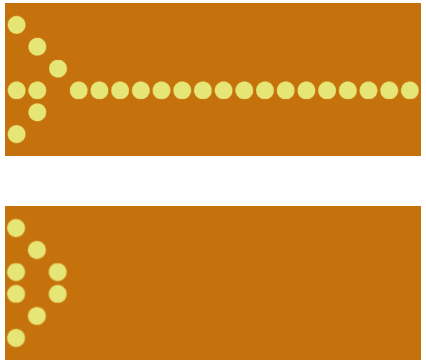
If 1 and 0 out of order, flip a coin to decide whether to swap them.



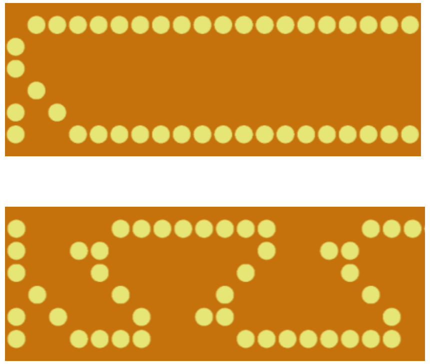


Deterministic circuits

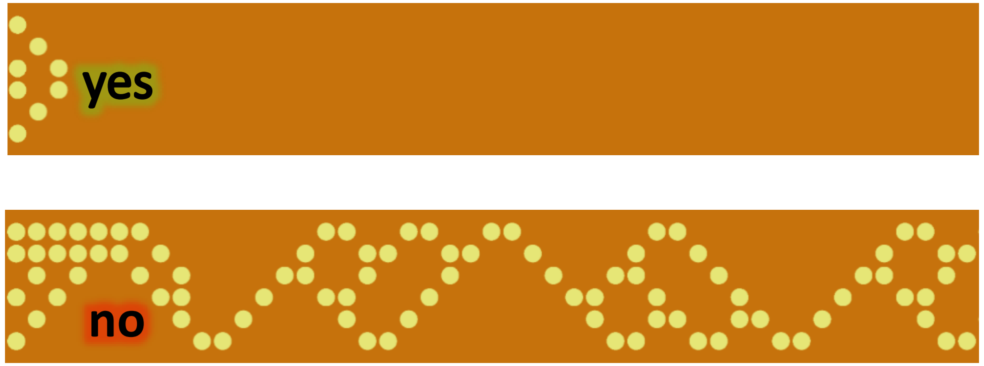
PARITY



MULTIPLEOF3



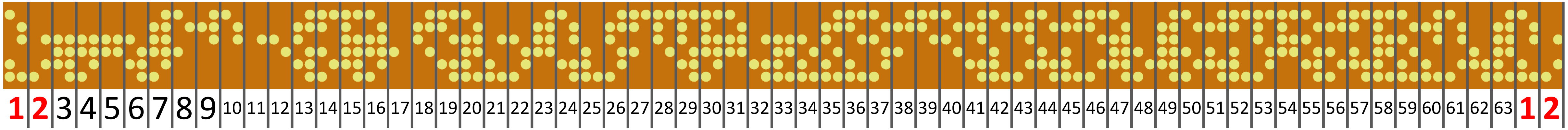
PALINDROME



answer yes/no question

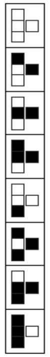
CYCLE63

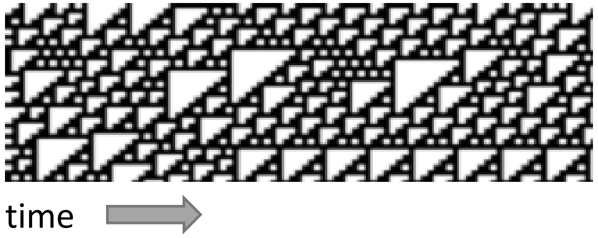
"count" as high as possible

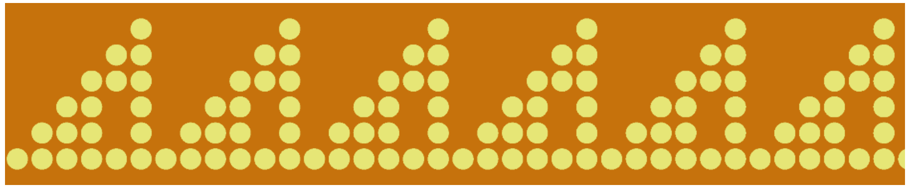


RULE110

simulate cellular automata







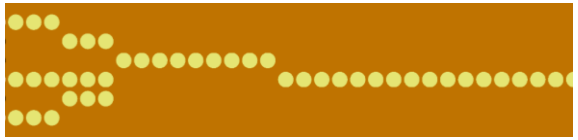
Theorem: Rule 110 can efficiently execute <u>any</u> algorithm.

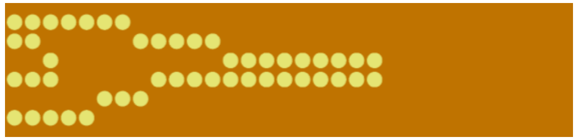
[Cook, <u>Complex Systems</u> 2004]

[Neary, Woods, <u>ICALP</u> 2006]

Randomized circuits

LAZYPARITY





RANDOMWALKINGBIT

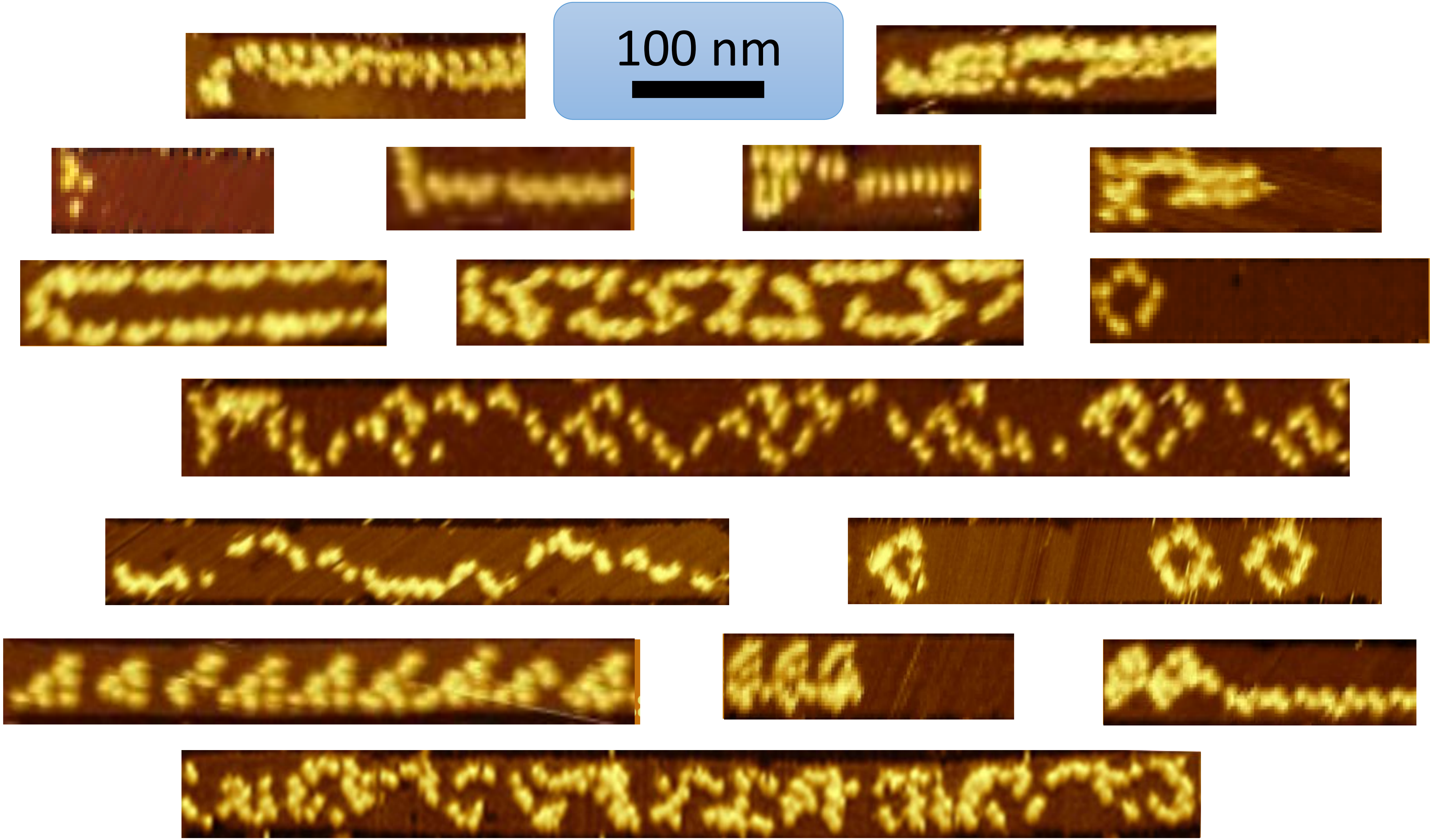
DIAMONDSAREFOREVER

FAIRCOIN

use biased coin to
simulate unbiased coin

Pr [] = Pr [] = ½

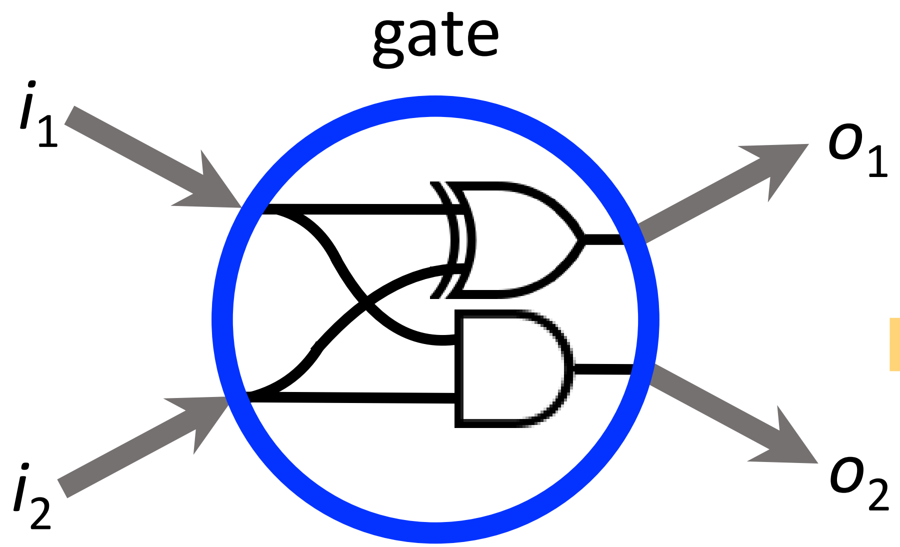
for **any** (positive) probabilities for the randomized gate


