

Molecular computing with DNA: theory and implementation

Damien Woods

Joint work with: David Doty,
Cameron Myhrvold, Joy Hui, Felix Zhou,
Peng Yin, Erik Winfree



**Maynooth
University**
National University
of Ireland Maynooth



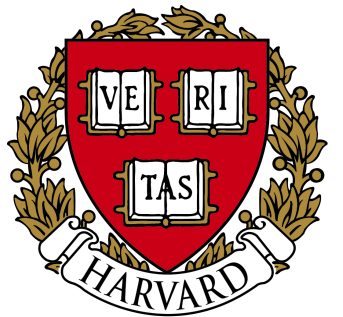
Hamilton Institute

Caltech

Inria

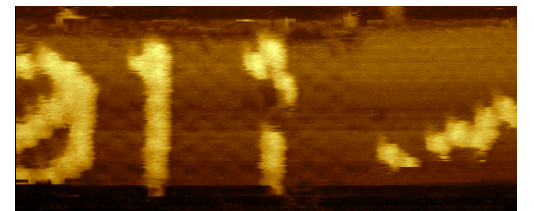
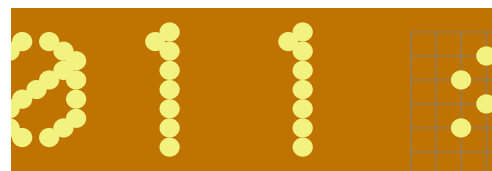


UC Davis



Harvard

Theorem: Let T be a
tile assembly system ...



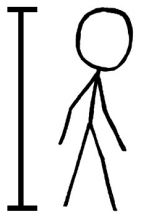
Building stuff



Ljubljana Marshes Wheel. 5k years old

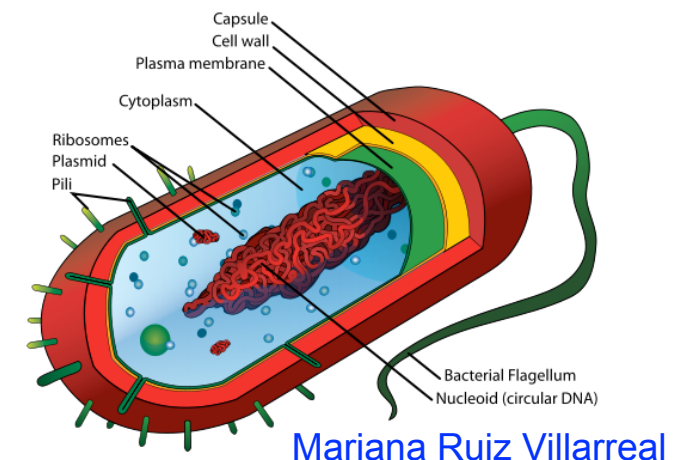


Newgrange, Ireland. 5.2k years old

- **Building stuff by hand:** use tools! Great for scale of $10^{+/-2} \times$ 
- **Building tools that build stuff:** specify target object with a computer program that then controls the manufacturing process

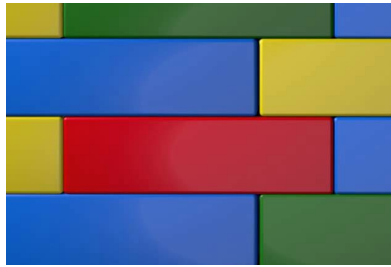


- **Programming stuff to build itself:** for building stuff in small wet places where our hands or tools can't reach



Mariana Ruiz Villarreal

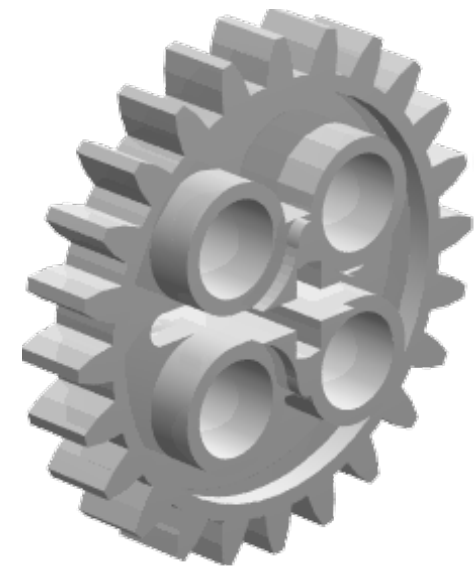
Stuff that builds itself



I want to stick
below blue & yellow
and above blue &
green

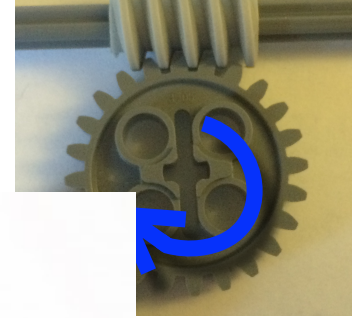
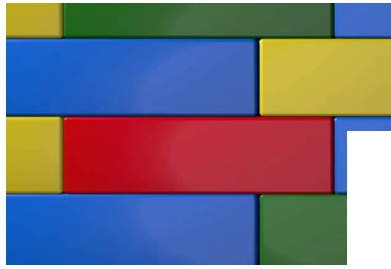


x10



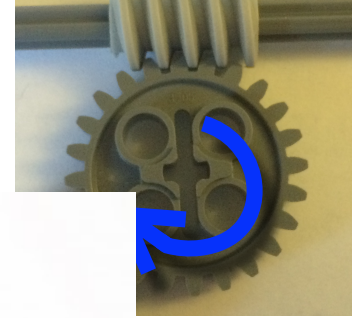
- Today you'll hear about self-assembling molecules that compute as they build themselves

Stuff that builds itself



- Today you'll hear about self-assembling molecules that compute as they build themselves

Stuff that builds itself



x10



- Today you'll hear about self-assembling molecules that compute as they build themselves

Biology is an expert at nanoscale engineering

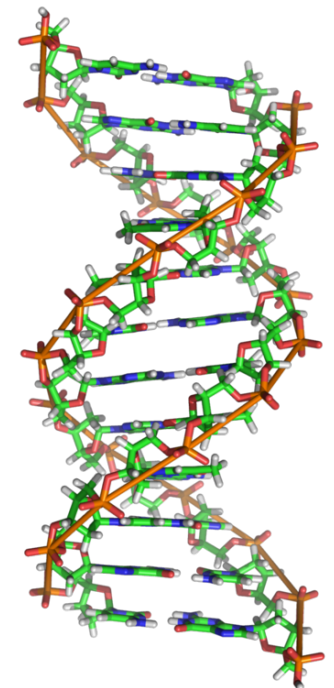
- Evolution: a long-term random and unpredictable process used by Biology, not a good way engineer (Too slow. What are the principles? Not reproducible. Caveat: Directed evolution in a controlled environment)
- We'd like to be able to design from the ground up:
 - using materials and processes we understand
 - using a hierarchy to handle complexity
 - systems that have the potential for computation



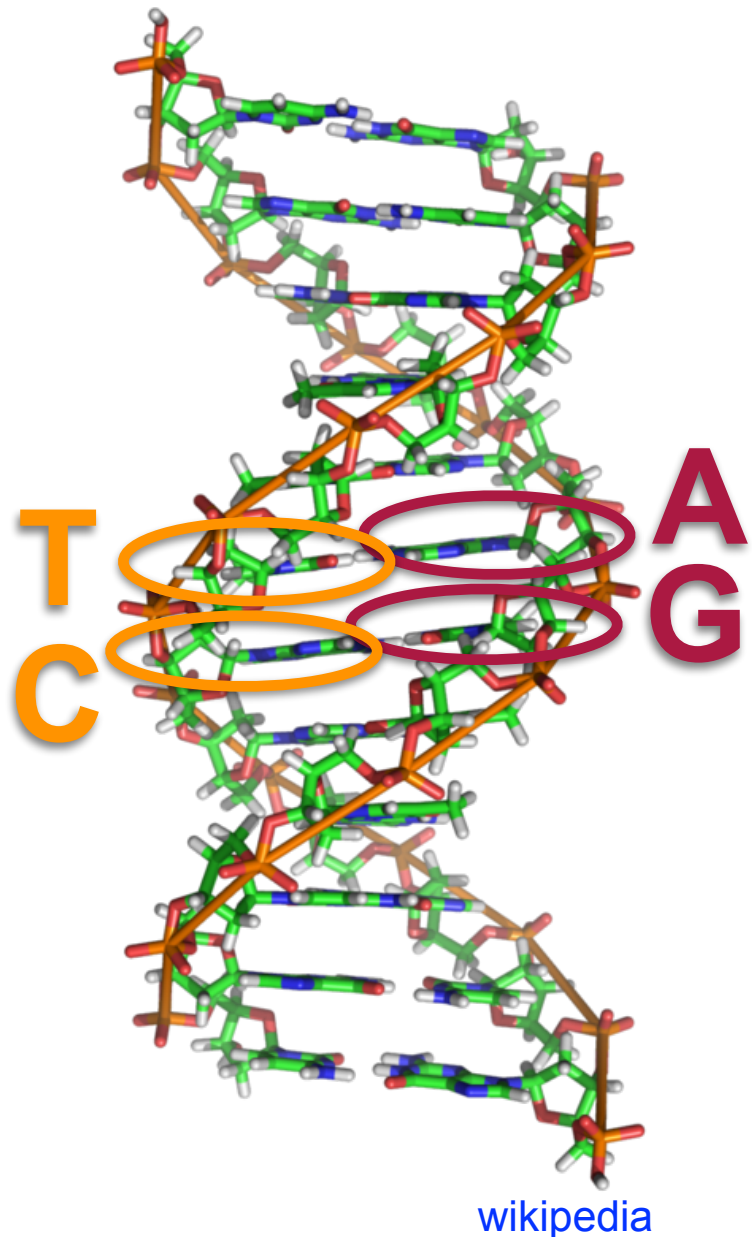
Newly hatched zebrafish,
3 days after zygote

Material

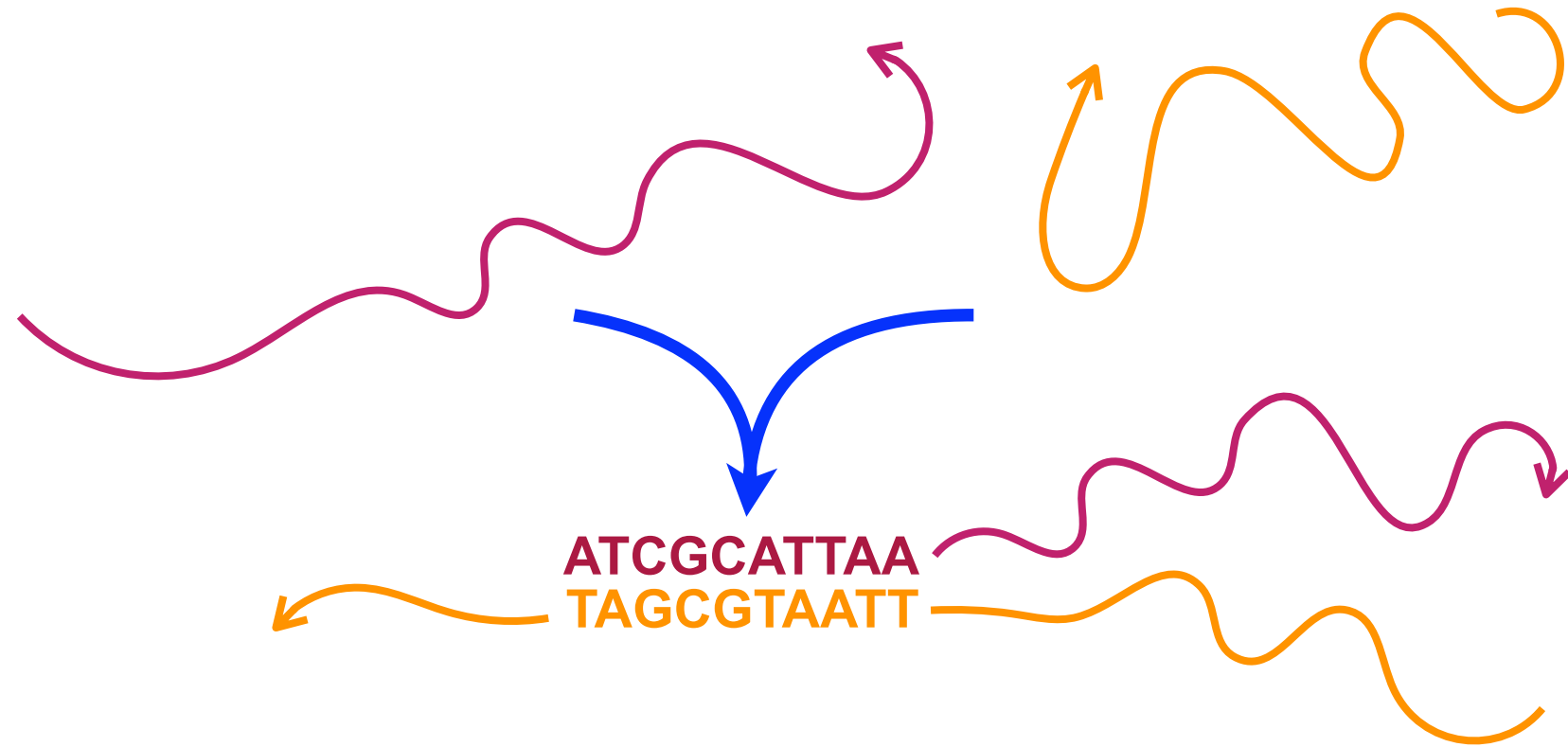
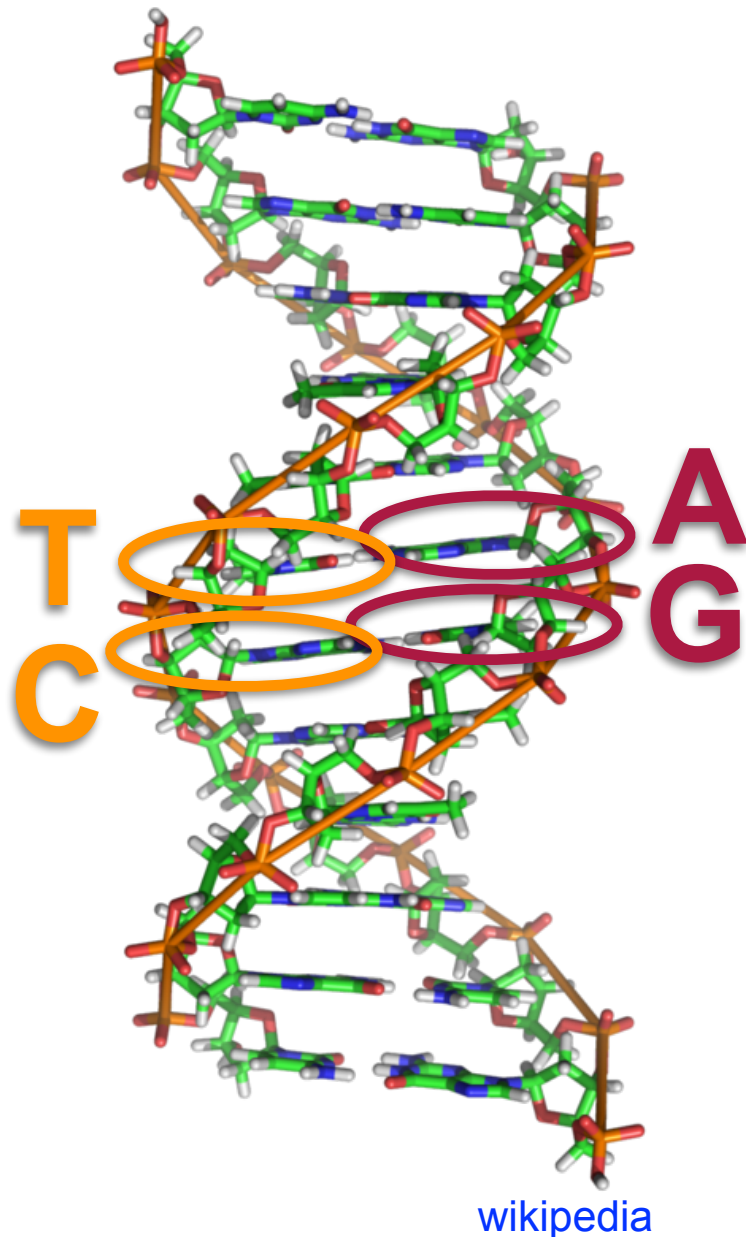
- DNA is a material that fits the bill! (Thanks Biology!)
- DNA is so predictable and well-understood that we can use it like a kind of nanoscale Lego



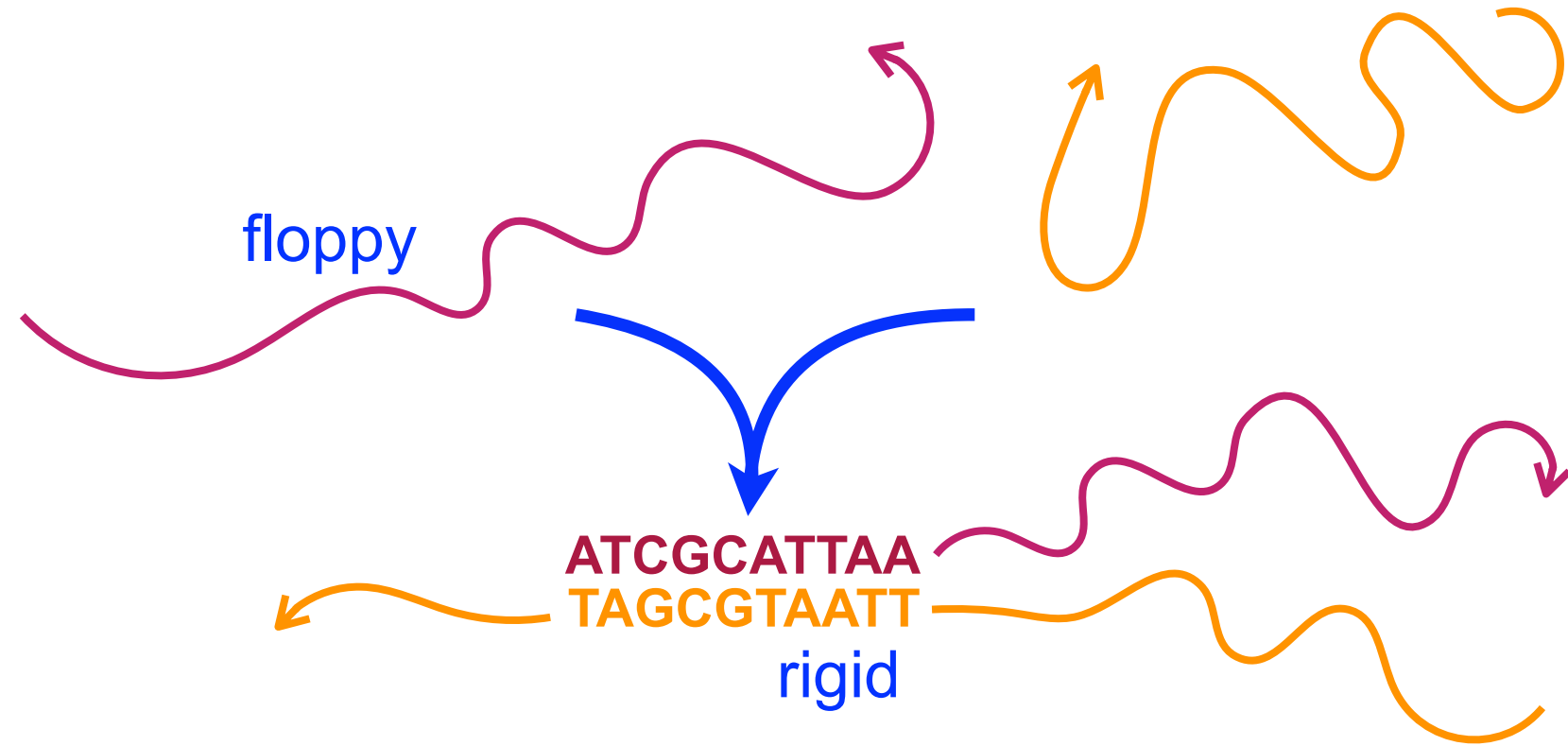
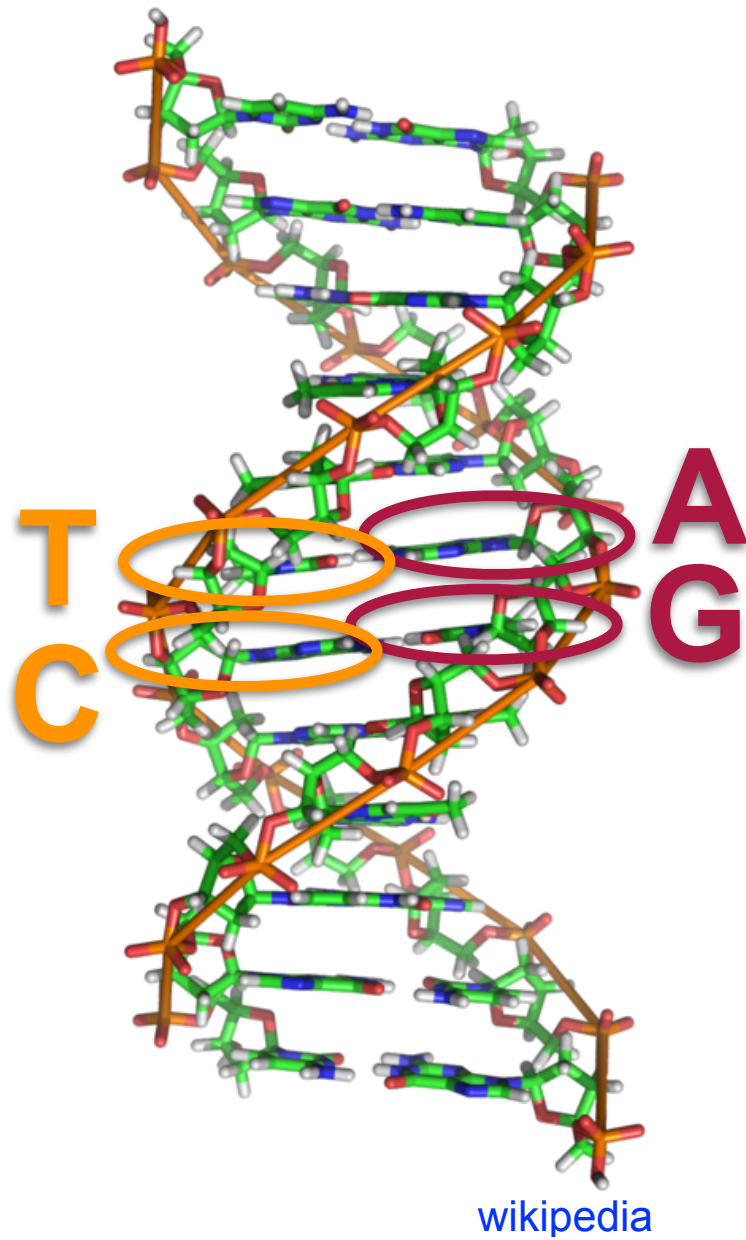
DNA & DNA tiles



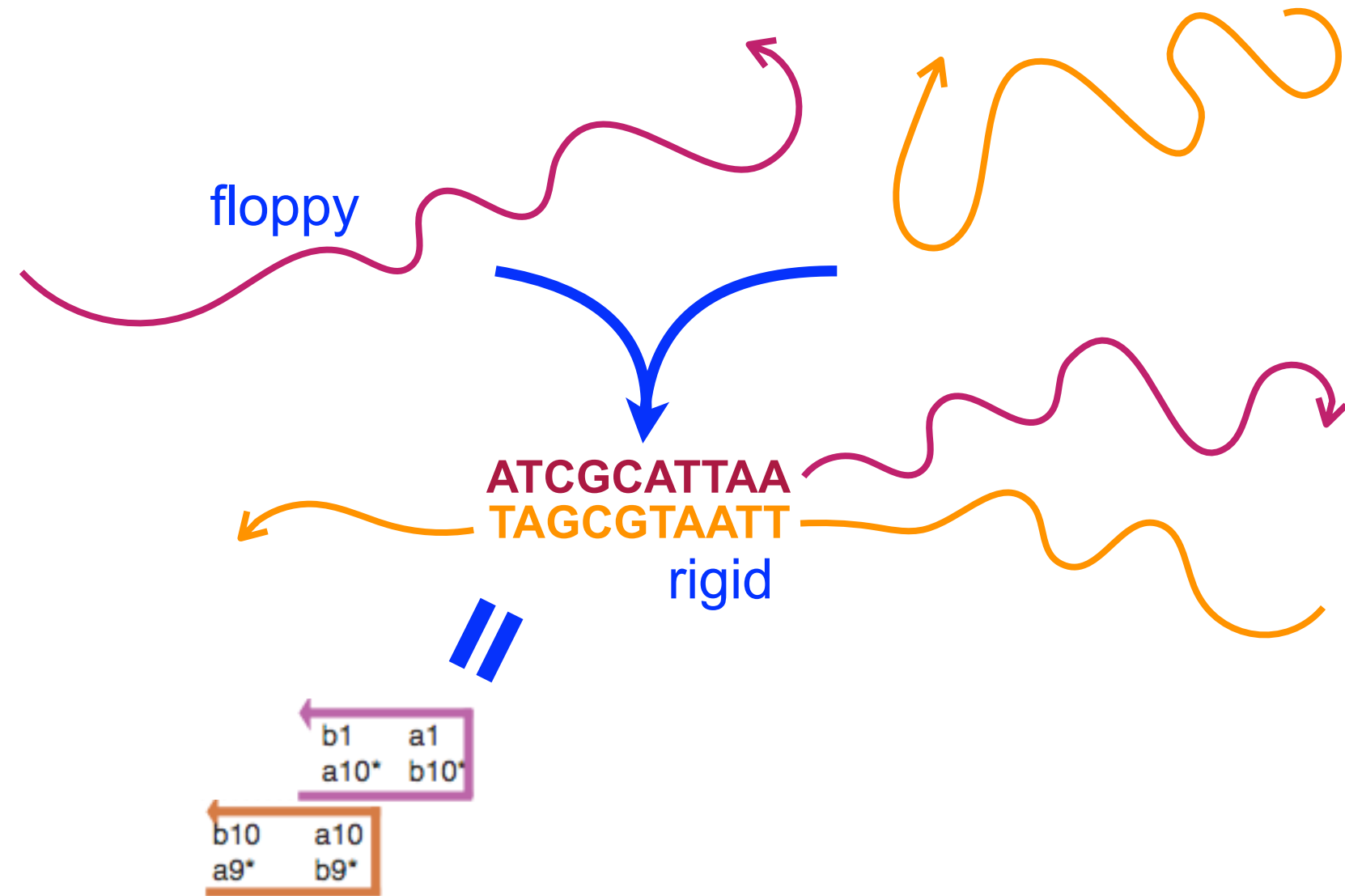
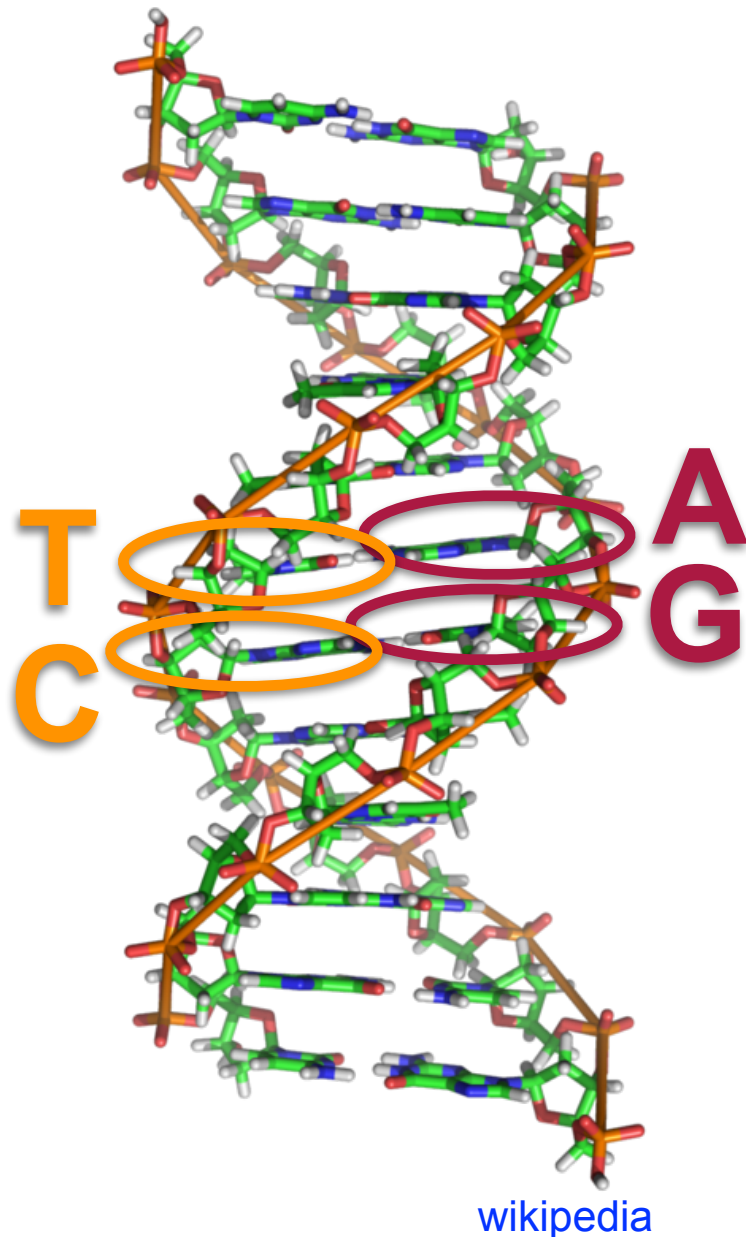
DNA & DNA tiles



DNA & DNA tiles

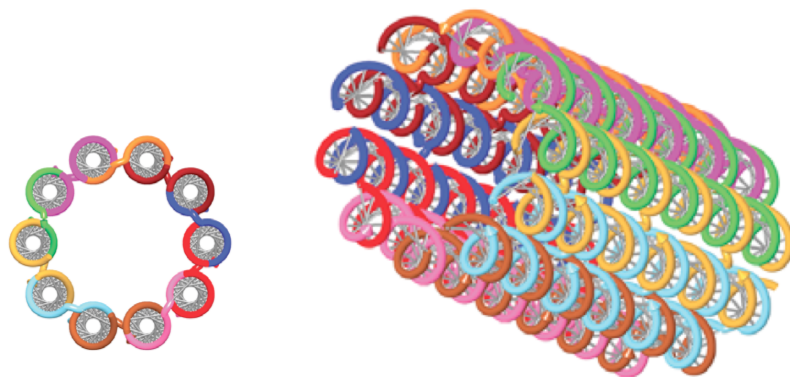
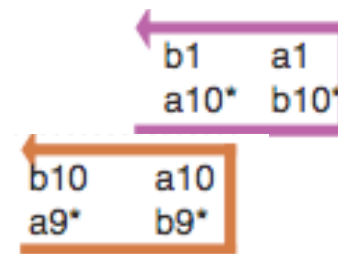
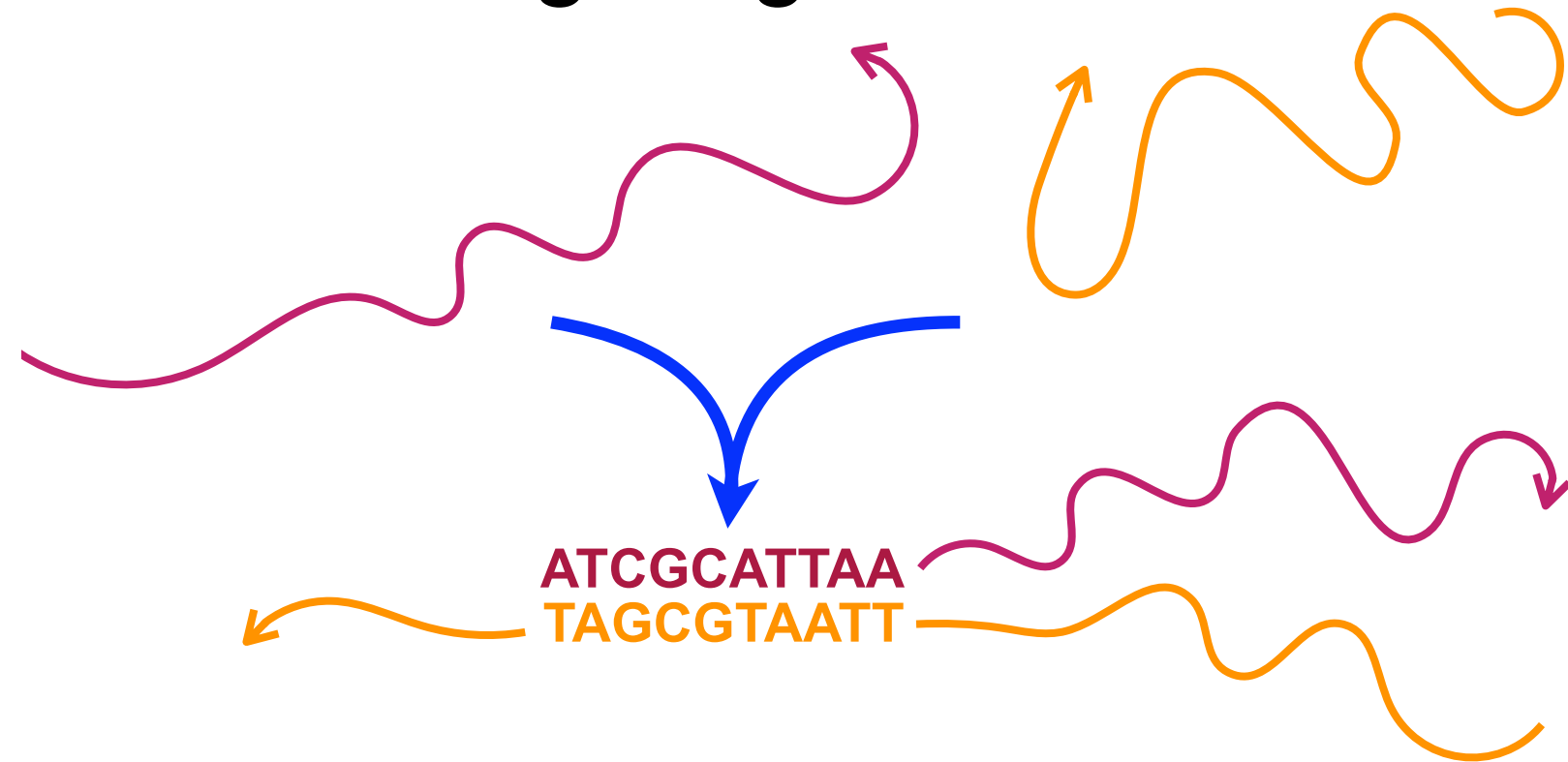


DNA & DNA tiles



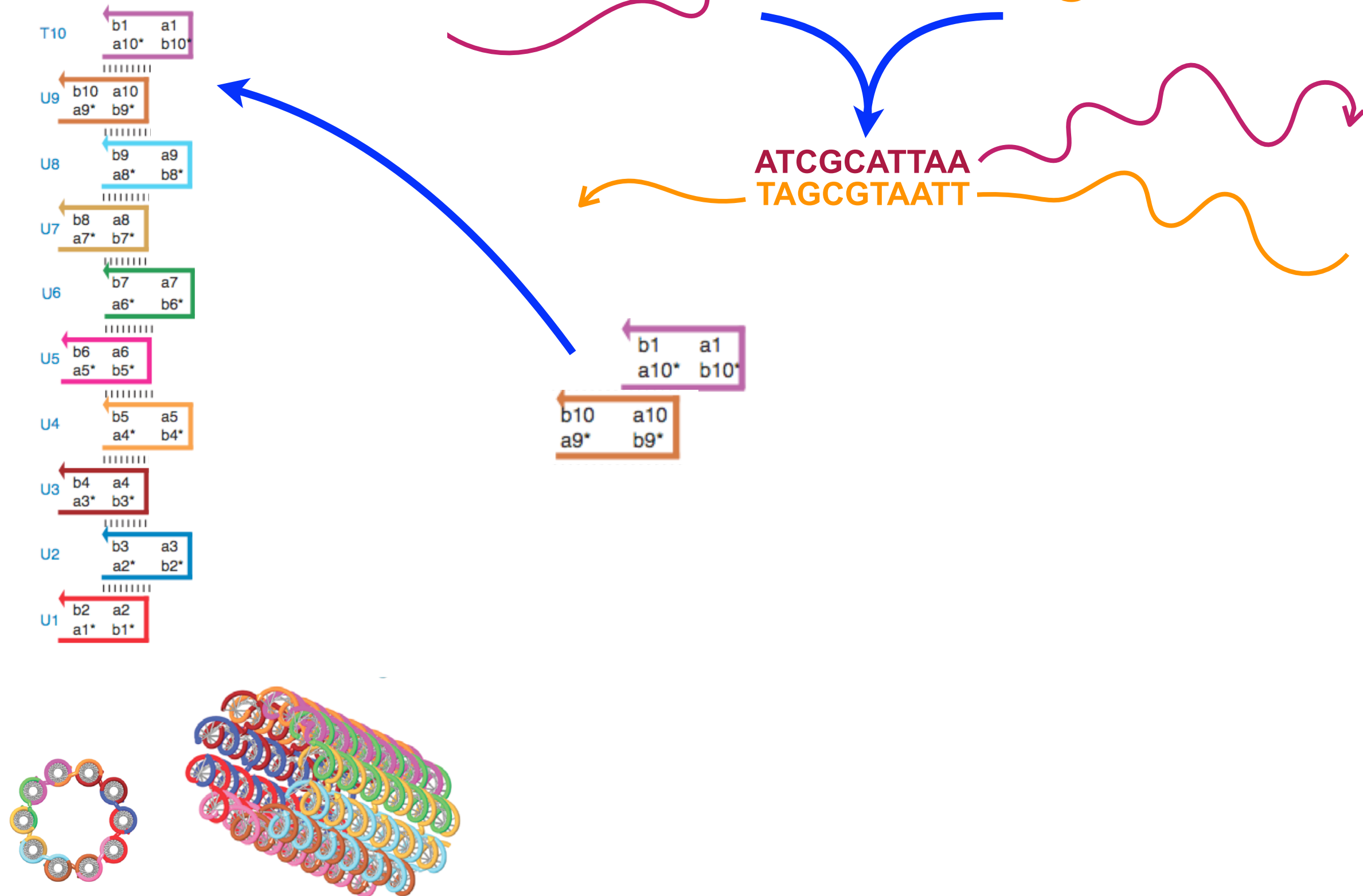
Example DNA nanostructure using single-stranded tiles

- Yin, Hariadi, Sahu, Choi, Park, LaBean, Reif. Science. 2008



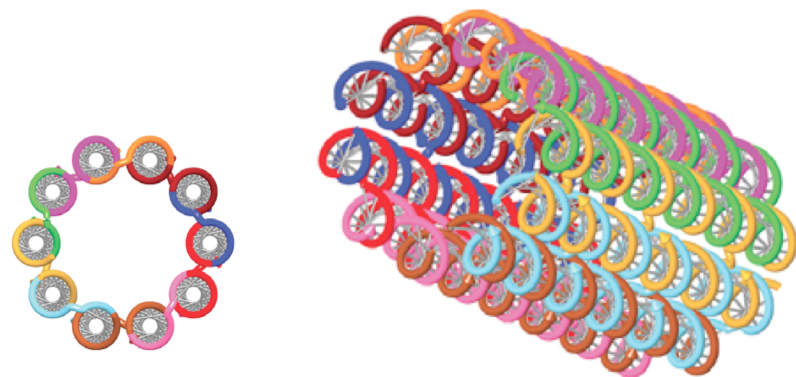
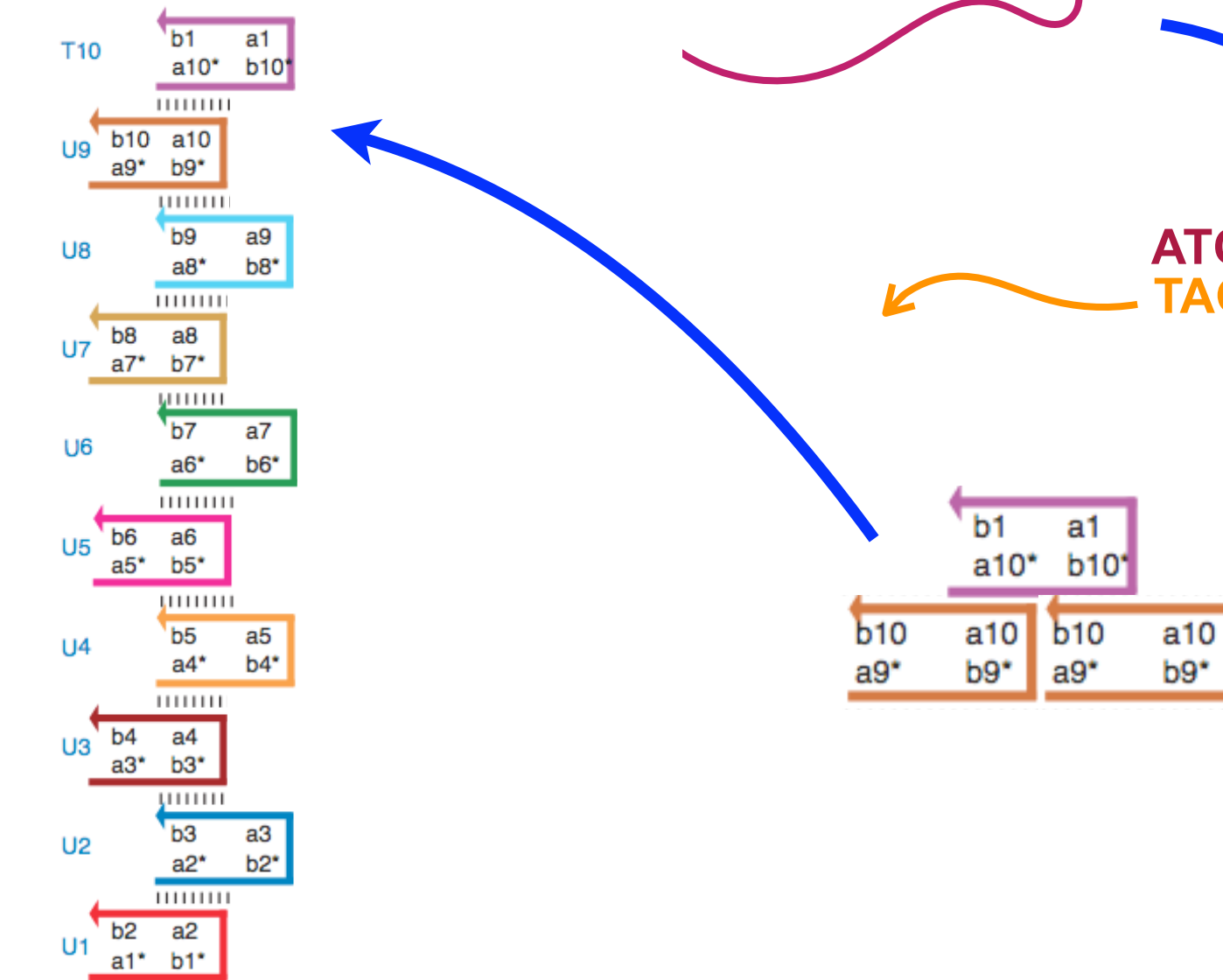
Example DNA nanostructure using single-stranded tiles

- Yin, Hariadi, Sahu, Choi, Park, LaBean, Reif. Science. 2008



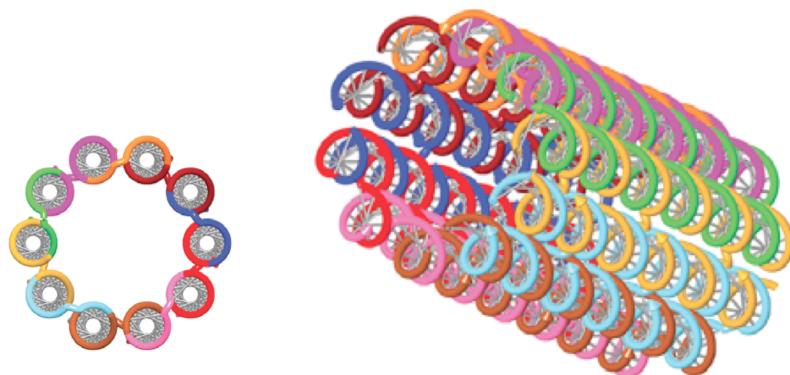
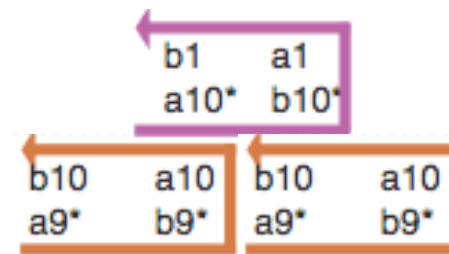
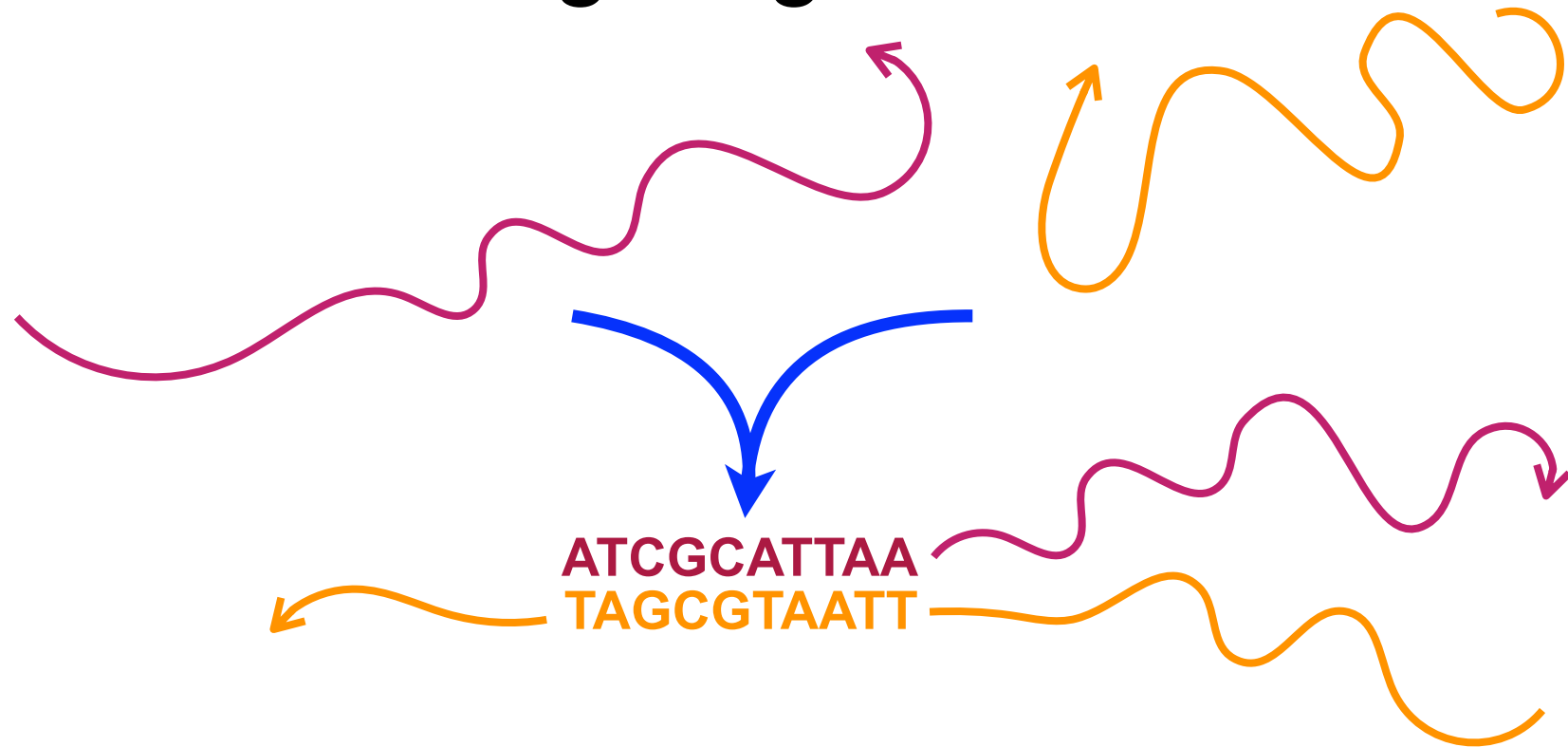
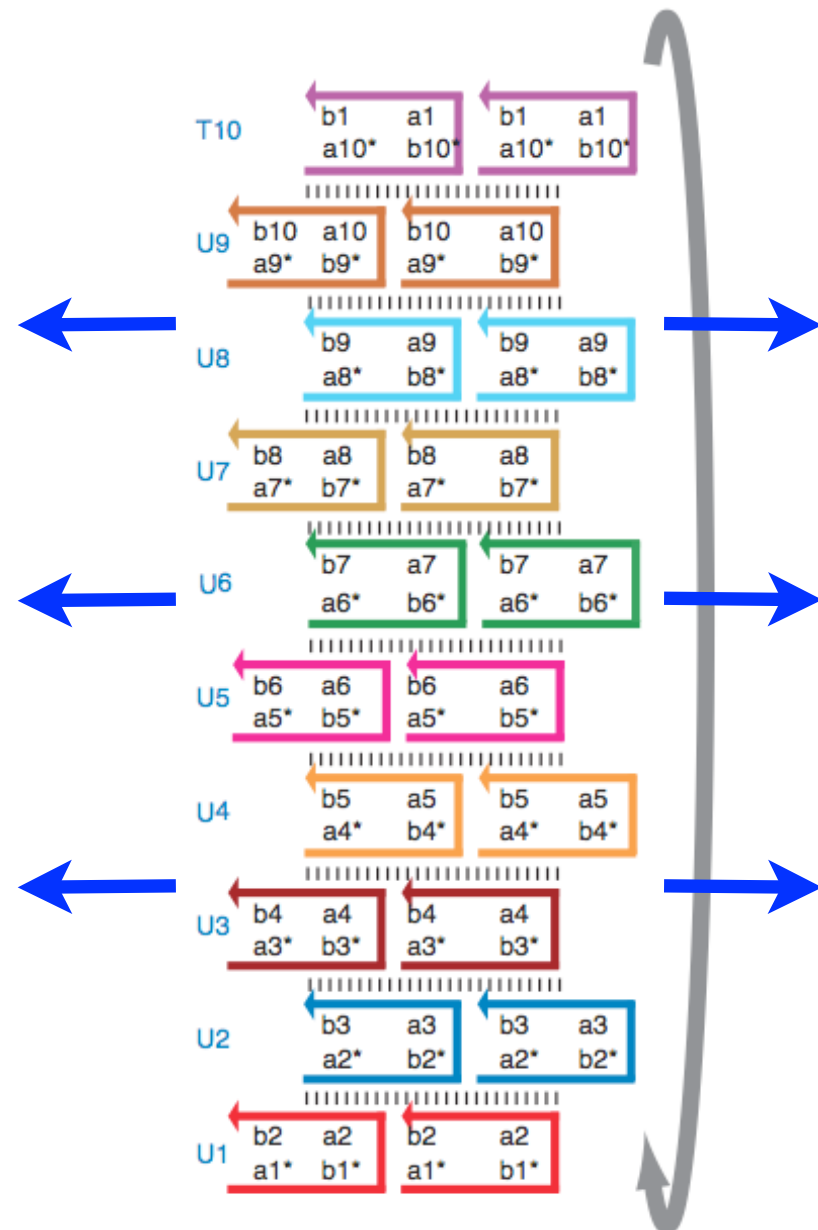
Example DNA nanostructure using single-stranded tiles