100 nm

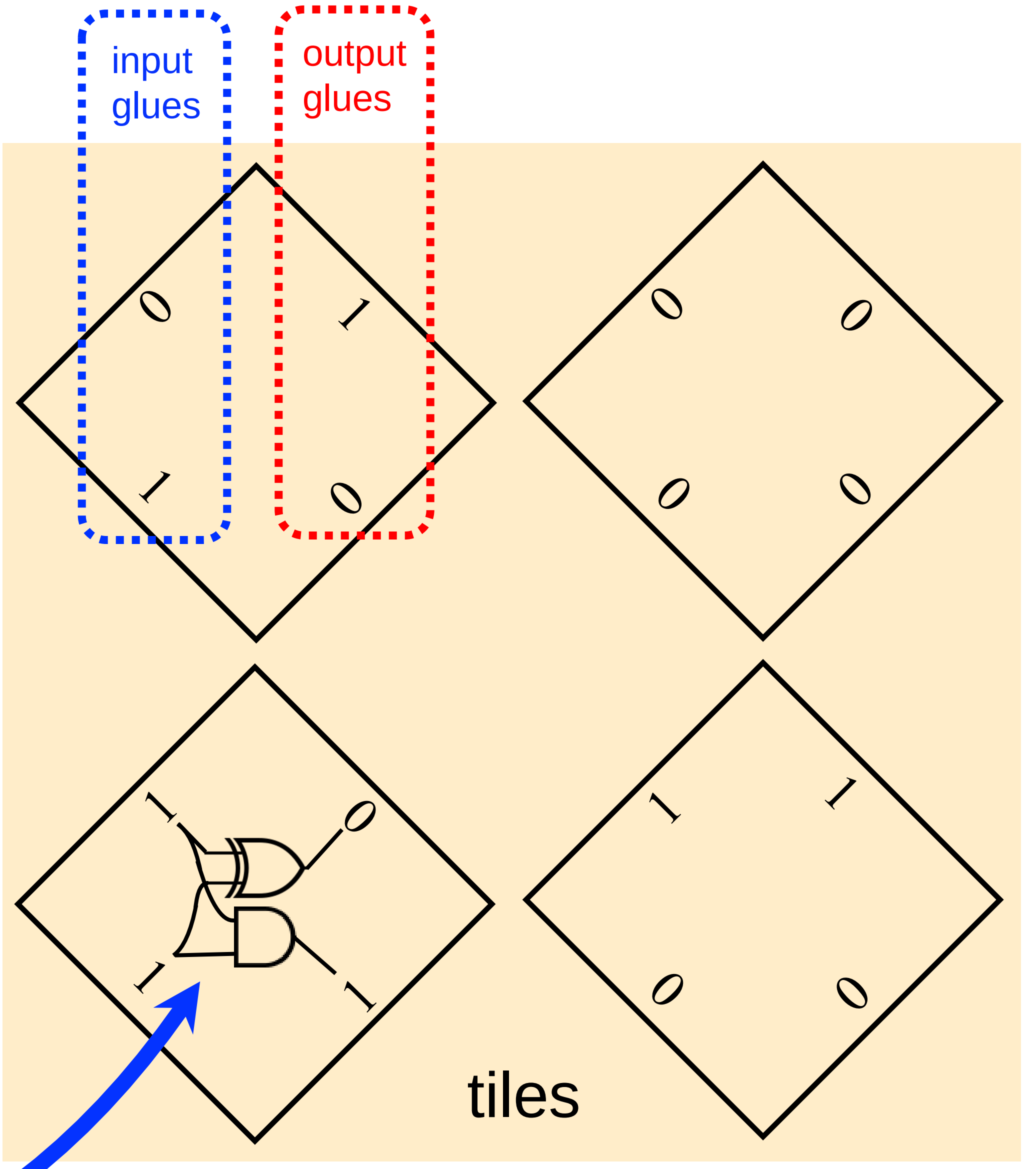
Hierarchy of abstractions

Bits:	Boolean circuits compute
➡ **Tiles:**	**Tile growth implements circuits**
DNA:	DNA strands implement tiles

Gates → Tiles

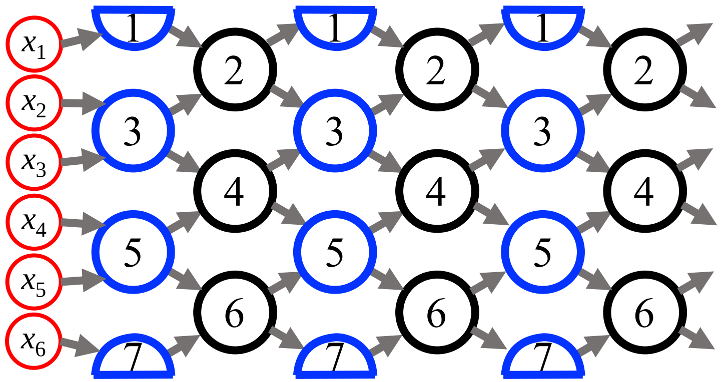


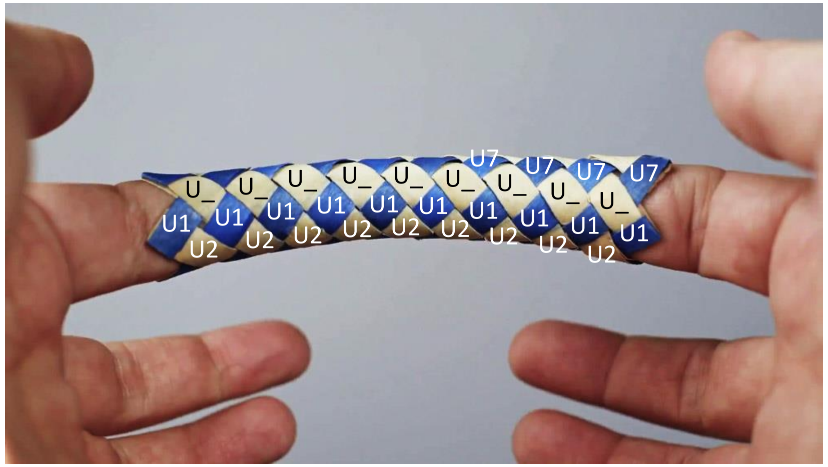
i_1	i_2	o_1	o_2
0	0	0	0
0	1	1	0
1	0	1	0
1	1	0	1

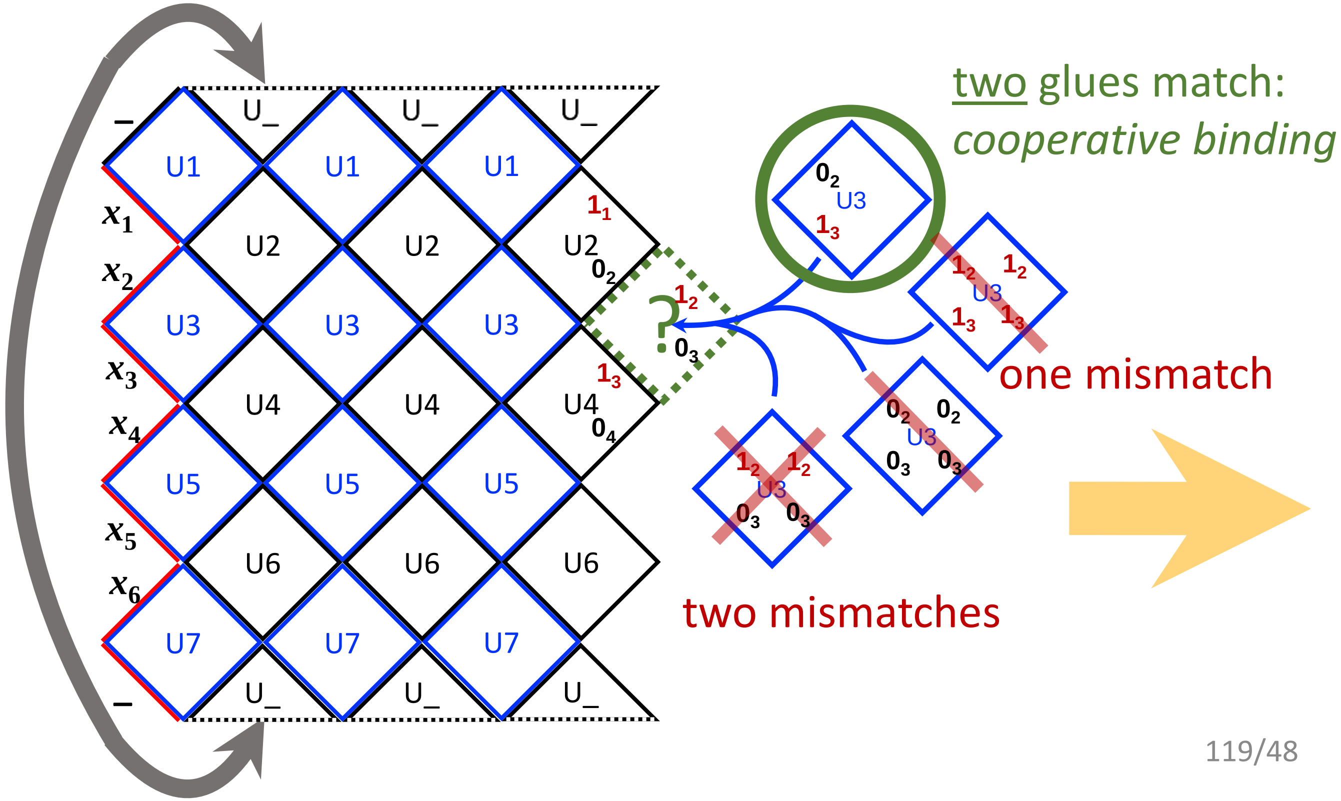


truth table row is encoded by a **tile** with 4 **glues** encoding bits

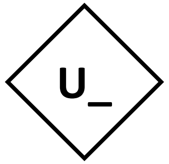
How tiles compute while growing (algorithmic self-assembly)







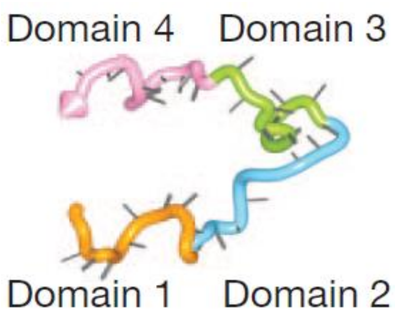
"data-free" tile wraps top to bottom to form a tube

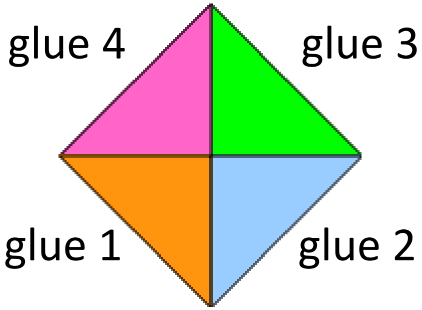


Hierarchy of abstractions

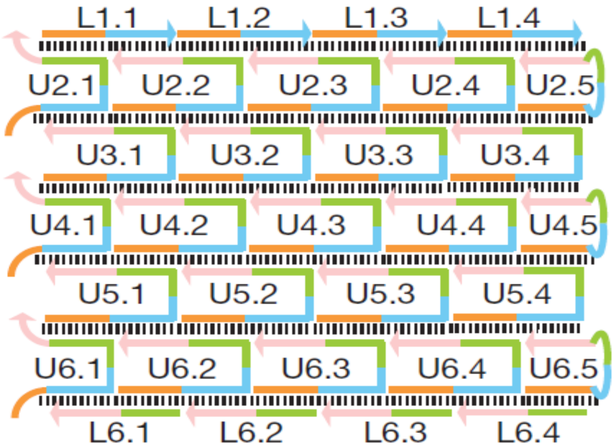
Bits:	Boolean circuits compute
Tiles:	Tile growth implements circuits
➡ **DNA:**	**DNA strands implement tiles**

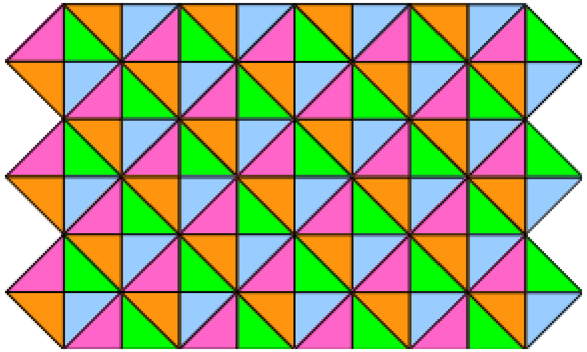
DNA single-stranded tiles





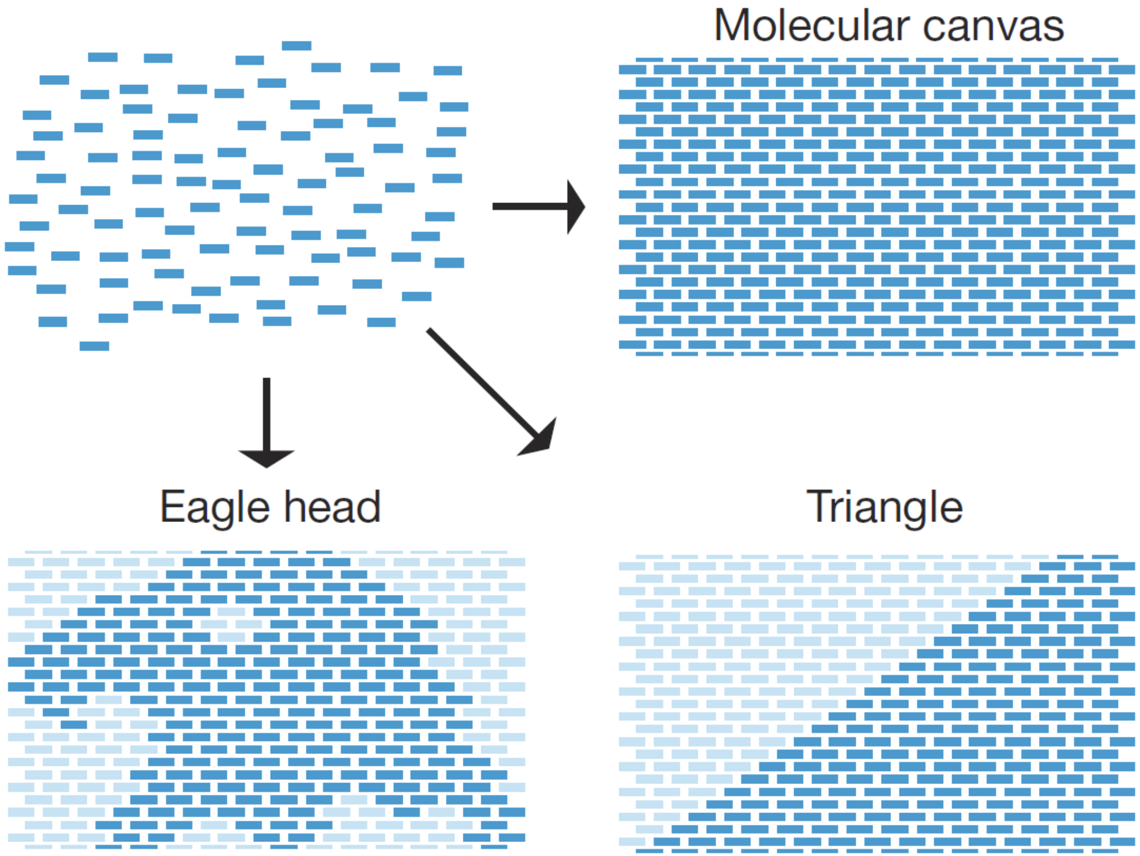
assembly





Yin, Hariadi, Sahu, Choi, Park, LaBean, and Reif.
Programming DNA tube circumferences.
<u>Science</u> 2008

Single-stranded tiles for making any shape



Bryan Wei, Mingjie Dai, and Peng Yin.
Complex shapes self-assembled from single-stranded DNA tiles.
Nature 2012.

Uniquely addressed self-assembly versus algorithmic

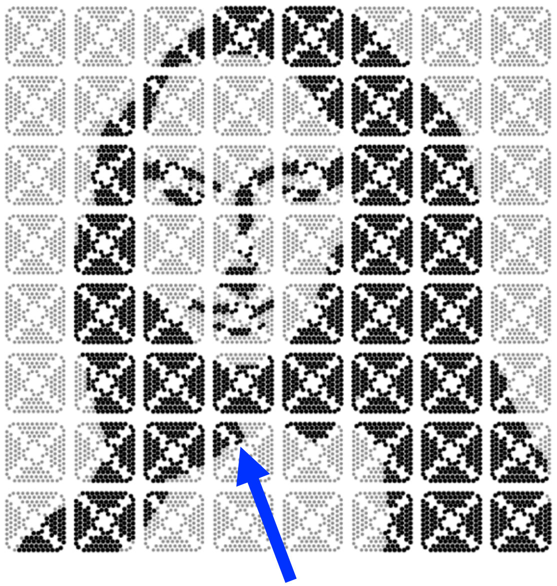
Unique addressing: each DNA "monomer" appears **exactly once** in final structure.

Algorithmic: DNA tiles are **reused** throughout the structure.

single DNA origami

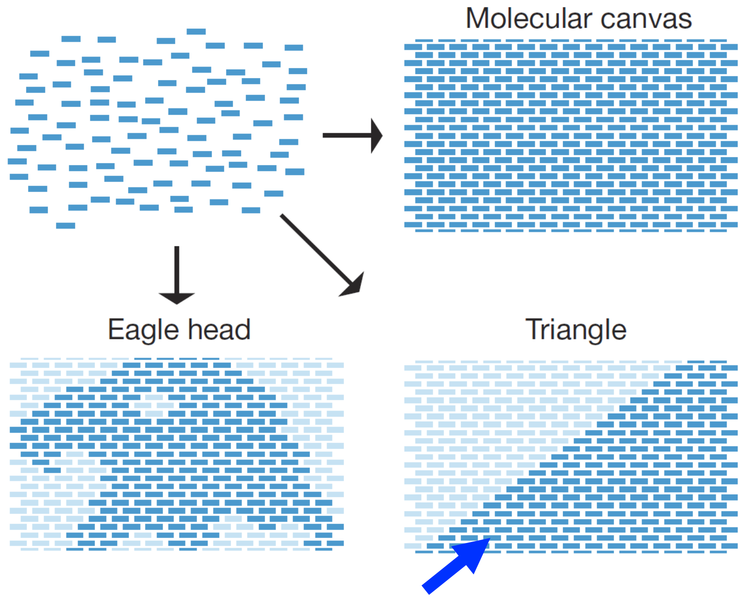
staple strand for position (4,2)

array of many DNA origamis



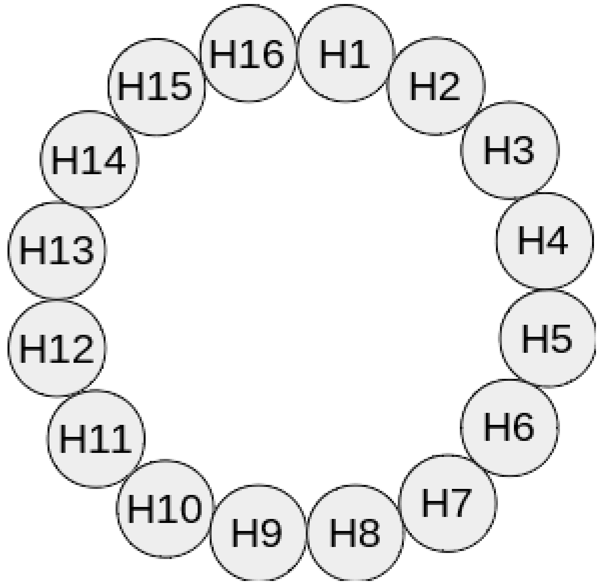
origami for position (4,2)