- Yin, Hariadi, Sahu, Choi, Park, LaBean, Reif. Science. 2008



Example DNA nanostructure using single-stranded tiles

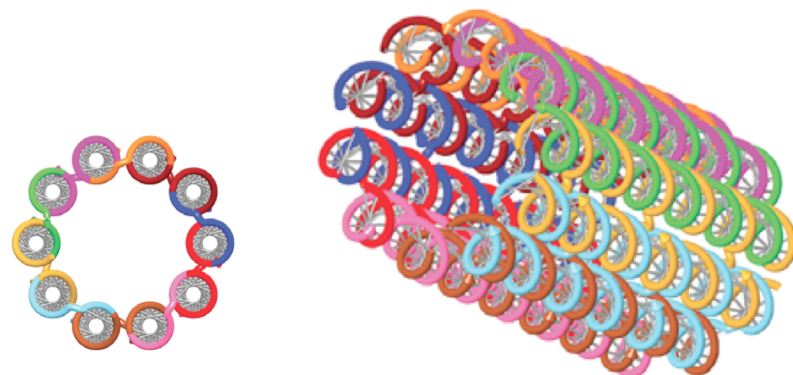
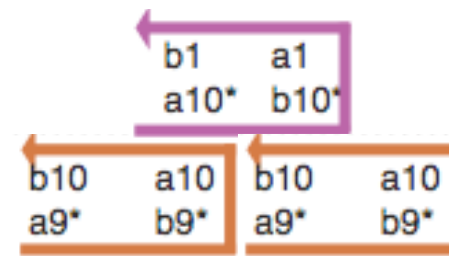
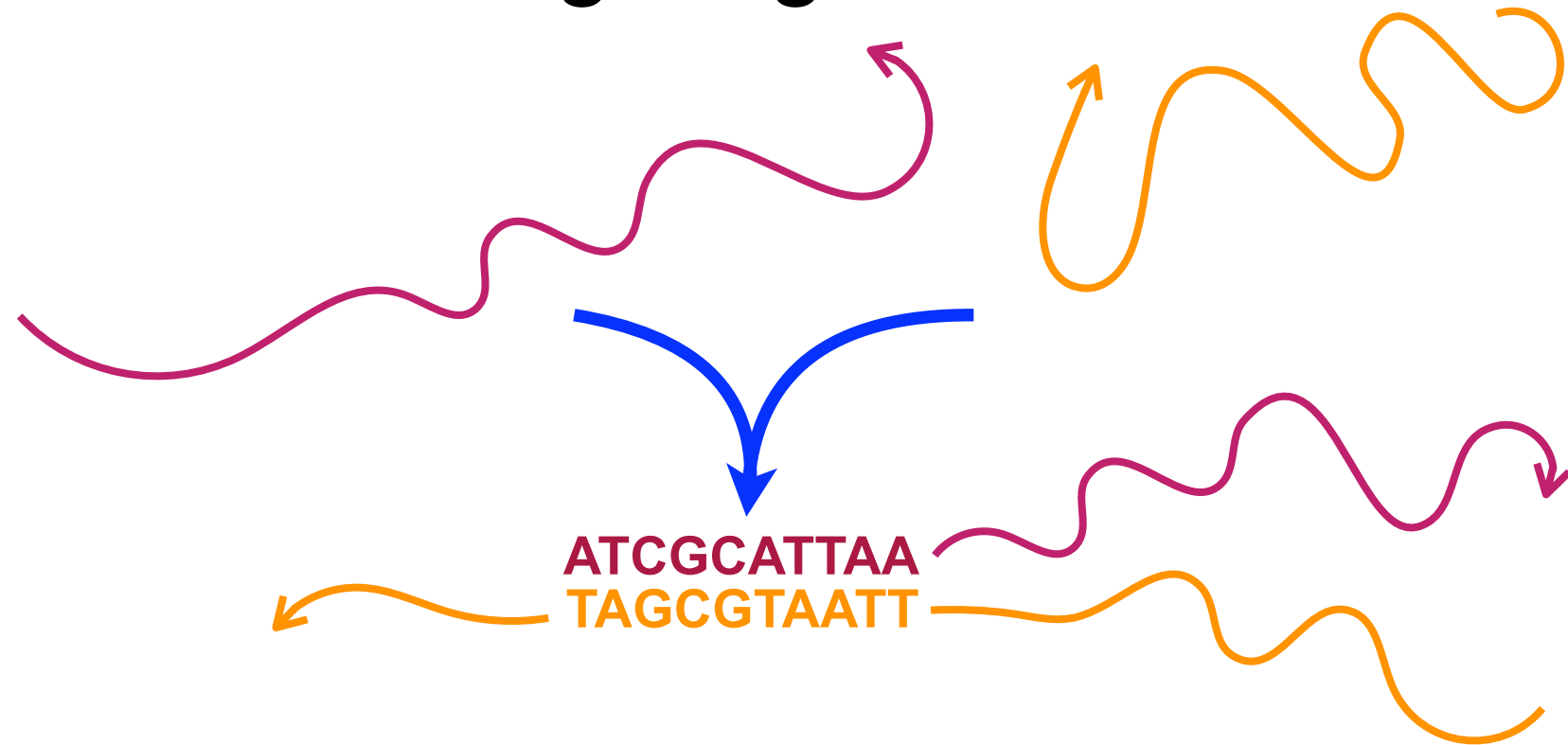
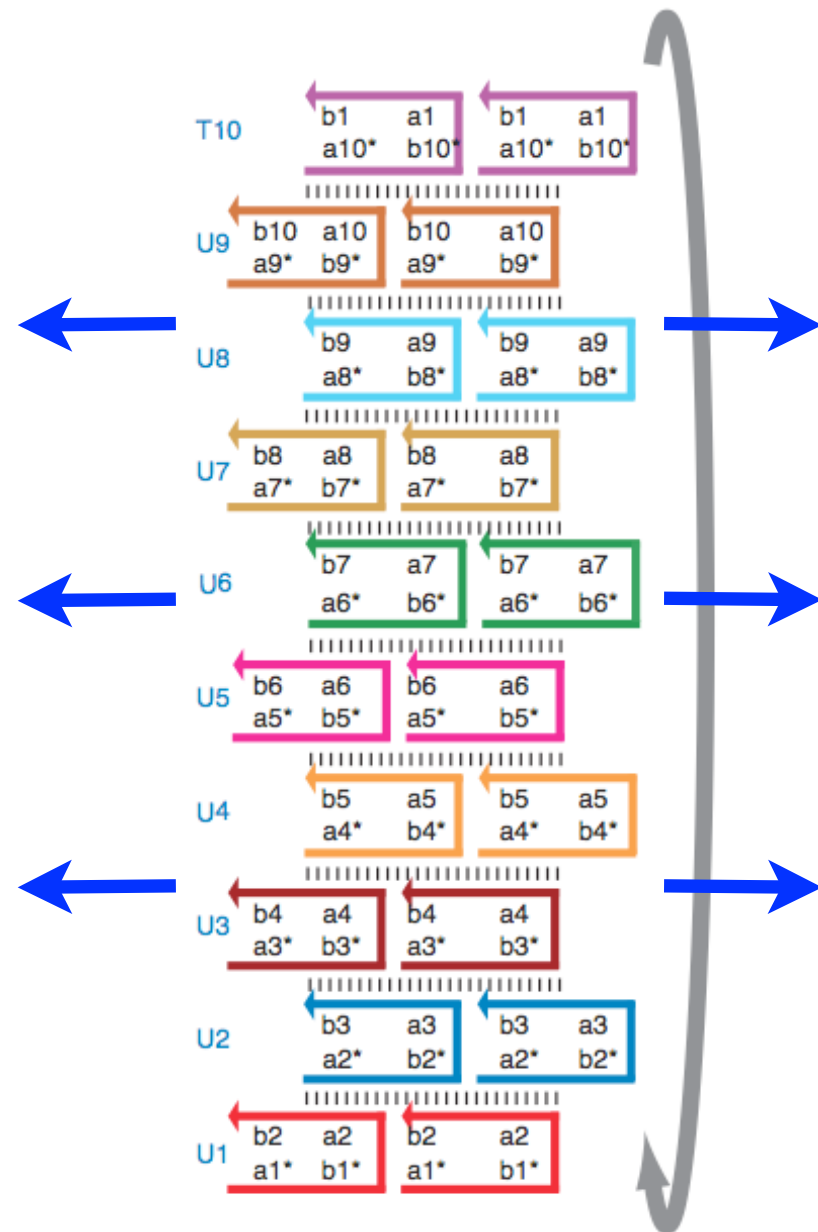
- Yin, Hariadi, Sahu, Choi, Park, LaBean, Reif. Science. 2008



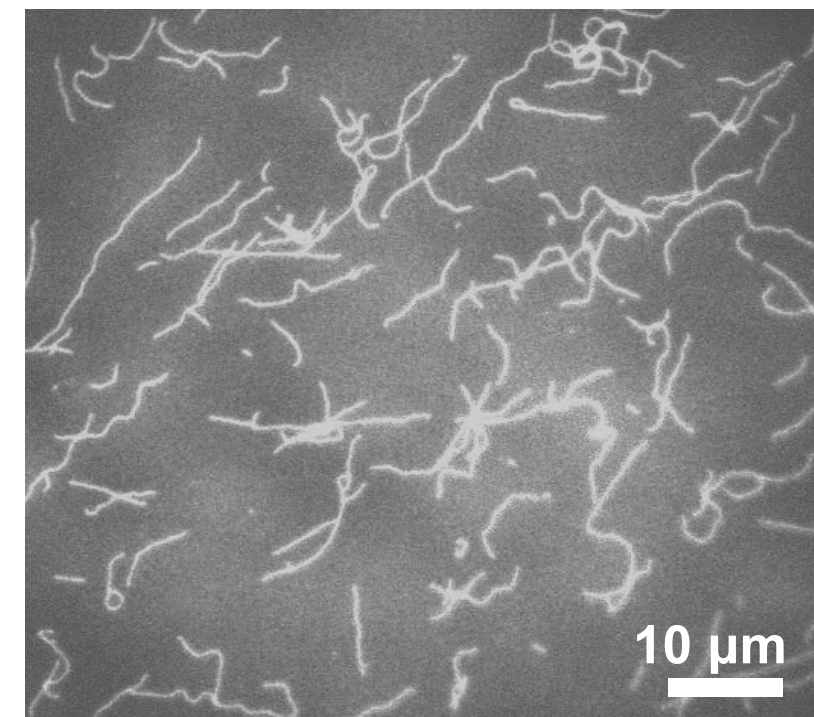
DNA nanotube!

Example DNA nanostructure using single-stranded tiles

- Yin, Hariadi, Sahu, Choi, Park, LaBean, Reif. Science. 2008



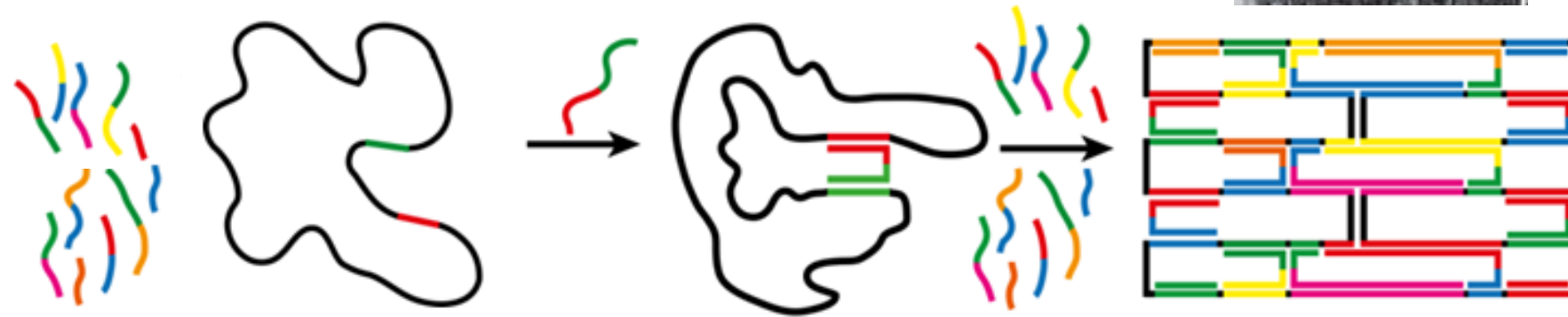
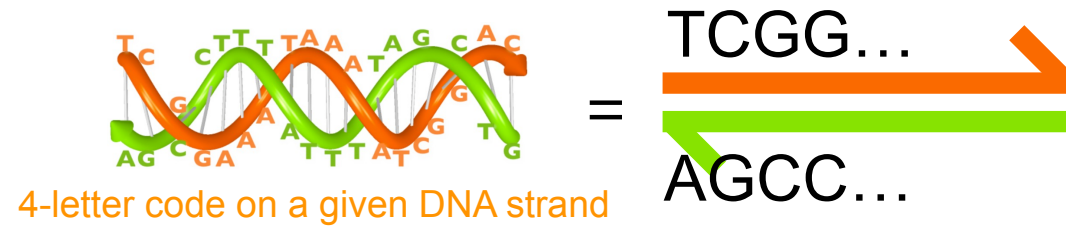
DNA nanotube!



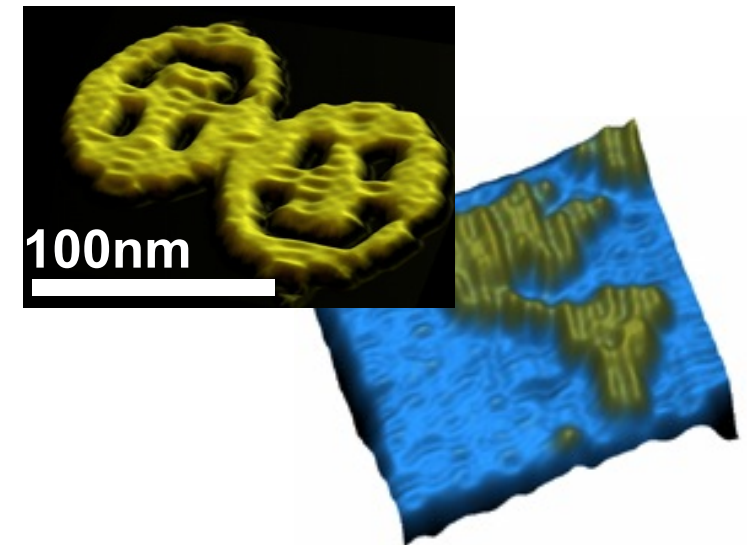
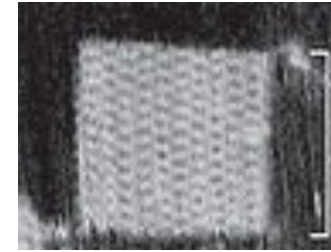
D Woods. Fluorescently labelled nanotubes

We made a “DNA nanotube” using small DNA strands, what else can strands do?

Background: DNA nanostructures



DNA origami



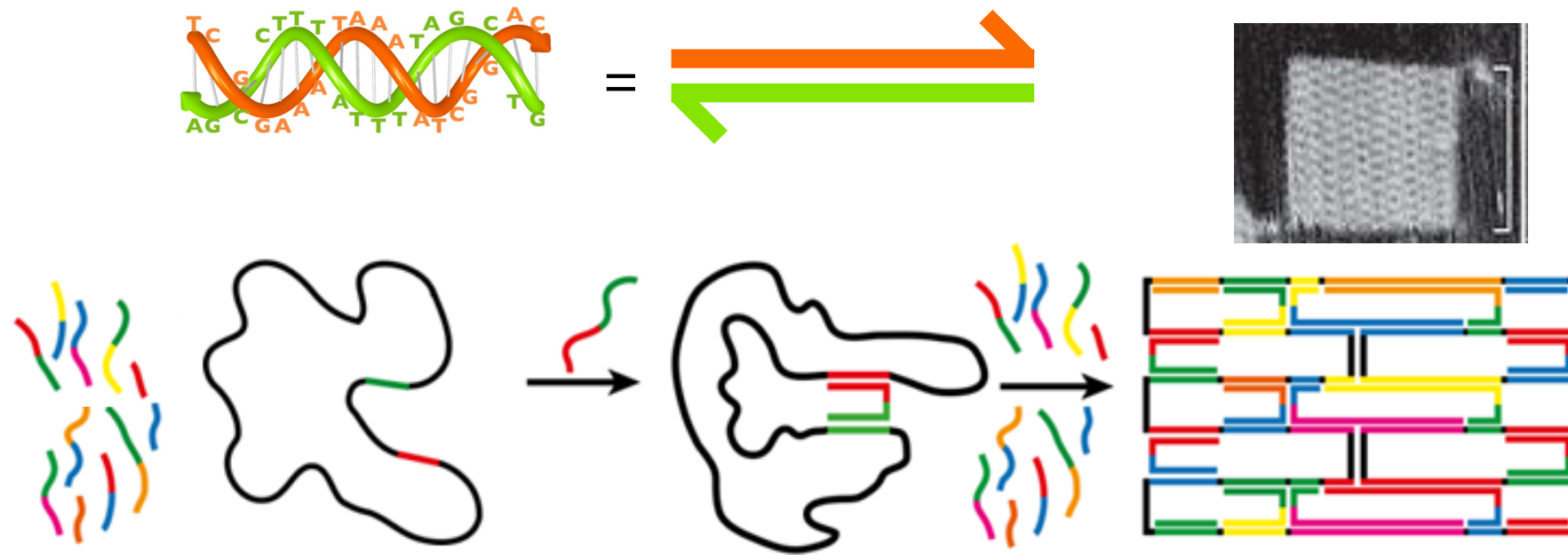
Rothemund. 2006 Nature

Example DNA nanostructure: DNA origami

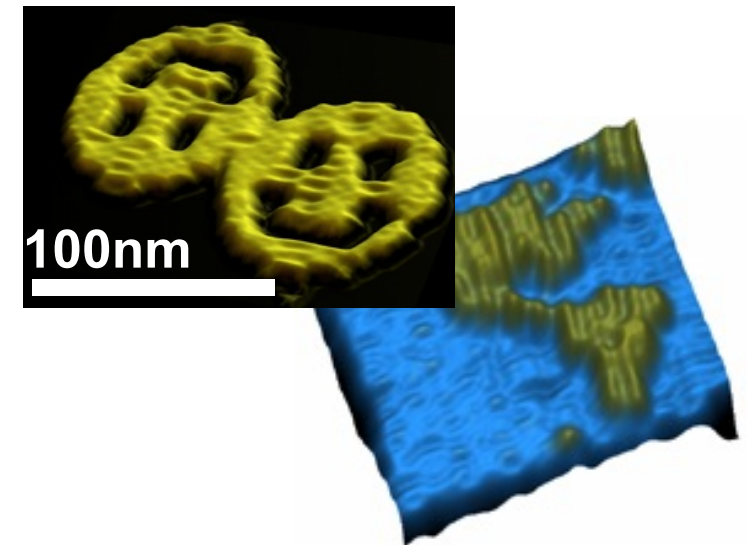


Movie by Shawn Douglas

Background: DNA nanostructures

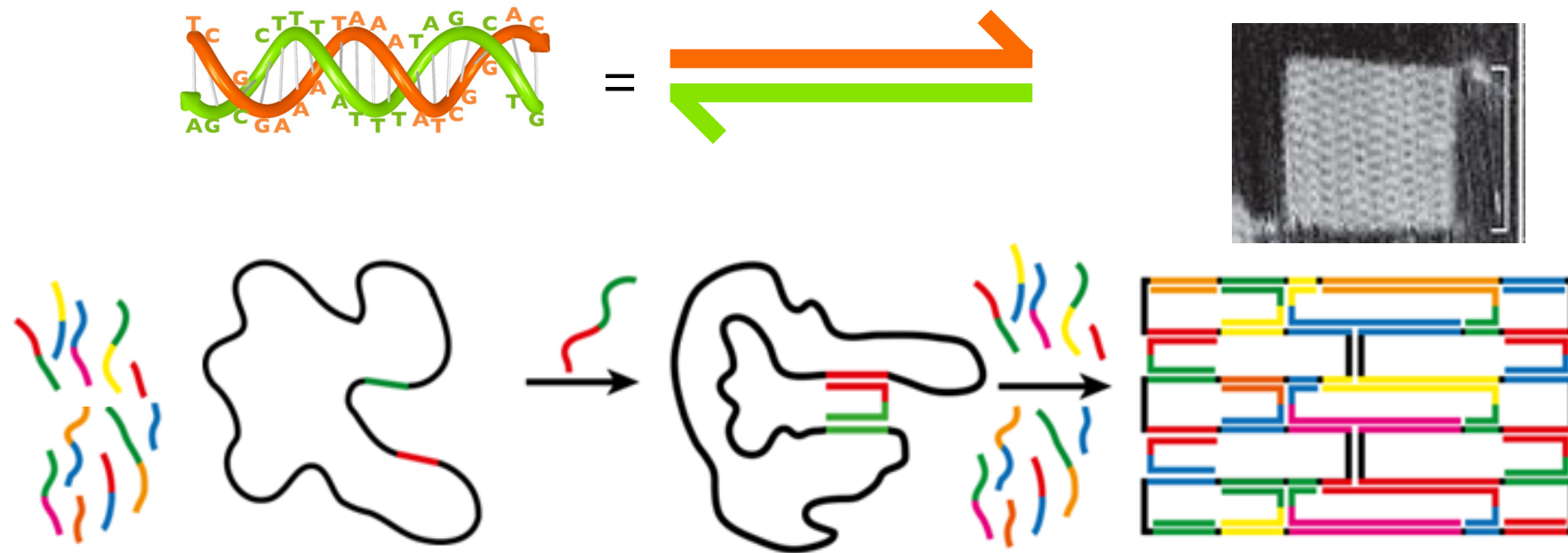


DNA origami

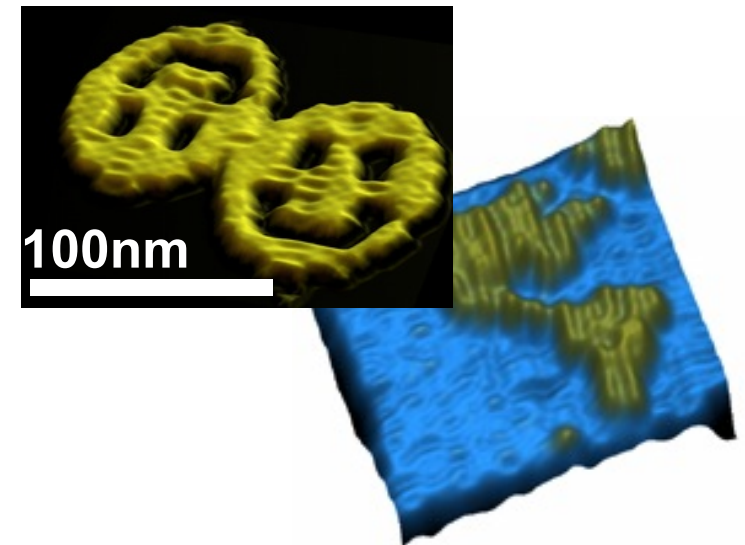


Rothemund. 2006 Nature

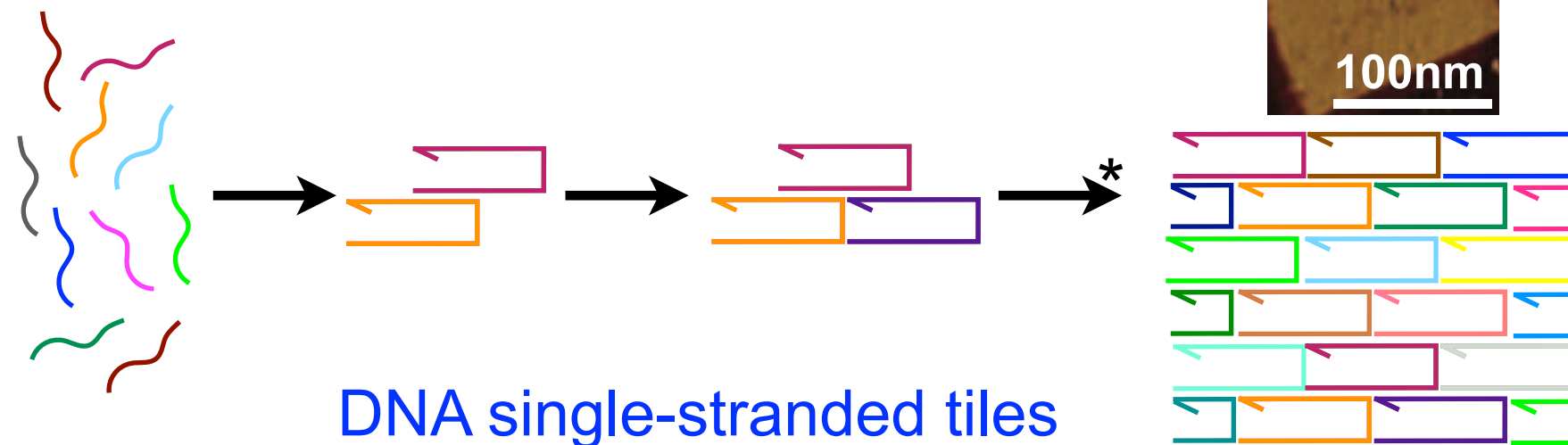
Background: DNA nanostructures



DNA origami



Rothemund. 2006 Nature

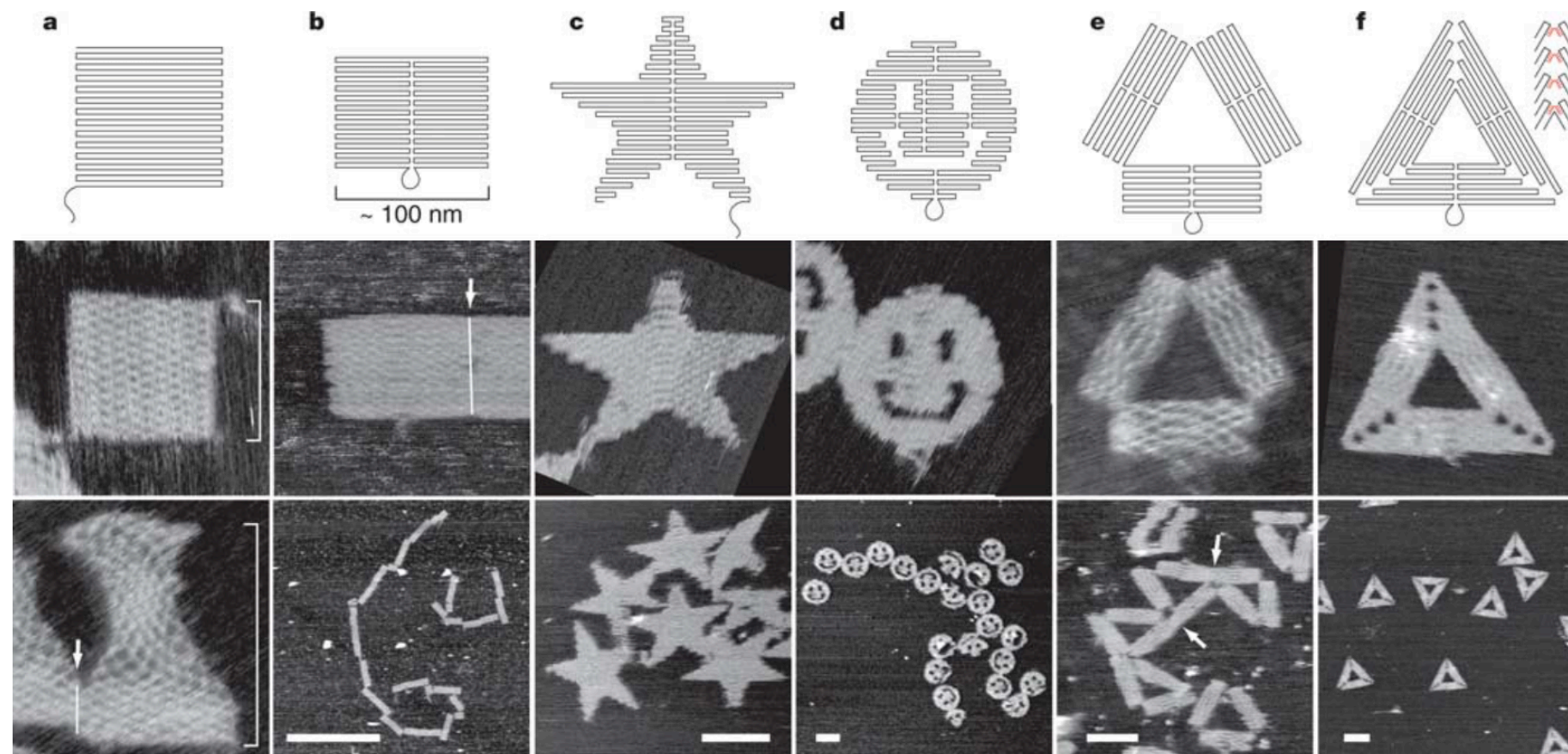


DNA single-stranded tiles



Wei, Dai, Yin. 2013 Nature

DNA nanostructure examples

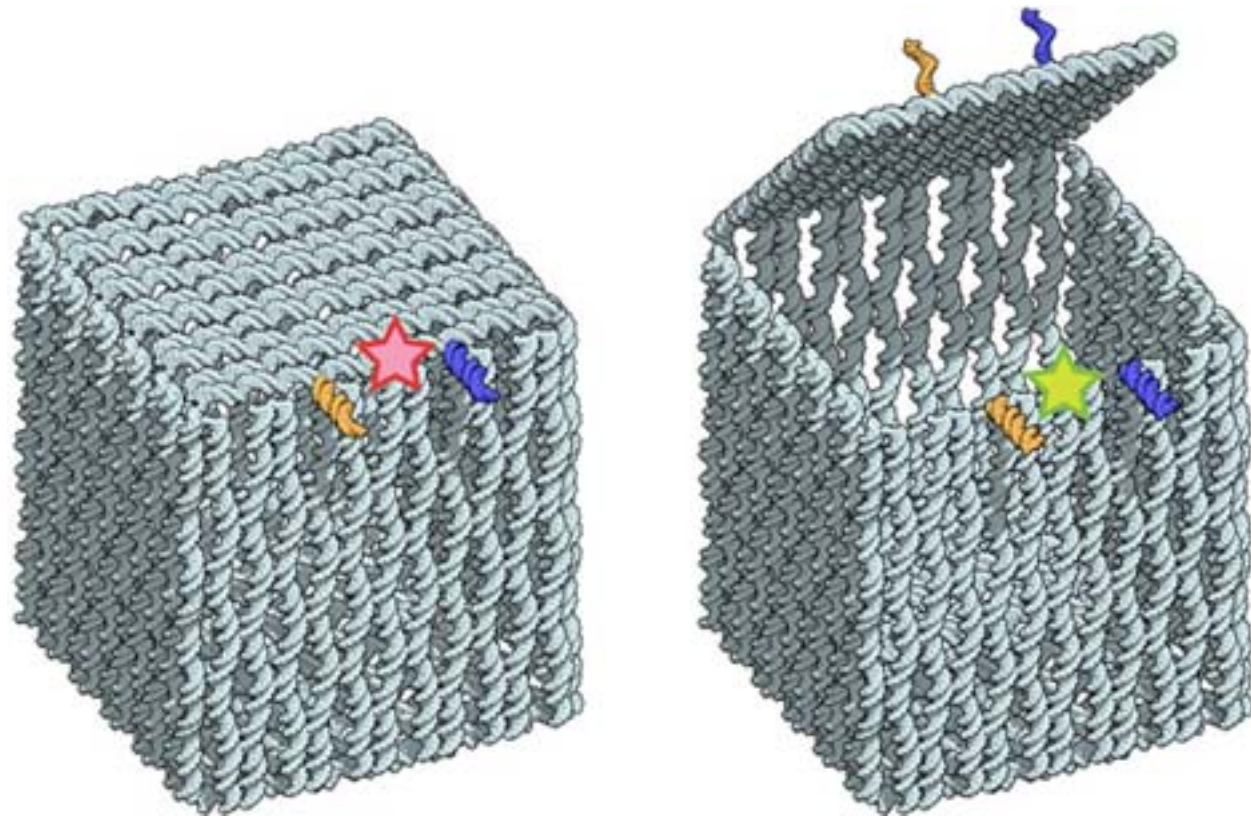


DNA origami: Rothemund, Nature 2006

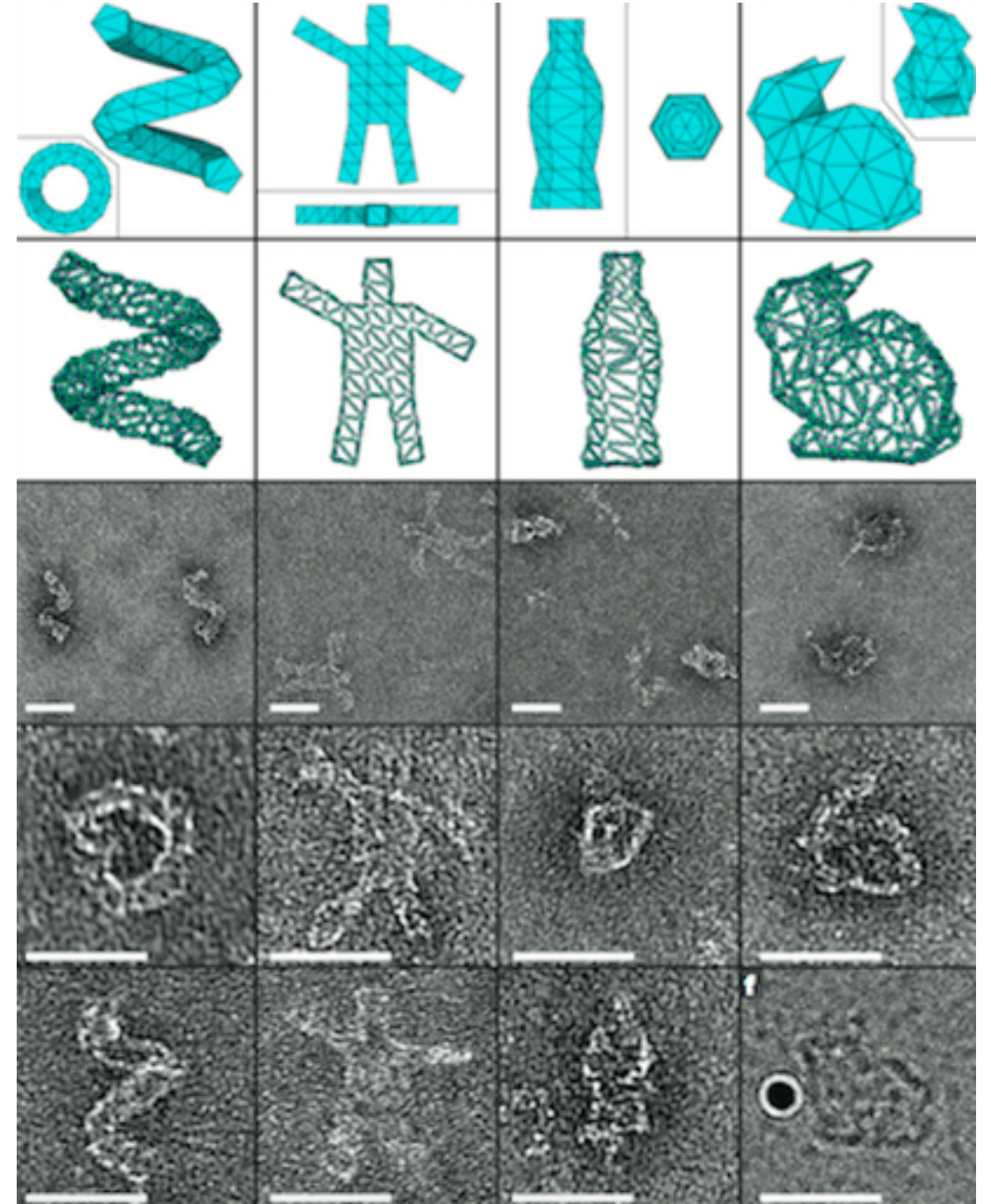


DNA single-stranded tiles: Wei, Dai, Yin, Nature 2012

3D shapes made out of DNA



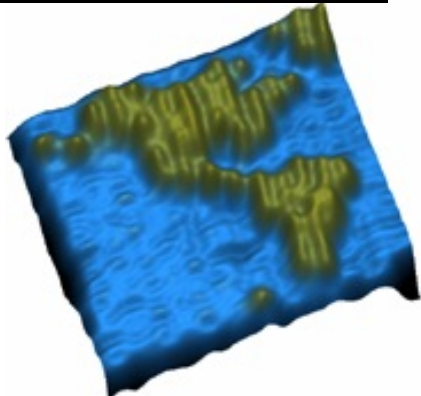
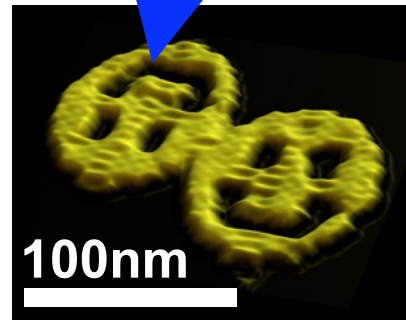
DNA origami box (that opens)
Andersen et al. Nature 2009.



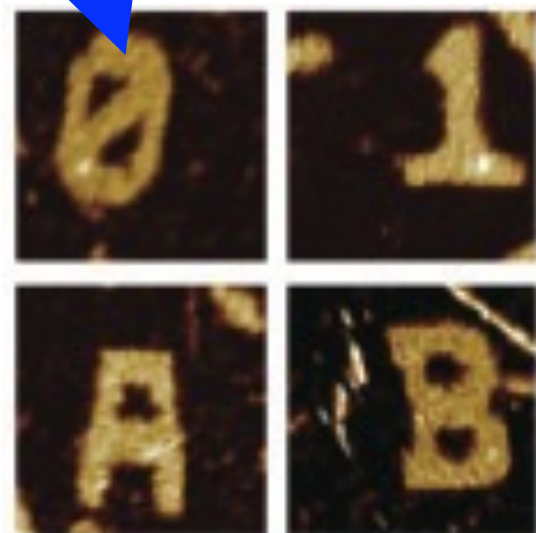
DNA origami 3D wireframe shapes
Benson, et al. Nature 2015

Nanostructure design via self-assembly

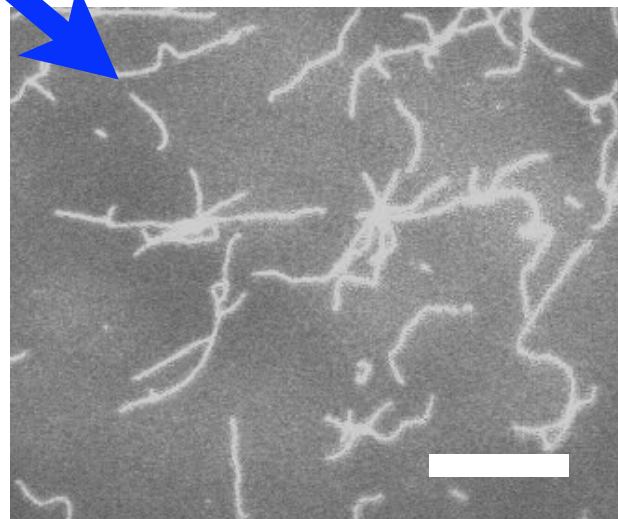
We tell the molecules **exactly** where to go



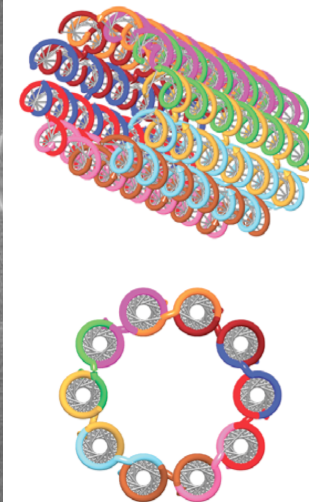
Rothemund
2006 Nature



Wei, Dai, Yin. 2013
Nature



Yin et al 2008 Science

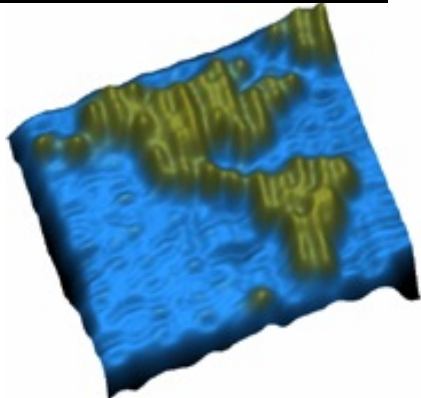
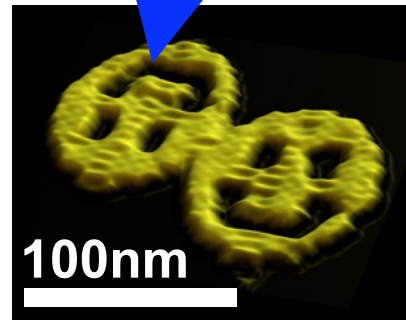


Nanostructure design via self-assembly

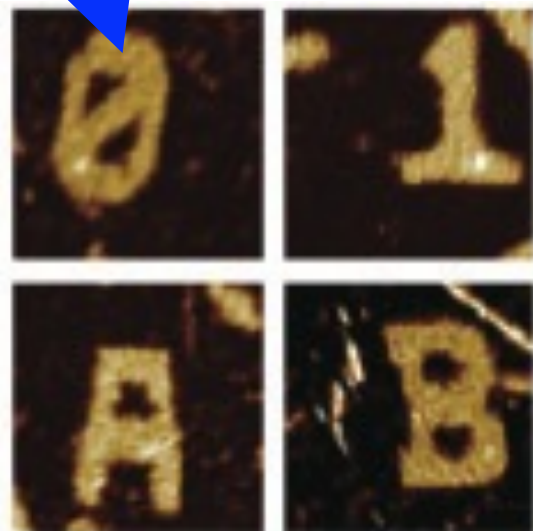
We tell the molecules **exactly** where to go



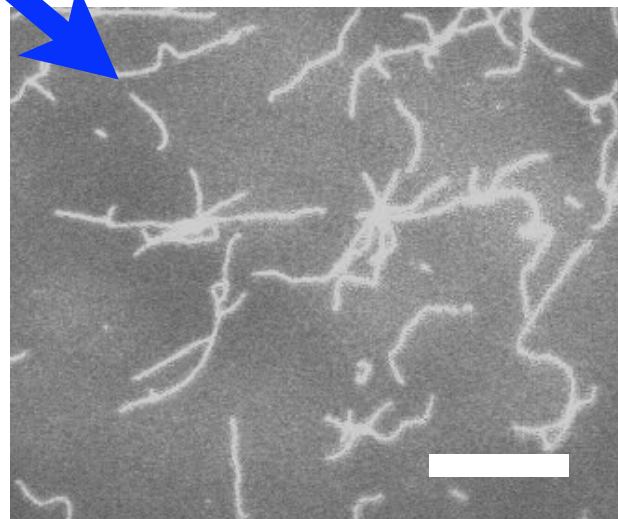
Can we have **smarter** molecules that decide where to go for themselves?