uniquely-addressed tiles

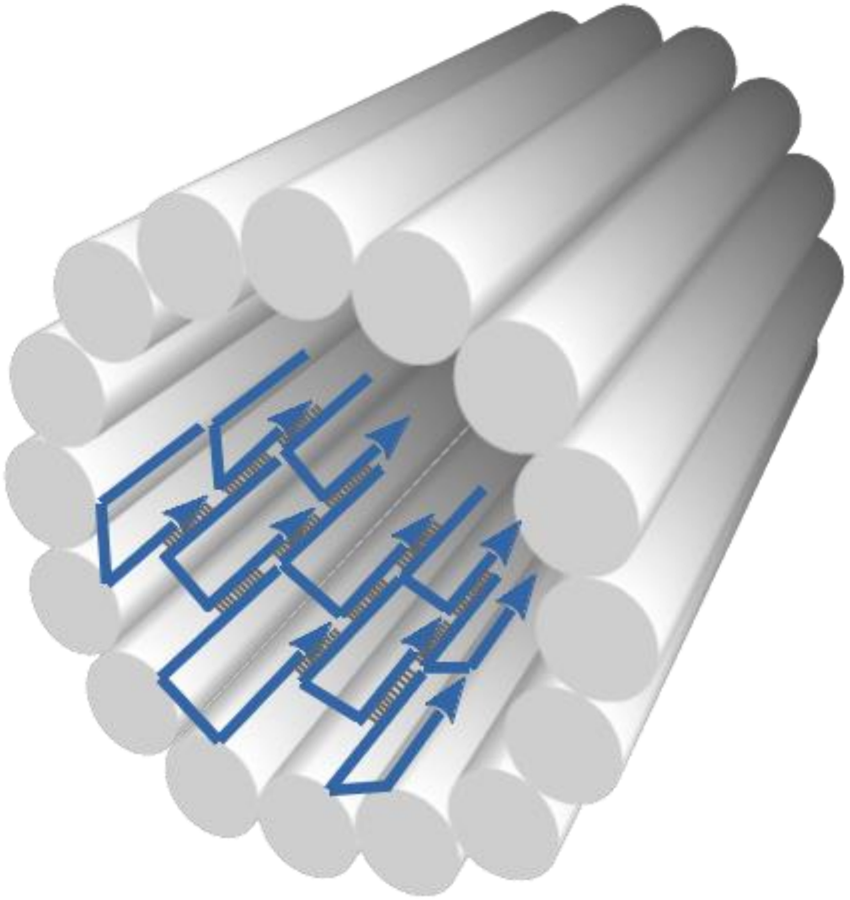


tile for position (4,2)

Single-stranded tile tubes

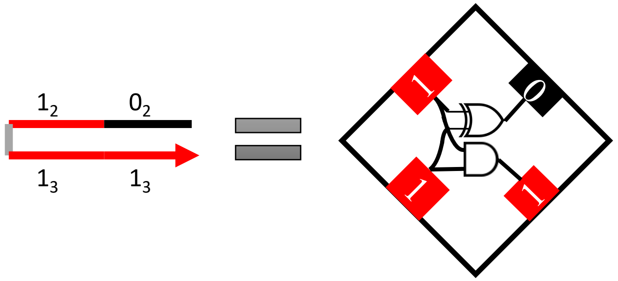


DNA-level diagram of 20-helix tube

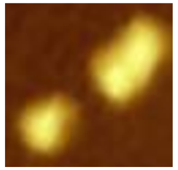


Yin, Hariadi, Sahu, Choi, Park, LaBean, and Reif. *Programming DNA tube circumferences*, Science 2008.

Seeded growth

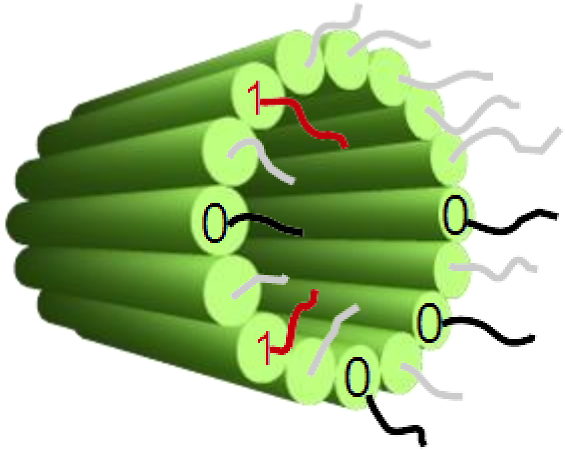


can later add streptavidin (5 nm wide protein) to bind biotins and visualize where the 1's are

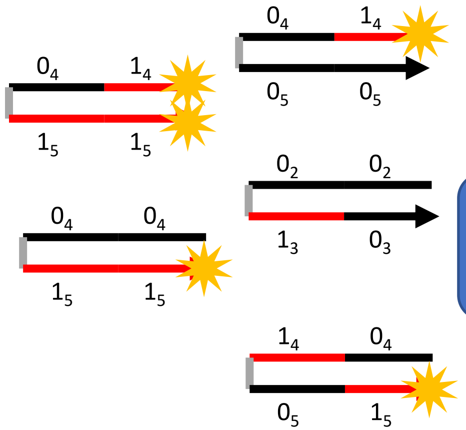


DNA origami seed

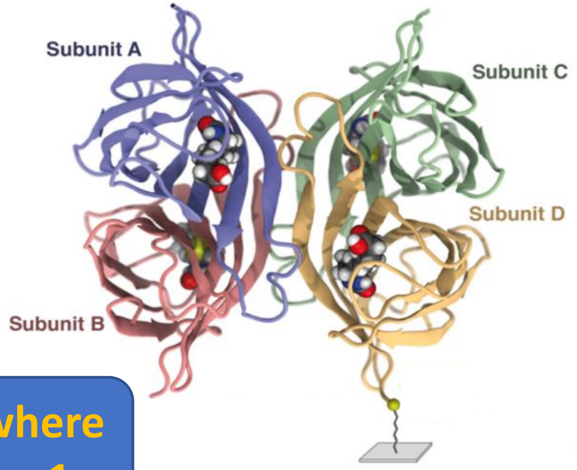
single-stranded "input-adapter" extensions encoding 6 input bits



single-stranded tiles implementing circuit gates

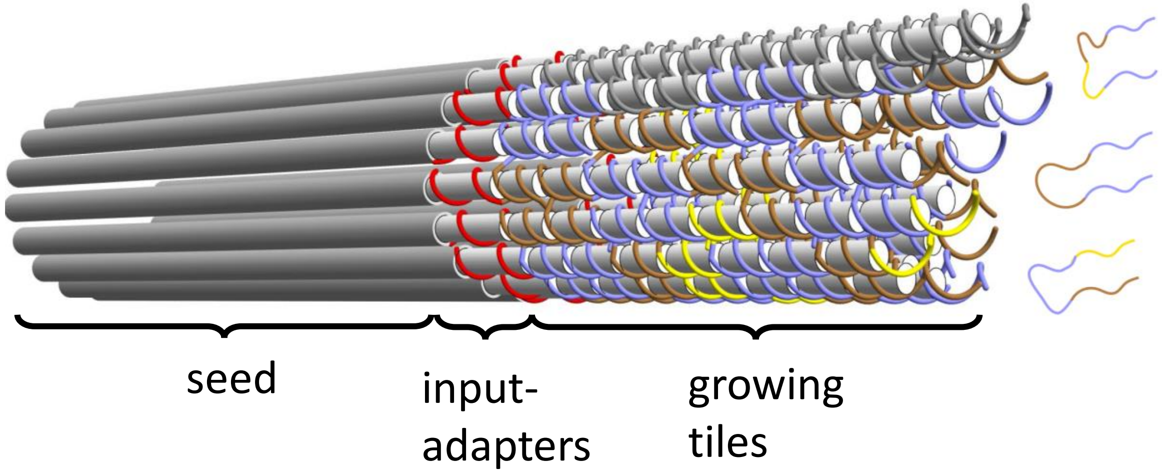


biotins where output = 1



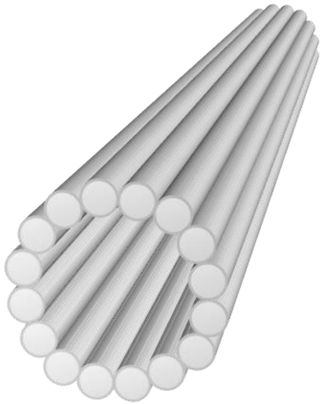
need barrier to nucleation (tile growth without seed);
[tile]=100 nM;
temperature=50.9° C