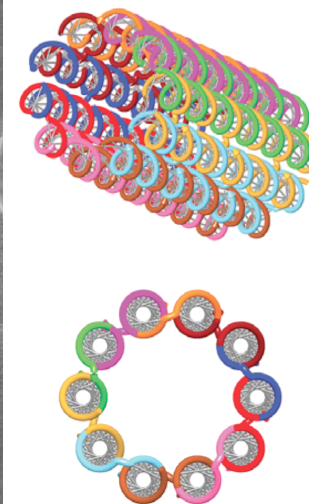
Rothemund
2006 Nature



Wei, Dai, Yin. 2013
Nature



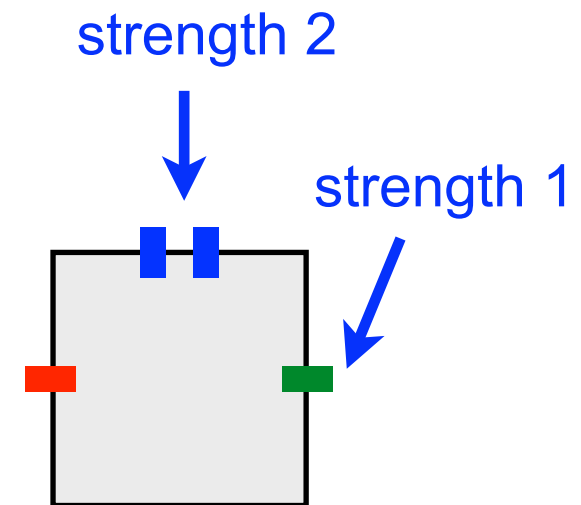
Yin et al 2008 Science



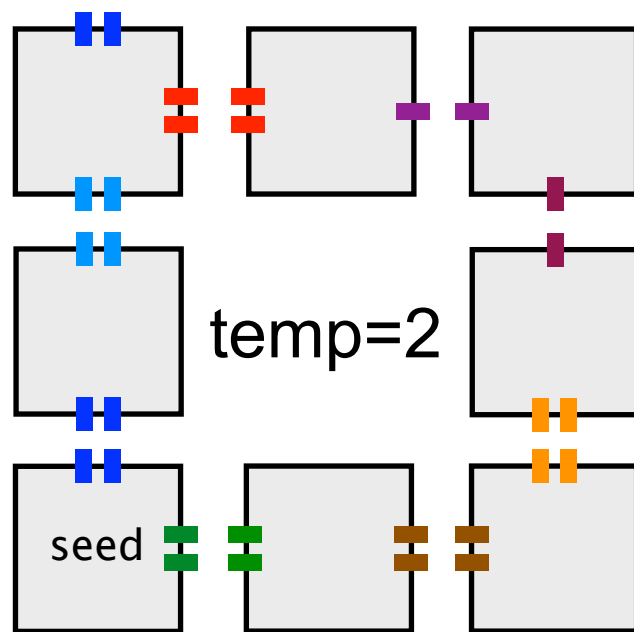
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



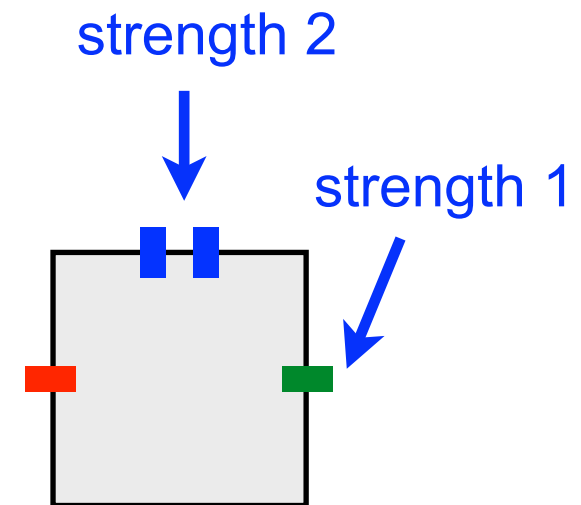
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

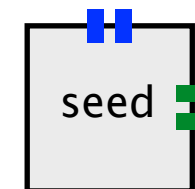
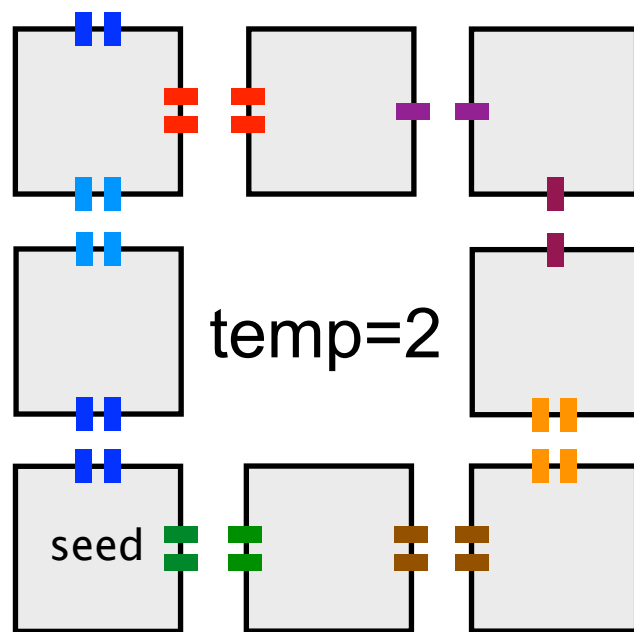
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



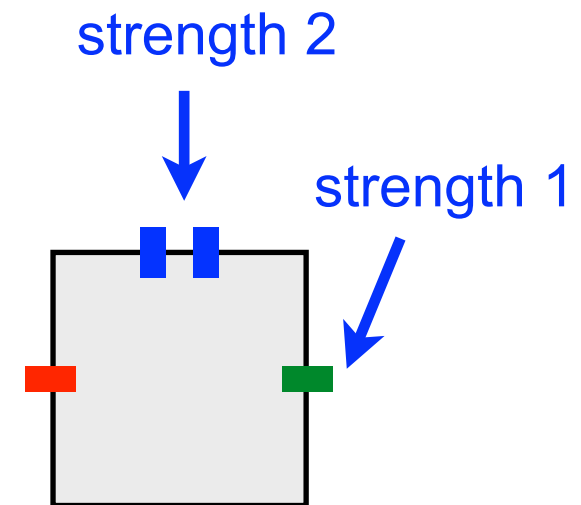
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

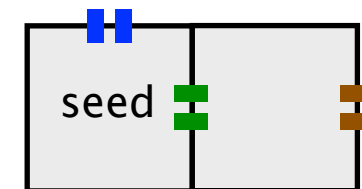
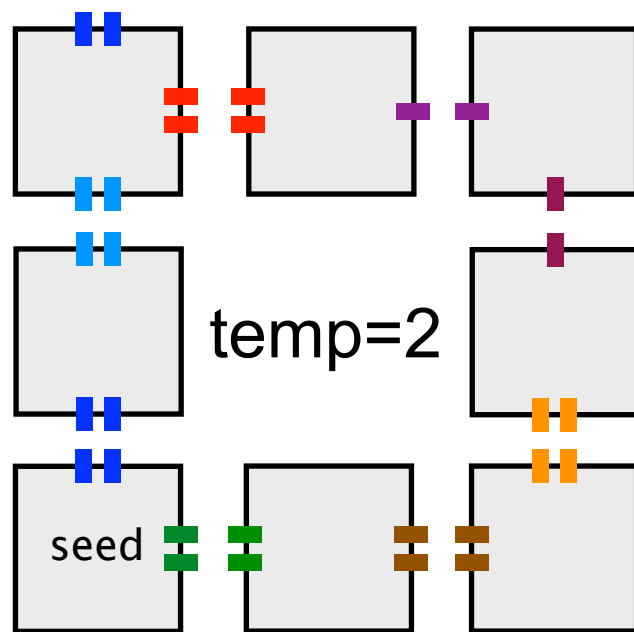
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



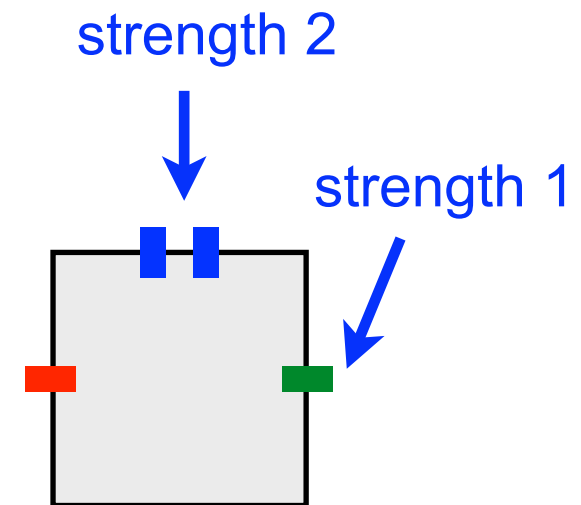
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

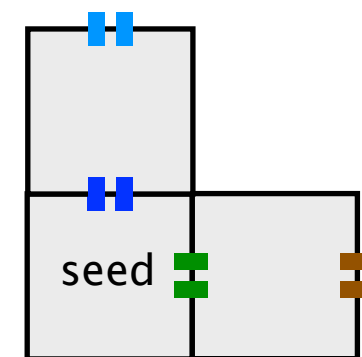
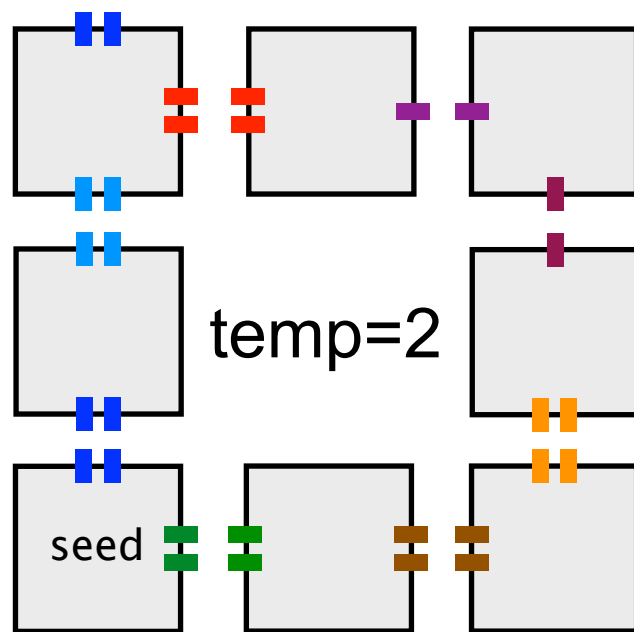
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



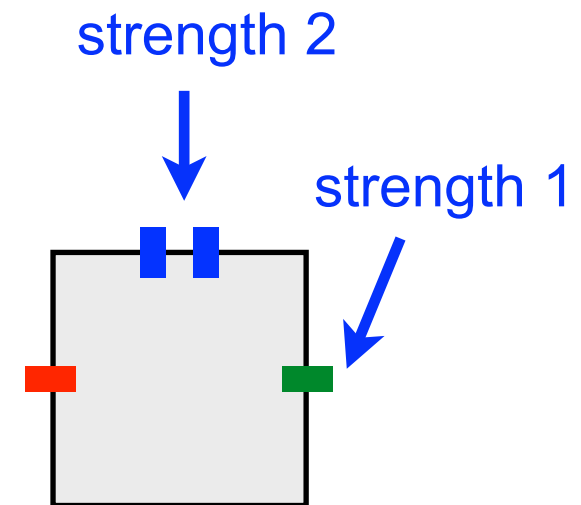
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

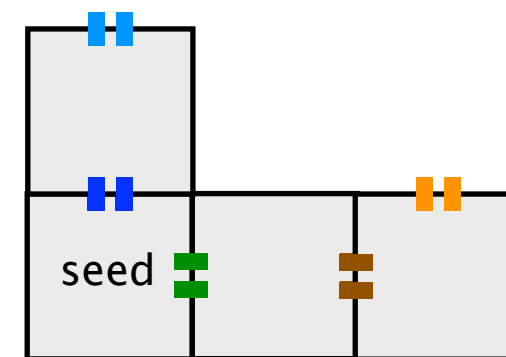
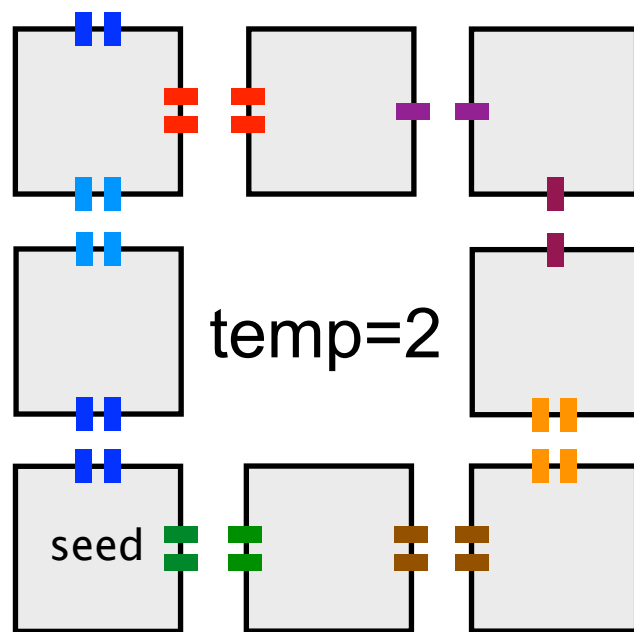
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



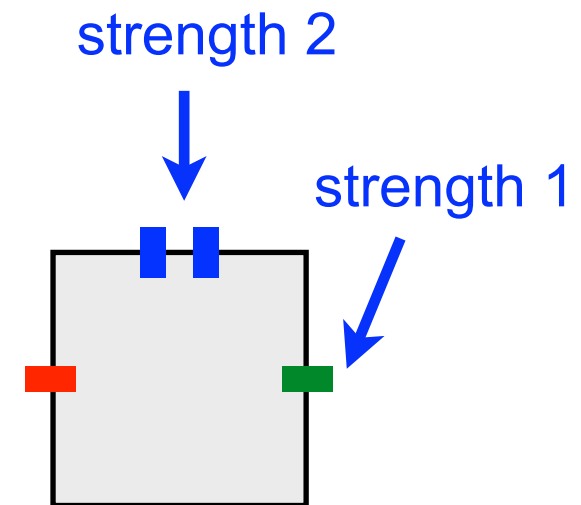
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

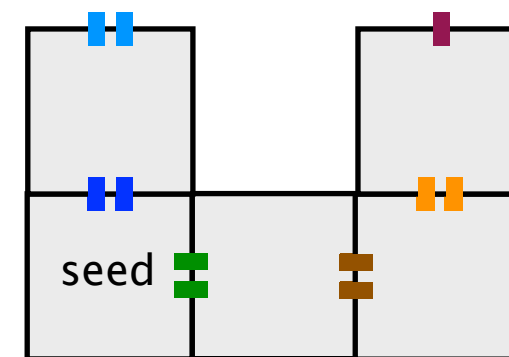
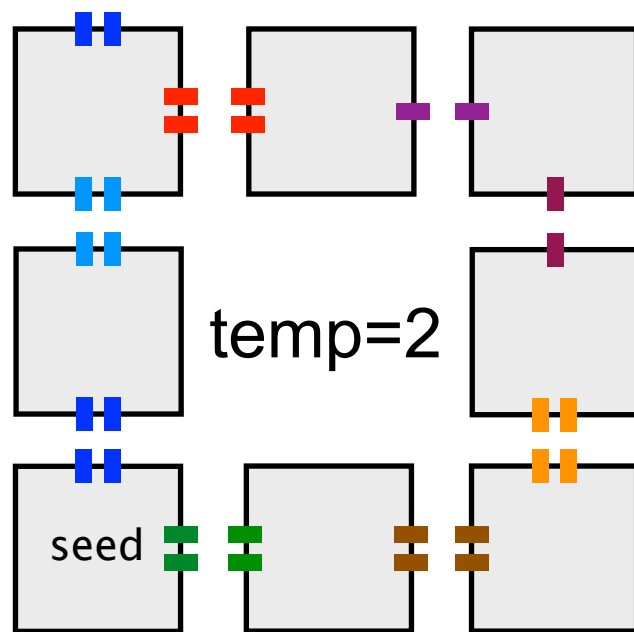
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



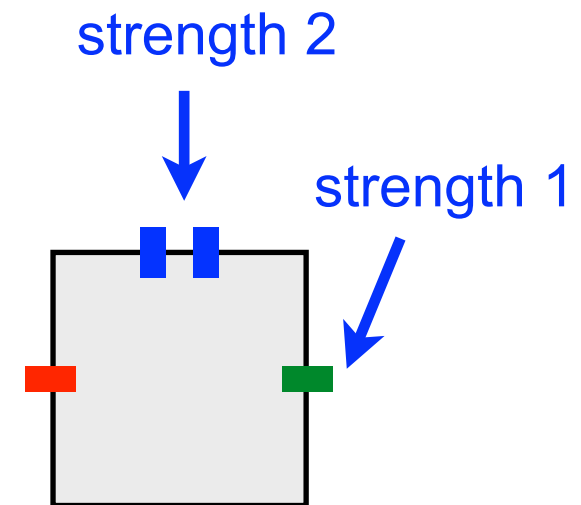
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

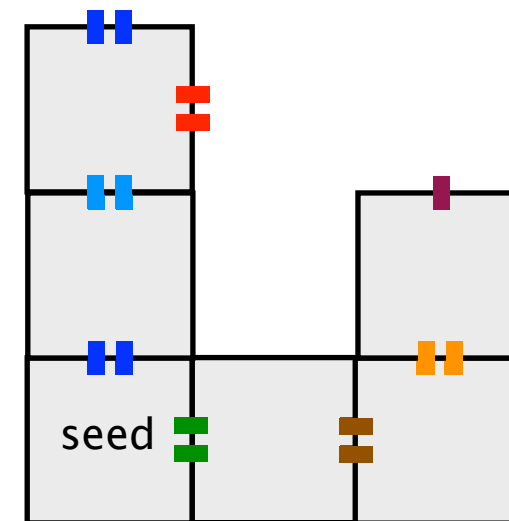
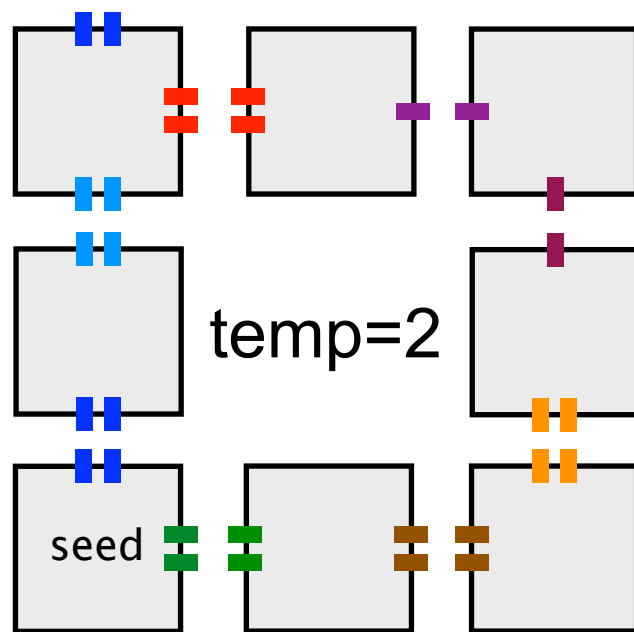
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



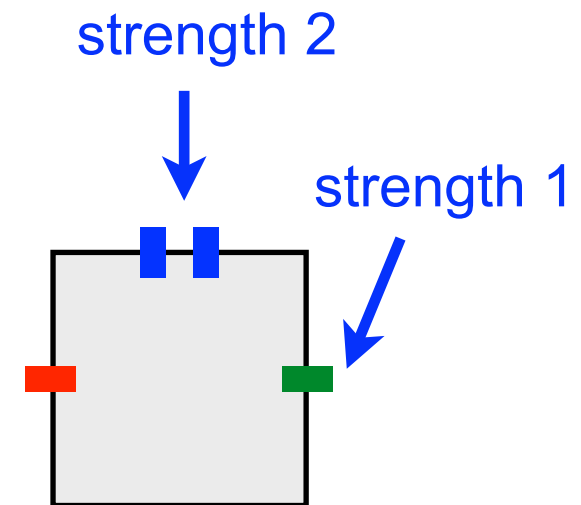
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

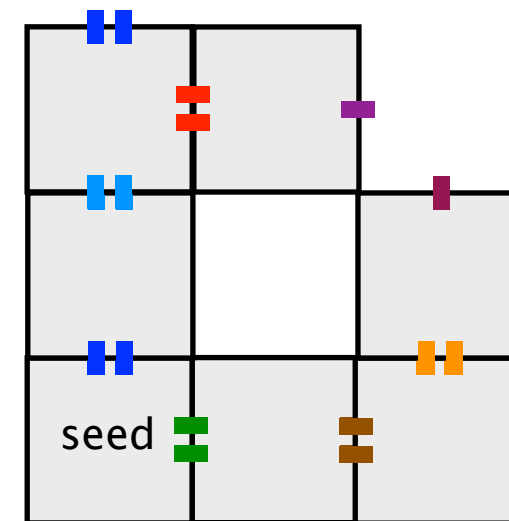
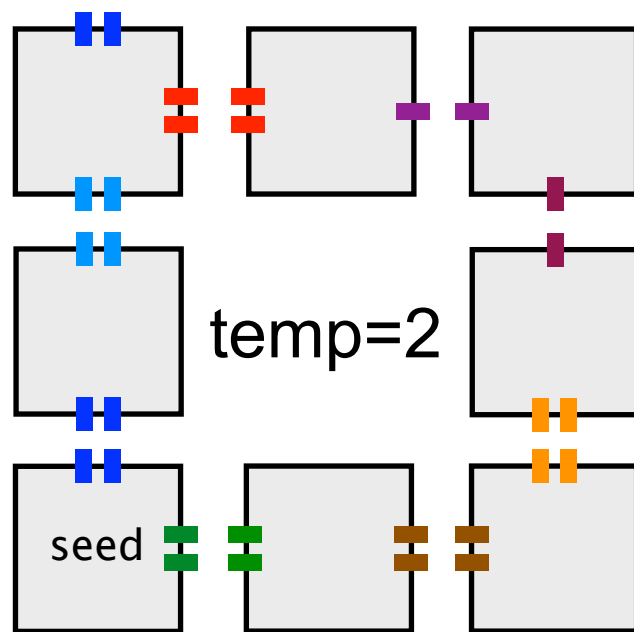
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



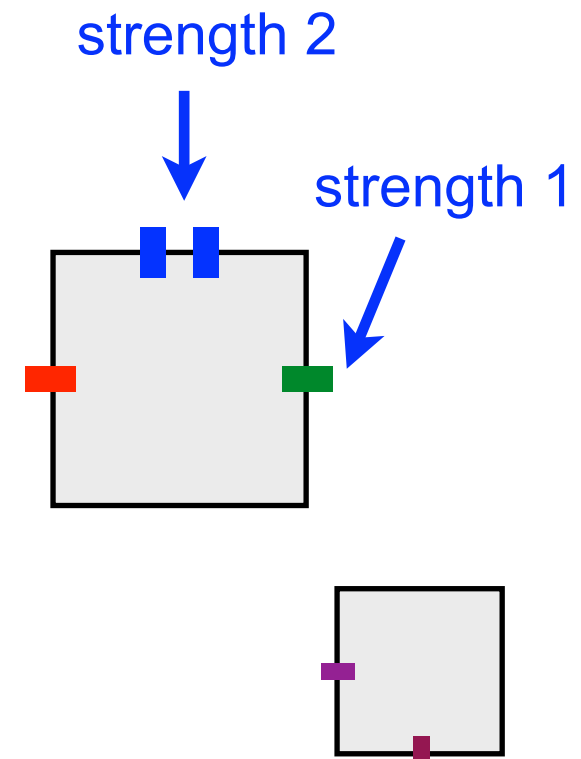
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

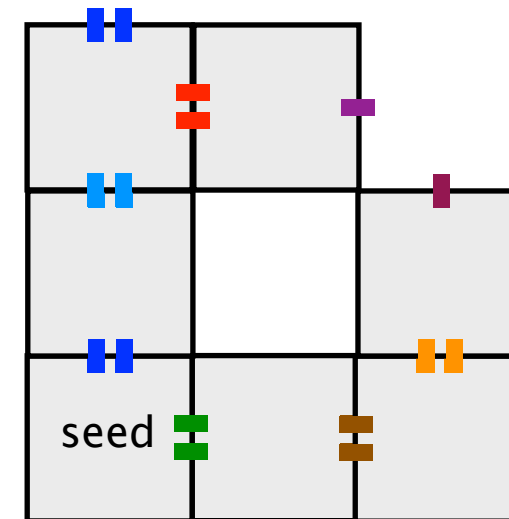
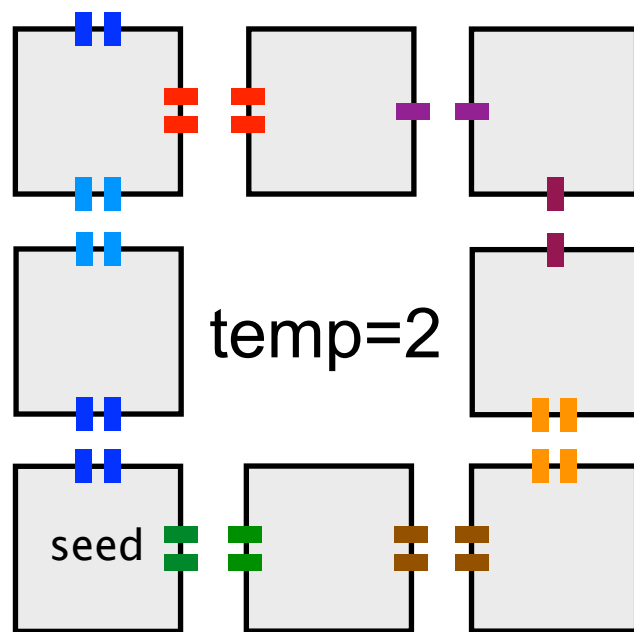
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



Model by Winfree, 1998



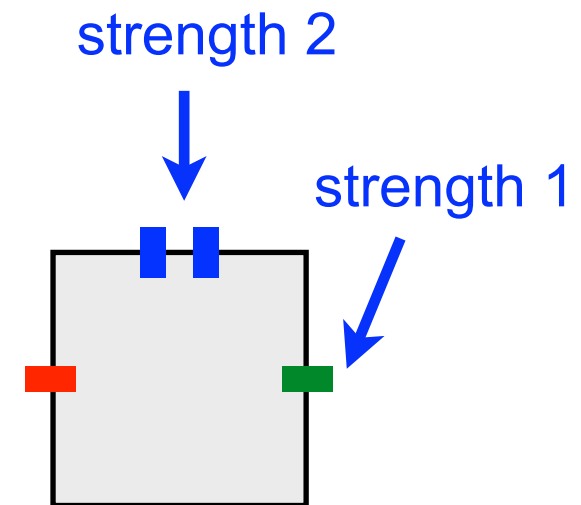
We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

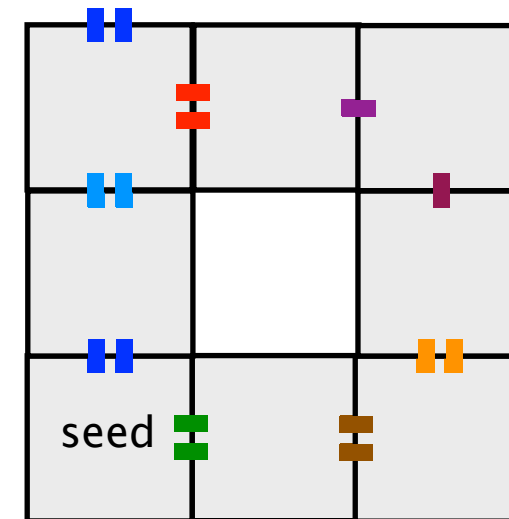
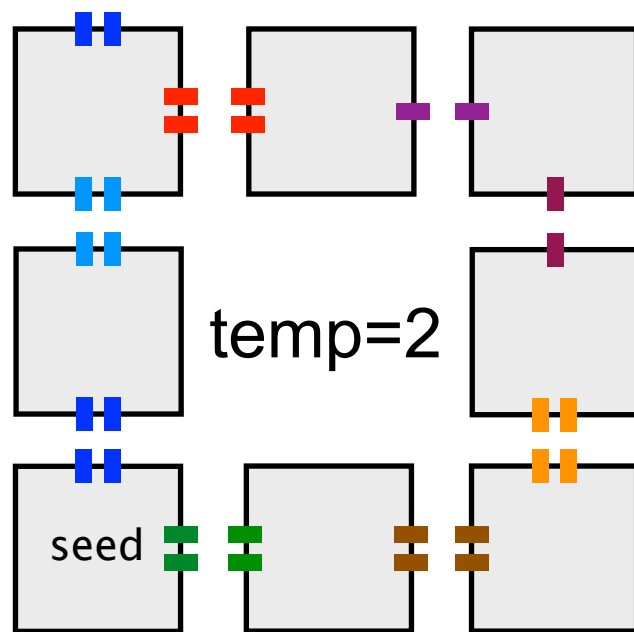
Computing with the abstract tile assembly model

An asynchronous cellular automaton model capturing dynamics of molecular binding

- **Square tiles**
 - finite set of tile types, unlimited supply of each type, non-rotatable
- Each side has a **glue** (colour) and **strength** (0,1,2,3,...)
- System has a **temperature** (e.g. 2)
- **Simple local binding rule:** A tile sticks to an assembly if enough of its glues match so that the sum of the strengths of the matching glues is at least the temperature



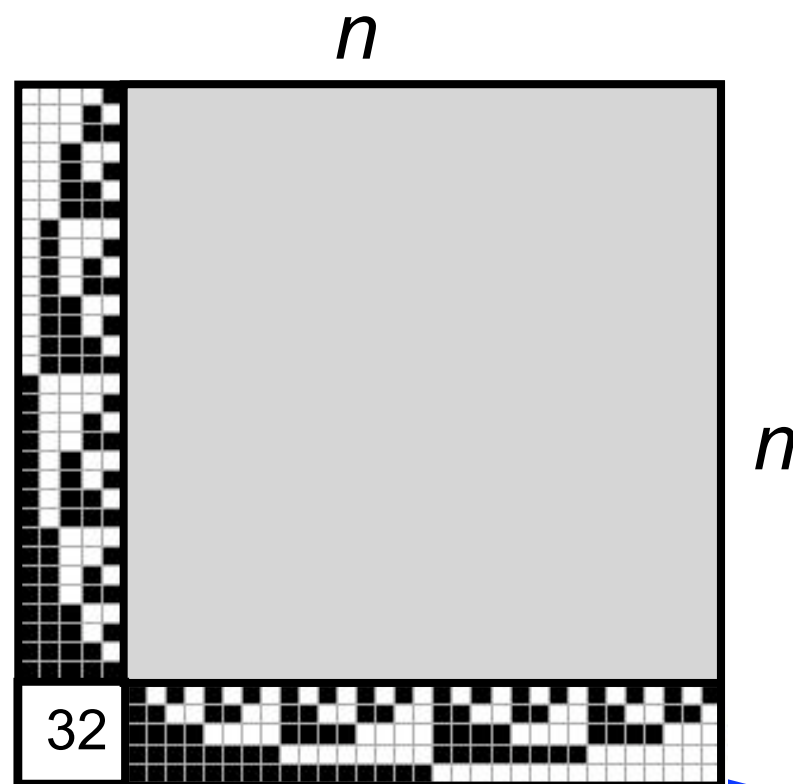
Model by Winfree, 1998



We can make these tiles out of DNA!

Small size, requires us to program in a bottom-up way

Algorithmic self-assembly **theory**: previous work



- Turing universality

Winfree, PhD Thesis. 1998



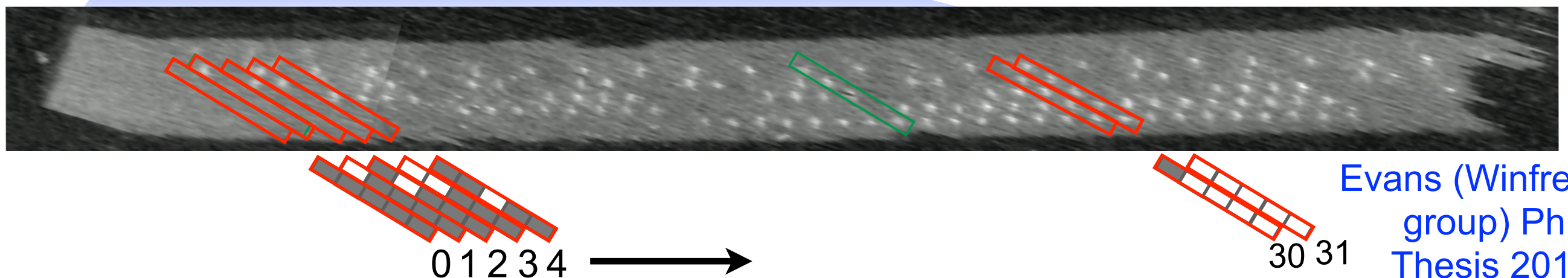
- Efficient assembly of simple shapes: $n \times n$ squares using $\Theta(\log n / \log \log n)$ tile types

Adleman, Cheng, Goel, Huang STOC 2001

Rothemund, Winfree. STOC 2000

- Efficient assembly of scaled shapes using a number of tile types roughly equal to the Kolmogorov complexity of the shape

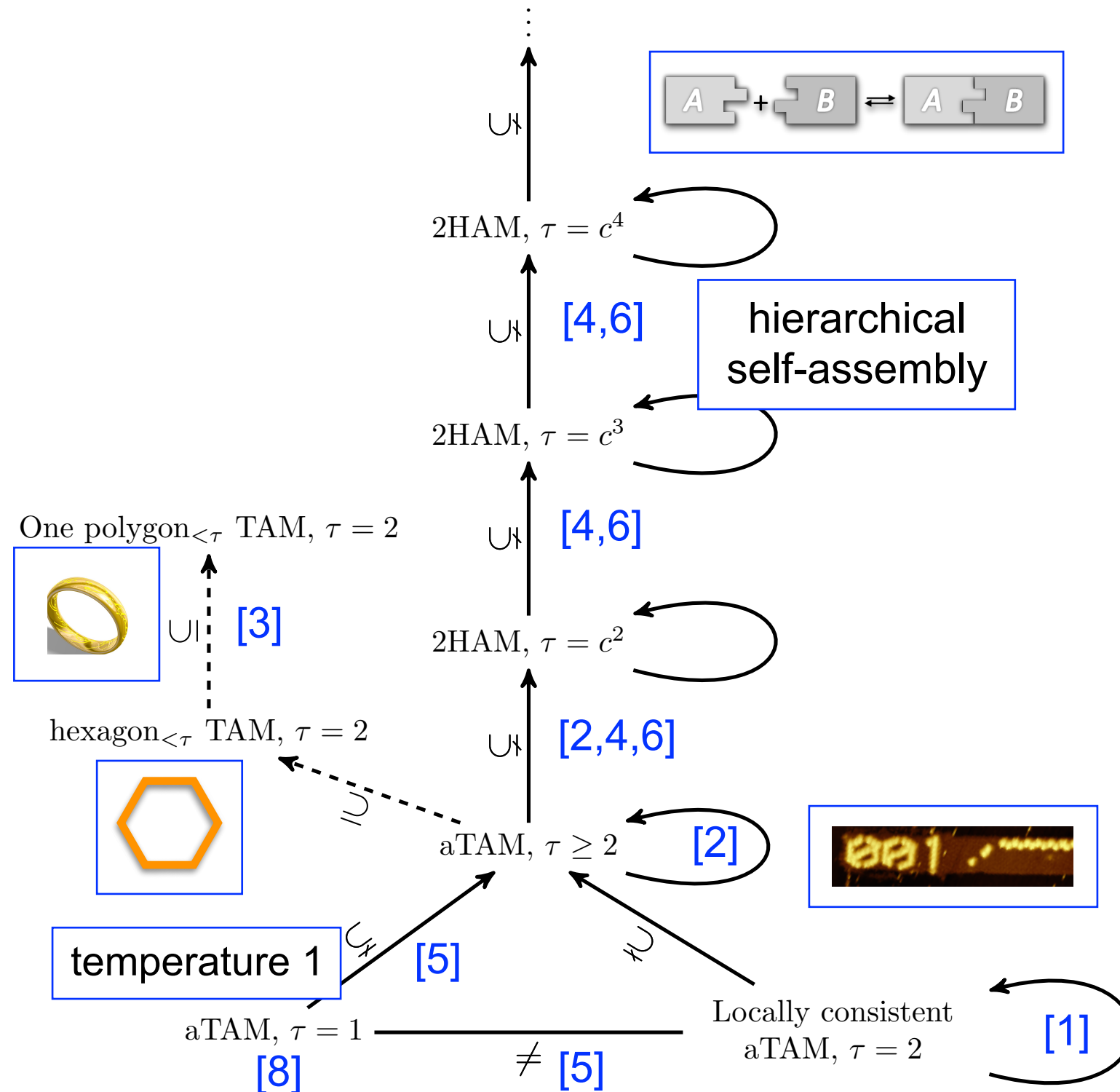
Soloveichik, Winfree. SICOMP 2007



Evans (Winfree group) PhD Thesis 2014

Algorithmic self-assembly theory: previous work

Simulation & *intrinsic* universality



Characterisations and comparisons of self-assembly models based on **simulation** between self-assembly systems

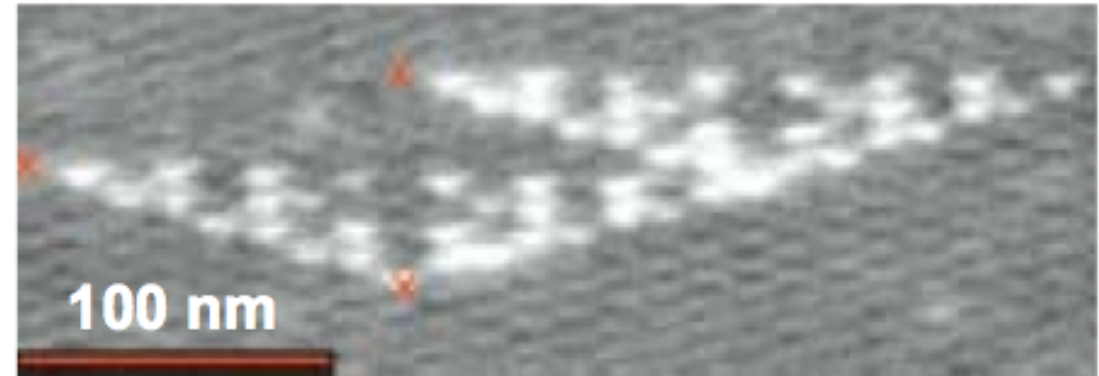
- [8] STOC 2017
- [7] Phil Trans Royal Soc. A. 2015
- [6] Algorithmica 2015
- [5] SODA 2014
- [4] ICALP 2014
- [3] ICALP 2013
- [2] FOCS 2012
- [1] STACS 2012

Complexity hierarchy for self-assembly

Algorithmic self-assembly experiments: previous work



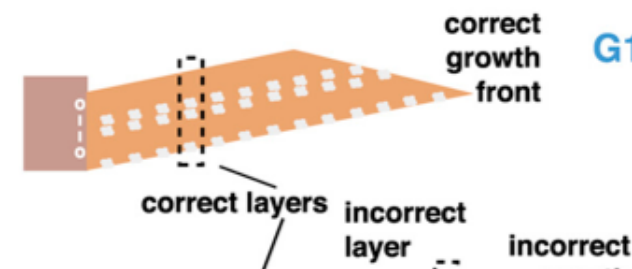
Bit Copying. Barish et al. 2009



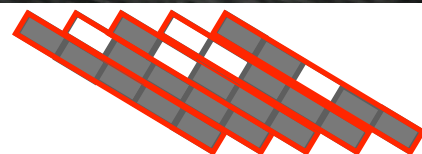
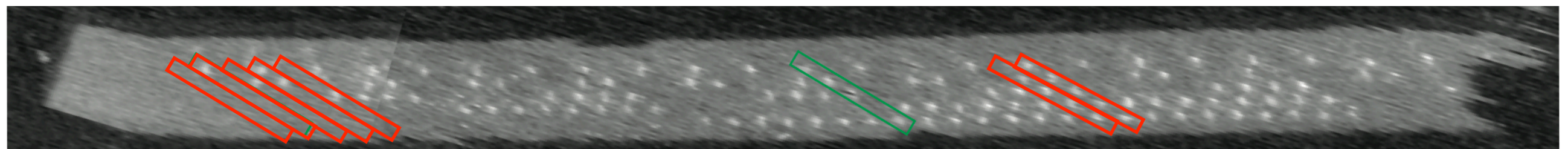
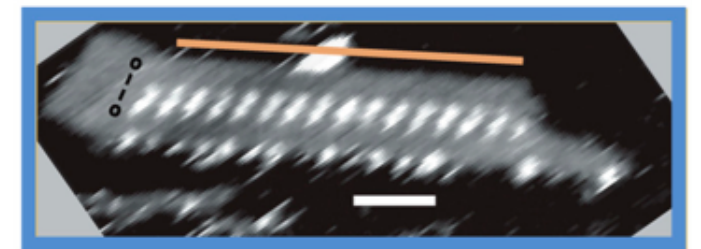
Sierpinski Triangles. Rothmund, Papadakis, Winfree. 2004



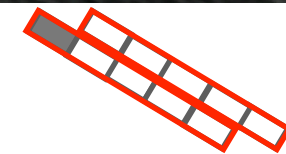
Counter. Barish et al. 2009



Copying & replication Schulman, Yurke, Winfree. PNAS. 2012



0 1 2 3 4



30 31

Evans, Winfree group. PhD Thesis 2014

Copying, Sierpinsky, binary counting to 31:
Can we run more algorithms?

Structure of talk

Copying, Sierpinski, binary counting to 31,
can we run more algorithms?

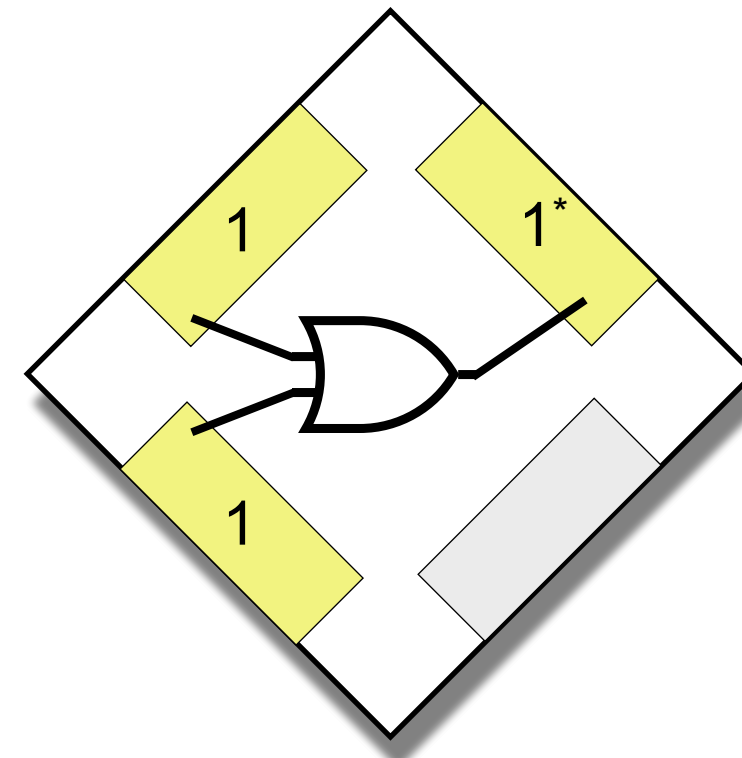
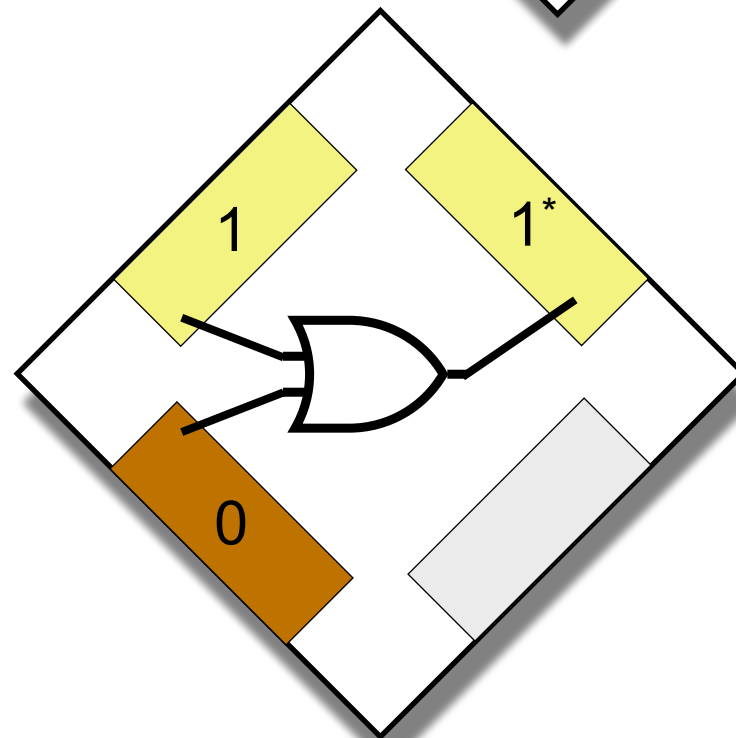
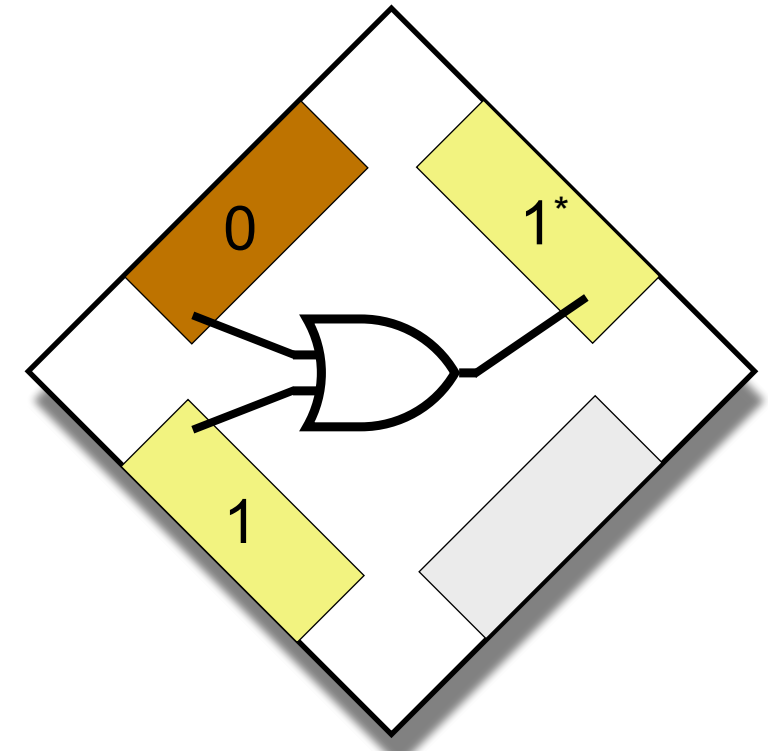
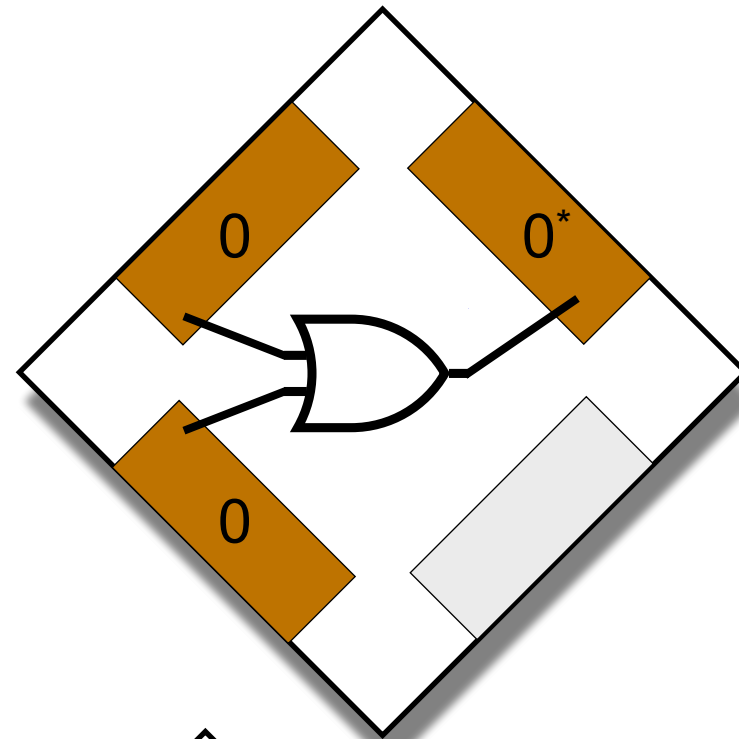
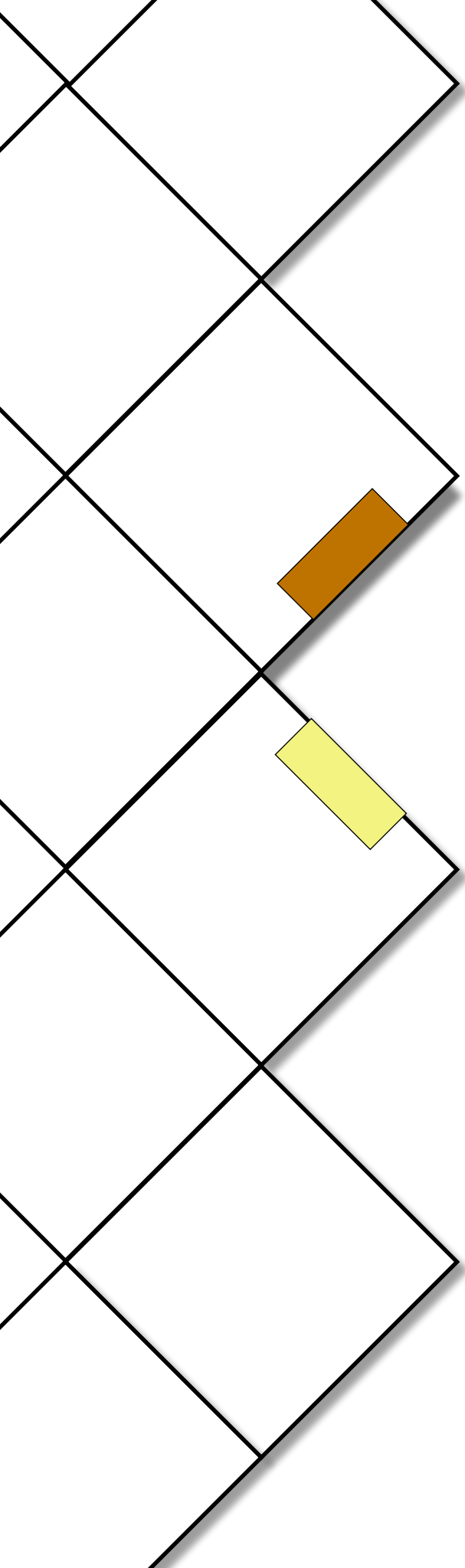
Theoretical circuit model

How it works: design and implementation

Experimental results

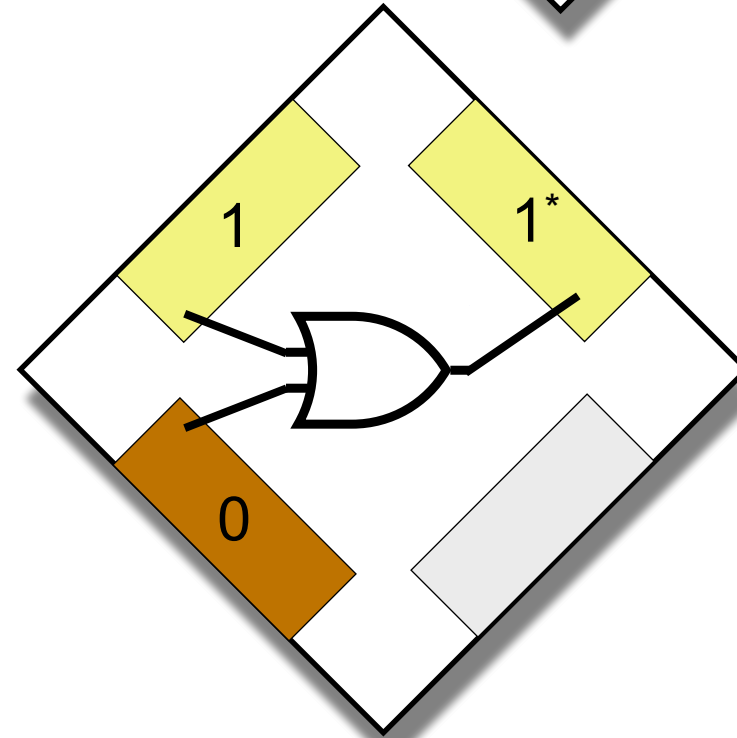
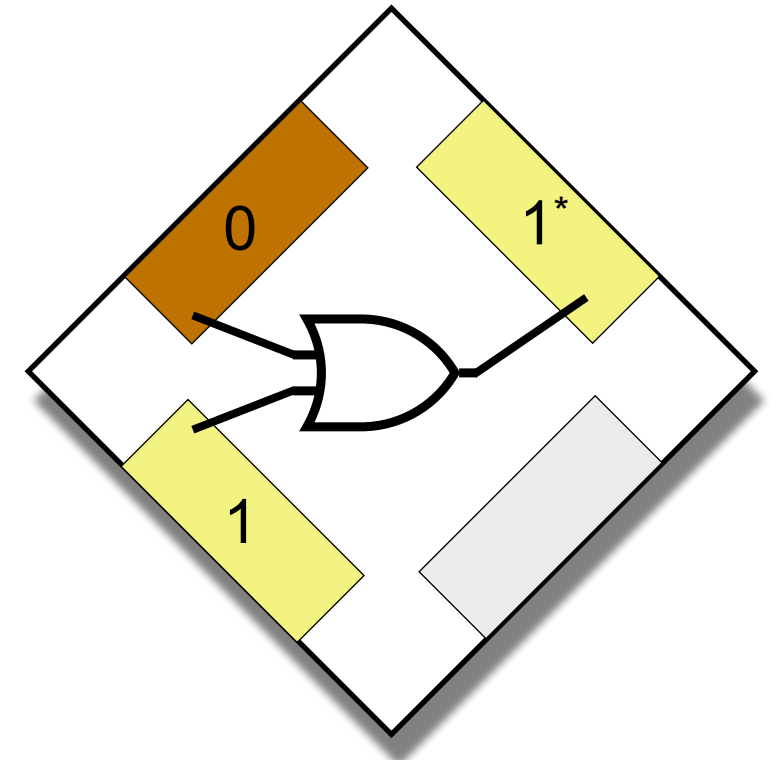
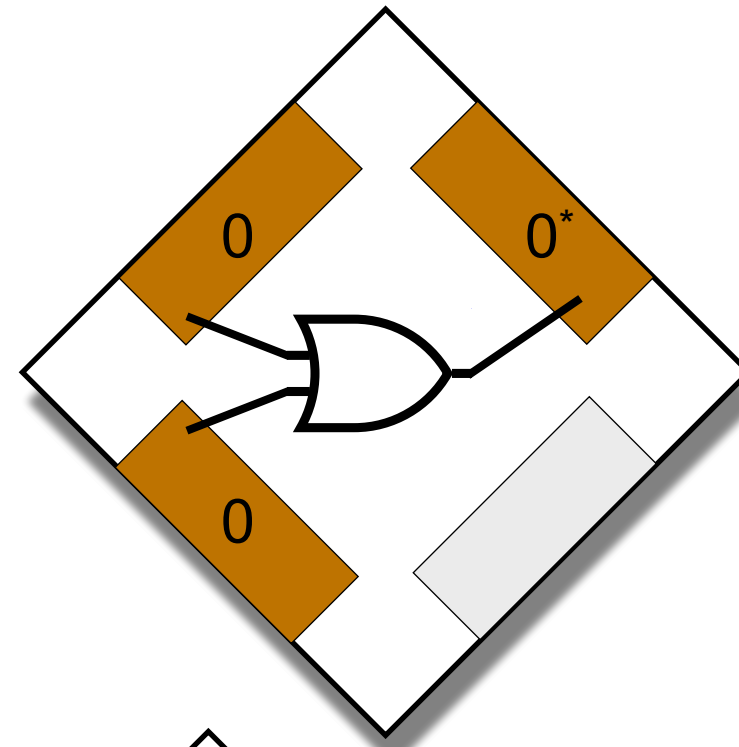
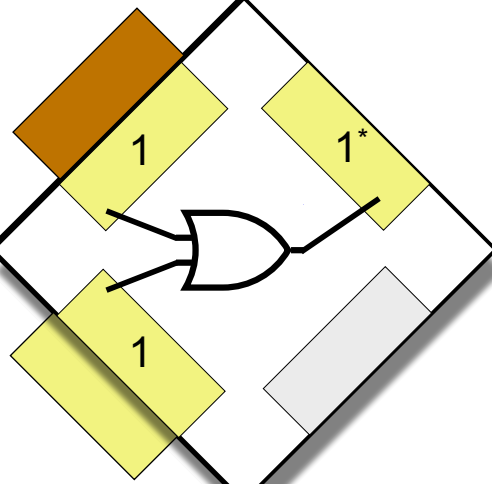
Smart self-assembly

logic gates: simple, yet powerful



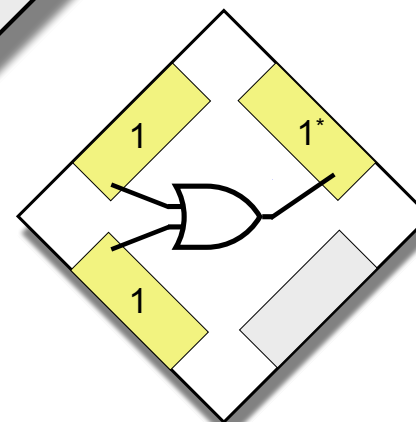
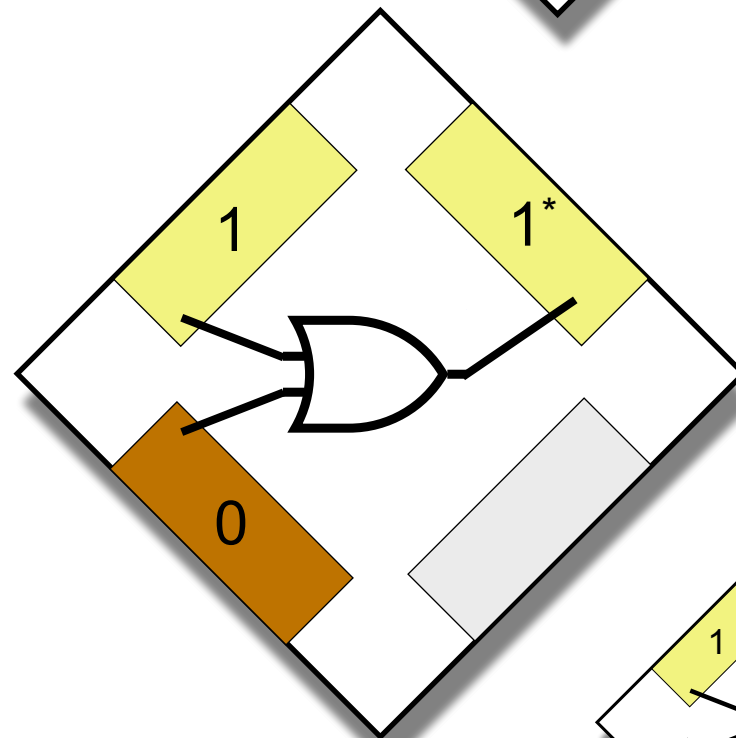
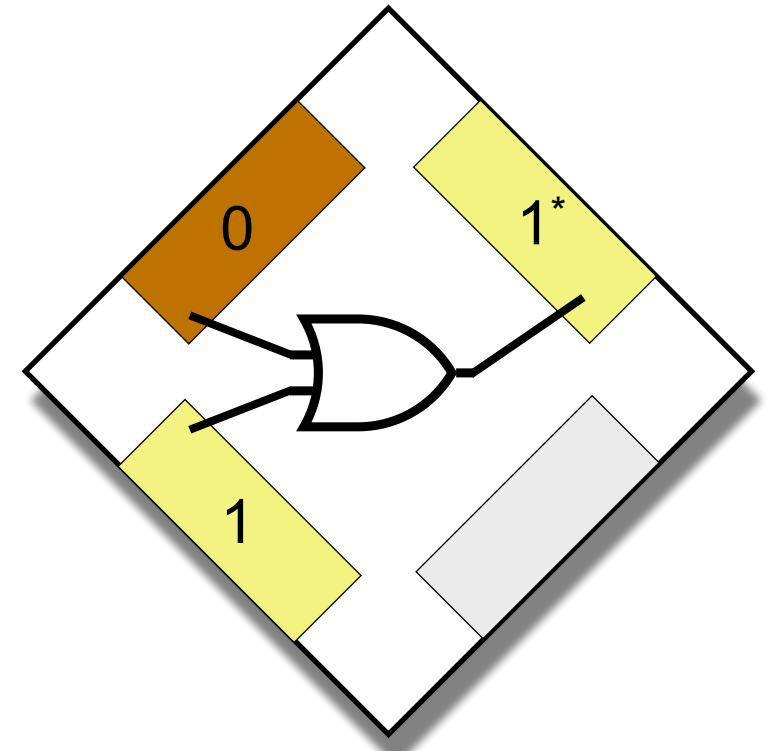
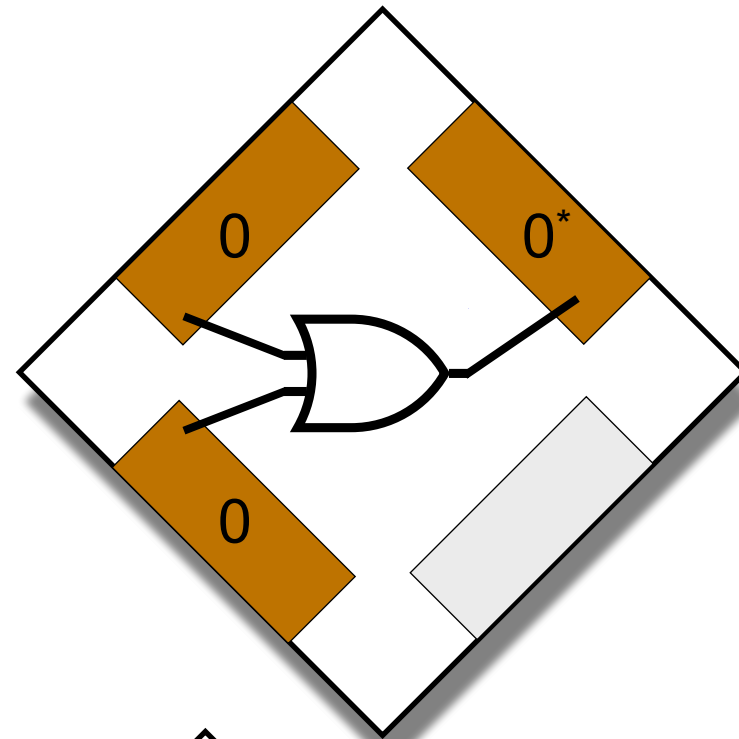
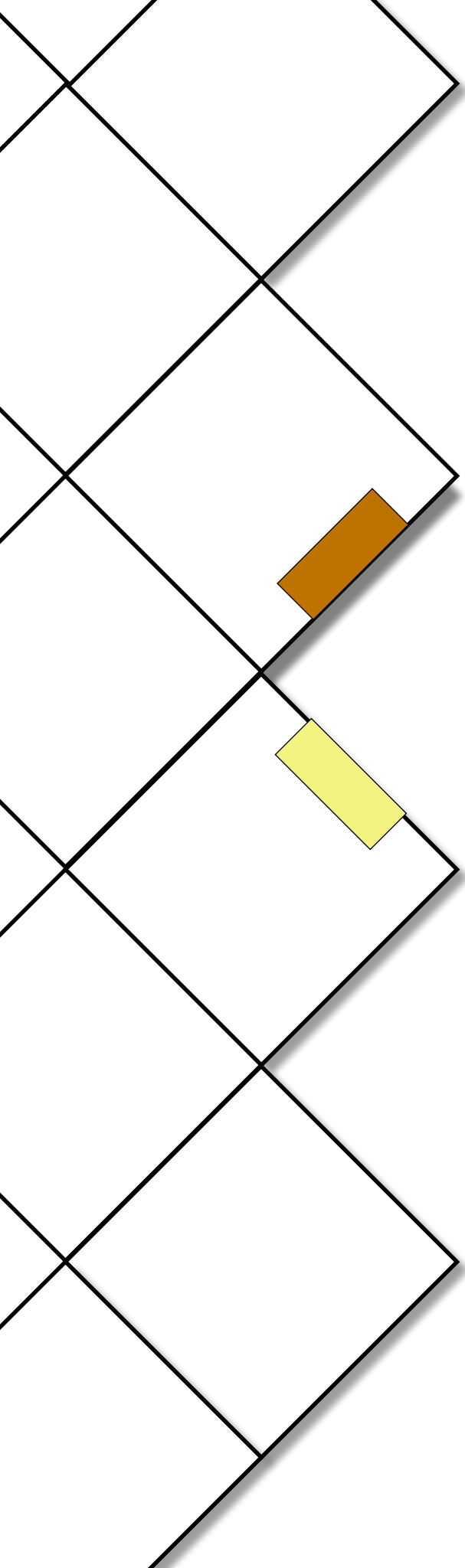
Smart self-assembly

logic gates: simple, yet powerful



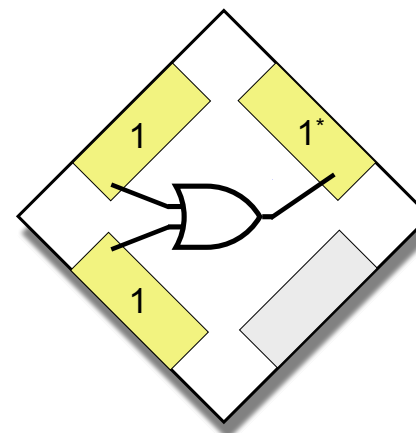
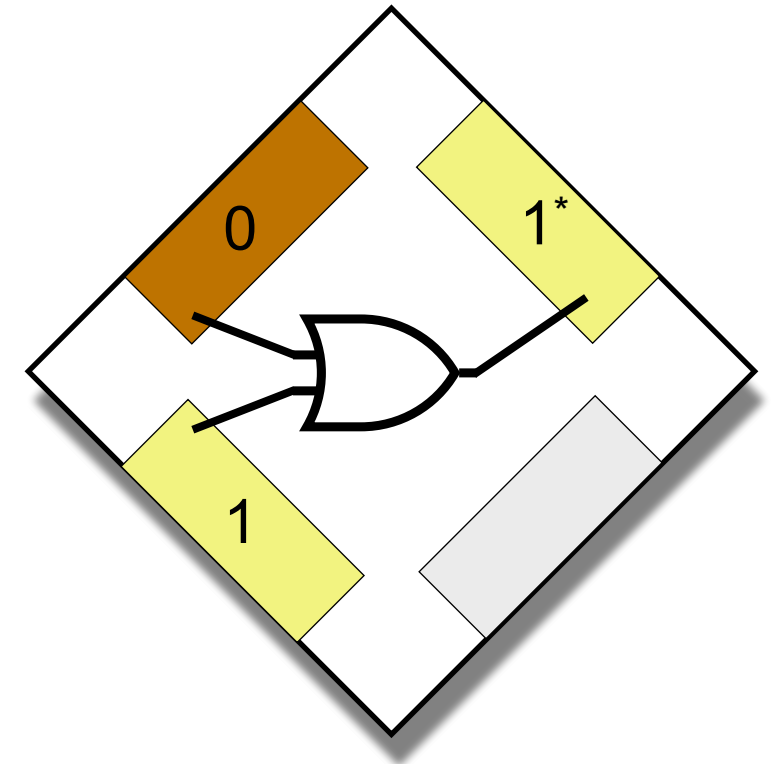
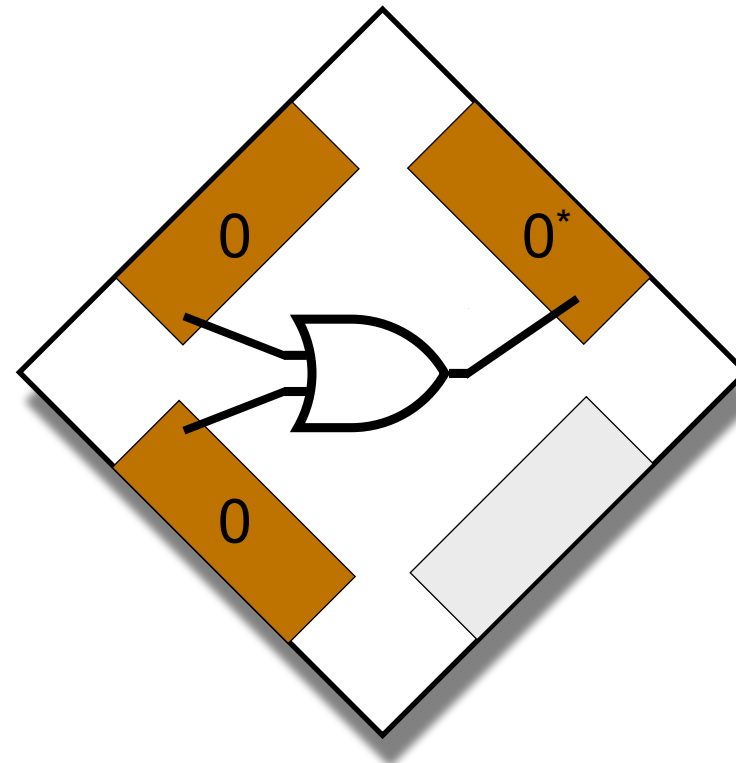
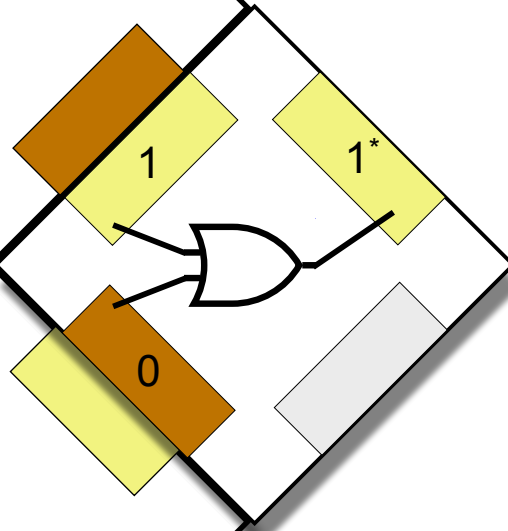
Smart self-assembly

logic gates: simple, yet powerful



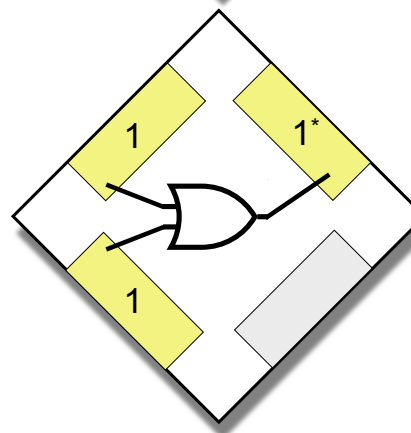
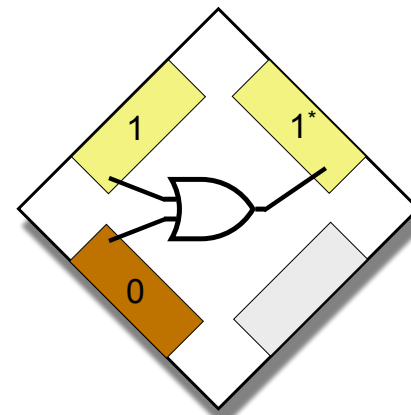
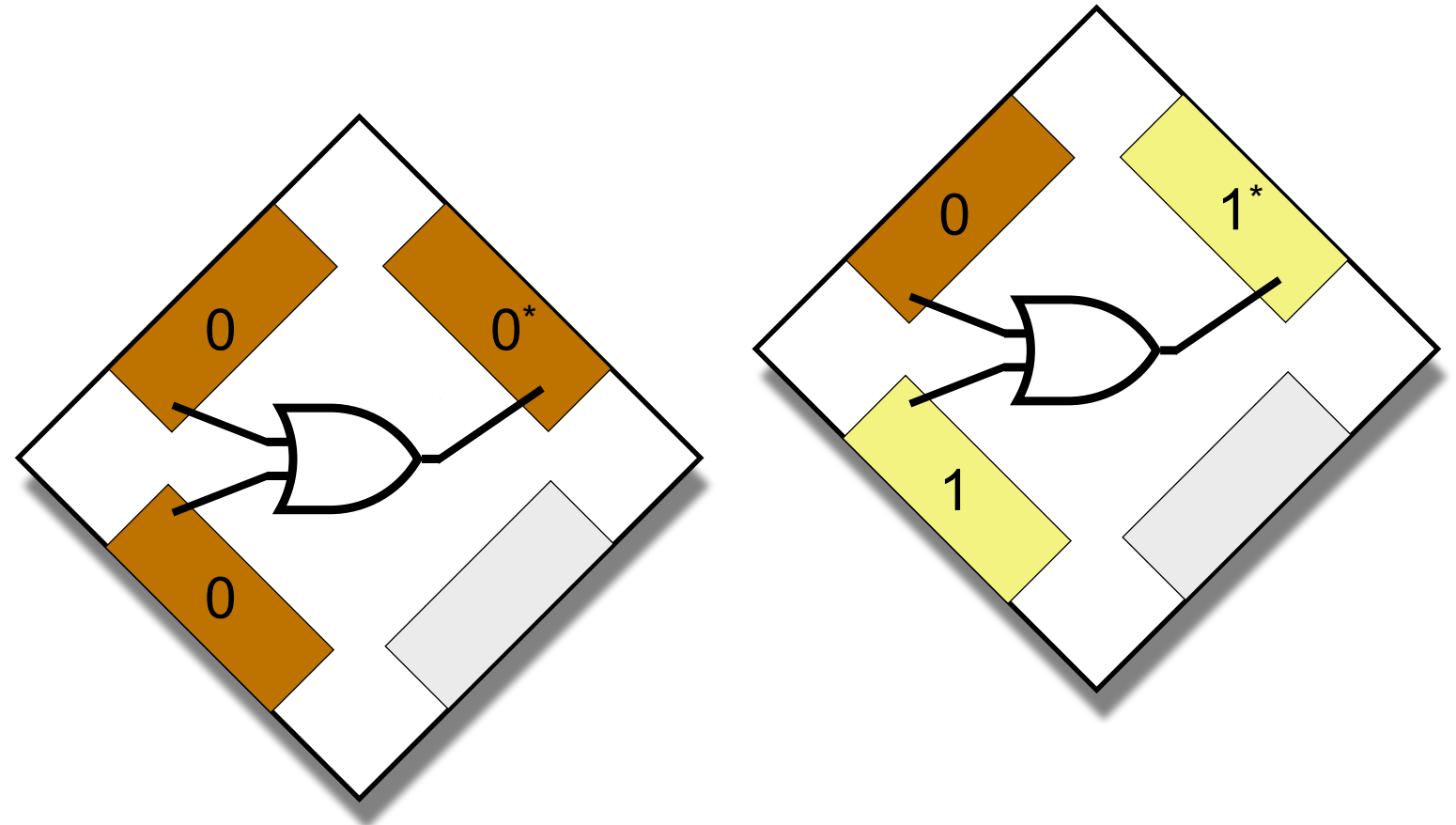
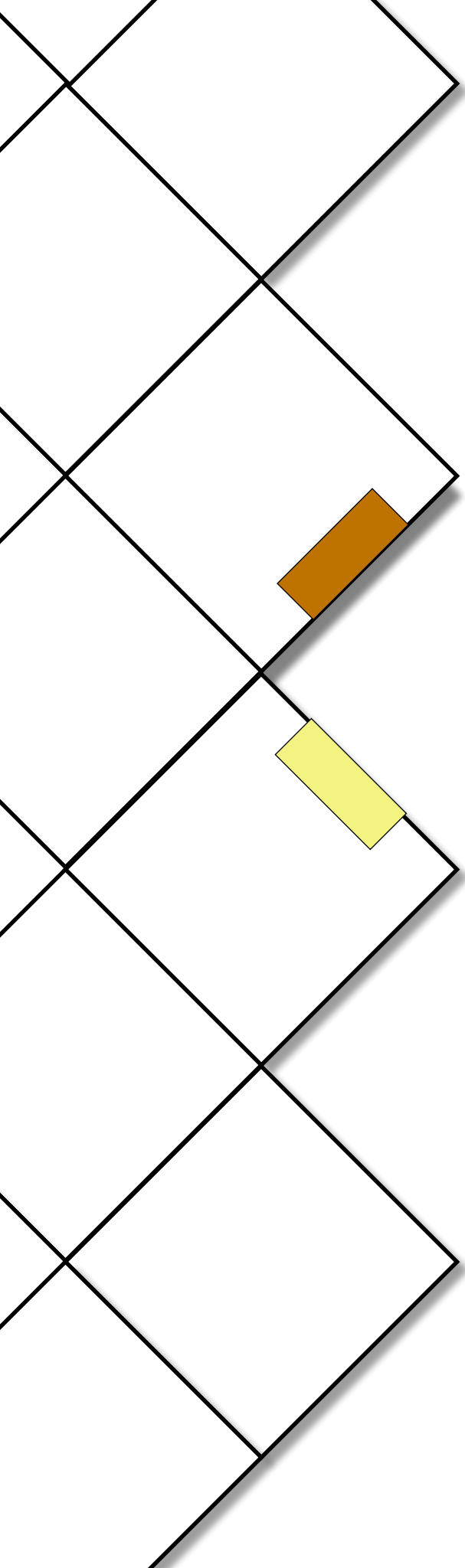
Smart self-assembly

logic gates: simple, yet powerful



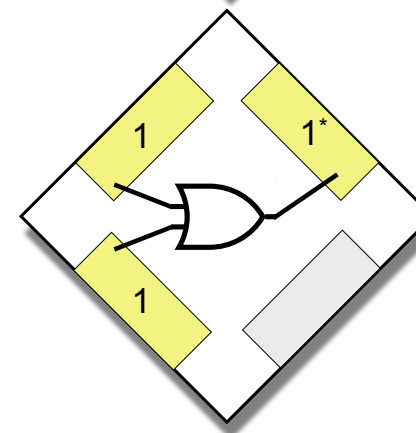
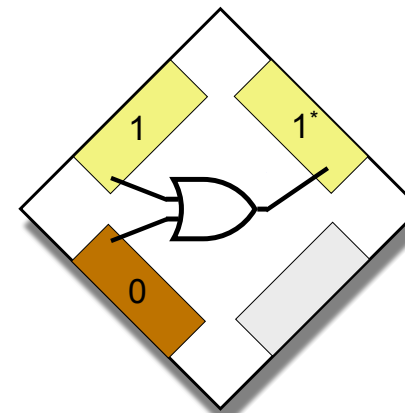
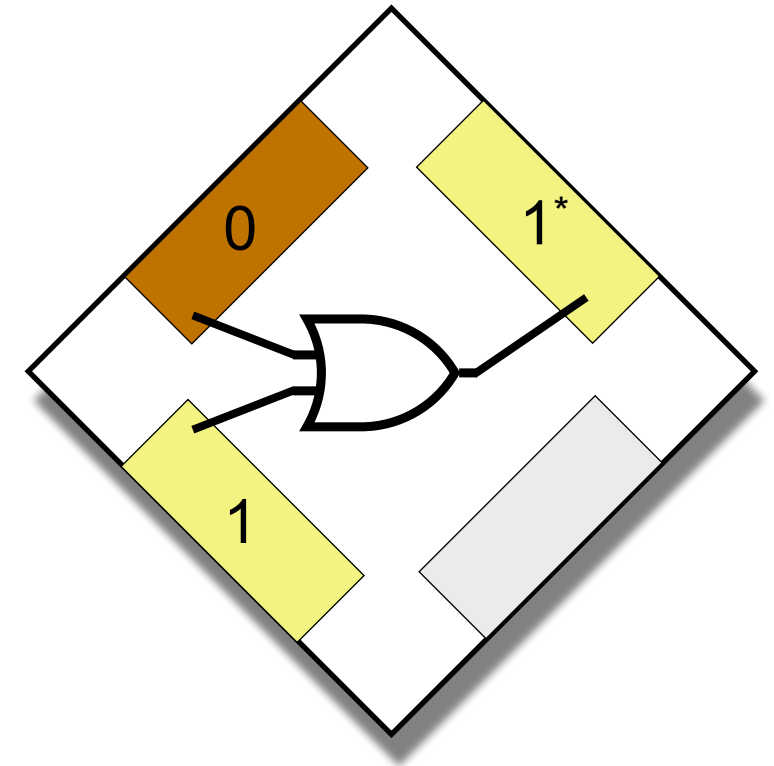
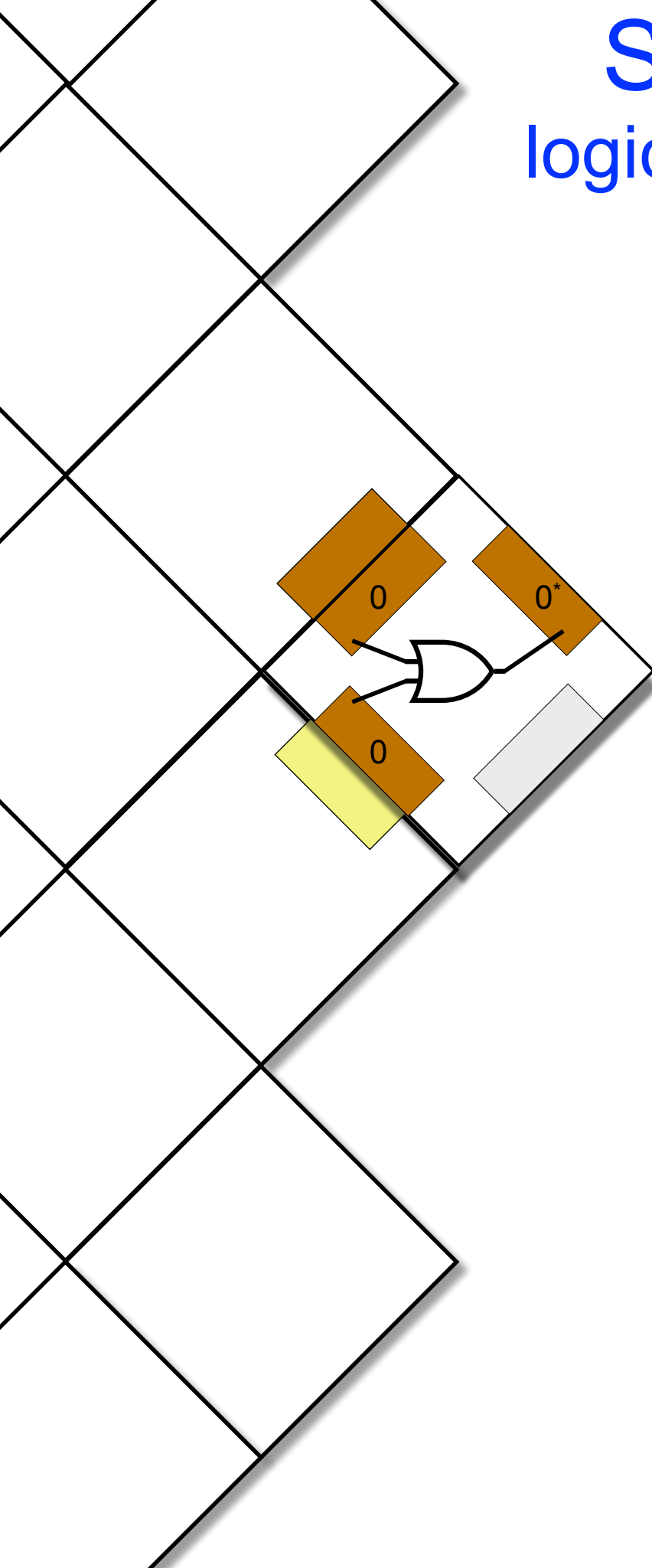
Smart self-assembly

logic gates: simple, yet powerful



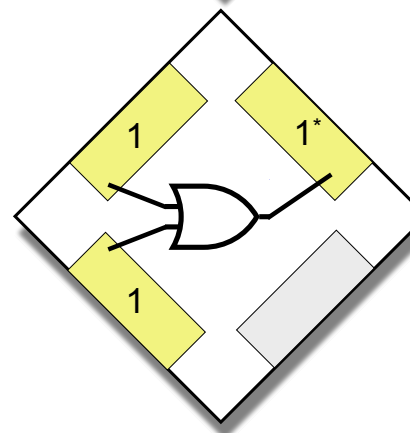
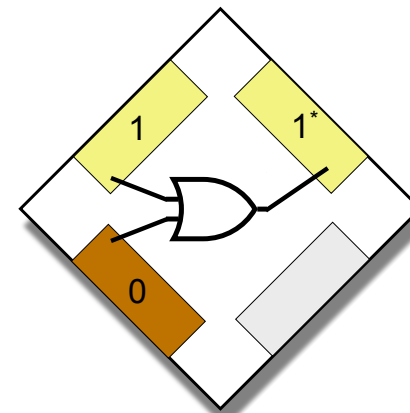
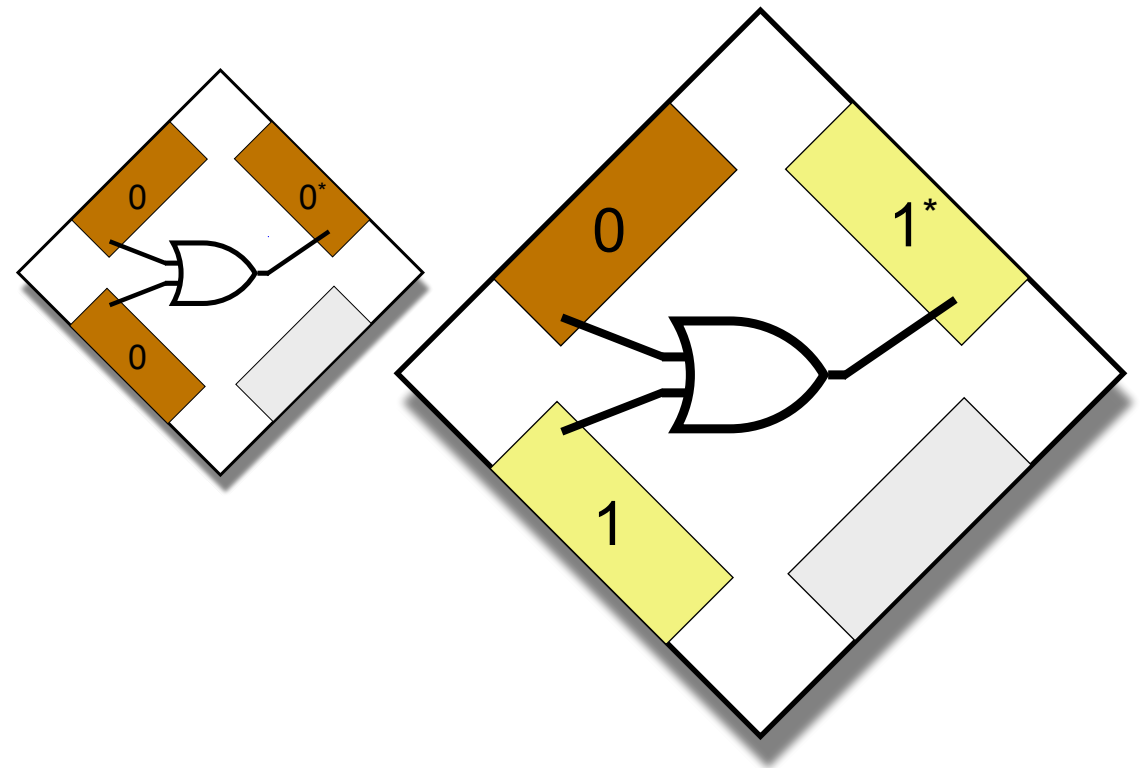
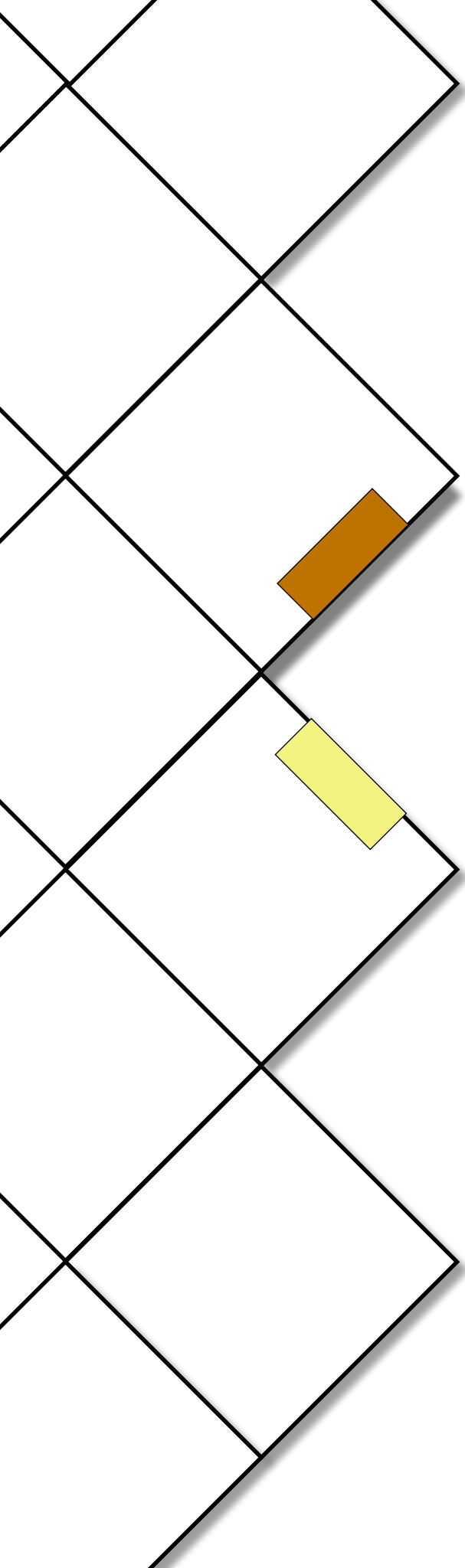
Smart self-assembly

logic gates: simple, yet powerful



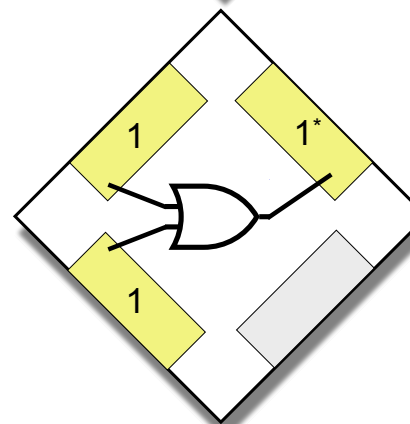
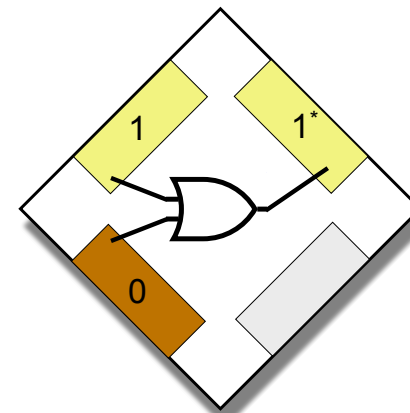
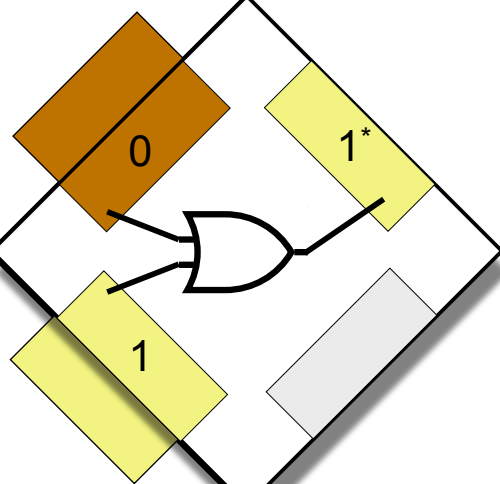
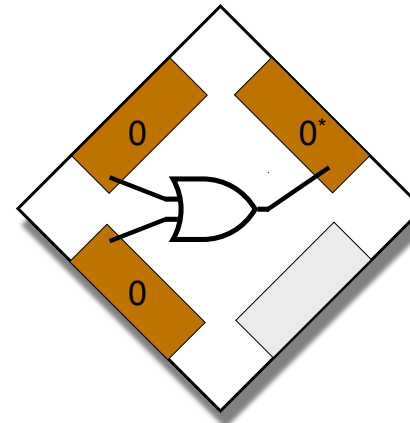
Smart self-assembly

logic gates: simple, yet powerful



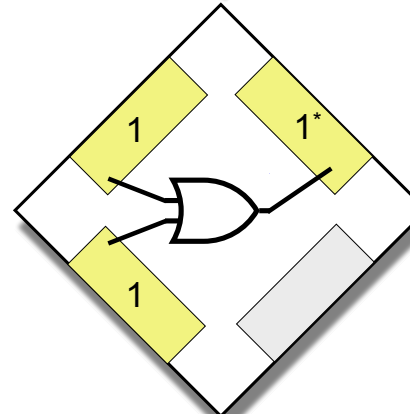
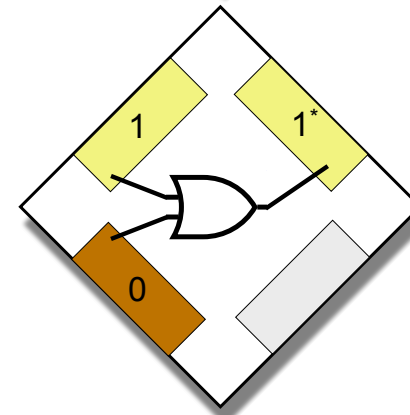
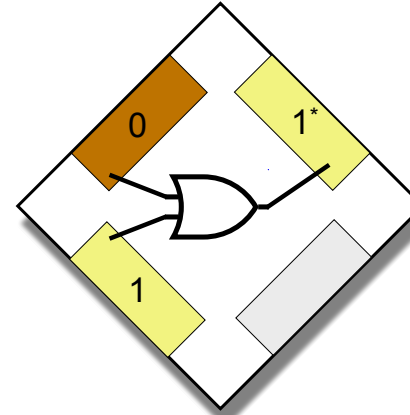
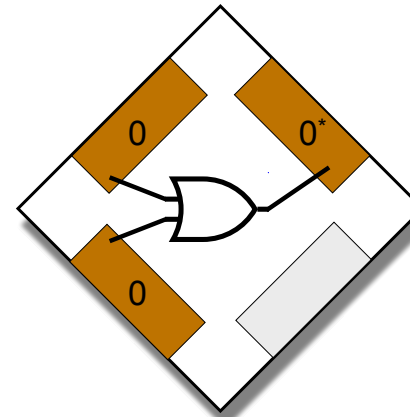
Smart self-assembly