hold 8-48 hours

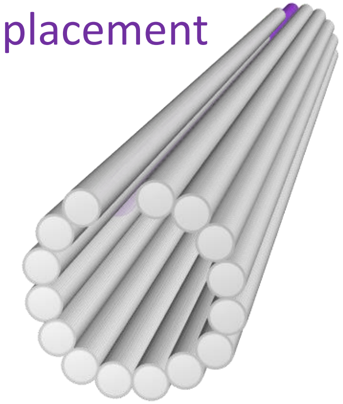


Tubes to ribbons

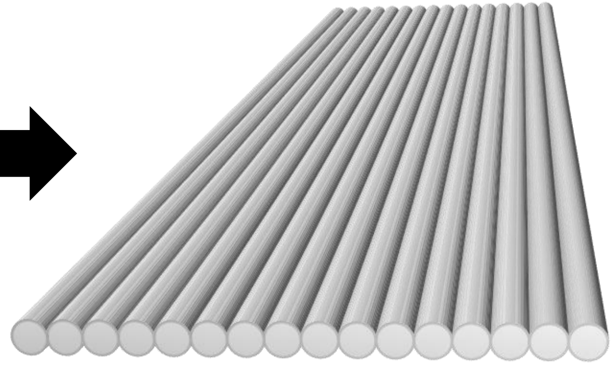
tube



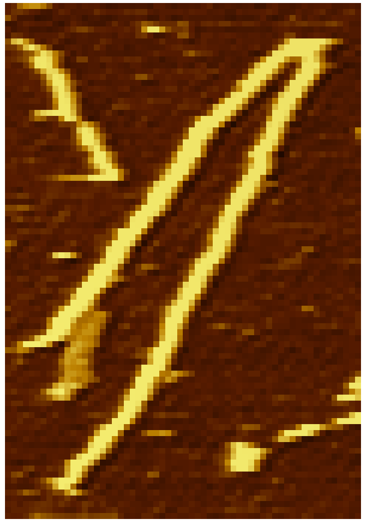
remove “seam” by
strand displacement



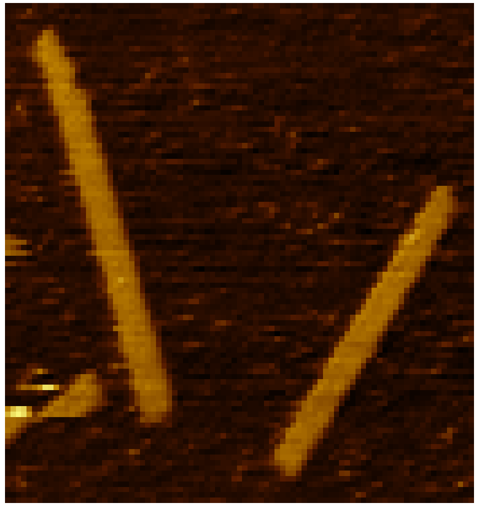
ribbon



AFM
image

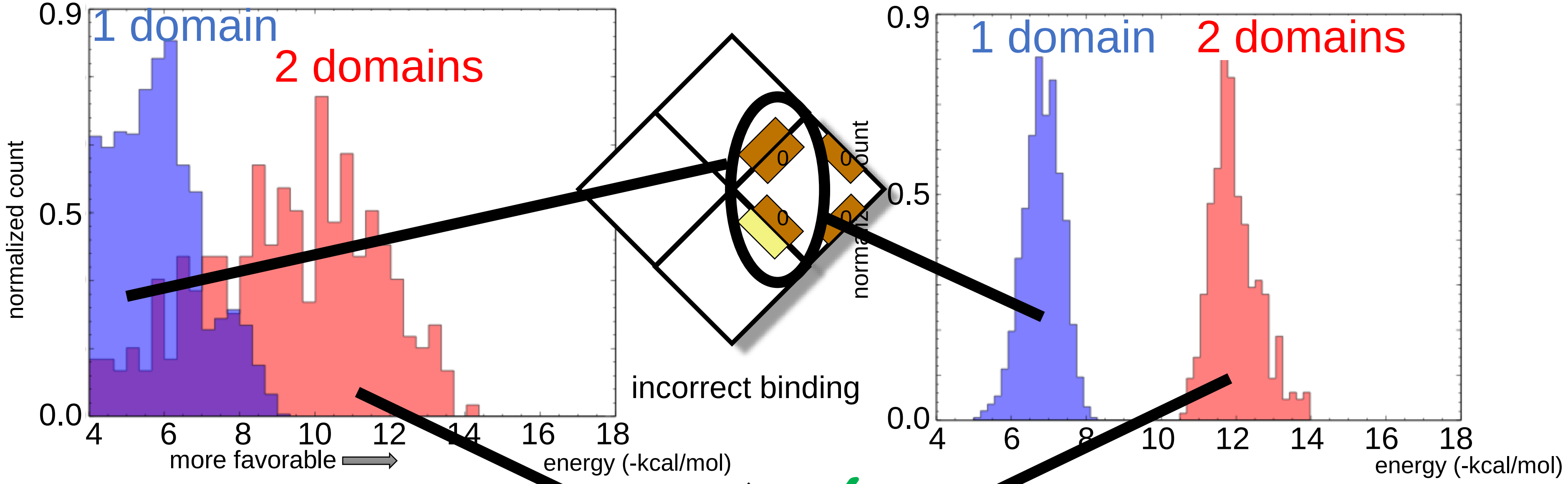


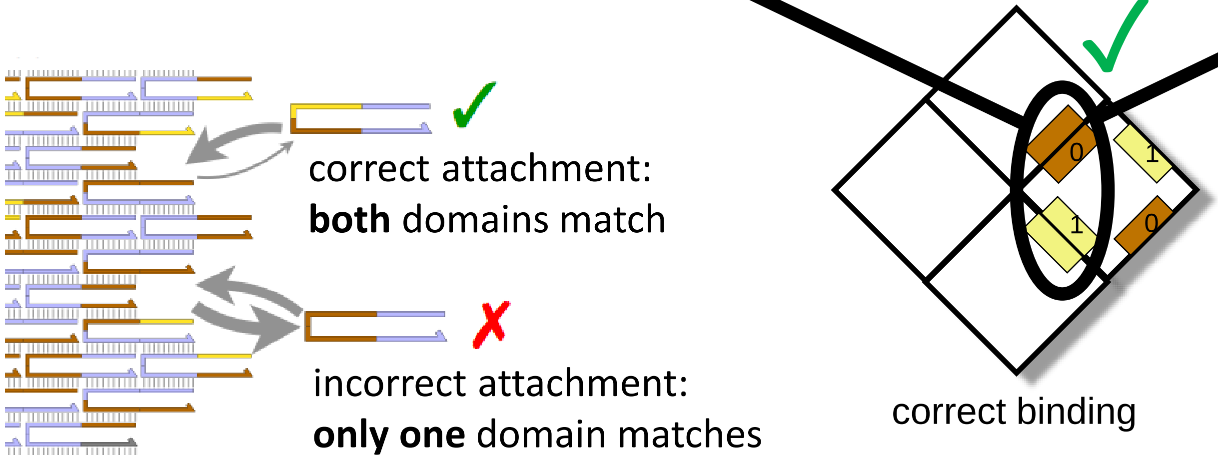
500 nm

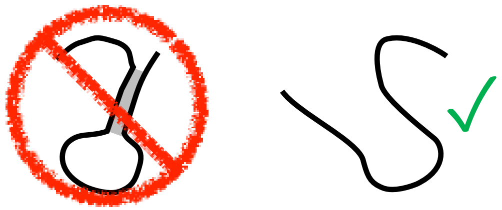


DNA sequence design

Random sequences vs designed sequences



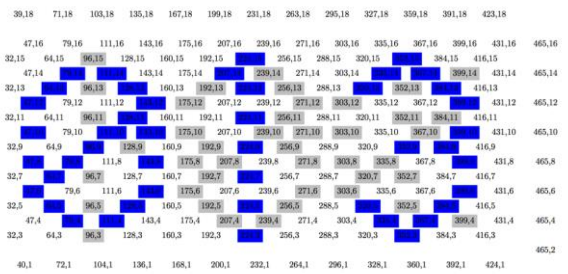




Other goals:

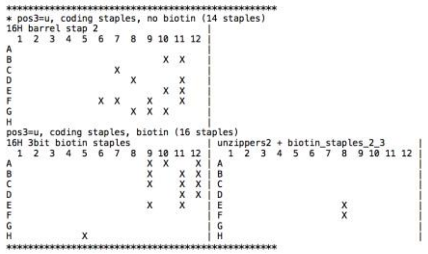
- low strand secondary structure
- low interaction between strands

Bar-coding origami seed for imaging multiple samples at once



some staples of origami seed have version with a biotin

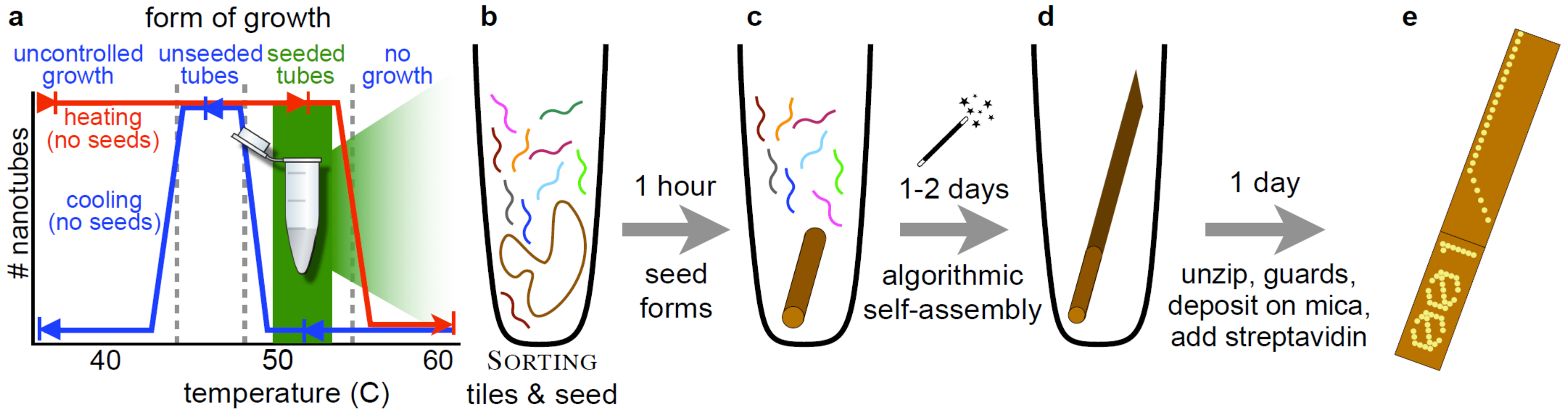
Generate plate map



represents some combination of circuit and input, e.g.,
013 = *“parity circuit, input=011010”*

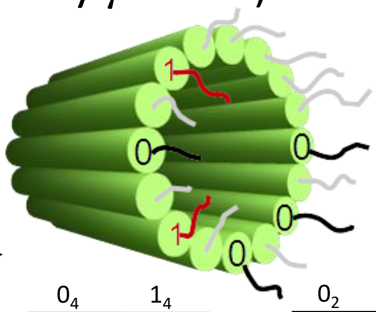
label with streptavidin

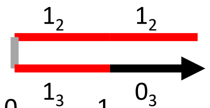
Experimental protocol

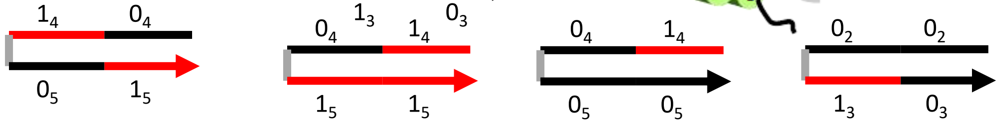


To execute circuit γ on input $x \in \{0,1\}^*$:

- Mix
  - origami seed (bar-coded to identify γ and x)
  - "adapter" strands encoding x
  - tiles computing γ



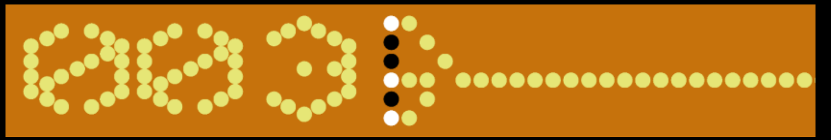




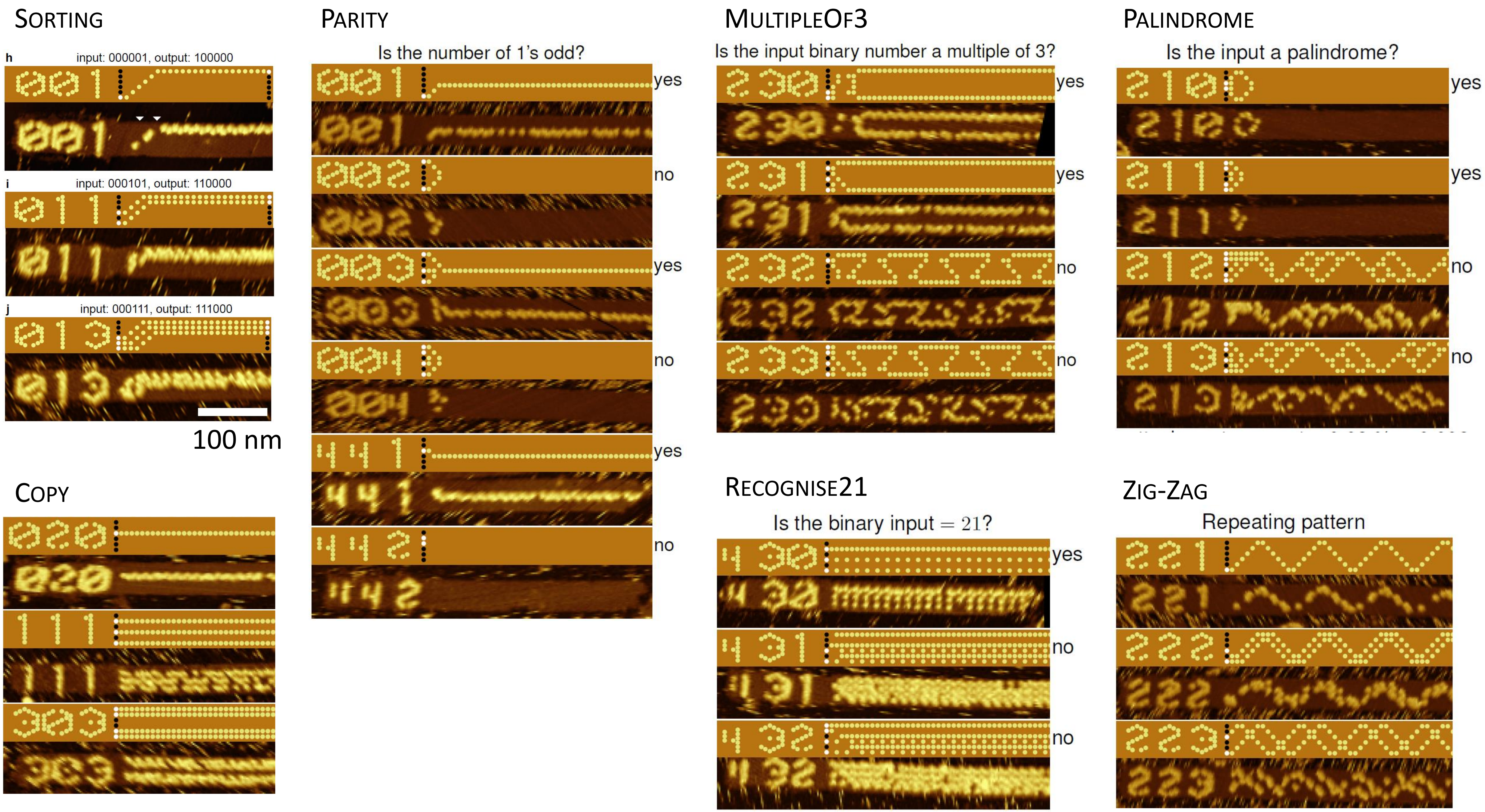
- Anneal 90° C to 50.9° C in 1 hour (*origami seeds form*)
- Hold at 50.9° C for 1-2 days (*tiles grow tubes from seed*)
- Add "unzipper" strands (remove seam to convert tube to ribbon)
- Add "guard" strands (complements of output sticky ends, to deactivate tiles)
- Deposit on mica, buffer wash, add streptavidin, AFM

Results

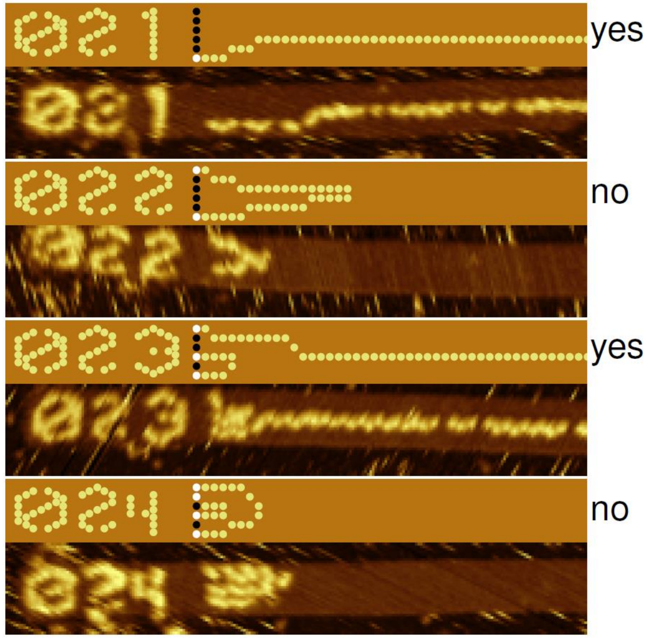
```
def test_parity():
    actual = parity('100101')

    expected =
```



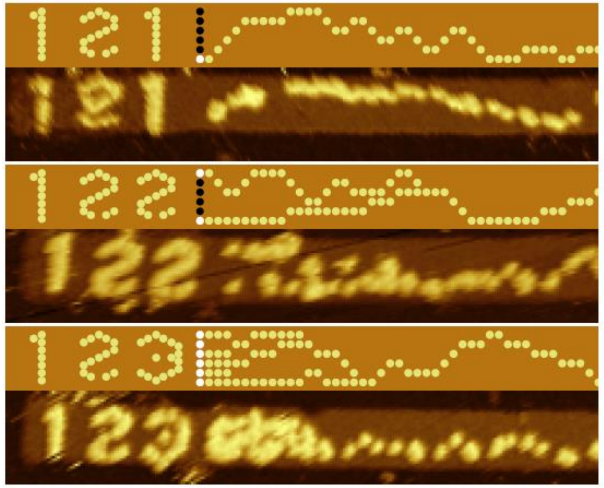
```
    assertEquals(expected, actual)
```


SORTING
h input: 000001, output: 100000
i input: 000101, output: 110000
j input: 000111, output: 111000
100 nm
COPY
PARITY
Is the number of 1's odd?
yes
no
yes
no
yes
no
MULTIPLEOF3
Is the input binary number a multiple of 3?
yes
yes
no
no
PALINDROME
Is the input a palindrome?
yes
yes
no
no
RECOGNISE21
Is the binary input = 21?
yes
no
no
ZIG-ZAG
Repeating pattern