logic gates: simple, yet powerful



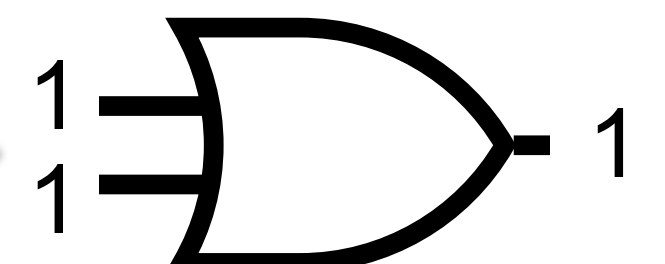
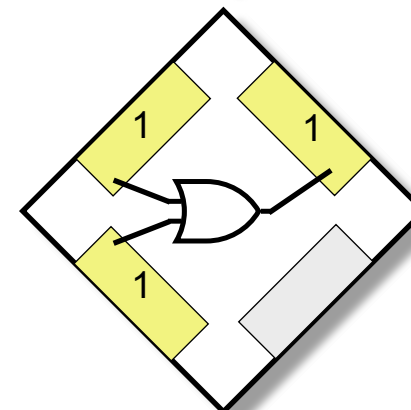
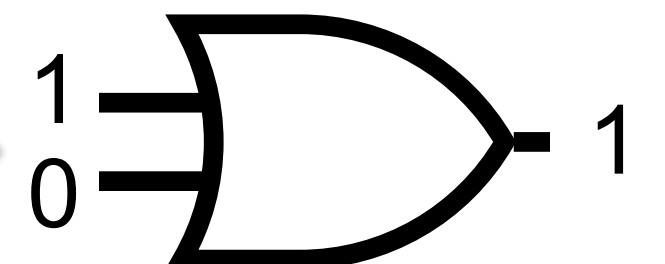
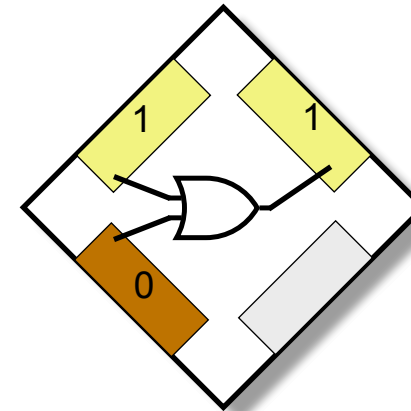
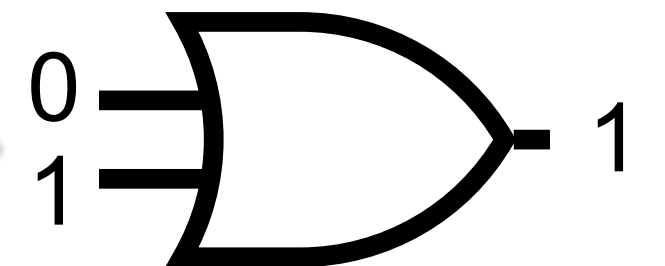
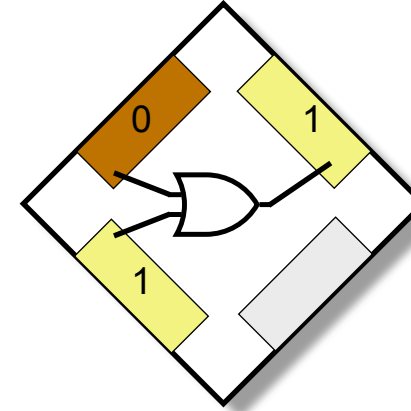
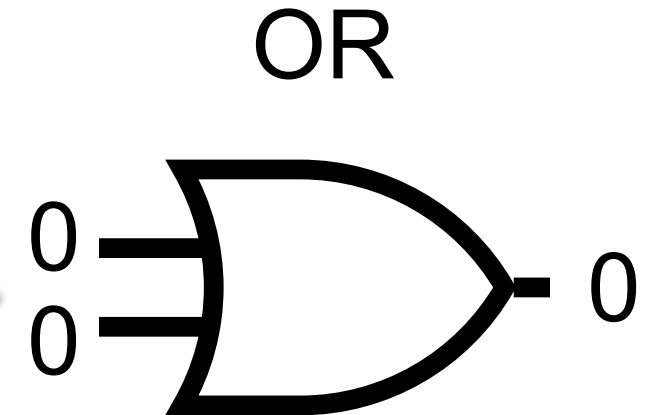
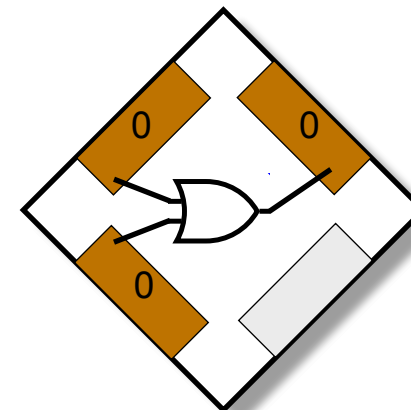
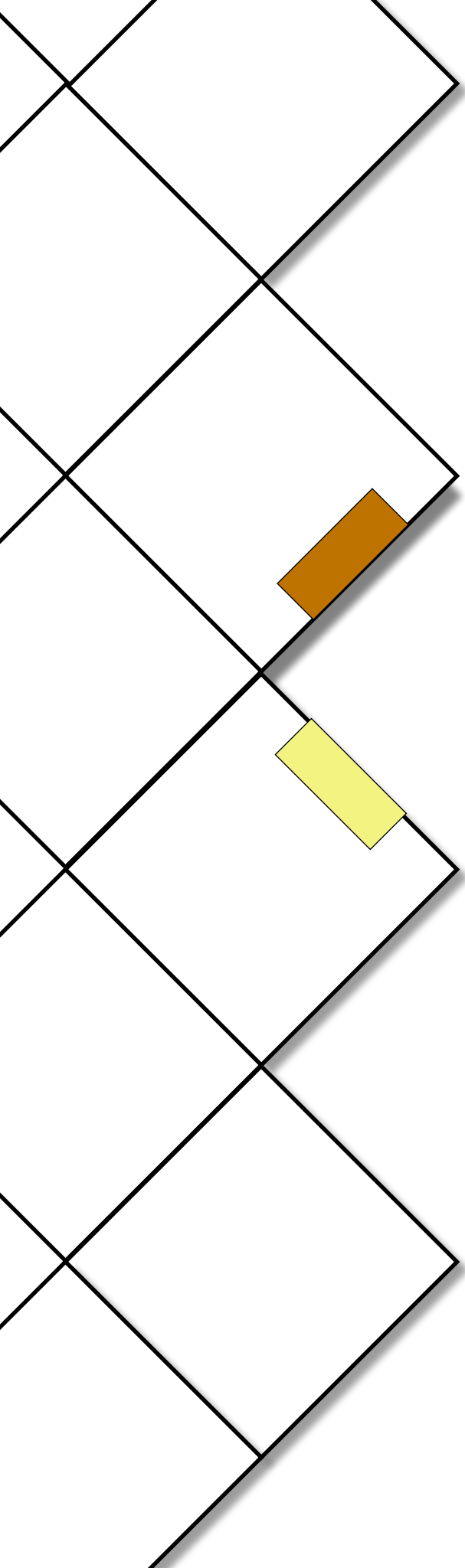
Smart self-assembly

logic gates: simple, yet powerful



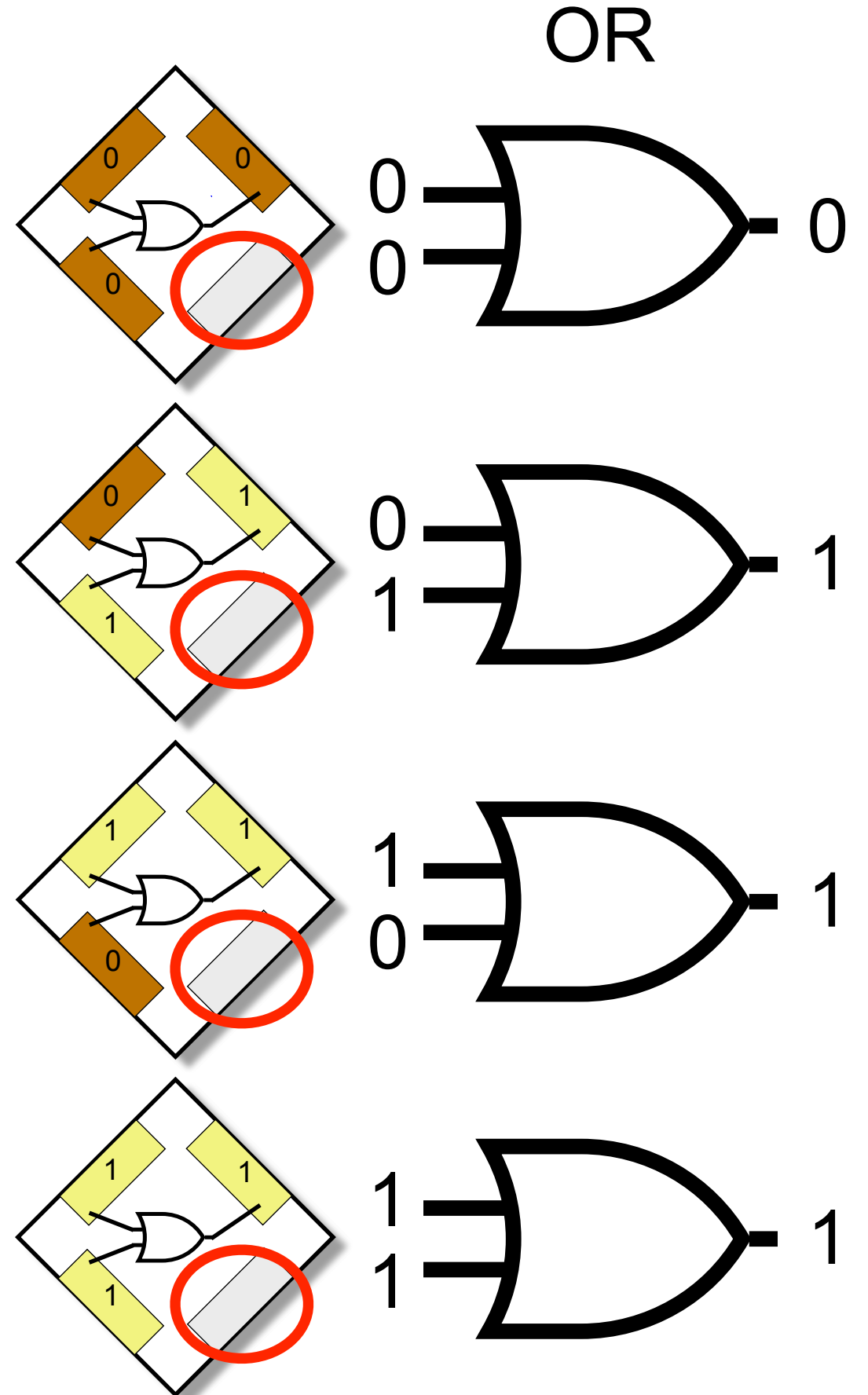
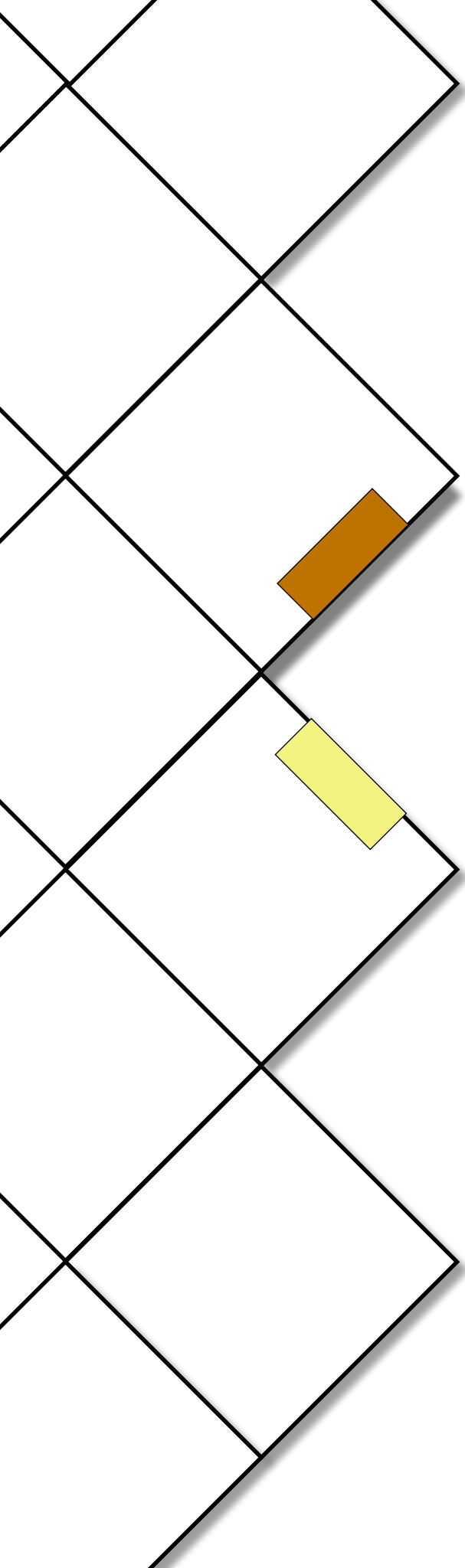
Smart self-assembly

logic gates: simple, yet powerful



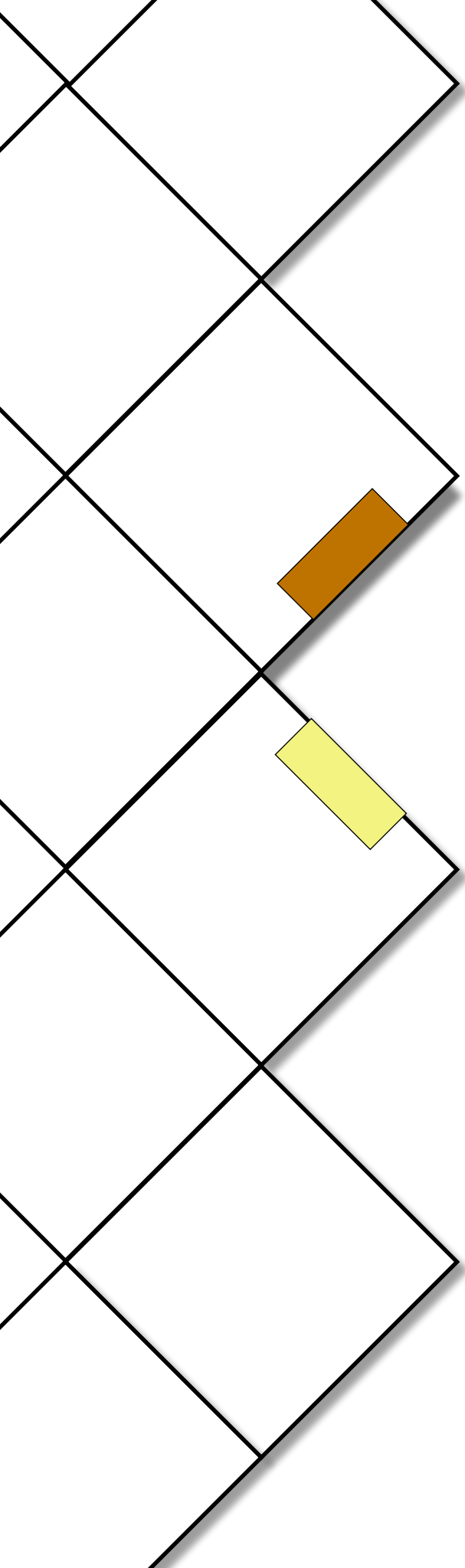
Smart self-assembly

logic gates: simple, yet powerful

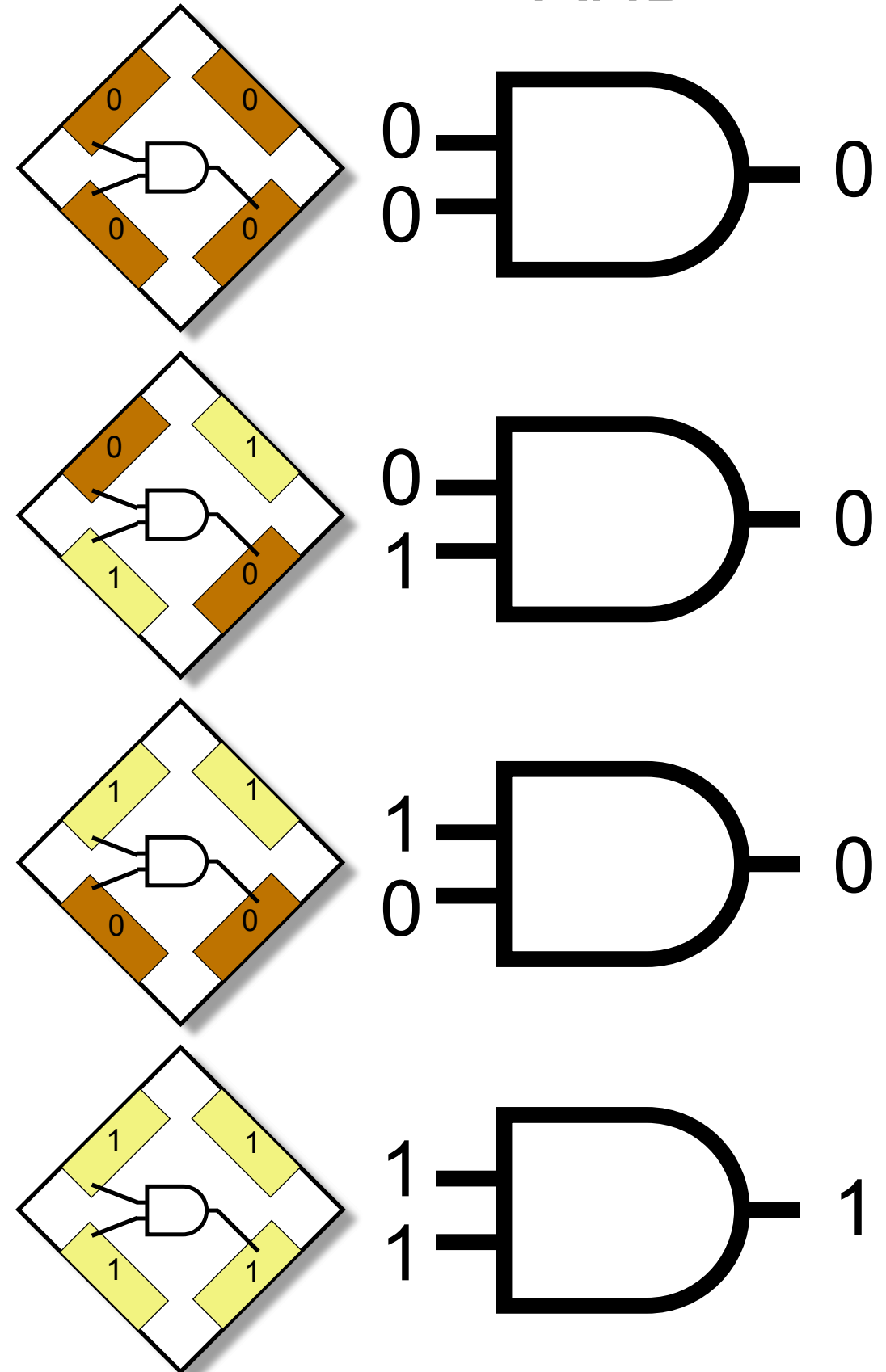


Smart self-assembly

logic gates: simple, yet powerful

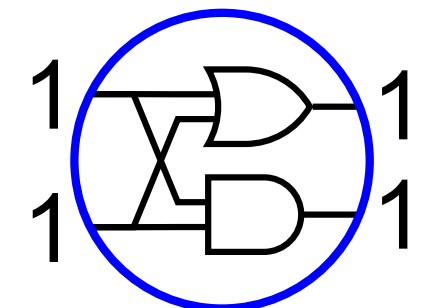
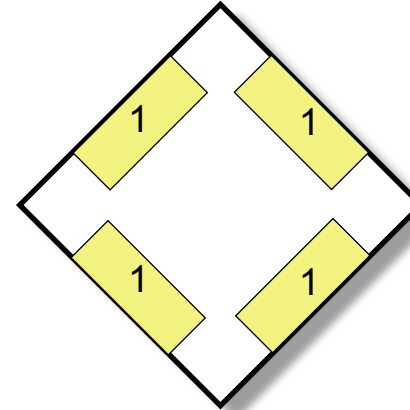
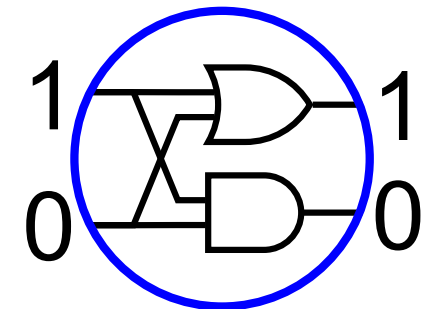
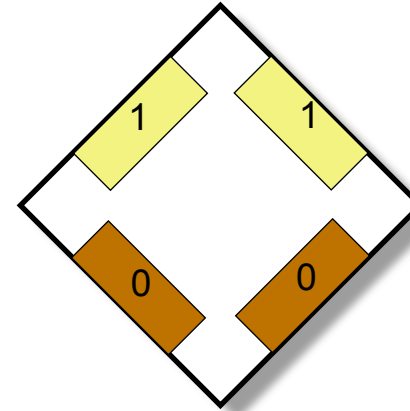
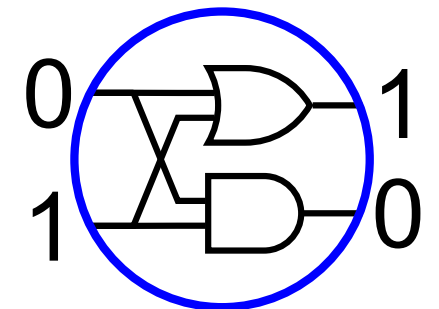
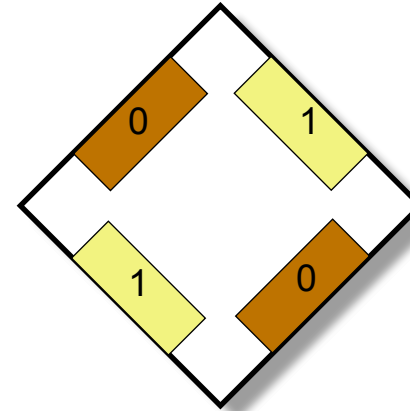
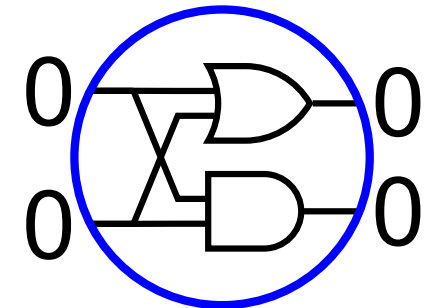
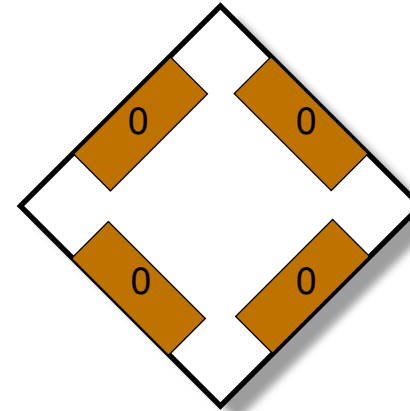
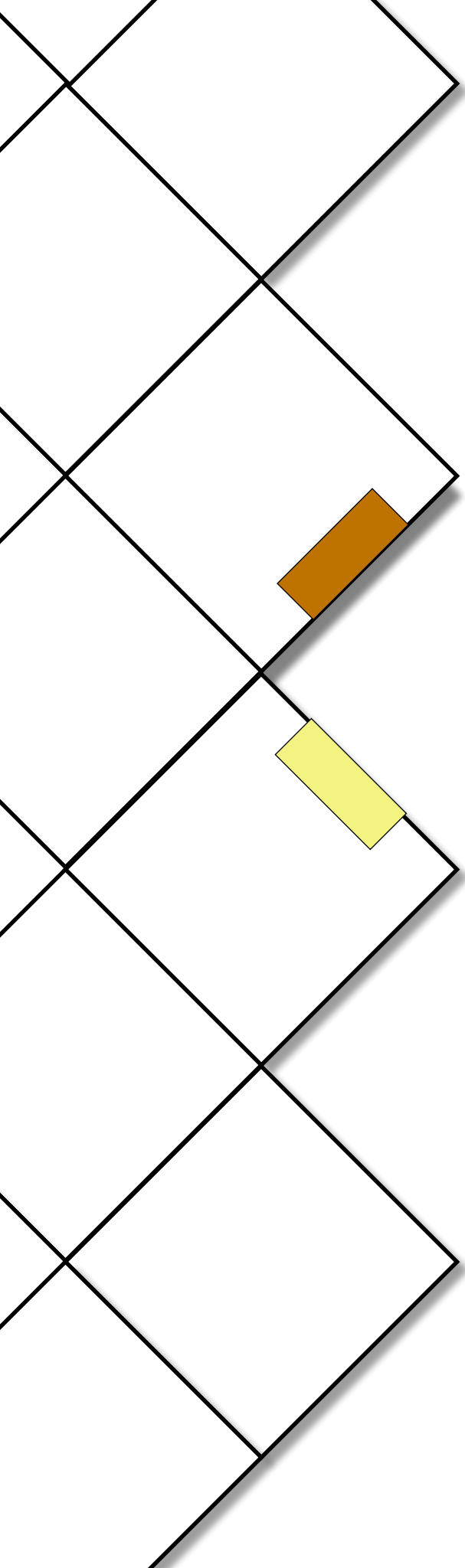


AND



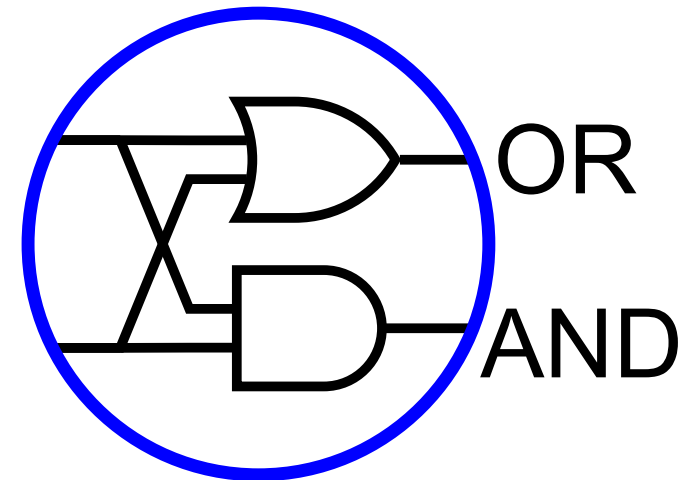
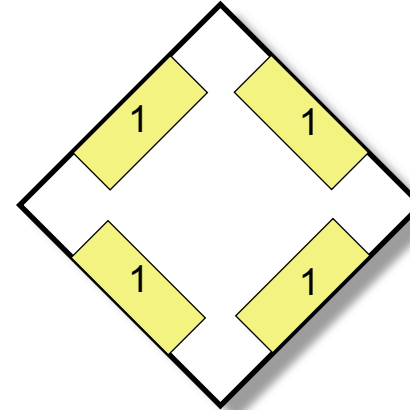
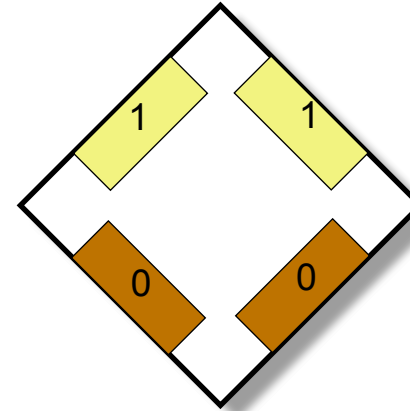
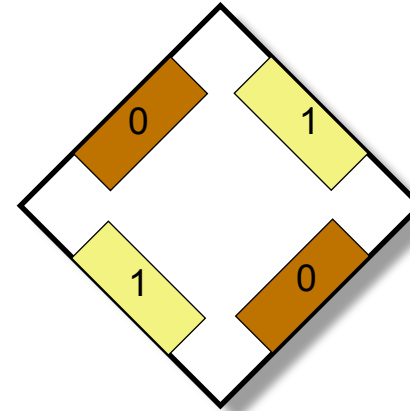
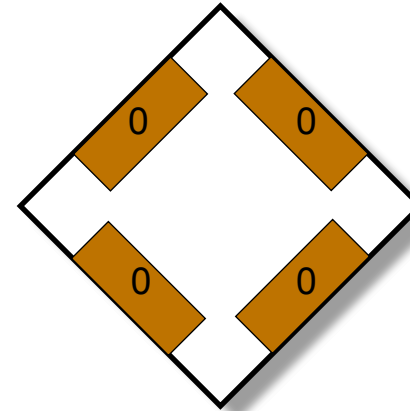
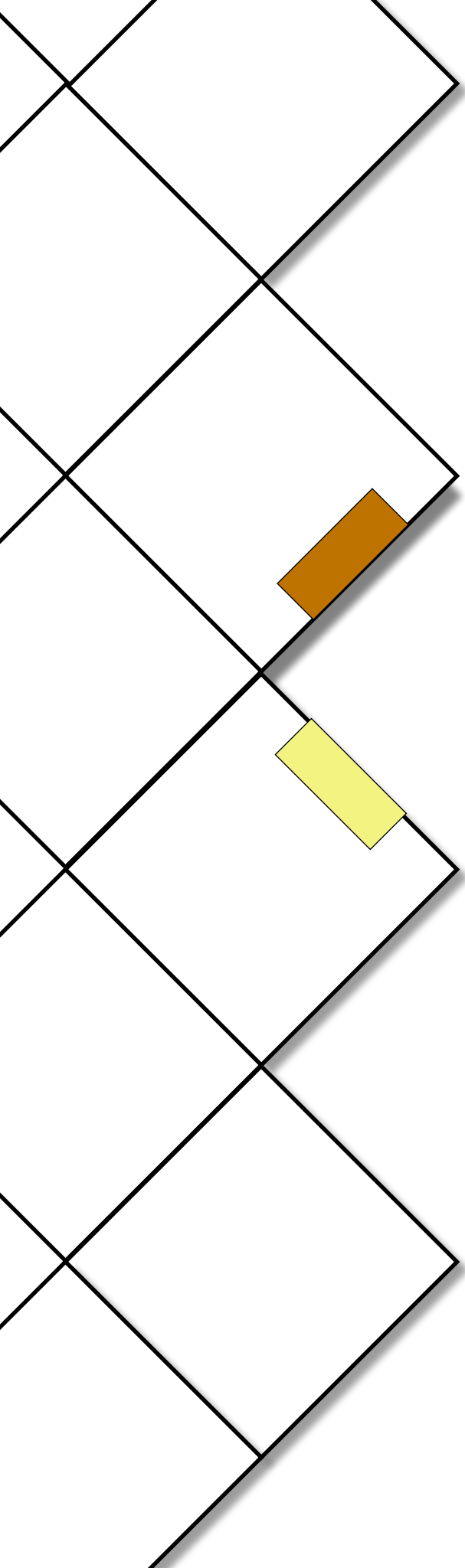
Smart self-assembly

logic gates: simple, yet powerful

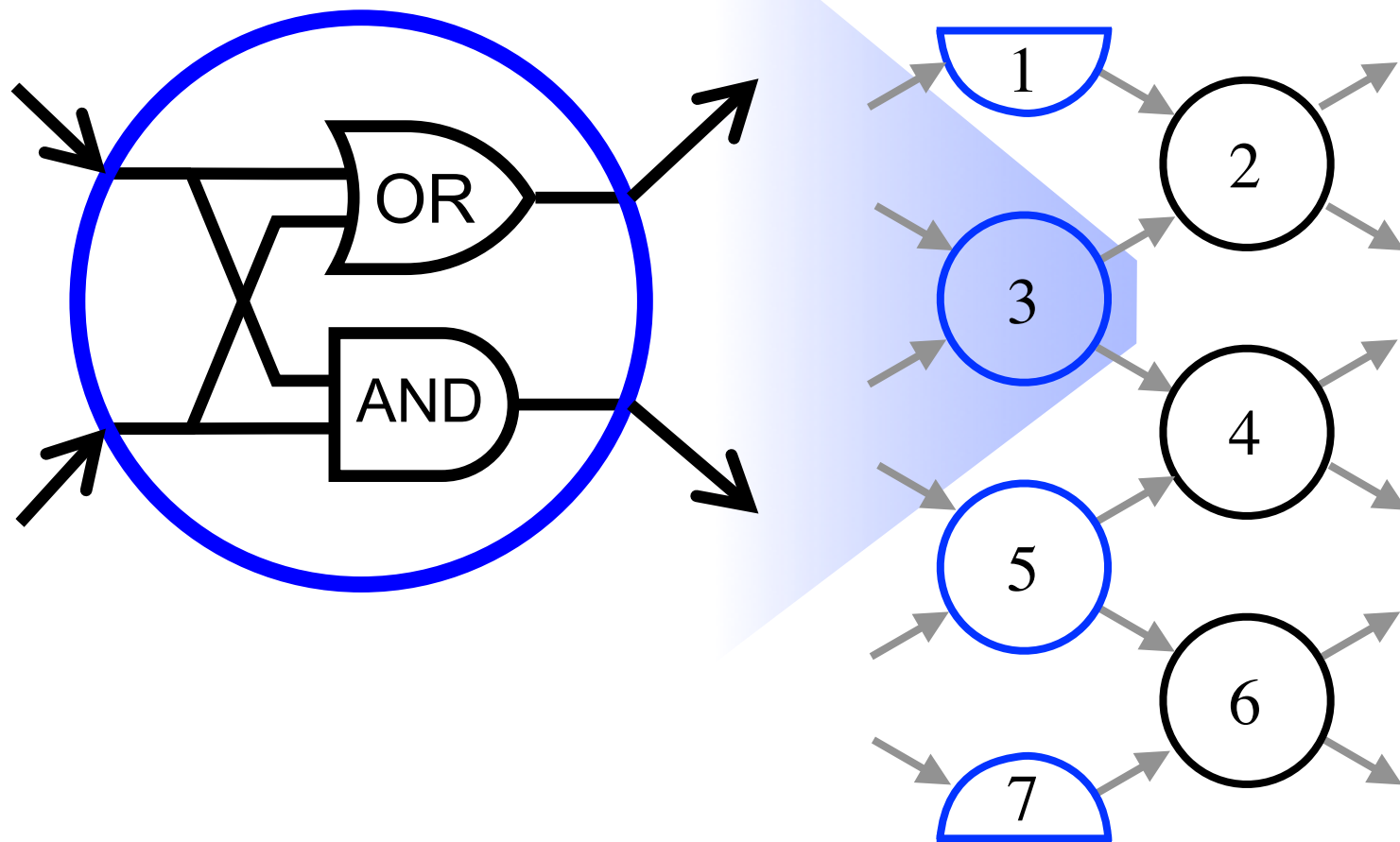


Smart self-assembly

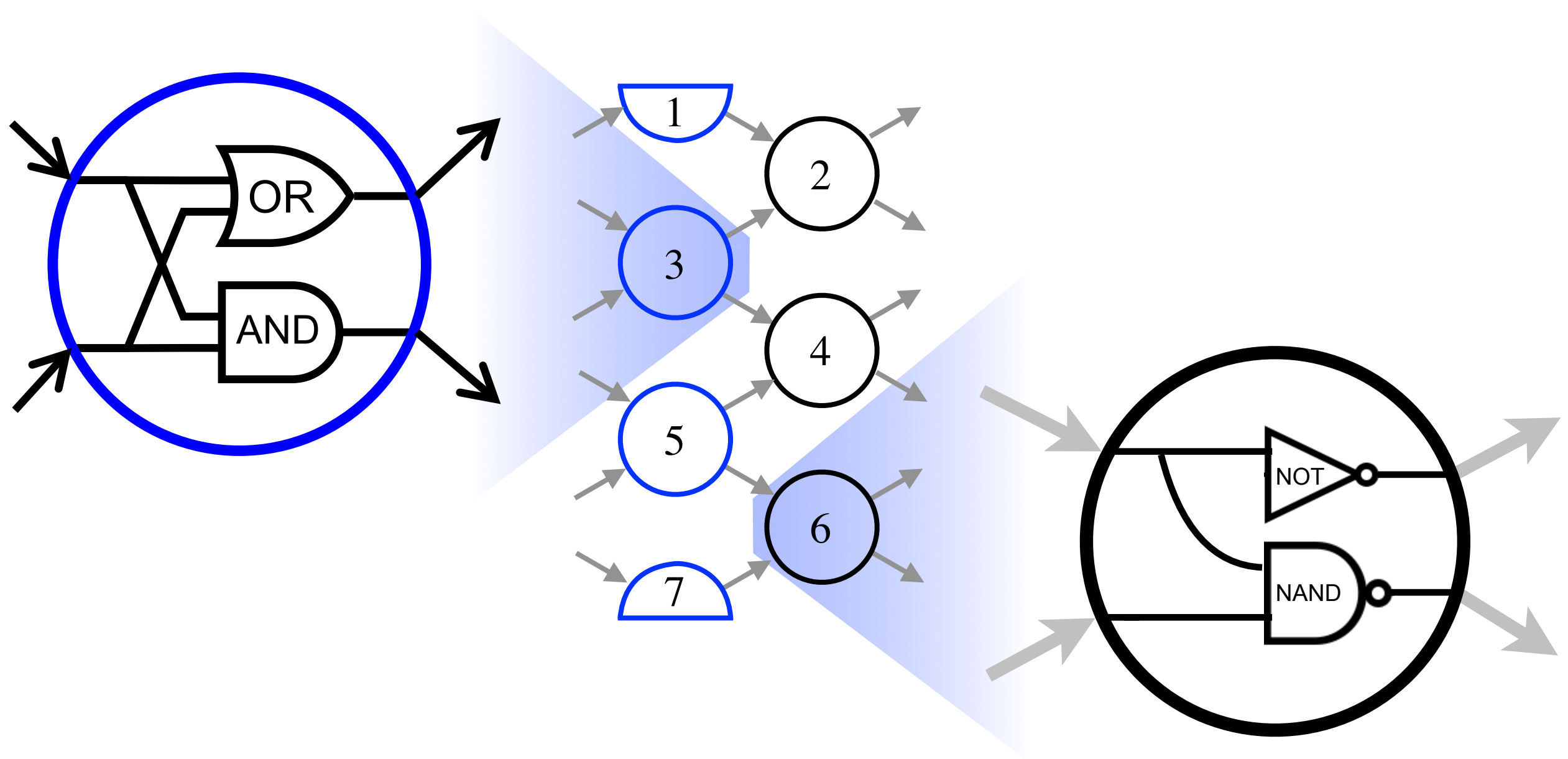
logic gates: simple, yet powerful



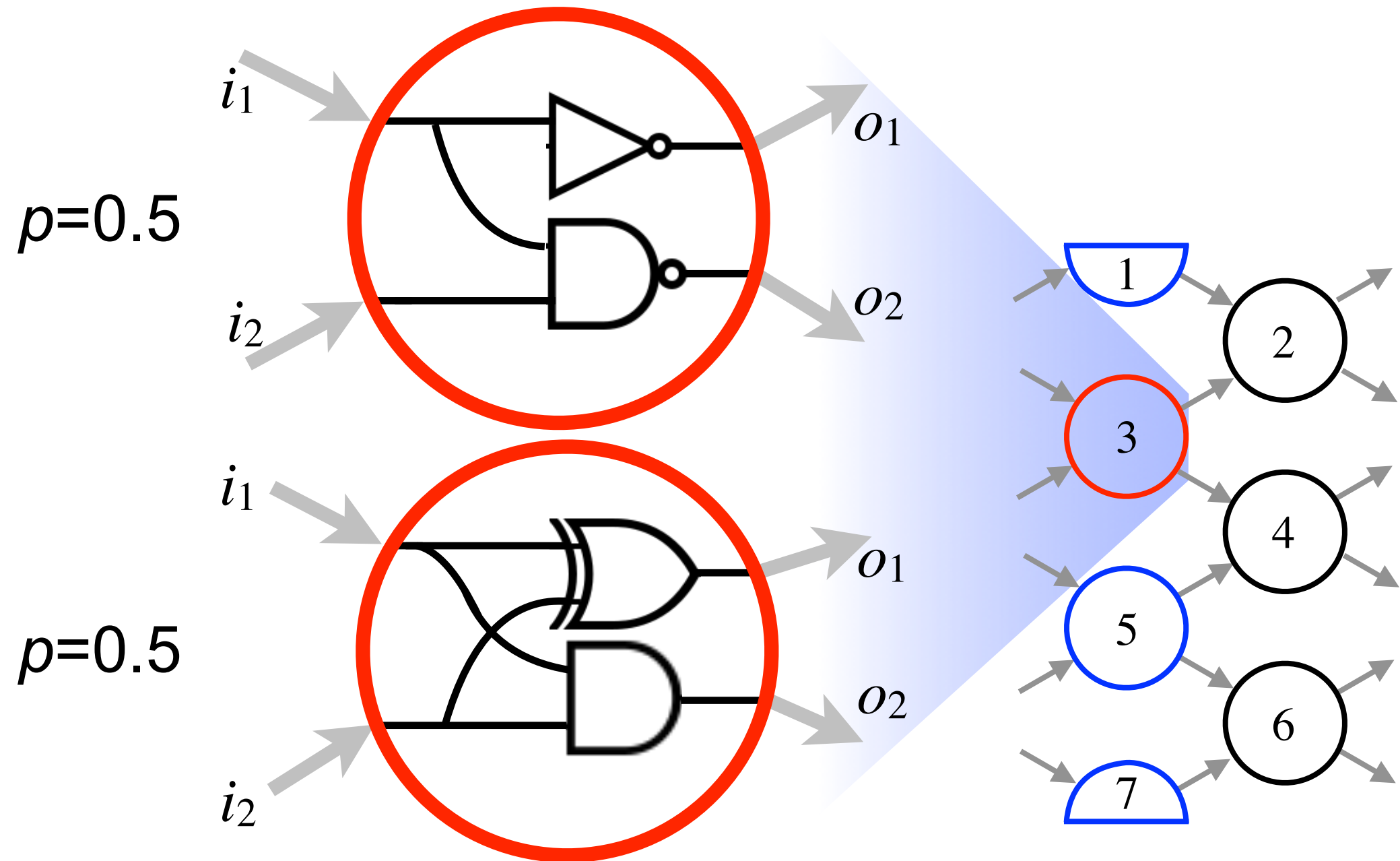
A local Boolean circuit model



A local Boolean circuit model

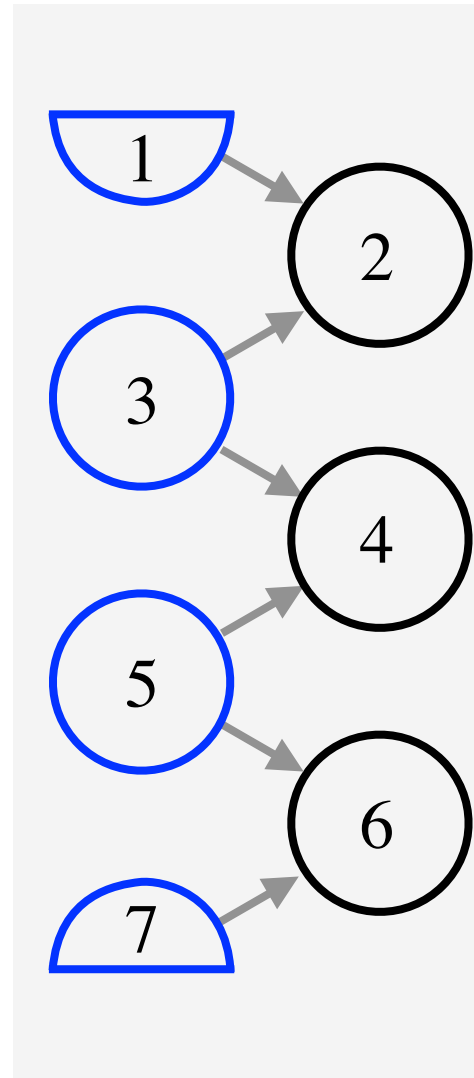


A local circuit model: randomised gates



A local Boolean circuit model

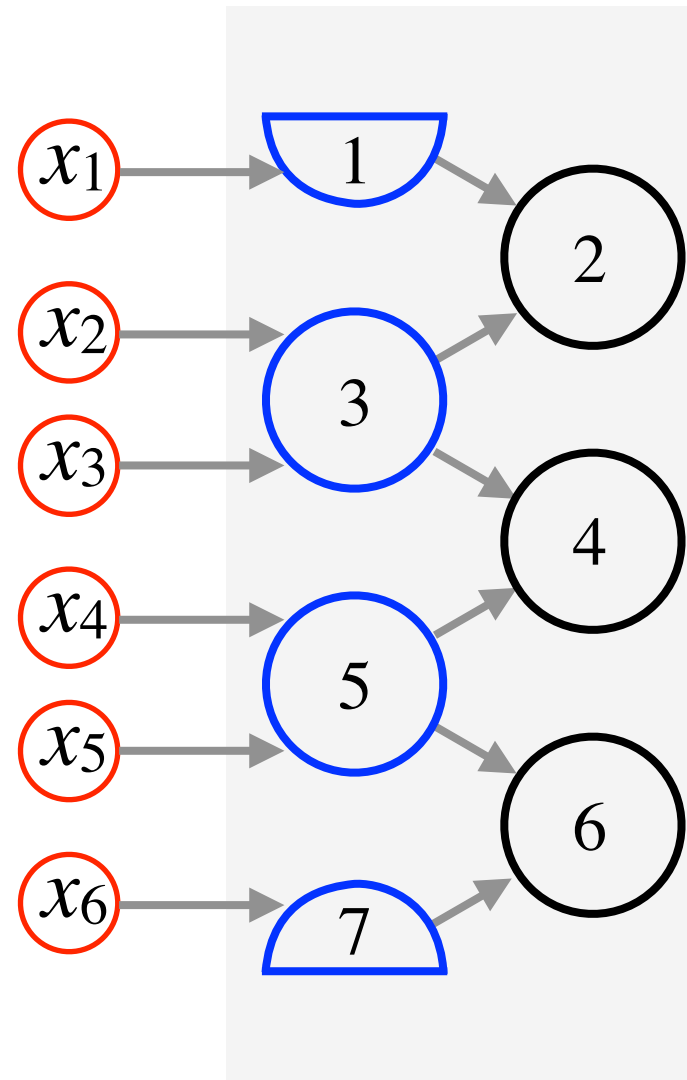
Programmer
specifies a layer



A local Boolean circuit model

Programmer
specifies a layer

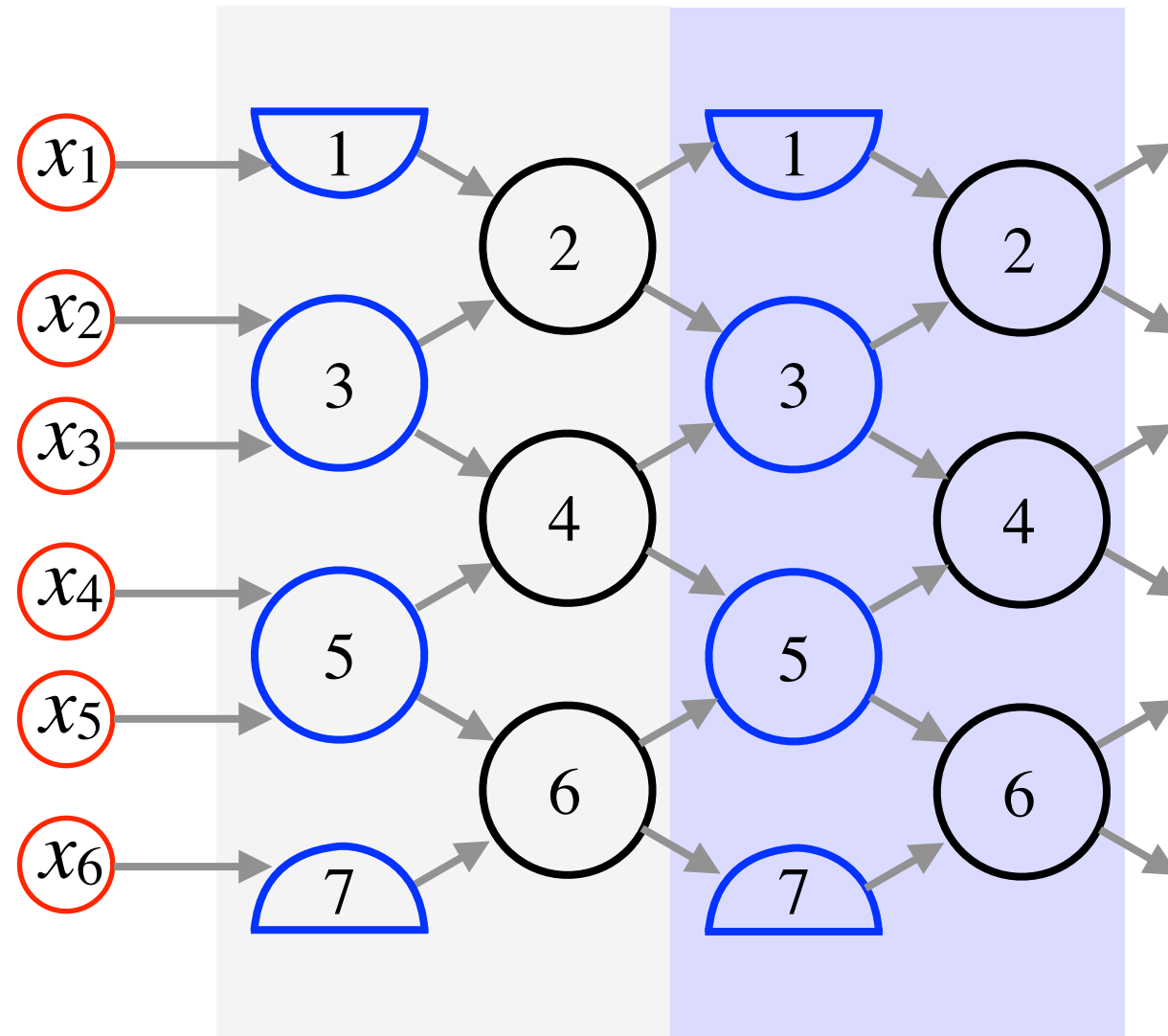
User gives n input
bits $x_k \in \{0,1\}$