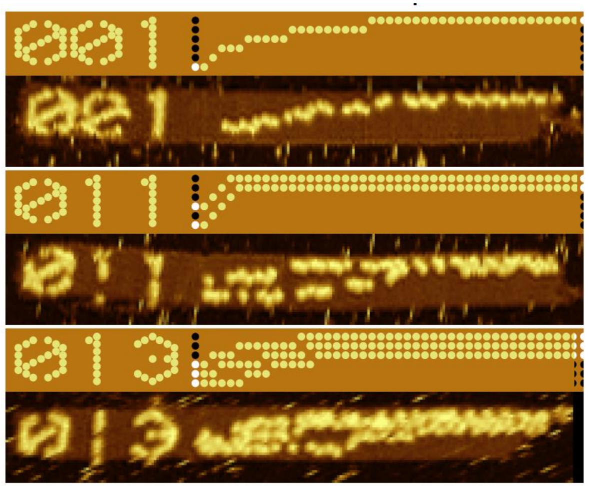
LazyParity



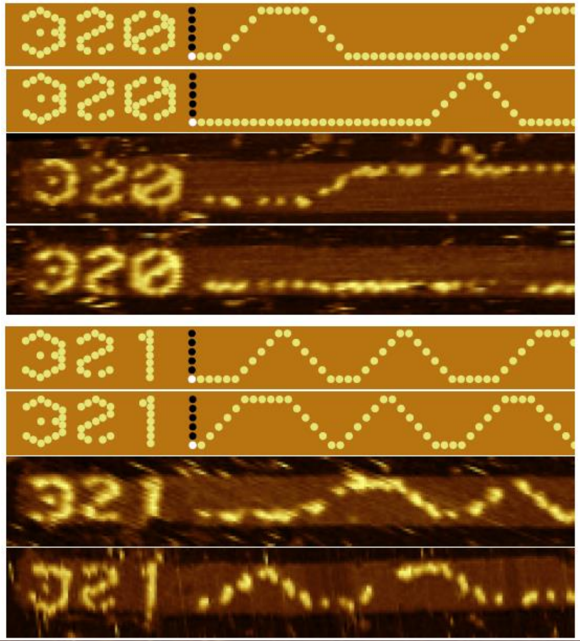
LeaderElection



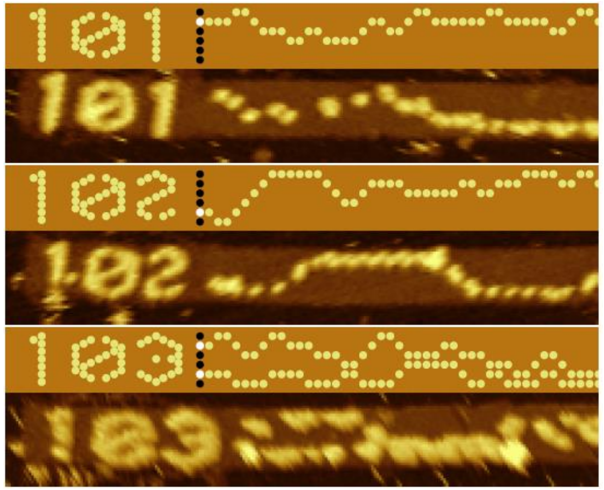
LazySorting



Waves

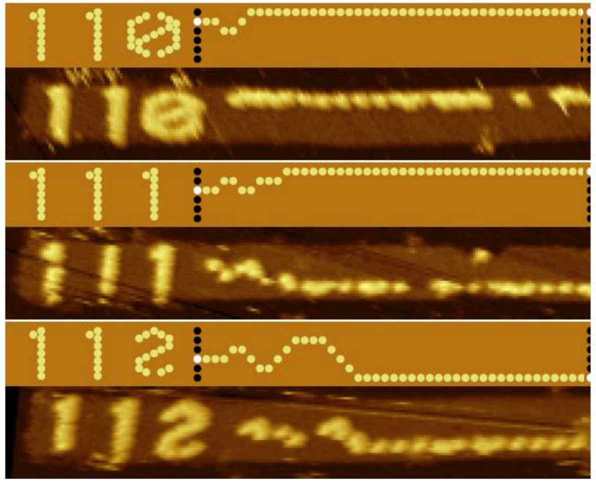


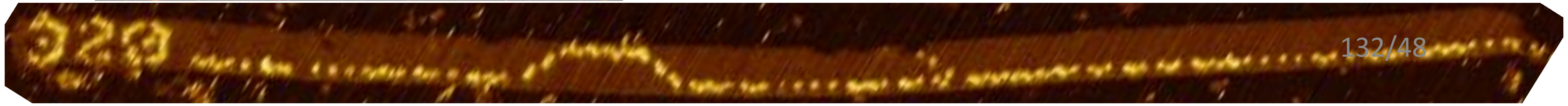
RandomWalkingBit



AbsorbingRandomWalkingBit

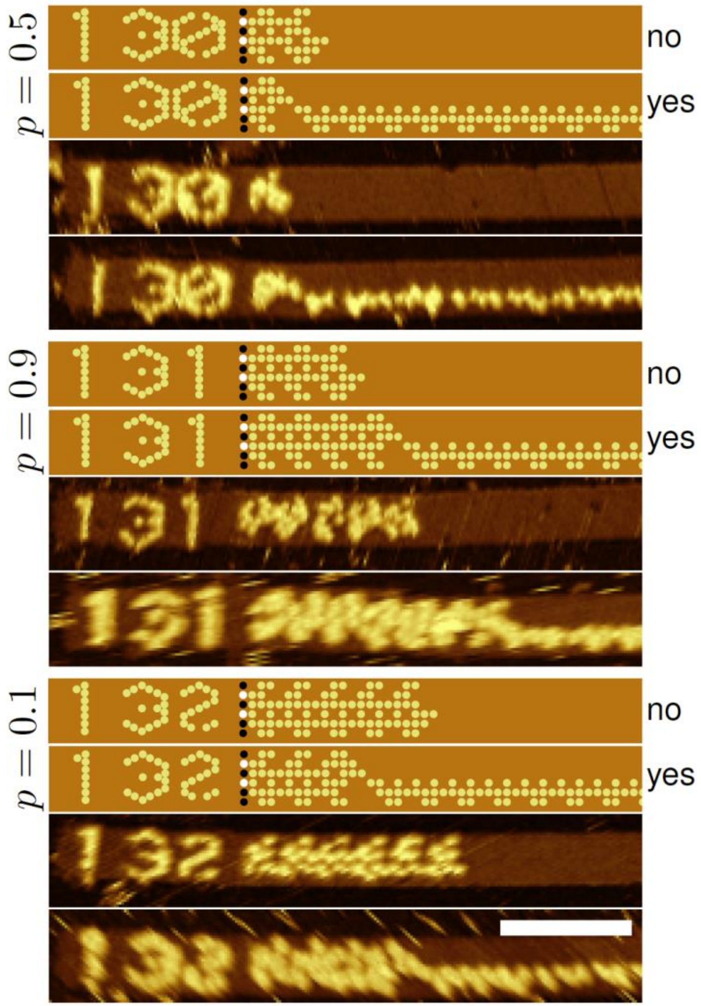
Random walker absorbs to top/bottom

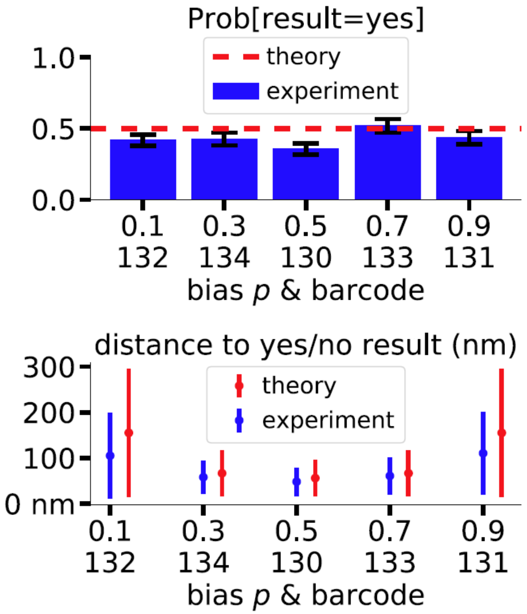




FAIRCOIN

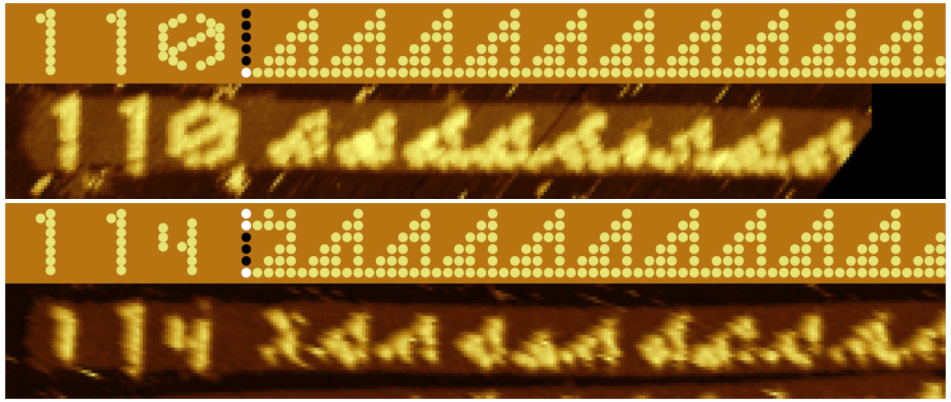
Unbiasing a biased coin





RULE110

Simulation of a cellular automaton



Counting to 63

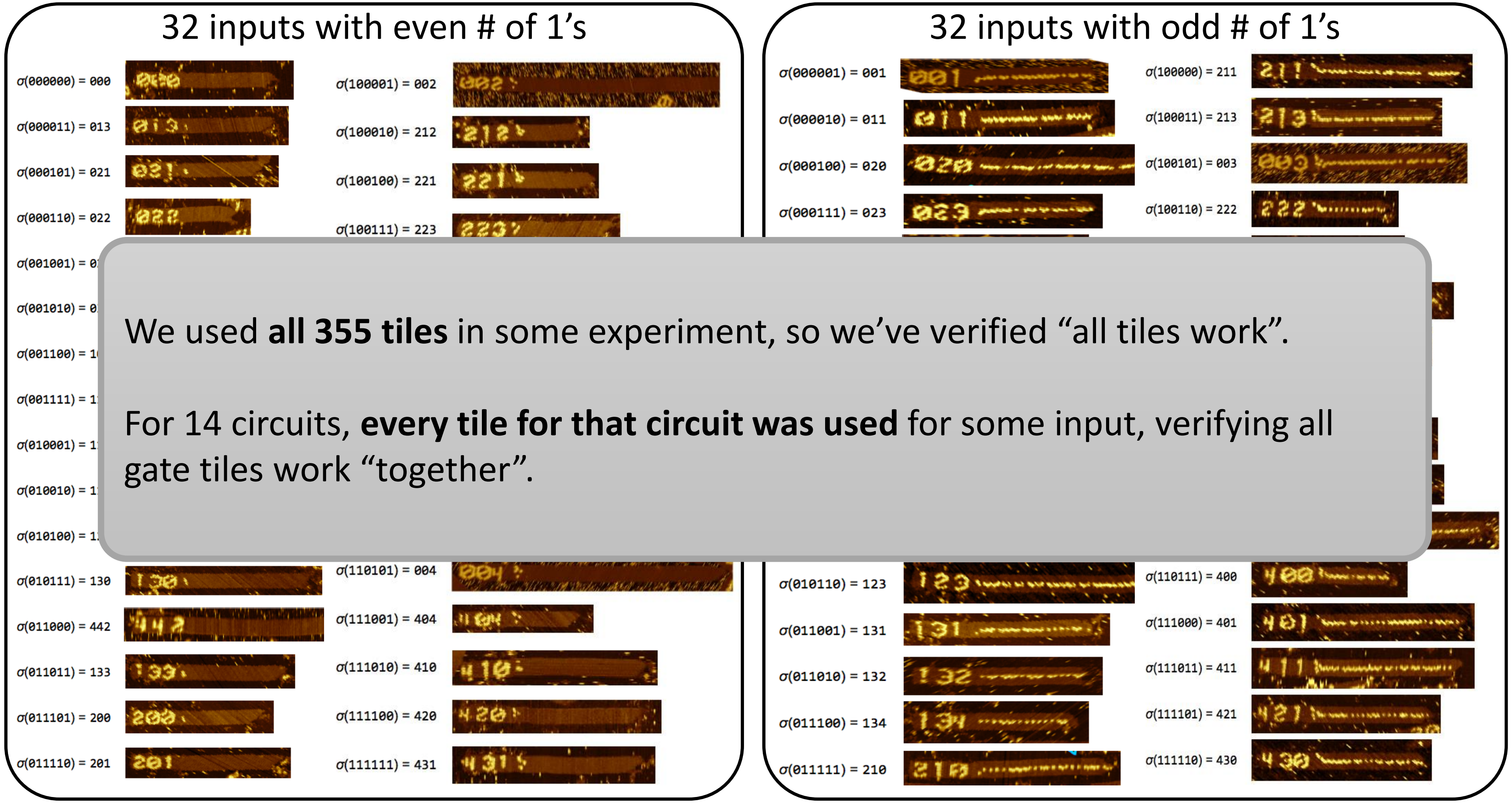
Circuit with 63 distinct strings

Is there a 64-counter?