A local Boolean circuit model

Programmer
specifies a layer

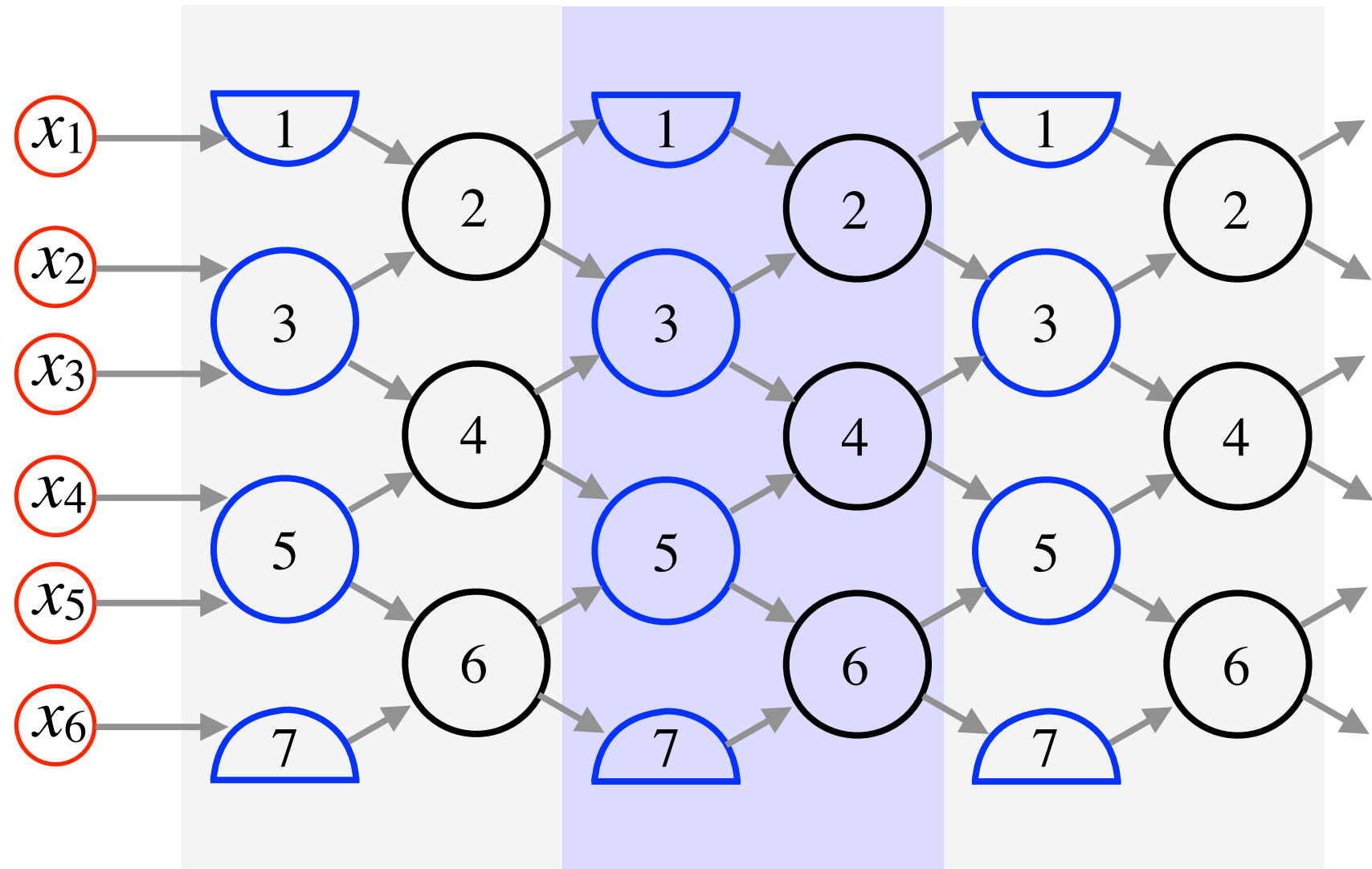
User gives n input
bits $x_k \in \{0,1\}$



A local Boolean circuit model

Programmer
specifies a layer

User gives n input
bits $x_k \in \{0,1\}$

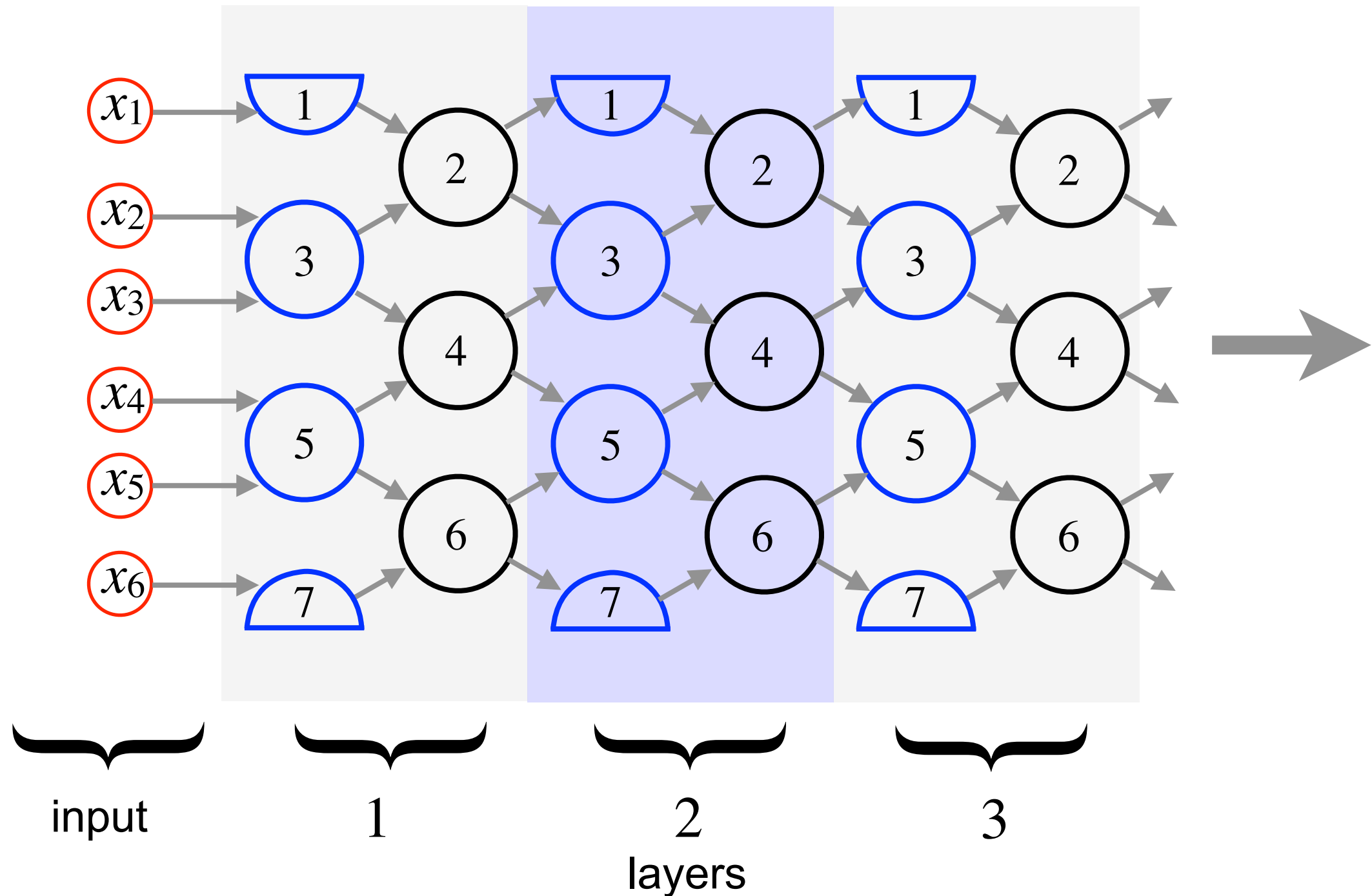


A local Boolean circuit model

Programmer
specifies a layer

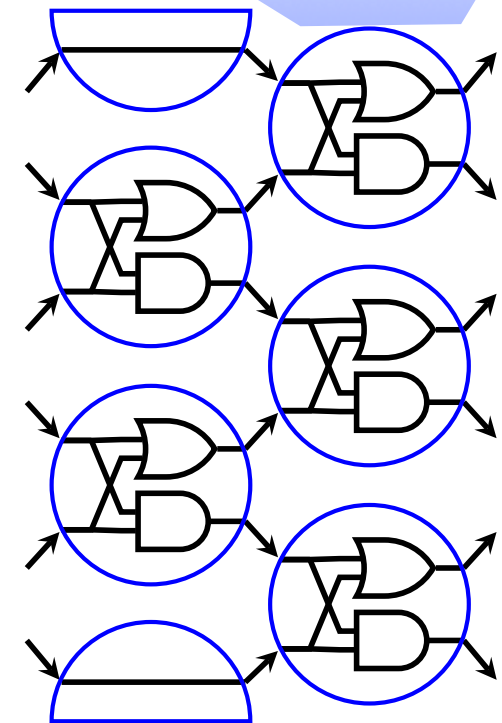
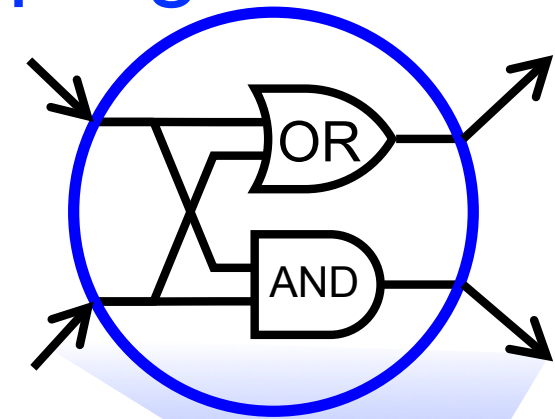
User gives n input
bits $x_k \in \{0,1\}$

Computation flows
from input gates to
layer 1, layer 2,
layer 3 ...

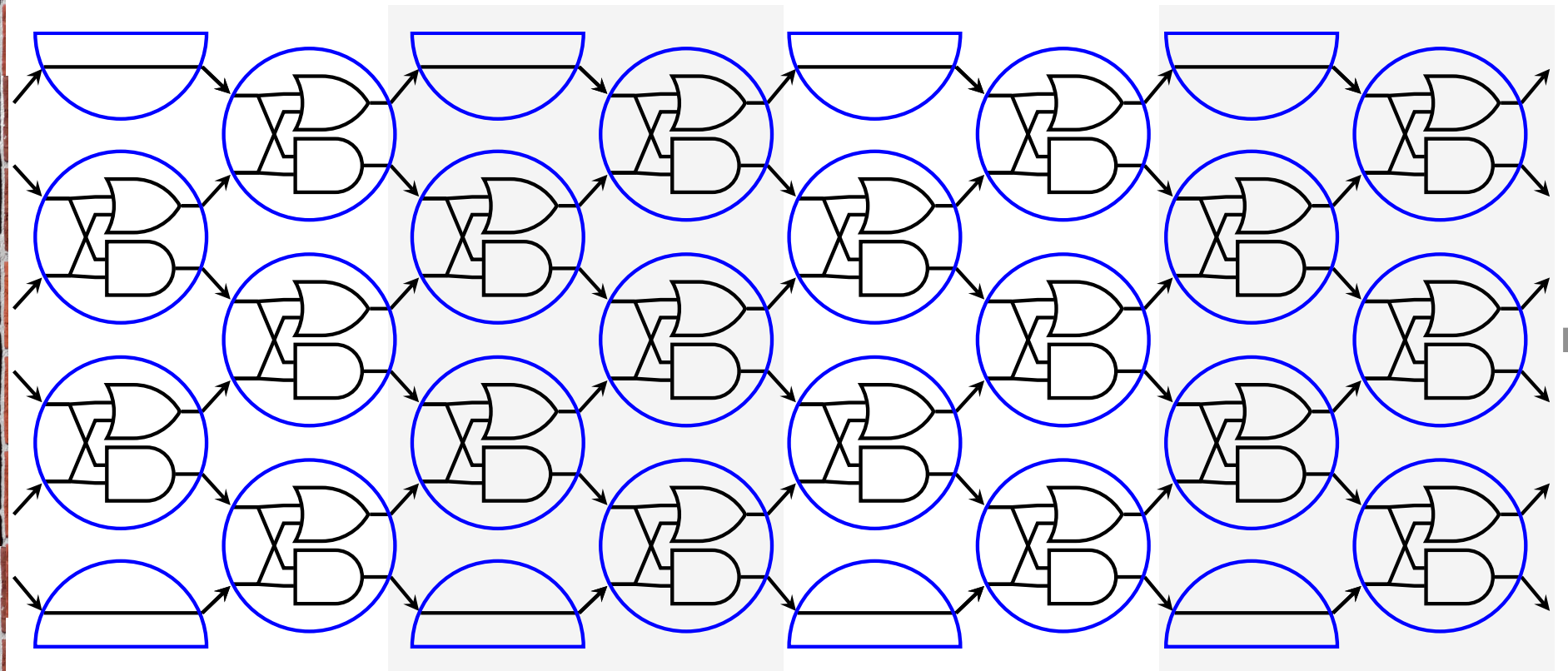


Example circuit

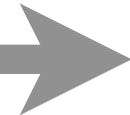
programmer



layer

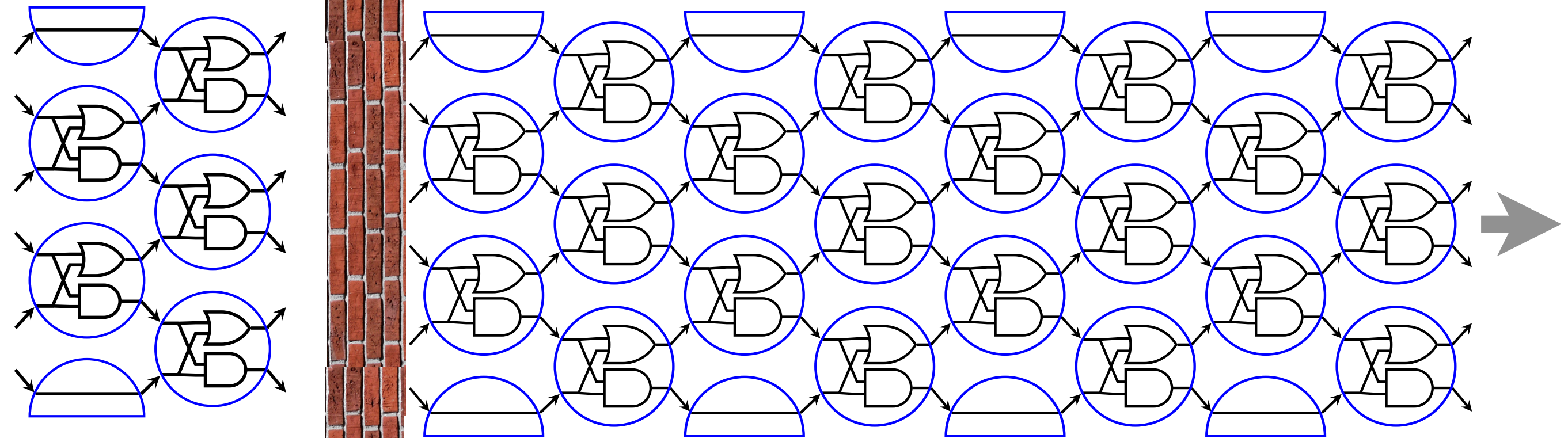


circuit



Example circuit

programmer

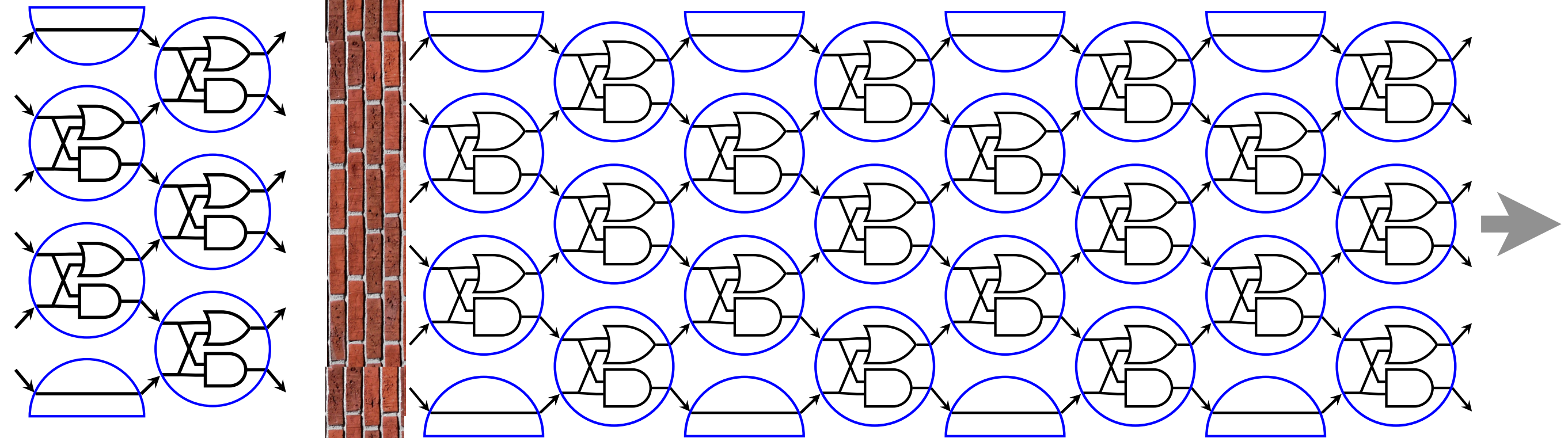


Example circuit

programmer

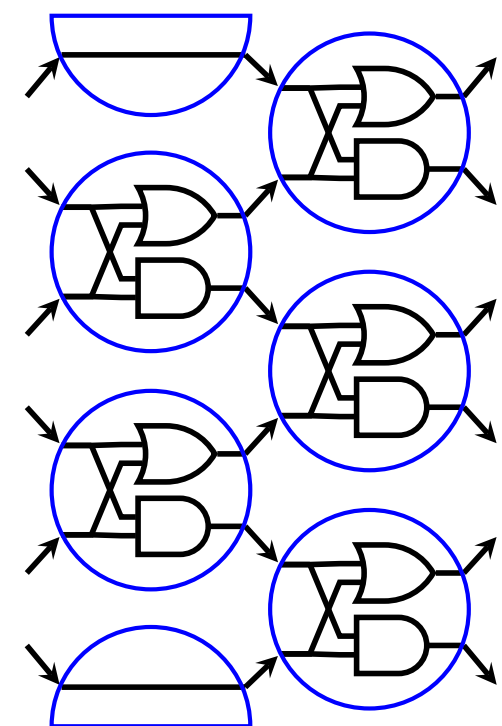
user

0
0
0
0
0
0
1



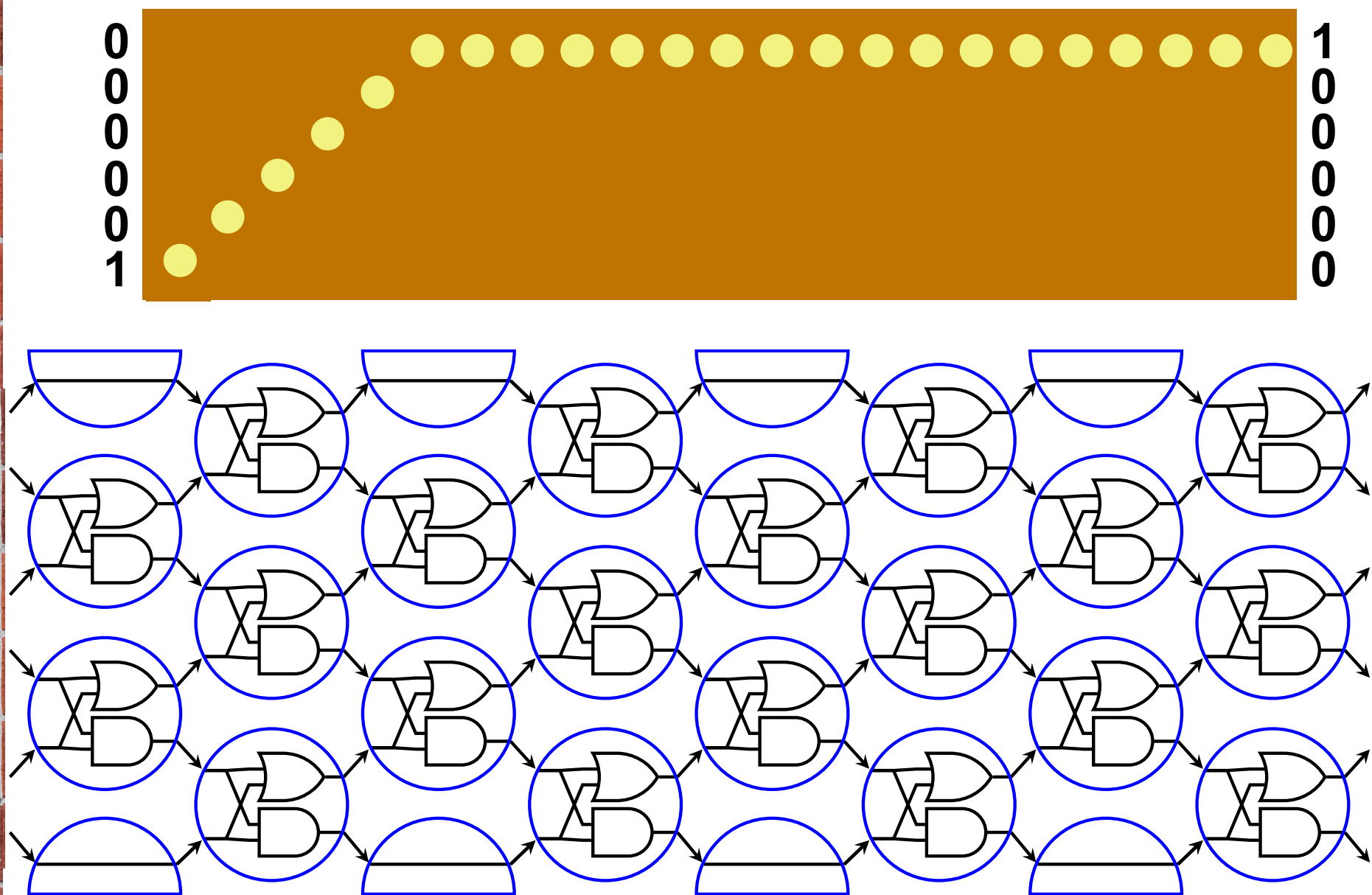
Example circuit

programmer



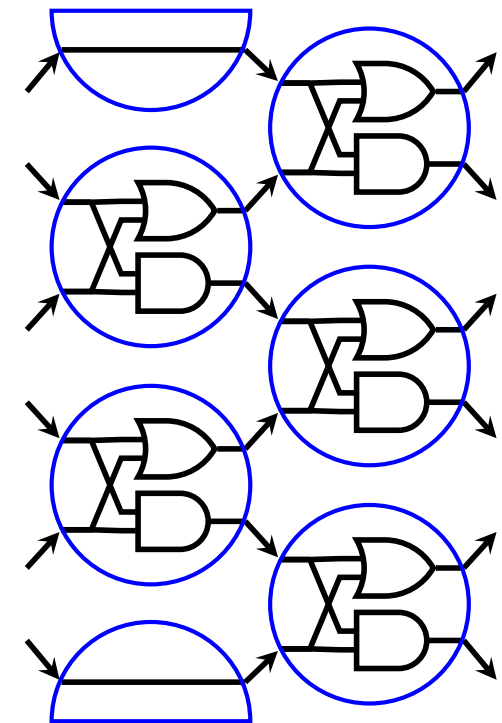
user

computation



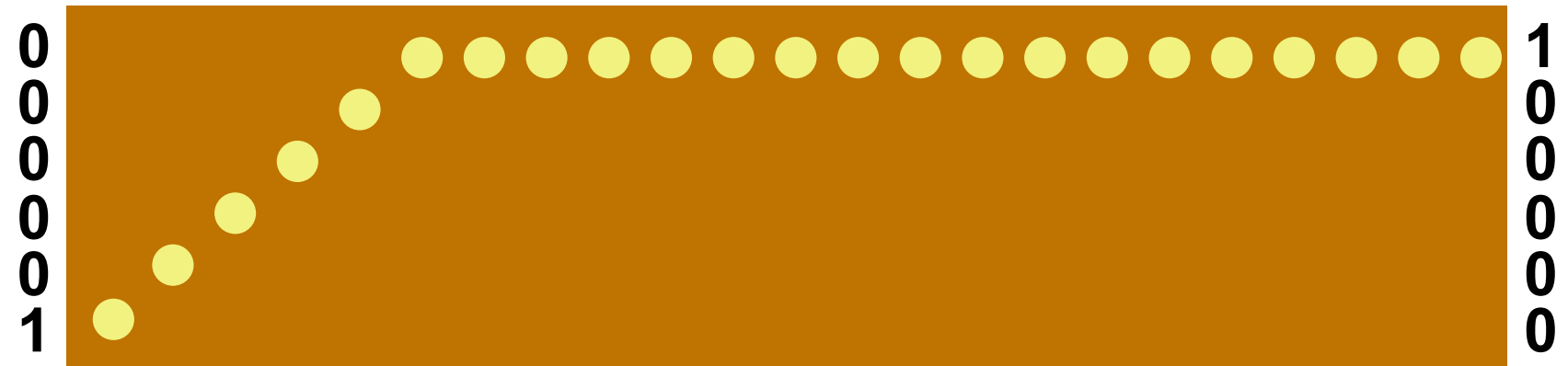
Example circuit

programmer



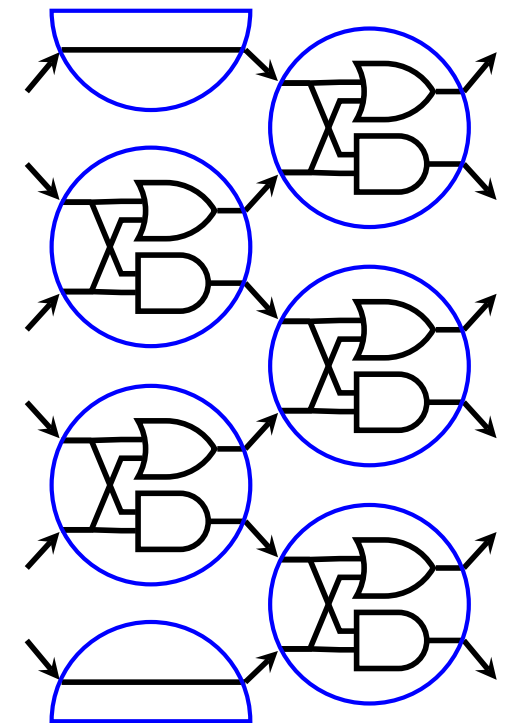
user

computation



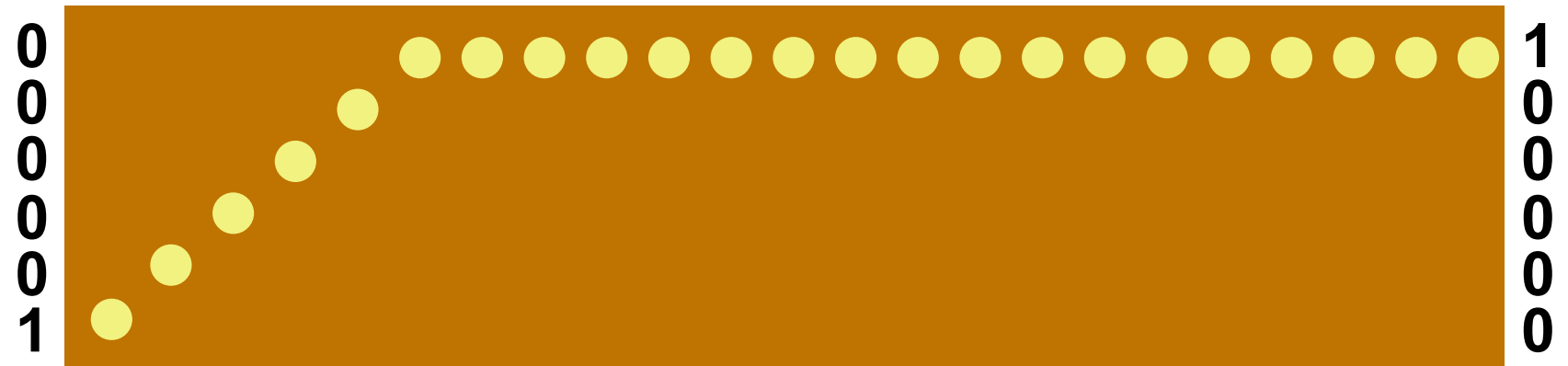
Example circuit: "SORTING"

programmer



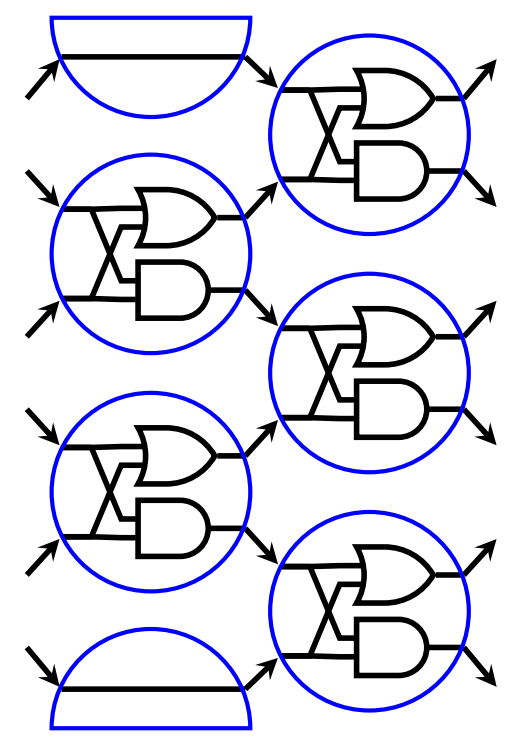
user

computation



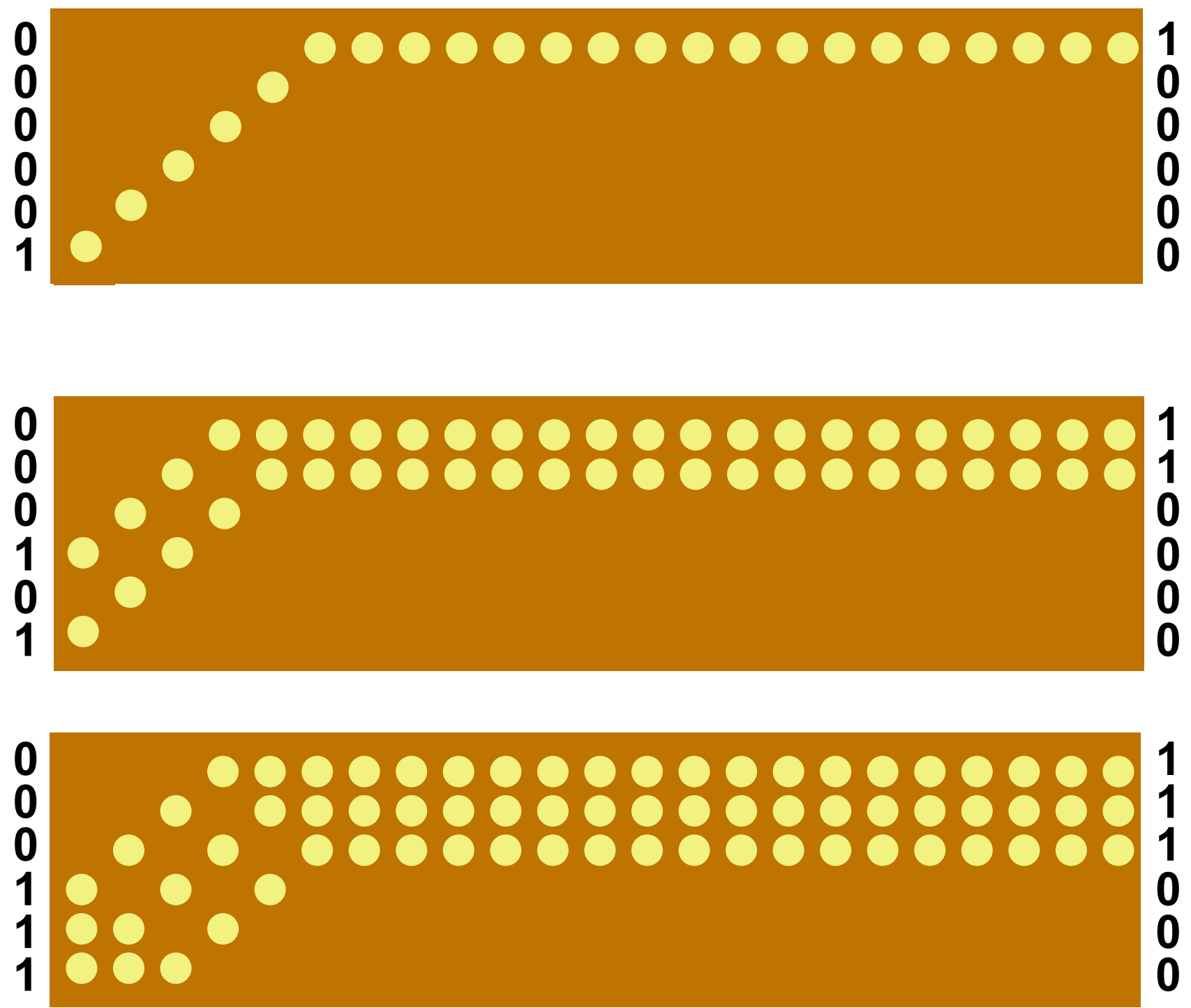
Example circuit: "SORTING"

programmer



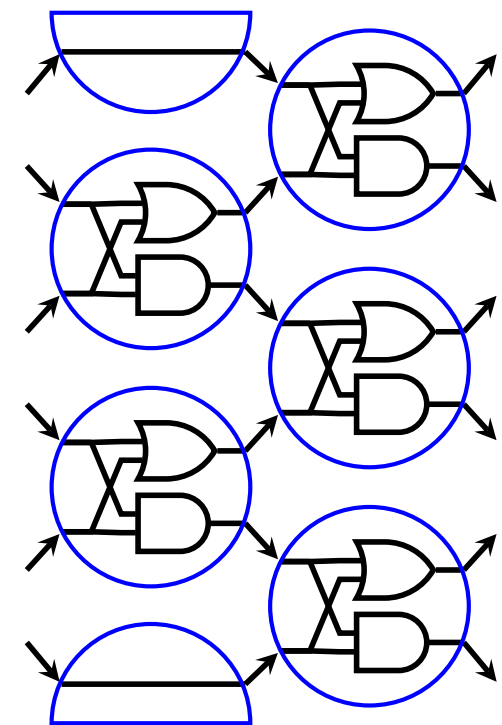
user

computation



Example circuit: "SORTING"

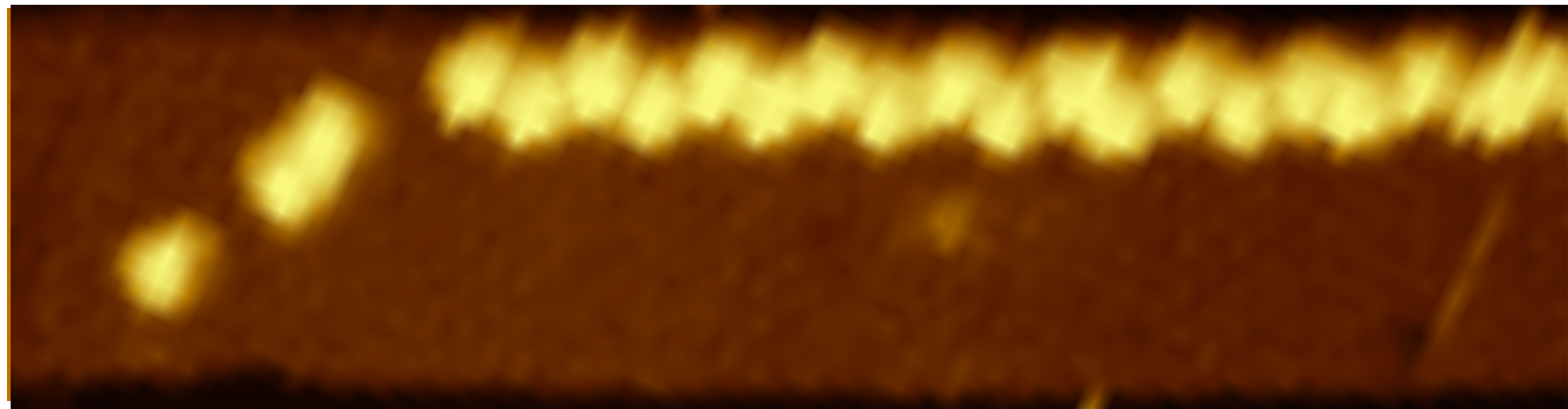
programmer



user

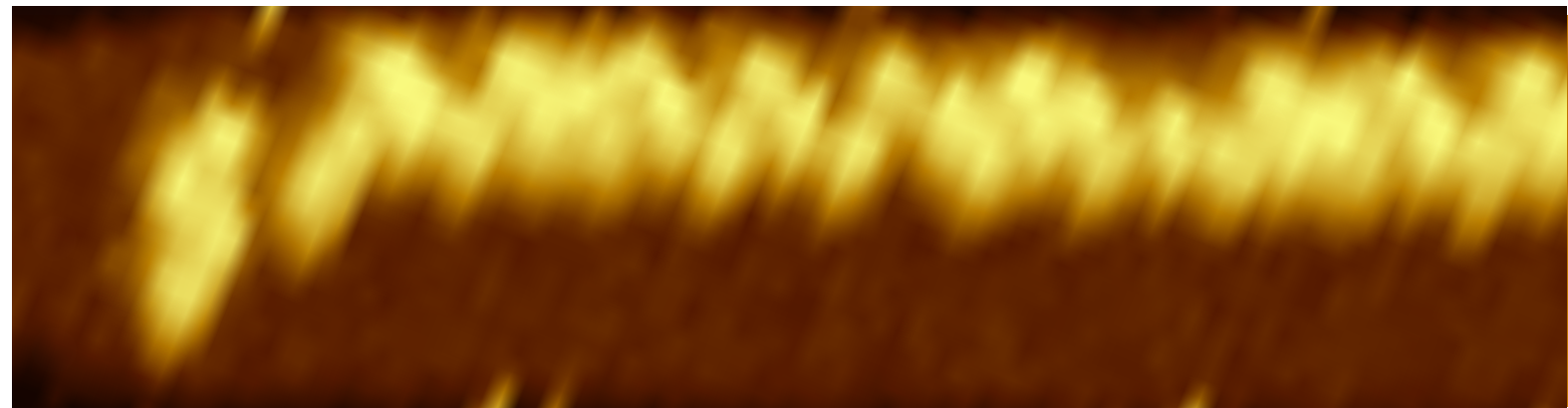
computation

0
0
0
0
0
1



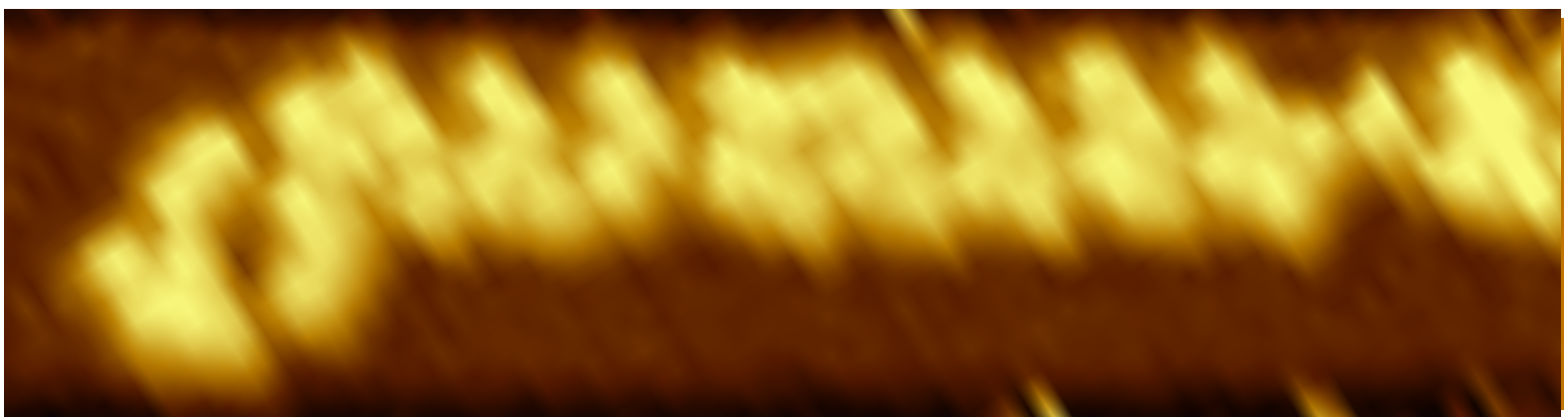
1
0
0
0
0
0

0
0
0
1
0
1



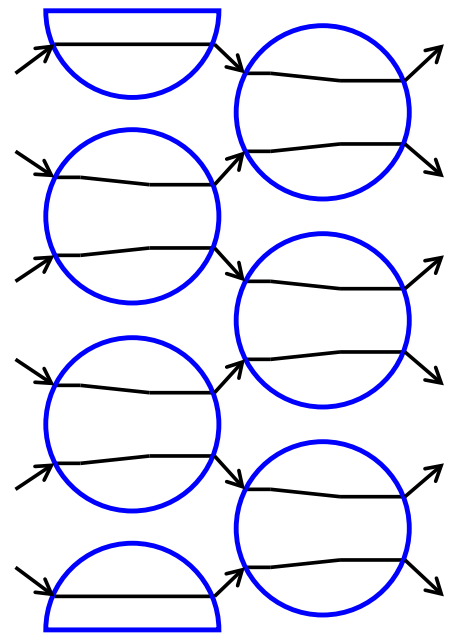
1
1
0
0
0
0

0
0
0
1
1
1



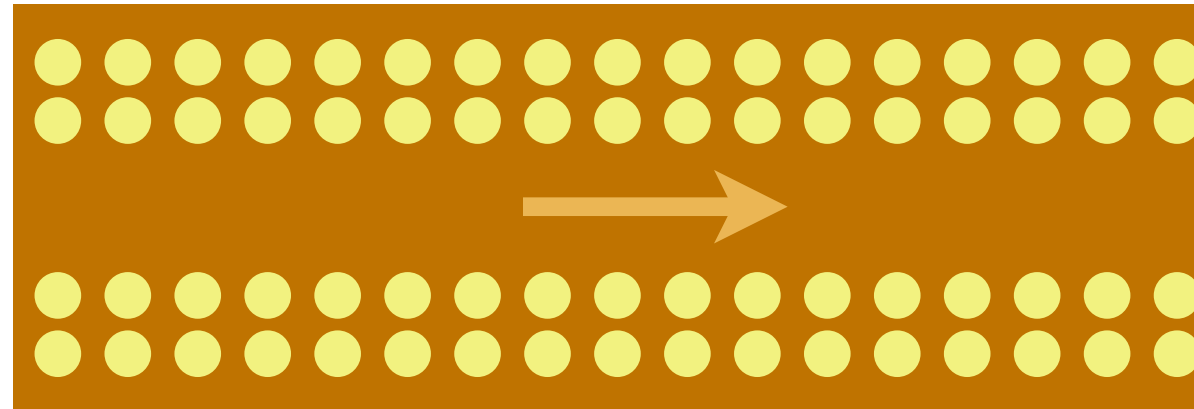
1
1
1
0
0
0

Example circuit: COPY bits to the right



input

1
1
0
0
1
1

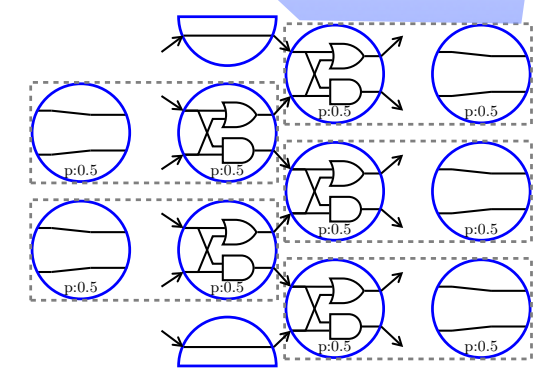
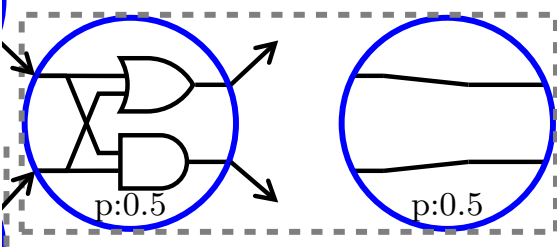


output

1
1
0
0
1
1

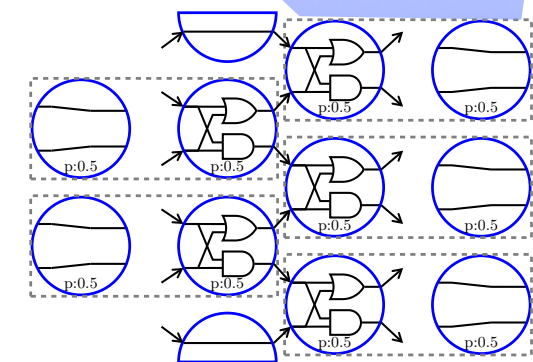
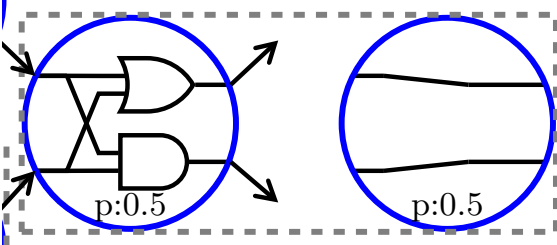
Example circuit: LAZYSORTING