No!
Proof by Tristan Stérin, Maynooth University
Consequence of following theorem:
No Boolean function computes an odd permutation if some output bit does not depend on all input bits.

Parity tested on all inputs

2^6 = 64 inputs with 6 bits



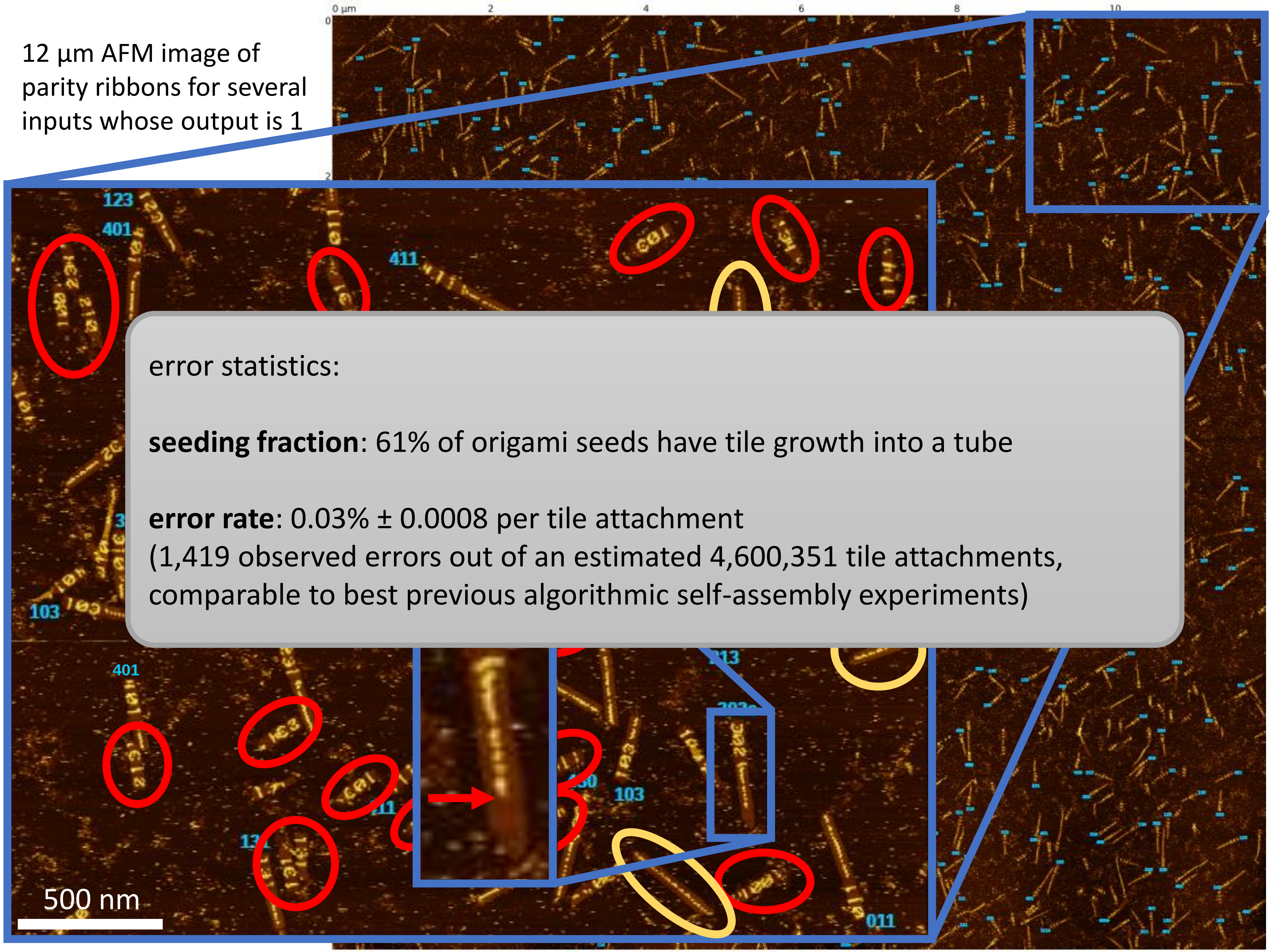
We used **all 355 tiles** in some experiment, so we've verified "all tiles work".

For 14 circuits, **every tile for that circuit was used** for some input, verifying all gate tiles work "together".

σ(6-bit input) = 3-digit barcode representing that input

150 nm

12 µm AFM image of parity ribbons for several inputs whose output is 1



error statistics:

seeding fraction: 61% of origami seeds have tile growth into a tube

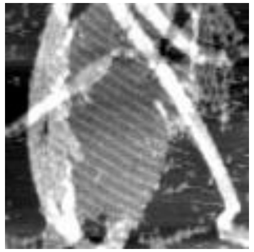
error rate: 0.03% ± 0.0008 per tile attachment
(1,419 observed errors out of an estimated 4,600,351 tile attachments, comparable to best previous algorithmic self-assembly experiments)

What did we learn?

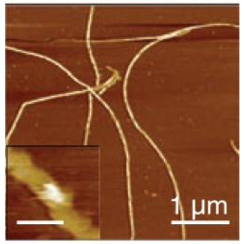
A small(ish) library of molecules can be reprogrammed to self-assemble reliably into many complex patterns, by processing information as they grow.

Contrasting with other self-assembly work:

more algorithmic control than **periodic** self-assembly

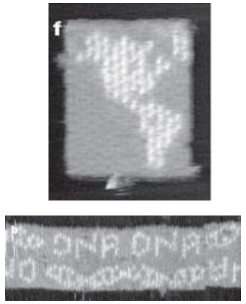


2D tile lattices (Winfree et al., *Nature* 1998)



1D tile tubes (Yin et al., *Science* 2008)

fewer types of DNA strands required than **uniquely-addressed** self-assembly

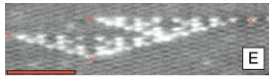


DNA origami (Rothemund, *Nature* 2006)

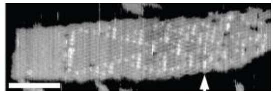
hard-coded tile lattice (Wei et al., *Nature* 2012)

order of magnitude more tile types available than previous **algorithmic** self-assembly

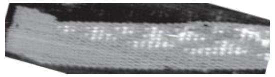
double-crossover tile lattices



(Rothemund et al., *PLoS Bio* 2004)



(Fujibayashi et al., *Nano Letters* 2008)



(Barish et al., *PNAS* 2009)

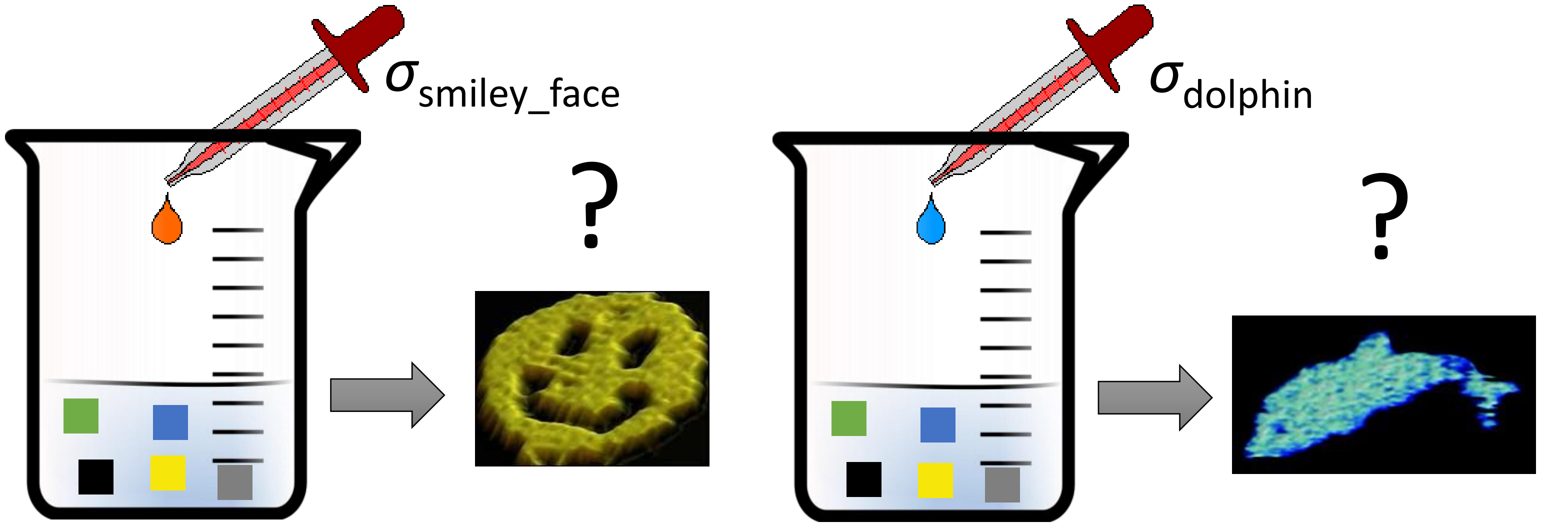
(Evans, *Ph.D. thesis* 2014)

Next big challenge: Algorithmically control shape

We "drew" interesting patterns on a boring shape (infinite rectangle)

Can we run algorithms to **grow interesting shapes**?

Theorem: There is a single set T of tile types, so that, for any finite shape S, from an appropriately chosen seed σ_S "encoding" S, T self-assembles S.



These tiles are universally programmable for building any shape.

[*Complexity of Self-Assembled Shapes*. Soloveichik and Winfree, SIAM Journal on Computing 2007]