programmer



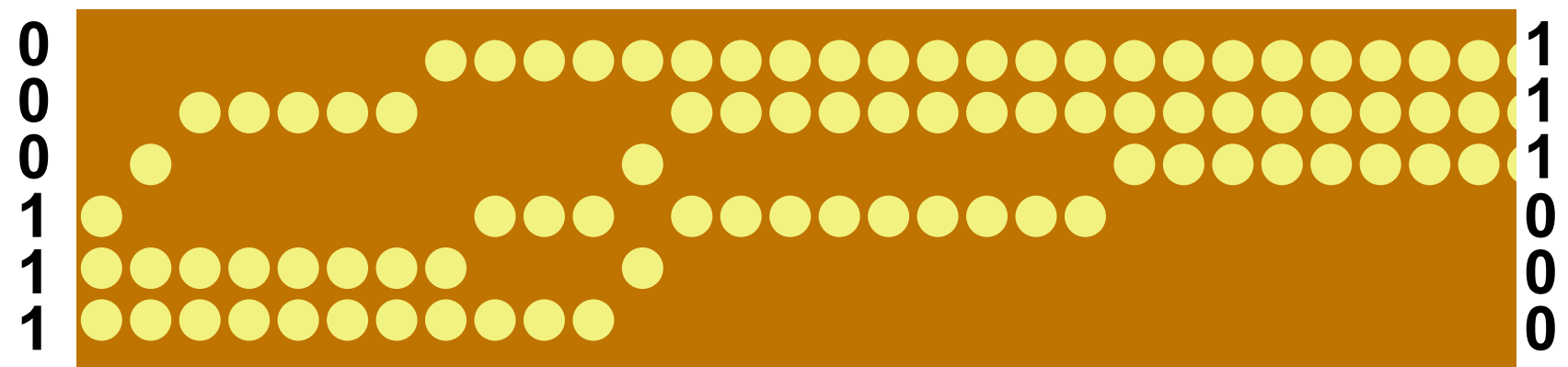
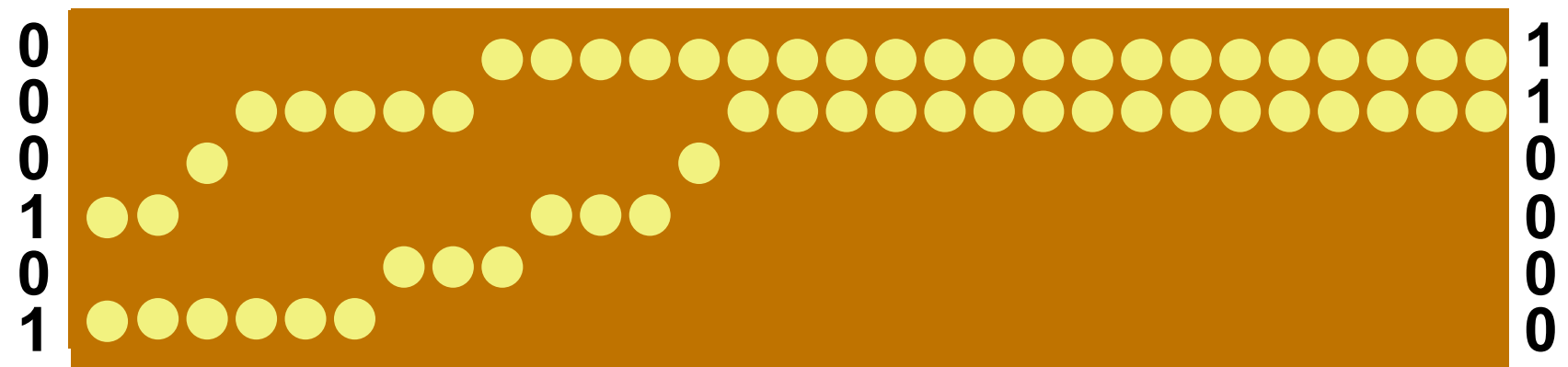
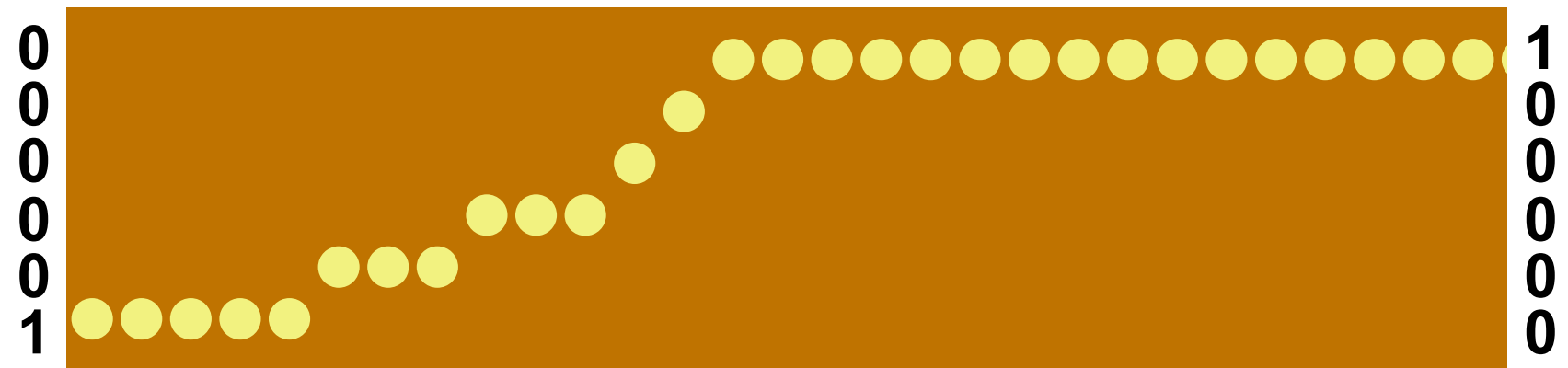
Example circuit: LAZYSORTING

programmer



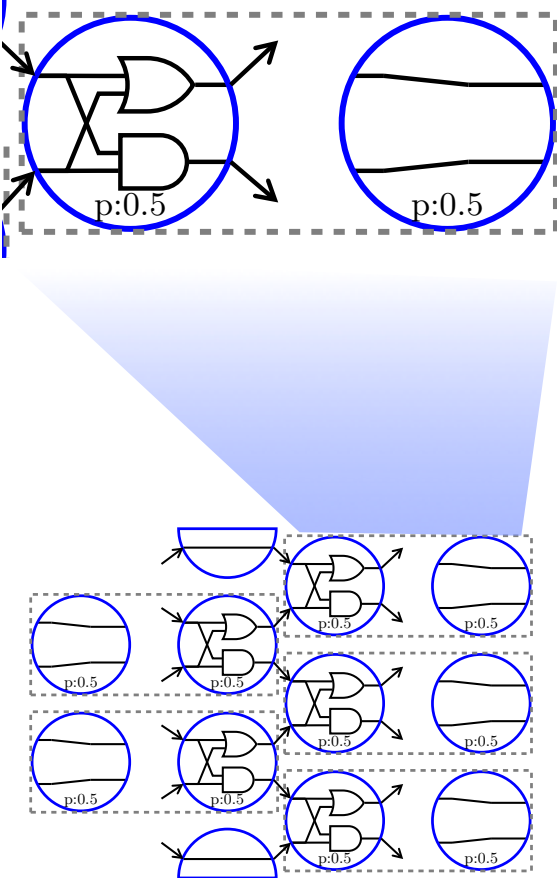
user

computation



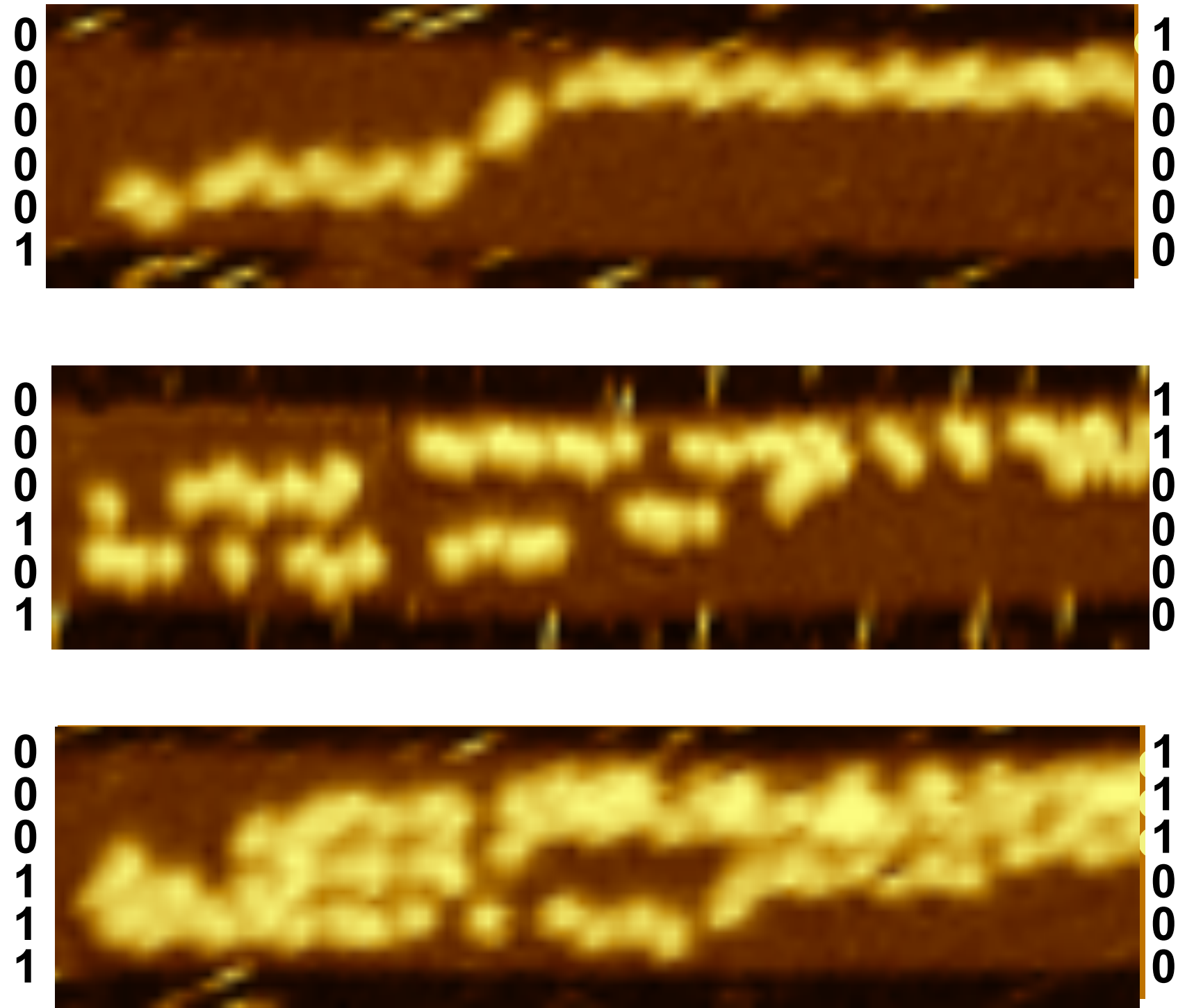
Example circuit: LAZYSORTING

programmer

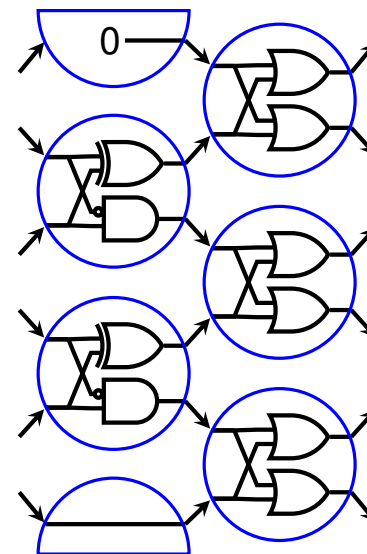


user

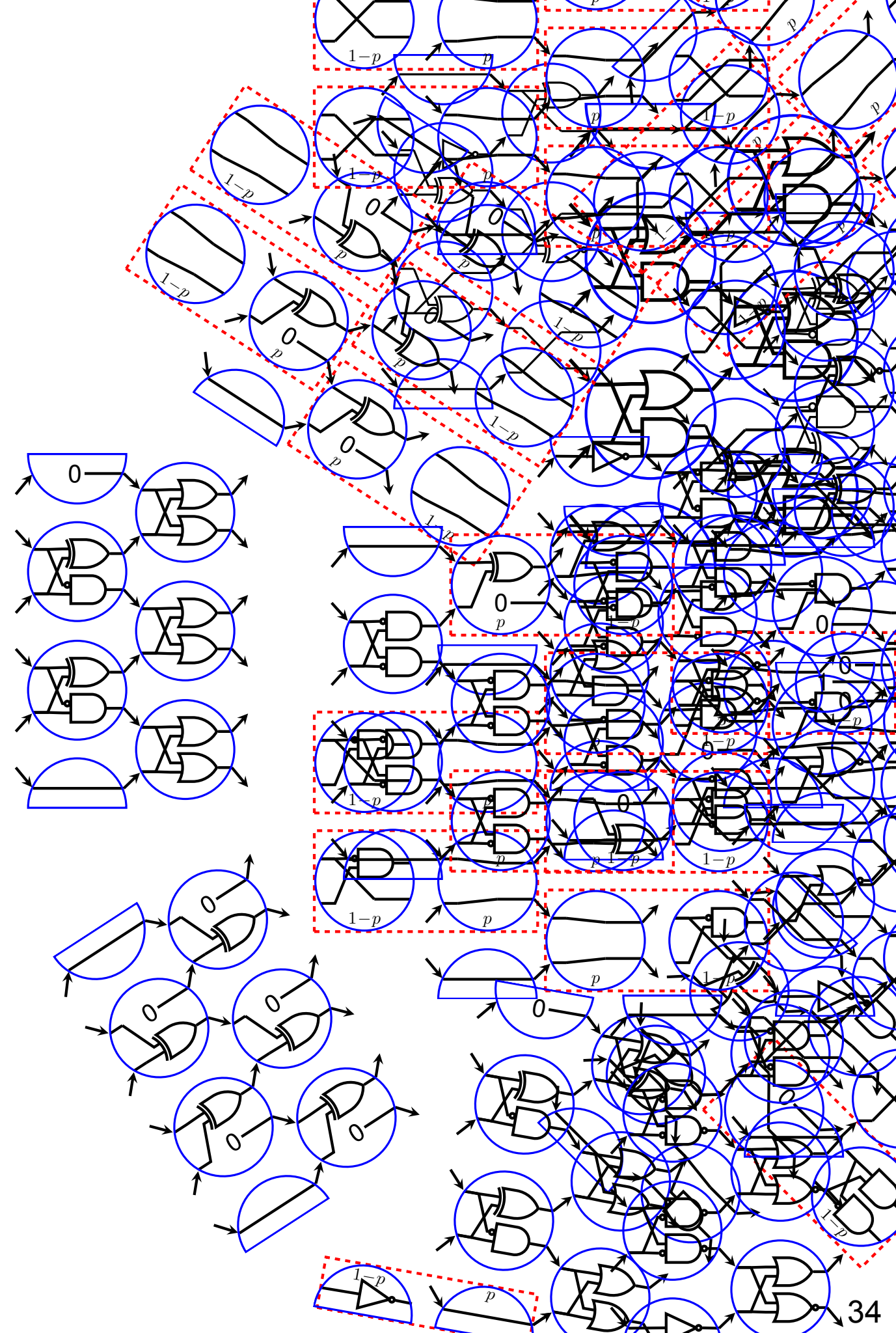
computation



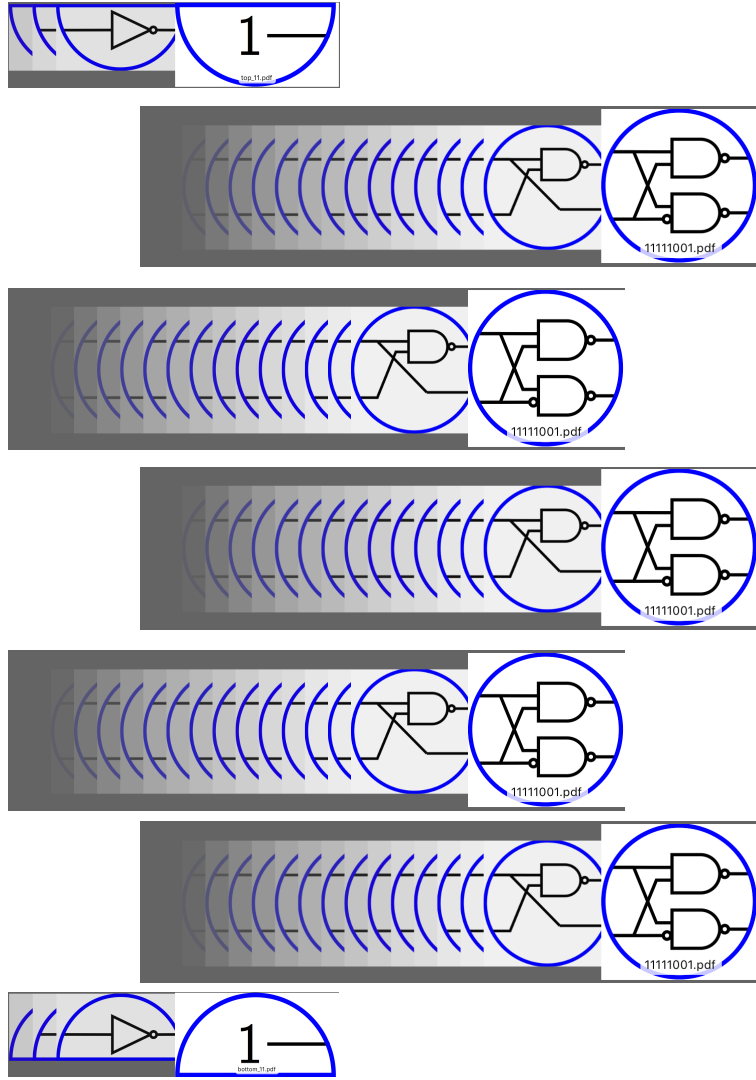
Which circuits to build?



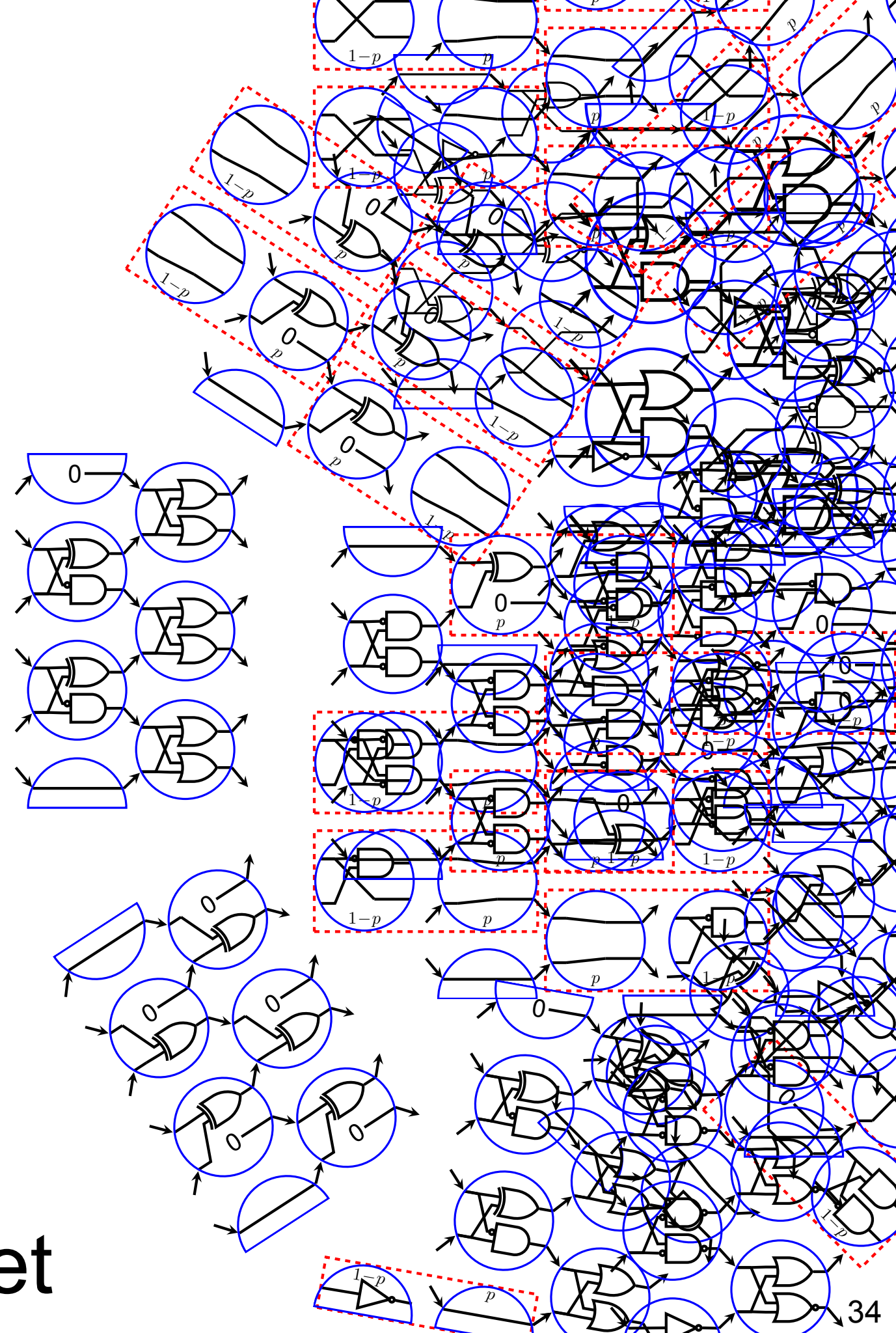
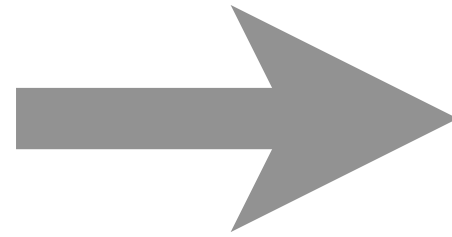
Which circuits to build?



Which circuits to build?



1,288 gates that
implement **any**
6-bit circuit



“Complete” 6-bit gate set

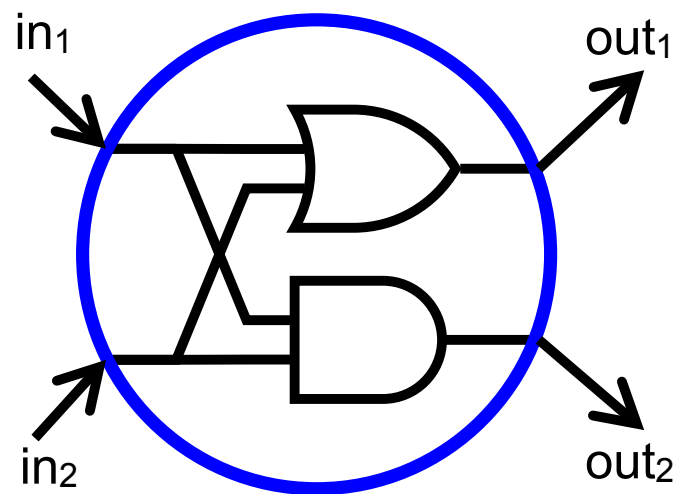
Structure

Theoretical circuit model

How it works: design and implementation

Experimental results

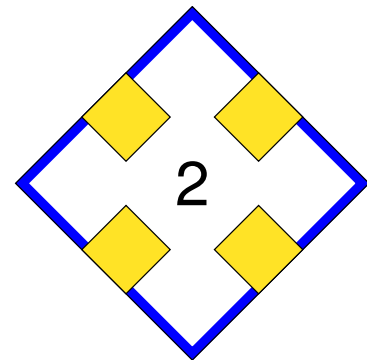
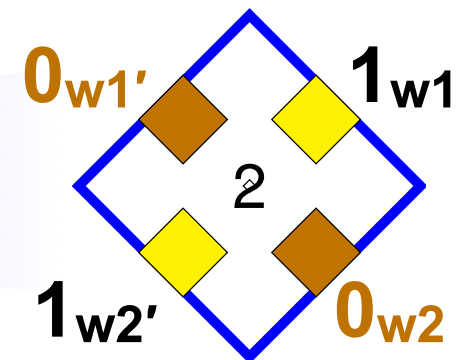
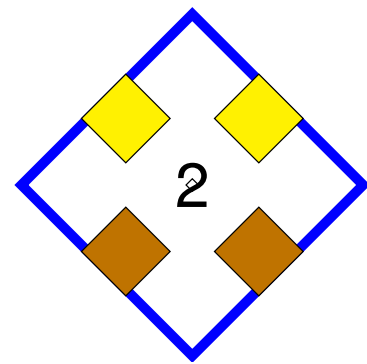
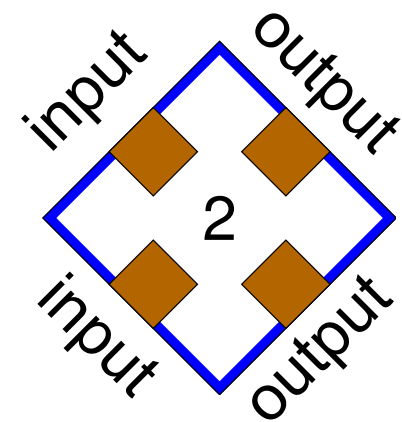
From circuits to square tiles



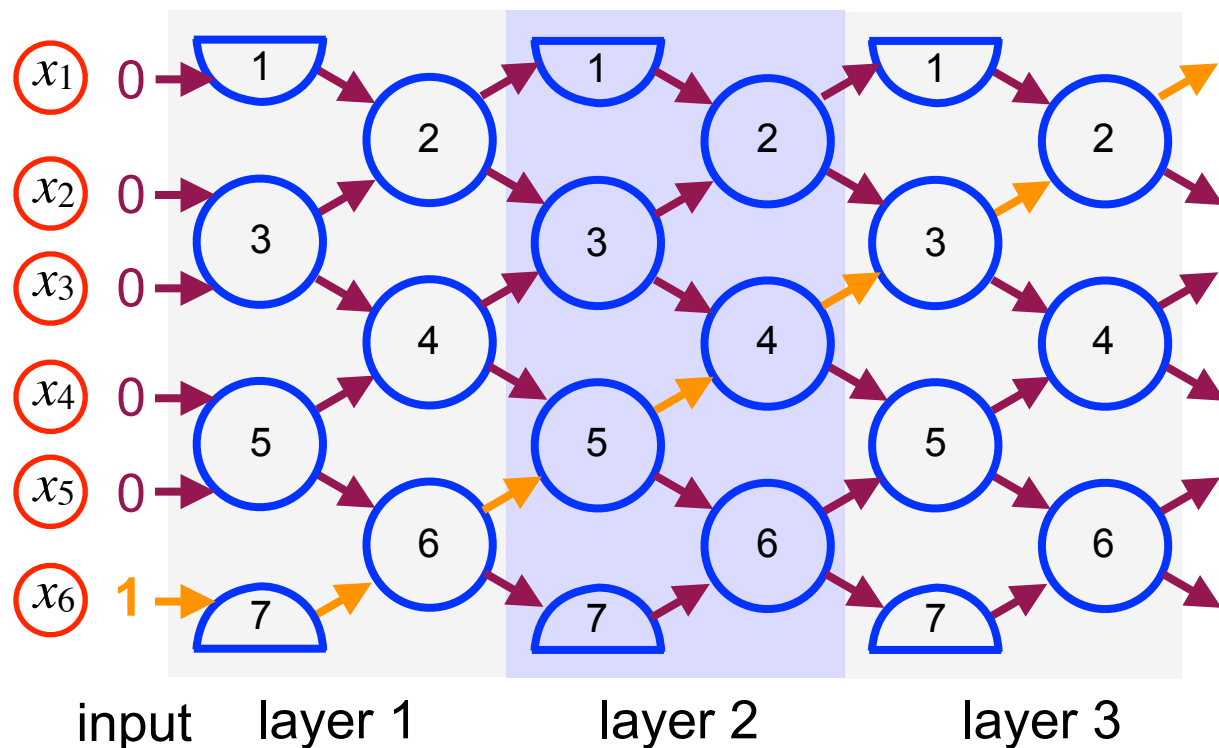
in ₁	in ₂	out ₁	out ₂
0	0	0	0
0	1	1	0
1	0	1	0
1	1	1	1

gate truth table

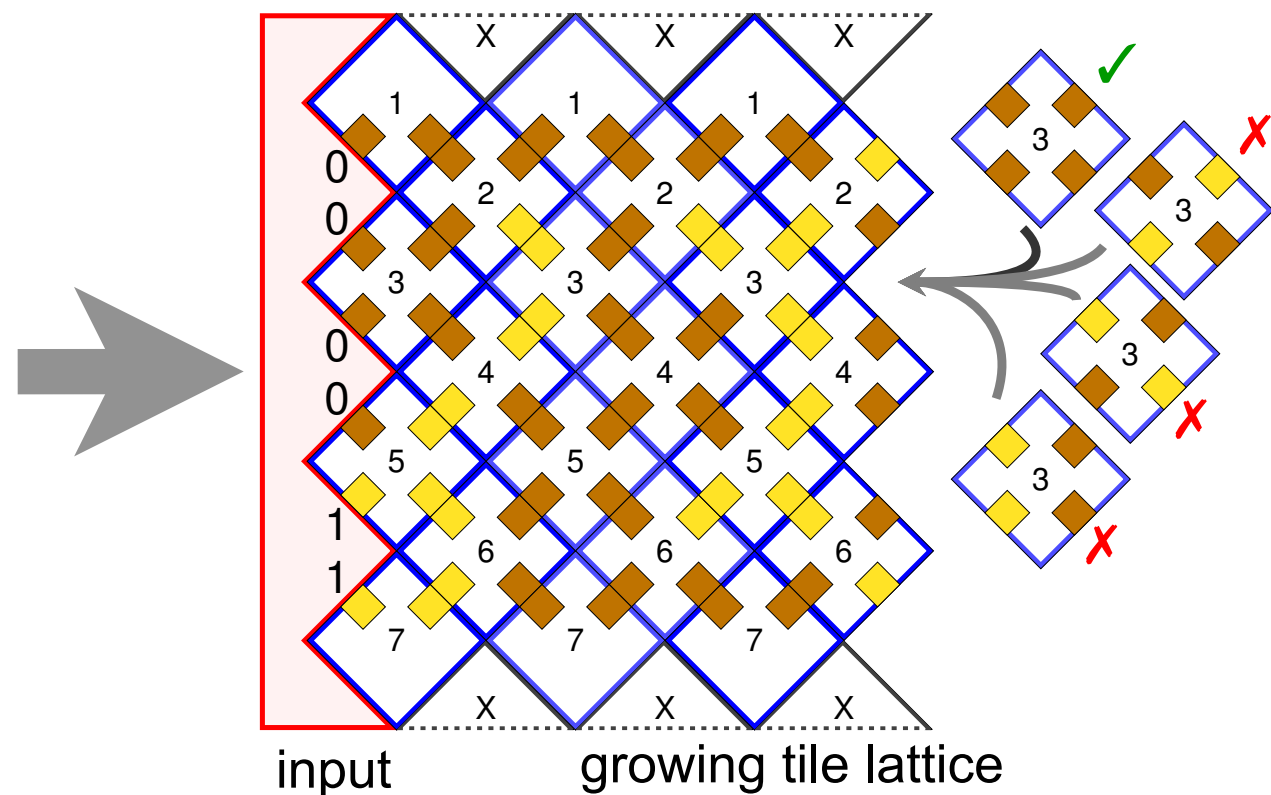
compile gate to
4 square tiles



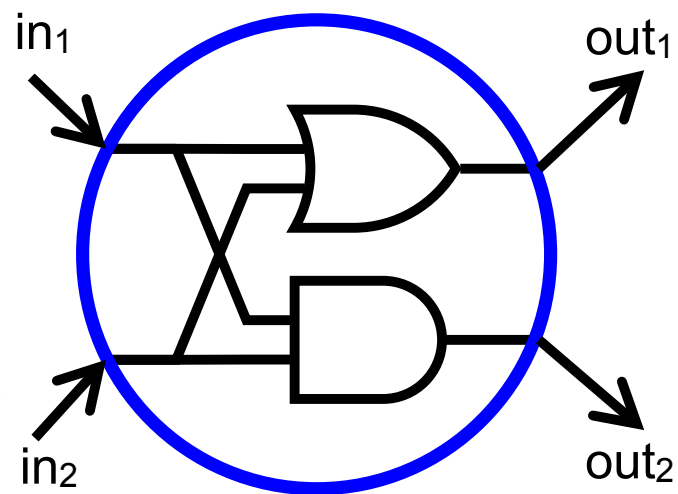
circuit computation



tile self-assembly



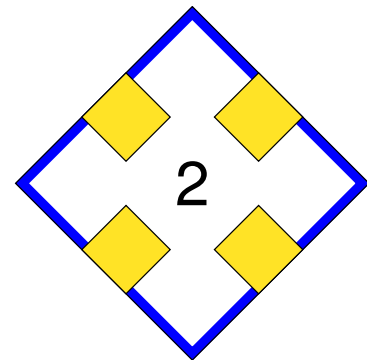
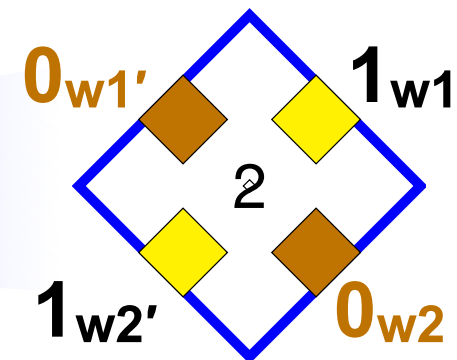
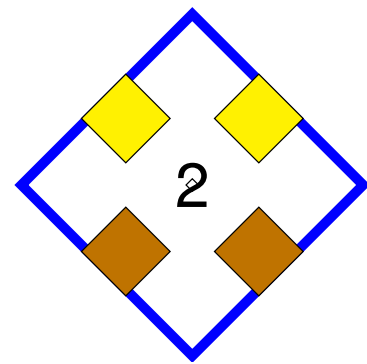
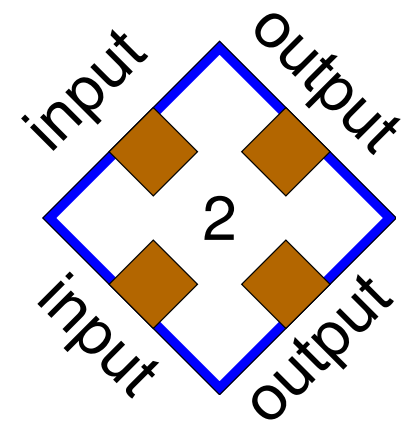
From circuits to square tiles



in ₁	in ₂	out ₁	out ₂
0	0	0	0
0	1	1	0
1	0	1	0
1	1	1	1

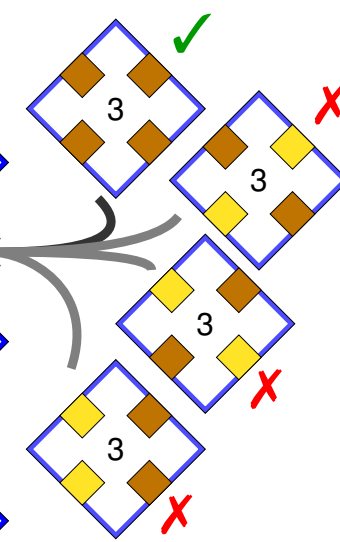
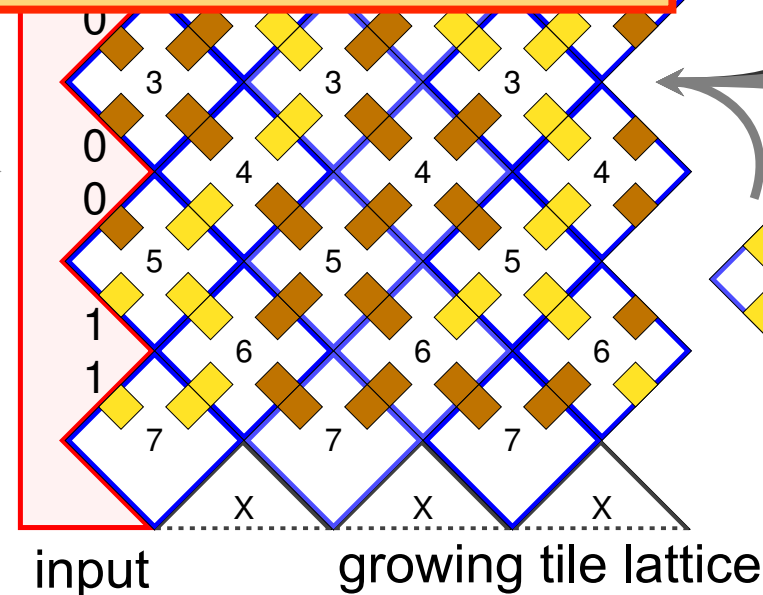
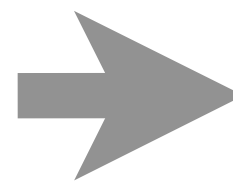
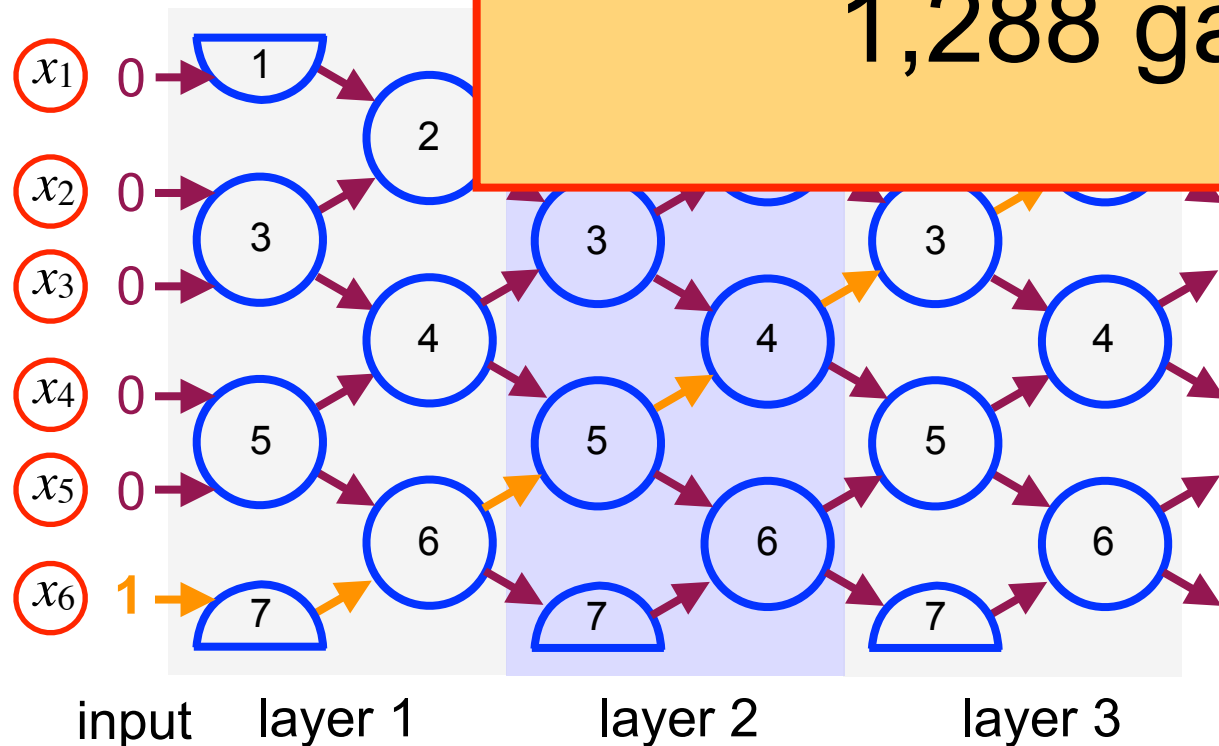
gate truth table

compile gate to
4 square tiles

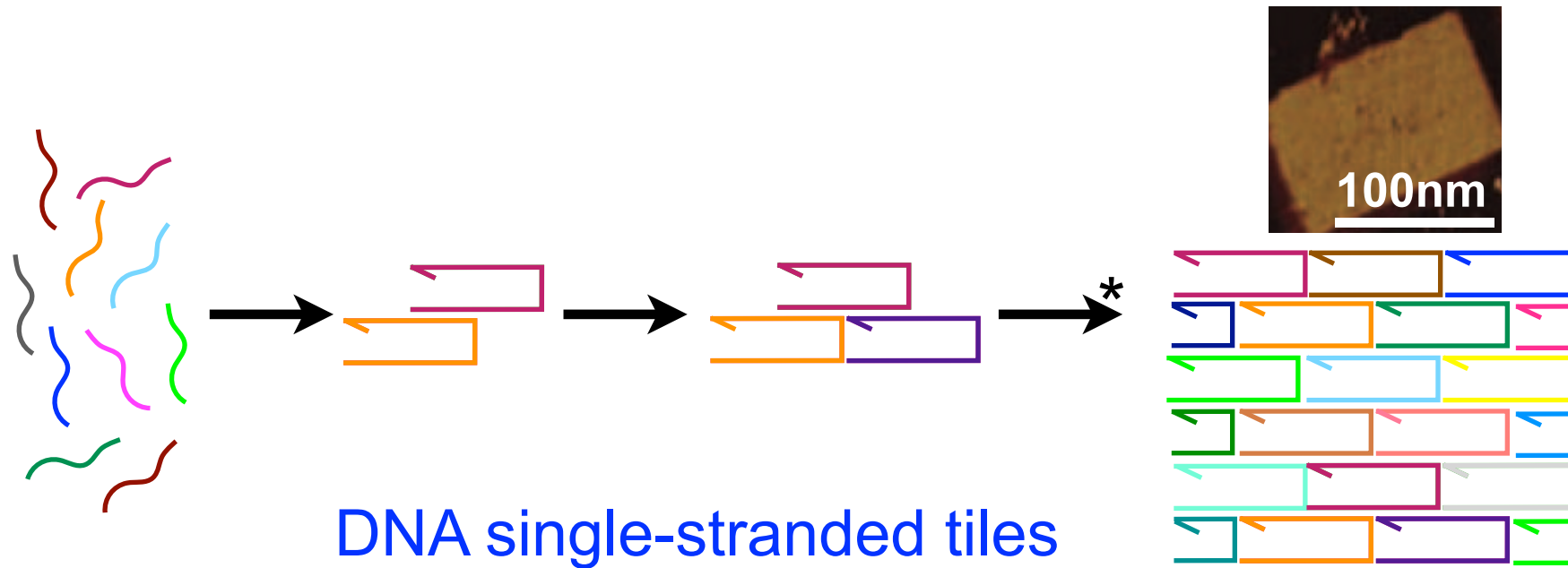


circuit

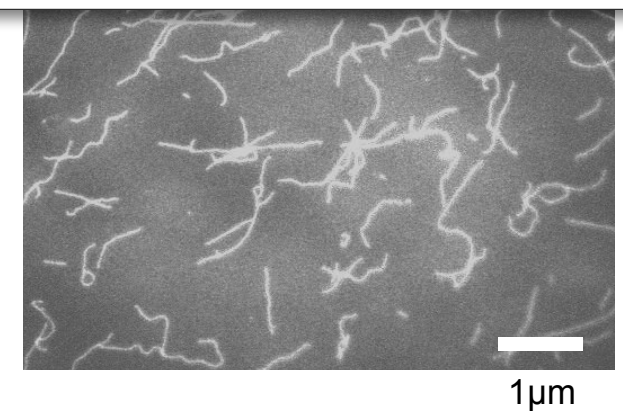
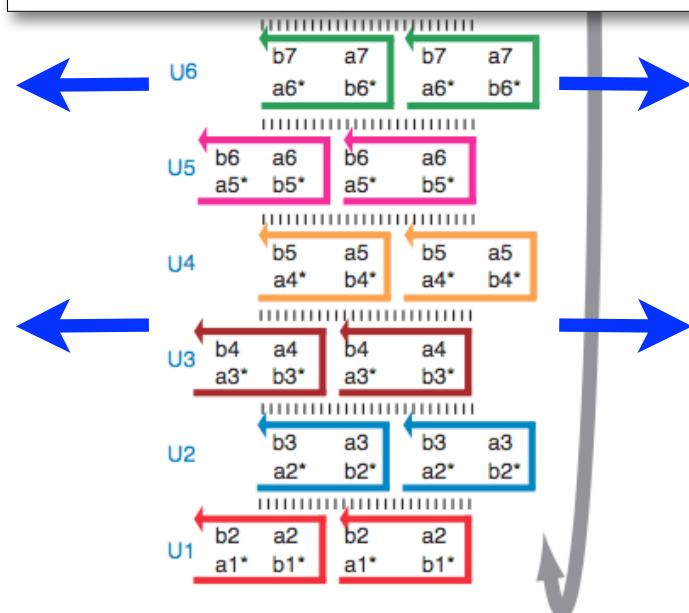
1,288 gates \rightarrow 89 tiles



Single-stranded tile motif

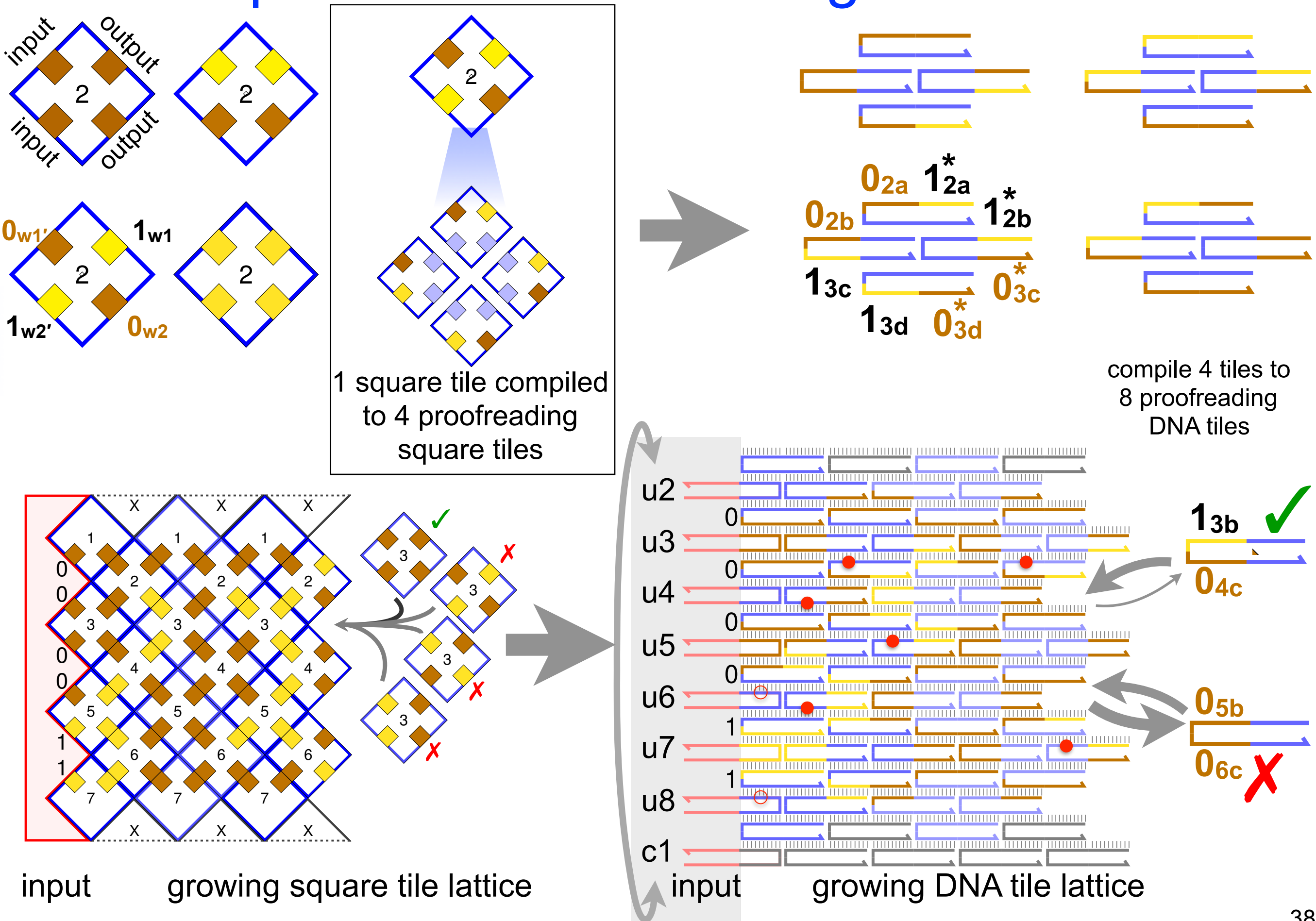


Wei, Dai, Yin. 2013 Nature

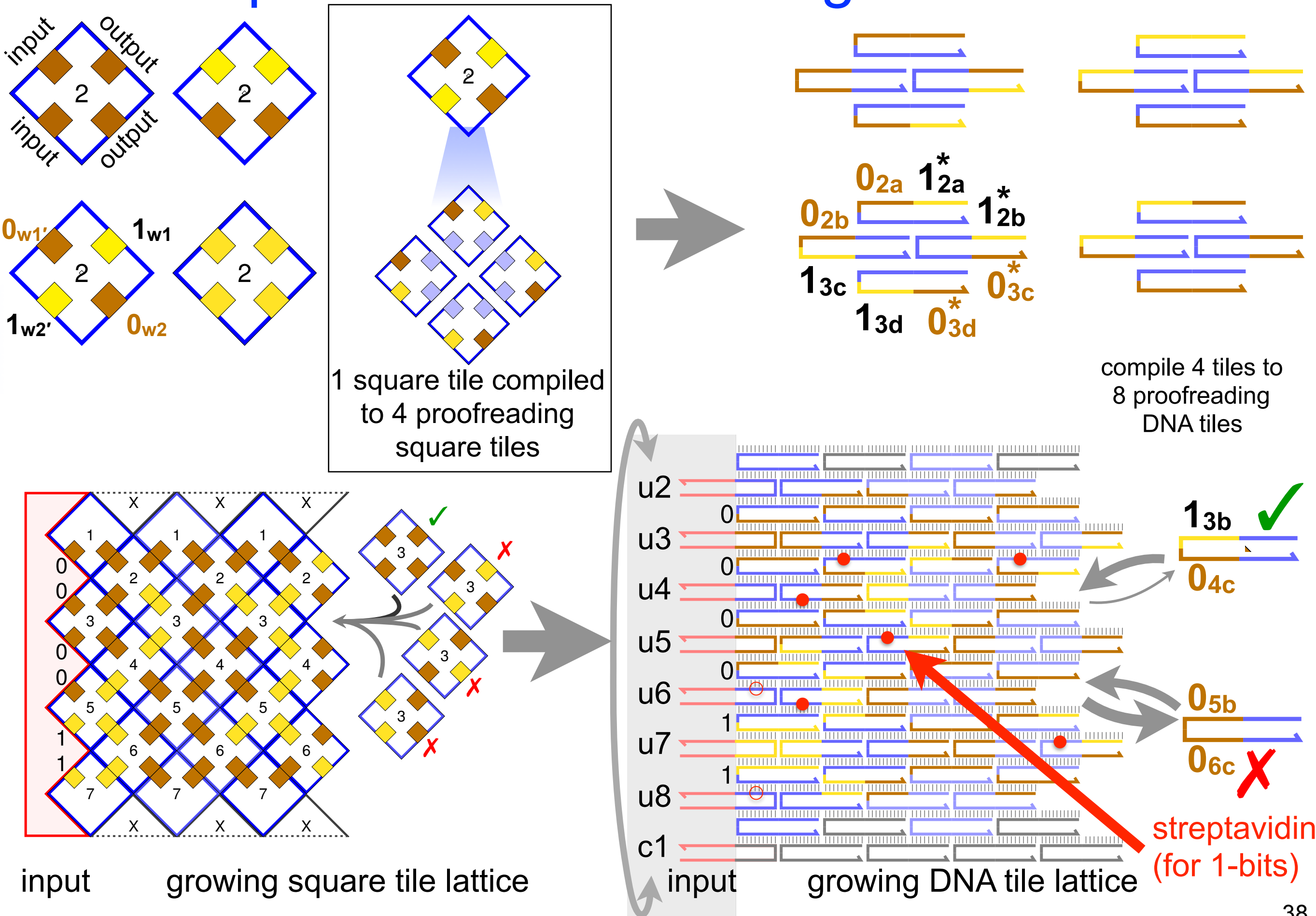


Yin, Hariadi, Sahu, Choi, Park,
LaBean, Reif. Science. 2008

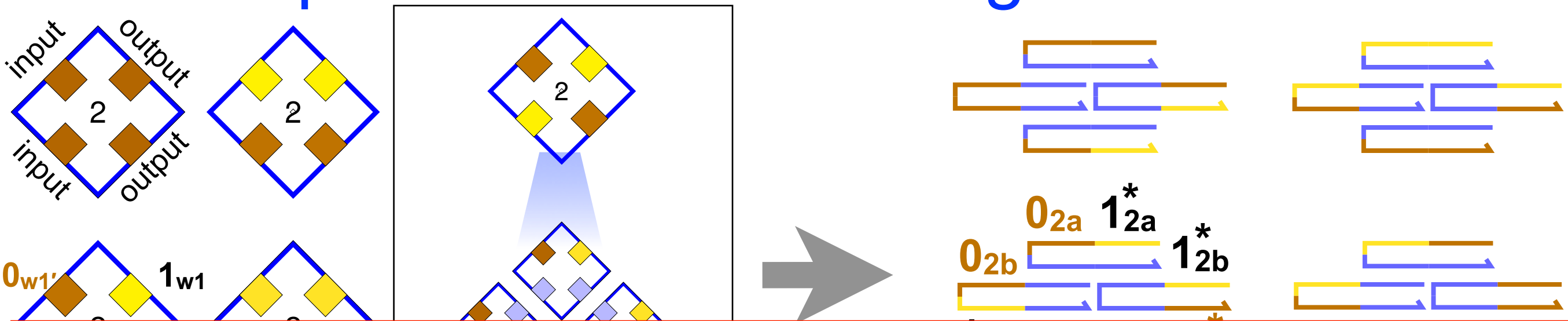
From square tiles to DNA single-stranded tiles



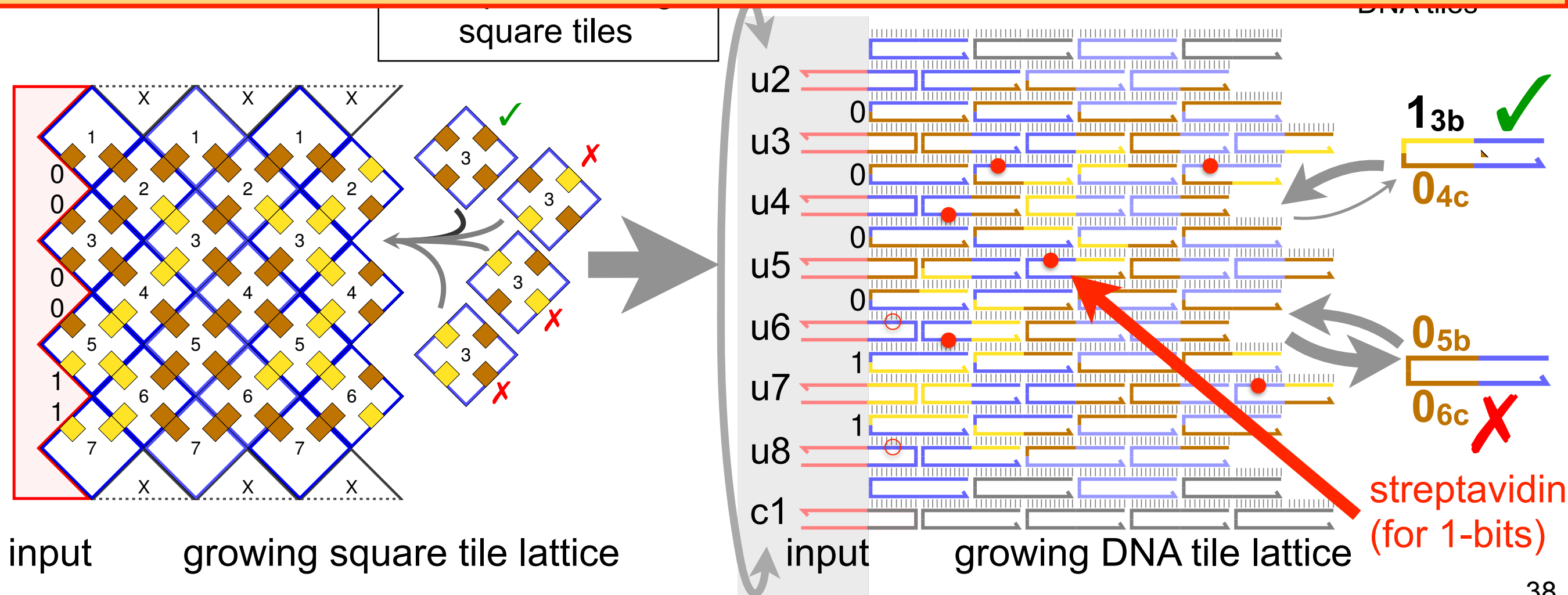
From square tiles to DNA single-stranded tiles



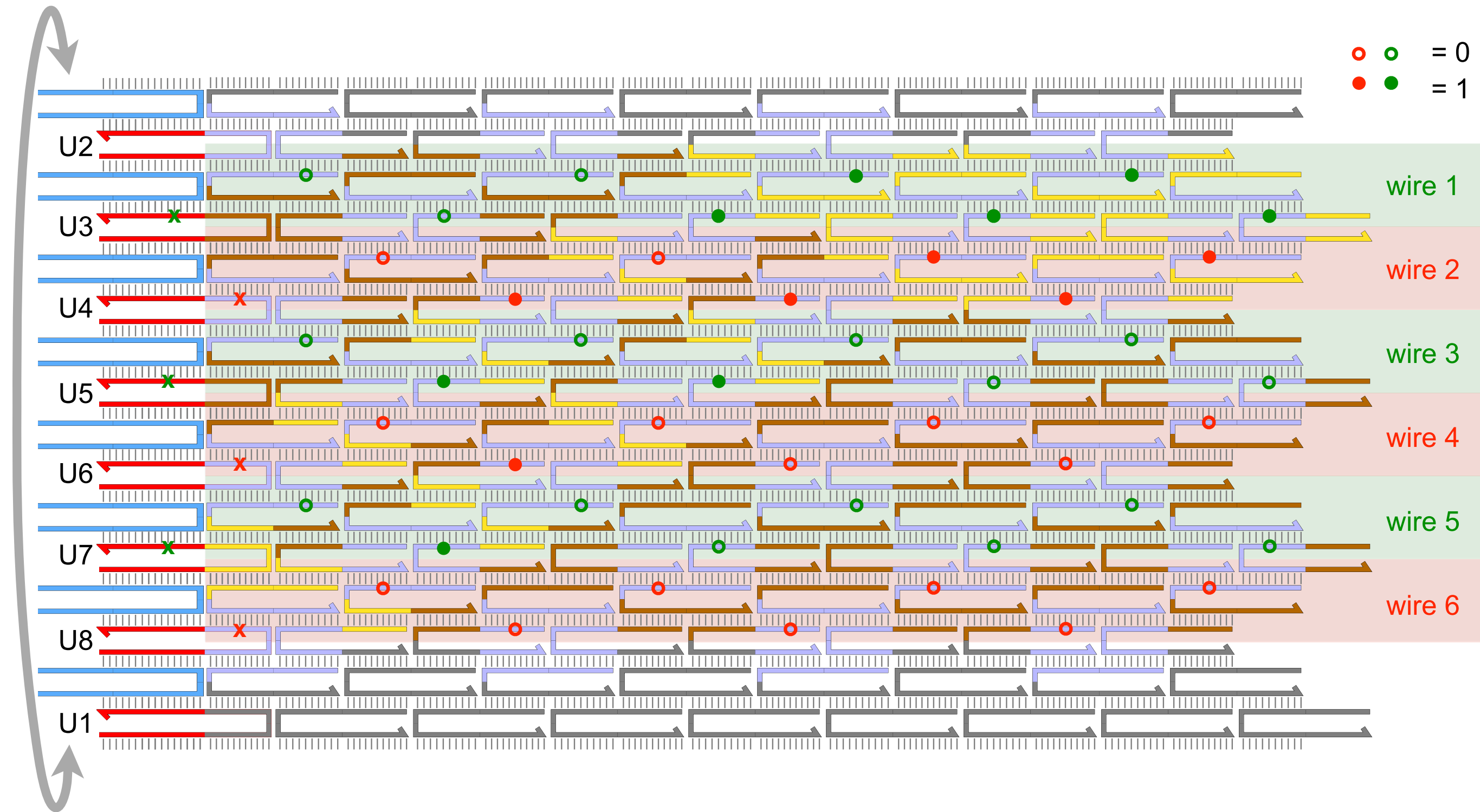
From square tiles to DNA single-stranded tiles



1,288 gates \rightarrow 89 tiles \rightarrow 355 tiles \rightarrow 355 DNA strands

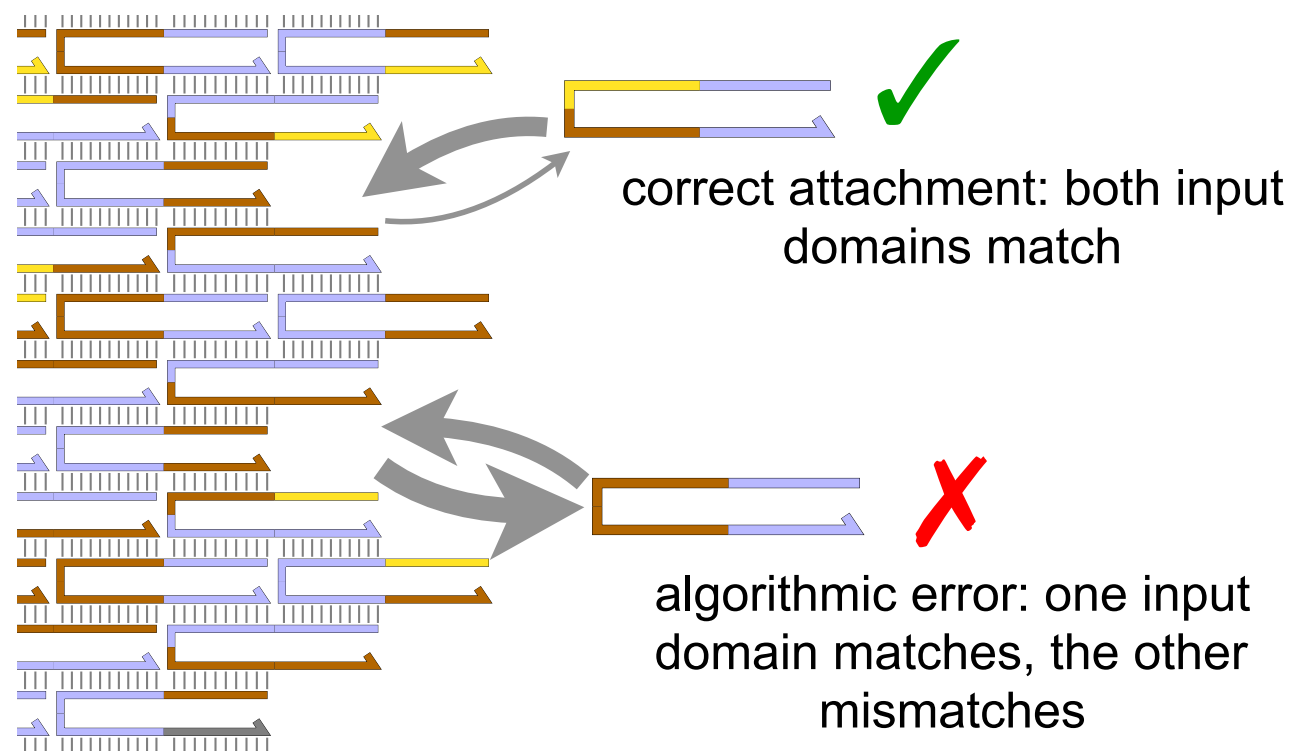


How the DNA tile lattice should look



DNA sequence design

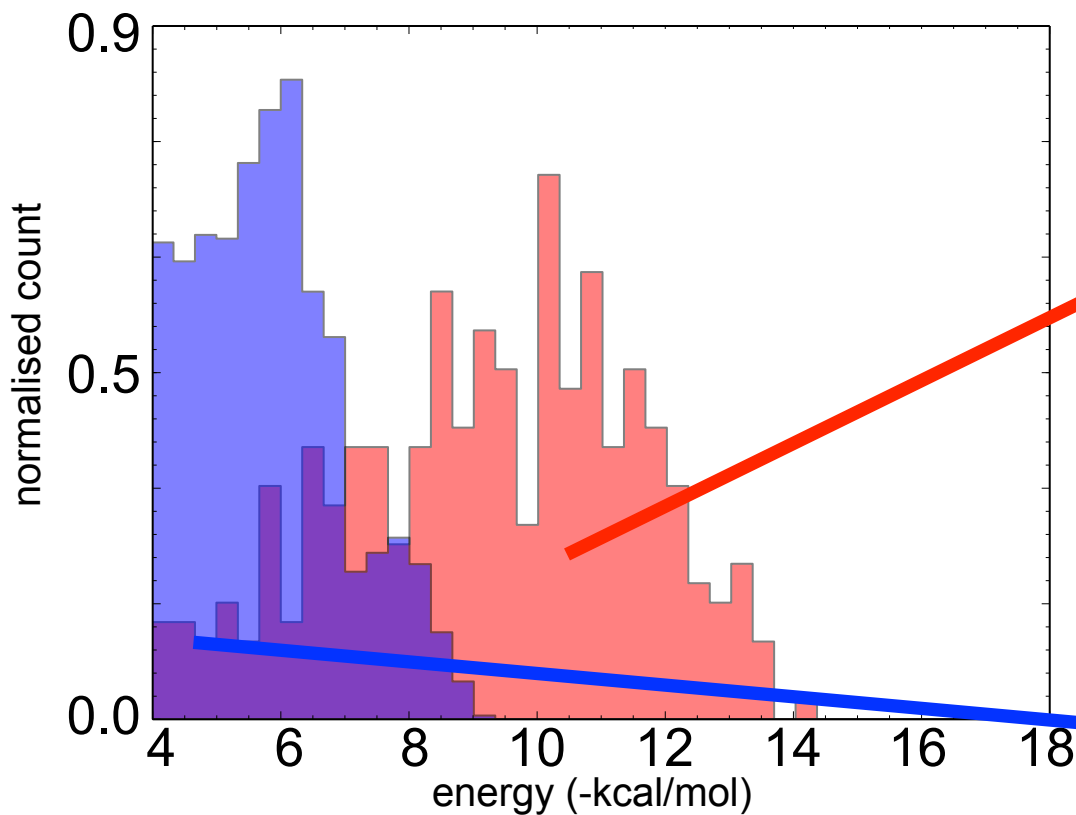
- Major challenge: We need to design DNA strands that bind when they should, and to not bind when they shouldn't
- The next slide summarises some of the issues



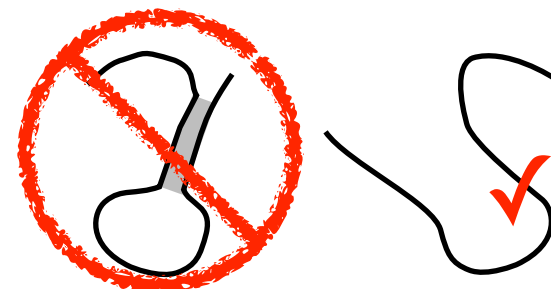
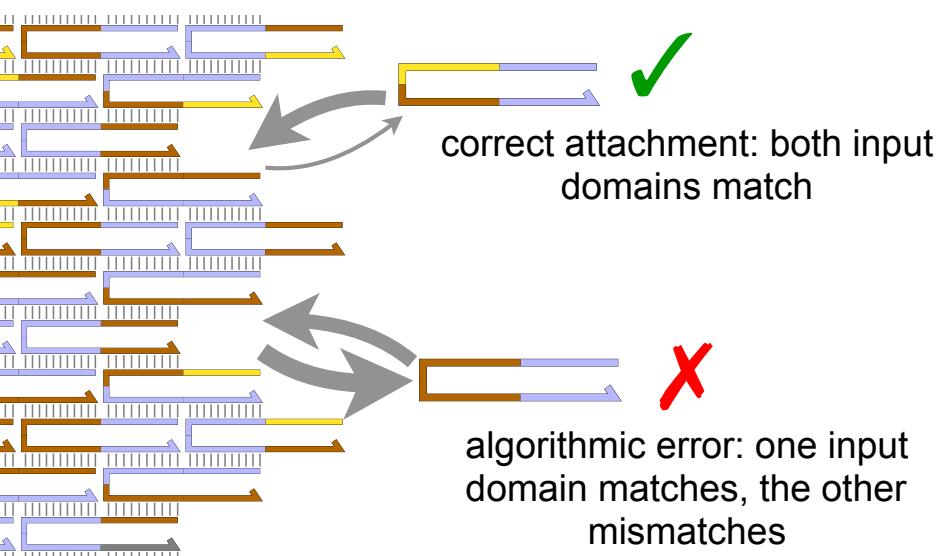
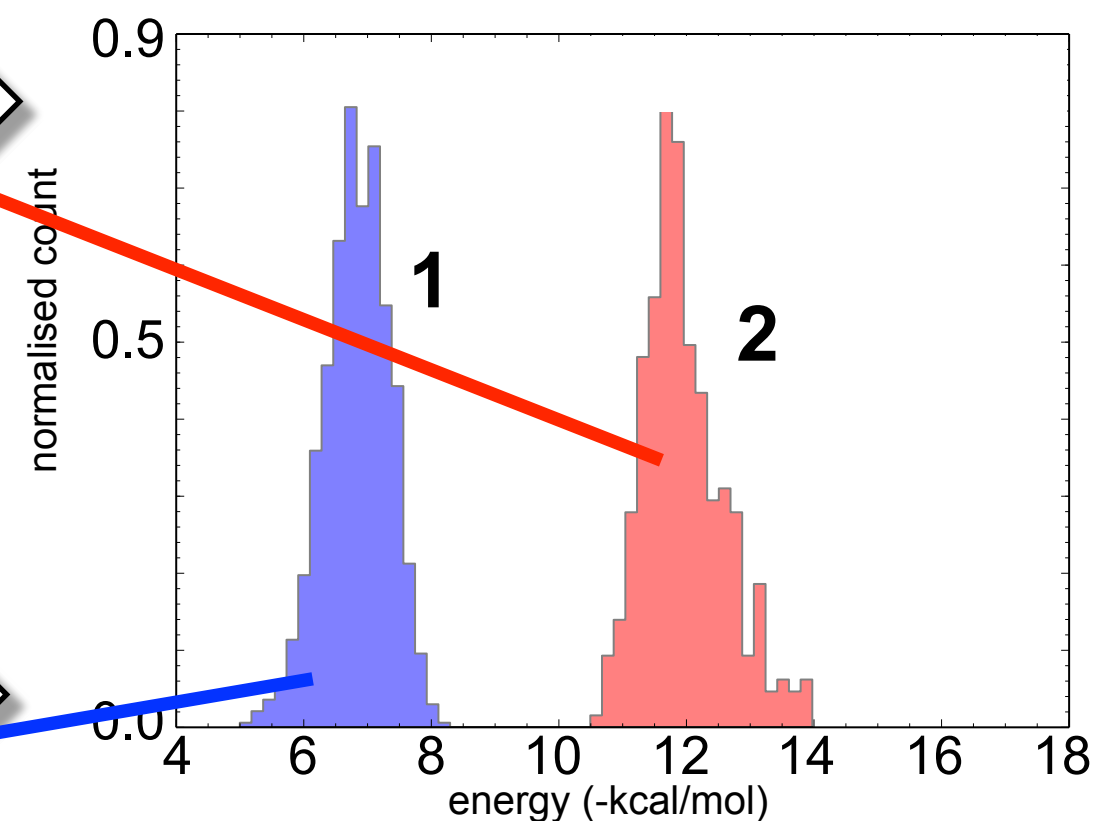
DNA sequence design

- Major challenge: We need to design DNA strands that bind when they should, and to not bind when they shouldn't
- Custom DNA sequence designer; built on top of Nupack & ViennaRNA

Random sequences



designed sequences



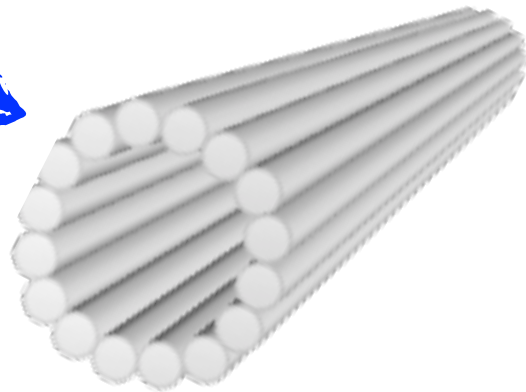
- **3. Strand ss**
- **4. Clean lattice**
- **5. Strand pairs**

Barcoded DNA origami seed

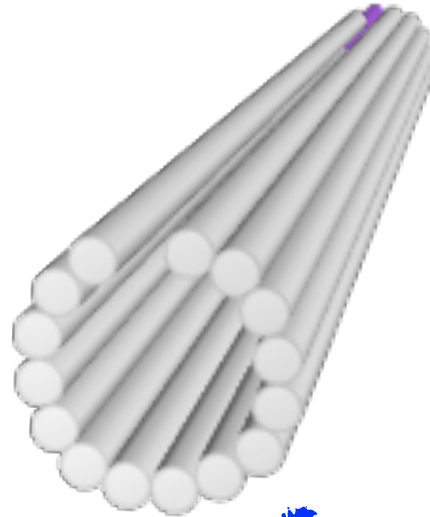
39,18	71,18	103,18	135,18	167,18	199,18	231,18	263,18	295,18	327,18	359,18	391,18	423,18	
47,16	79,16	111,16	143,16	175,16	207,16	239,16	271,16	303,16	335,16	367,16	399,16	431,16	465,16
32,15	64,15	96,15	128,15	160,15	192,15	224,15	256,15	288,15	320,15	352,15	384,15	416,15	
47,14	79,14	111,14	143,14	175,14	207,14	239,14	271,14	303,14	335,14	367,14	399,14	431,14	465,14
32,13	64,13	96,13	128,13	160,13	192,13	224,13	256,13	288,13	320,13	352,13	384,13	416,13	
47,12	79,12	111,12	143,12	175,12	207,12	239,12	271,12	303,12	335,12	367,12	399,12	431,12	465,12
32,11	64,11	96,11	128,11	160,11	192,11	224,11	256,11	288,11	320,11	352,11	384,11	416,11	
47,10	79,10	111,10	143,10	175,10	207,10	239,10	271,10	303,10	335,10	367,10	399,10	431,10	465,10
32,9	64,9	96,9	128,9	160,9	192,9	224,9	256,9	288,9	320,9	352,9	384,9	416,9	
47,8	79,8	111,8	143,8	175,8	207,8	239,8	271,8	303,8	335,8	367,8	399,8	431,8	465,8
32,7	64,7	96,7	128,7	160,7	192,7	224,7	256,7	288,7	320,7	352,7	384,7	416,7	
47,6	79,6	111,6	143,6	175,6	207,6	239,6	271,6	303,6	335,6	367,6	399,6	431,6	465,6
32,5	64,5	96,5	128,5	160,5	192,5	224,5	256,5	288,5	320,5	352,5	384,5	416,5	
47,4	79,4	111,4	143,4	175,4	207,4	239,4	271,4	303,4	335,4	367,4	399,4	431,4	465,4
32,3	64,3	96,3	128,3	160,3	192,3	224,3	256,3	288,3	320,3	352,3	384,3	416,3	465,2
40,1	72,1	104,1	136,1	168,1	200,1	232,1	264,1	296,1	328,1	360,1	392,1	424,1	

Choose which
staples have biotin
modifications

Form
16-helix
tube



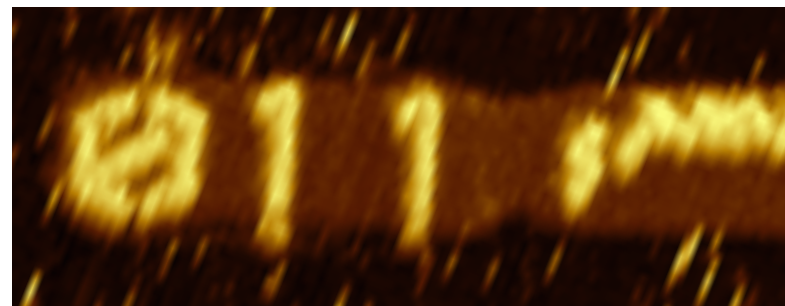
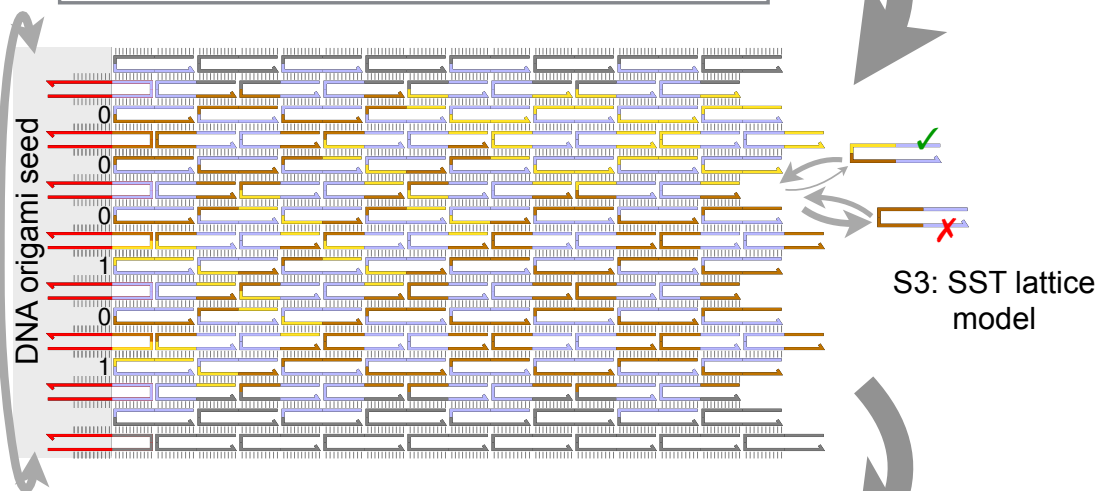
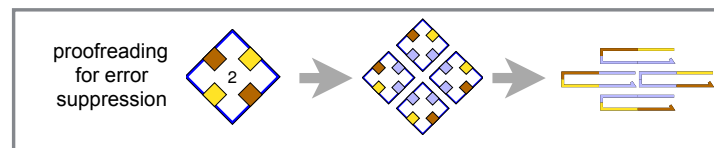
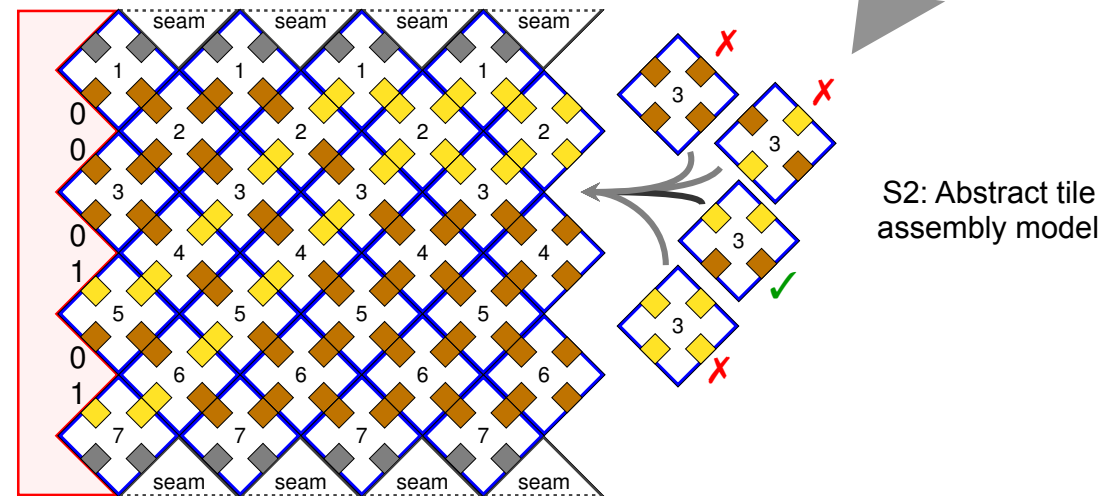
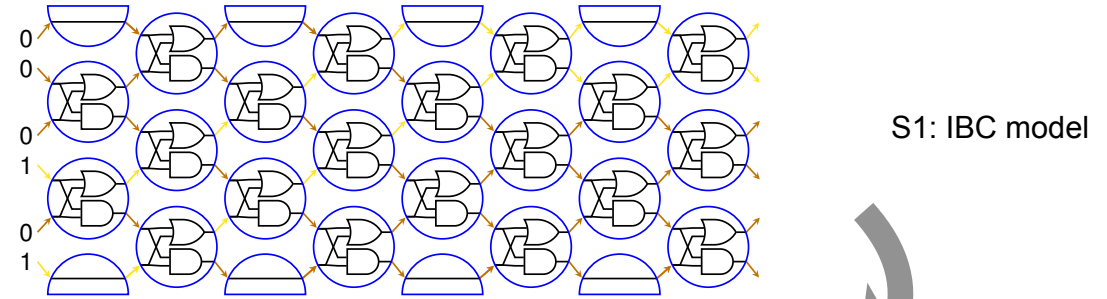
Unzip



add streptavidin
& image on mica



Abstraction hierarchy



S6-8:
Experimental
implementation
and results

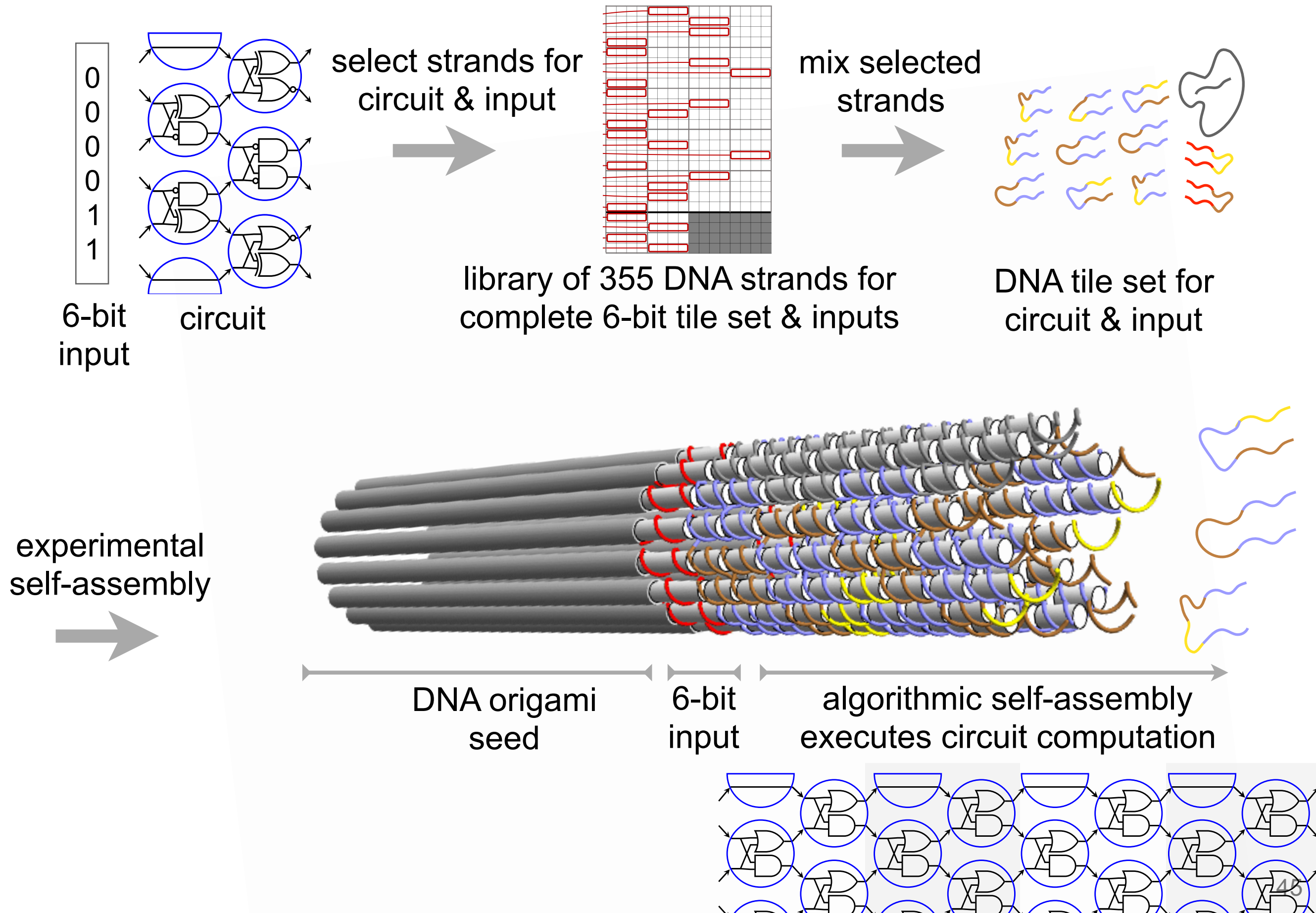
Structure

Theoretical circuit model

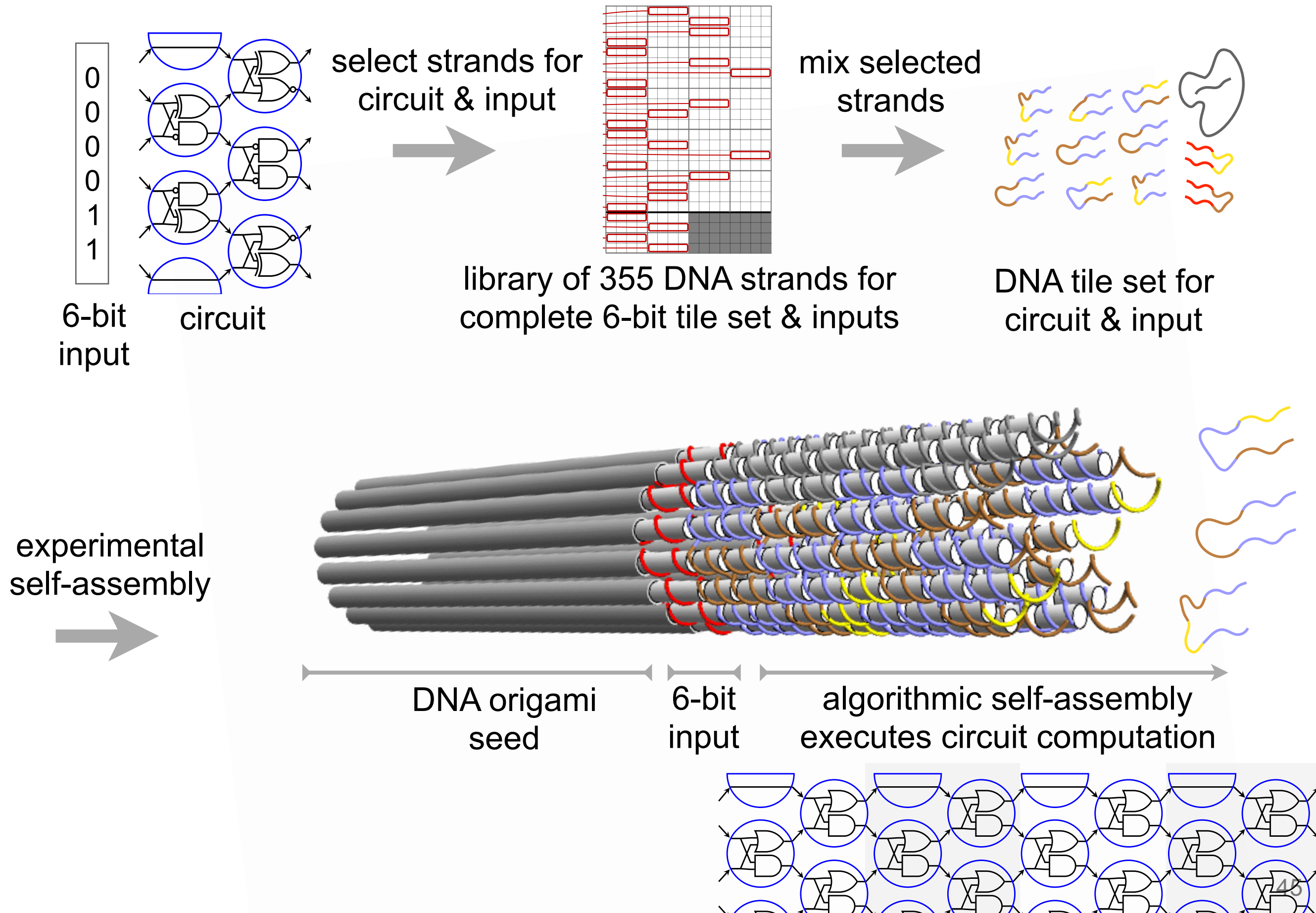
How it works: design and implementation

Experimental results

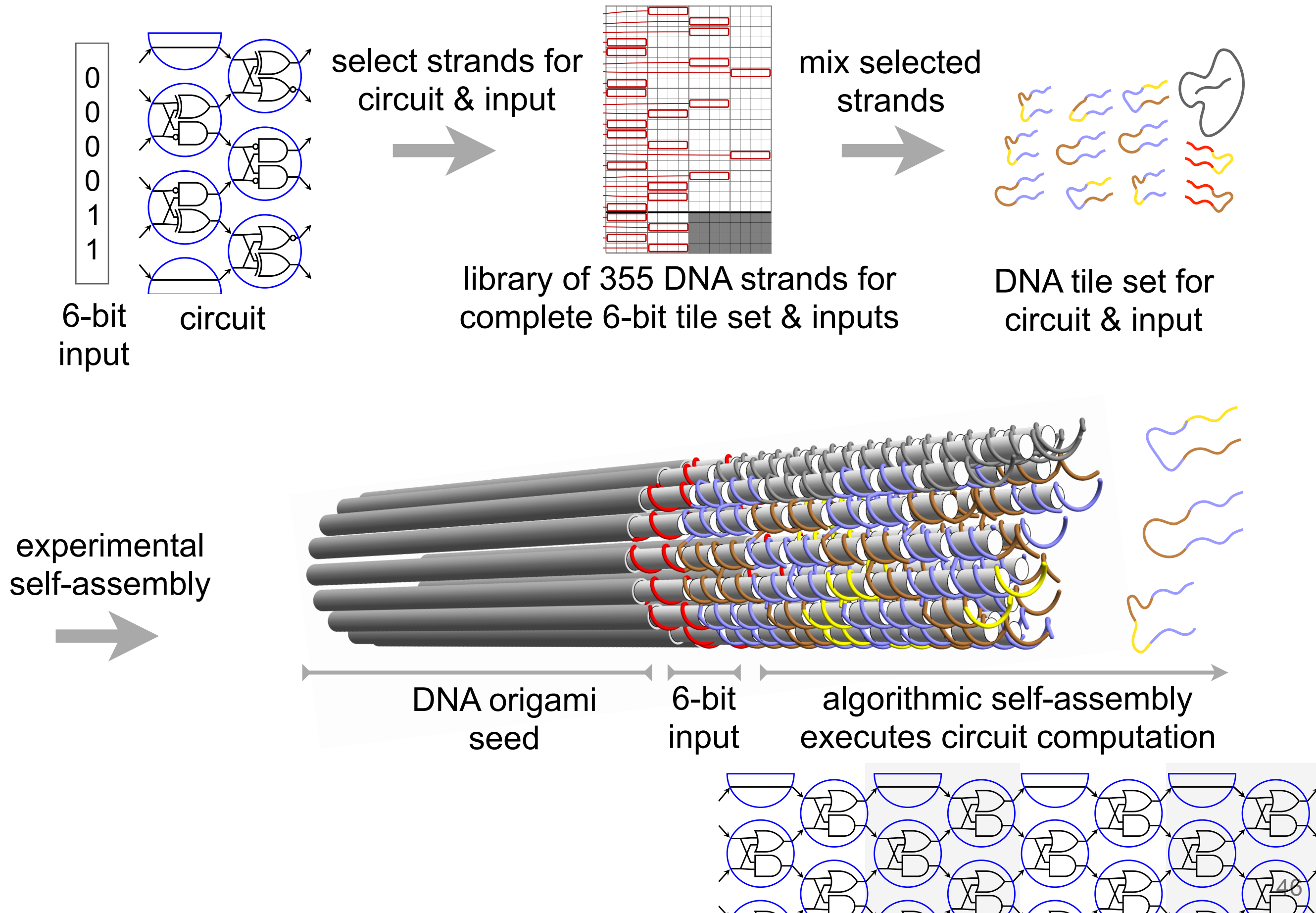
Schematic



Schematic

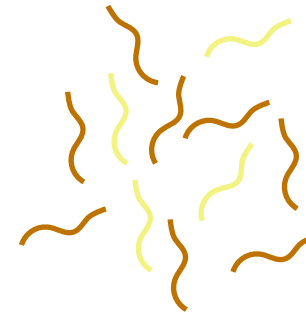
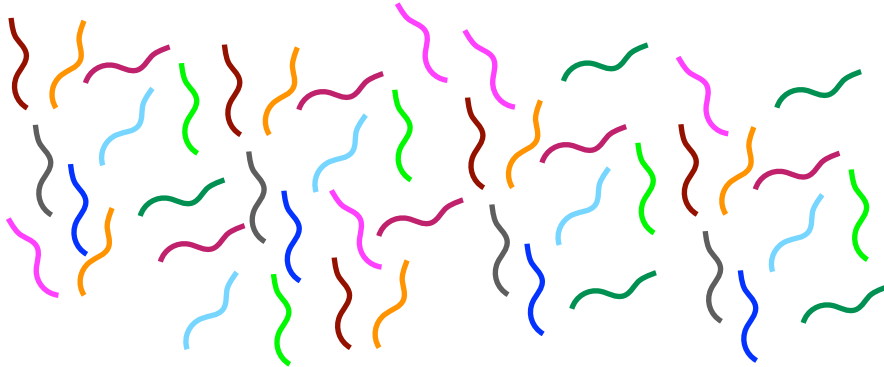


Schematic

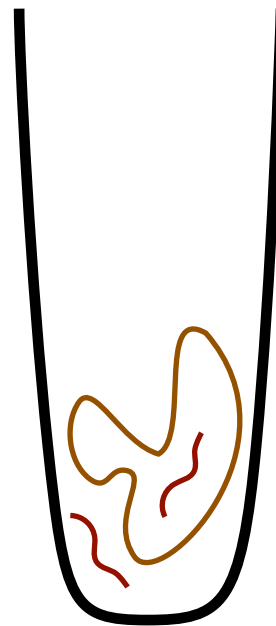


An example experiment: SORTING

355 tiles that
implement **any**
6-bit circuit



6-bit input
strands



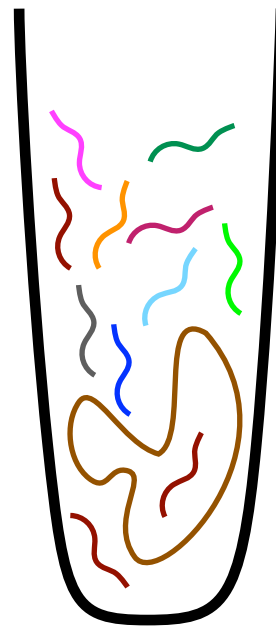
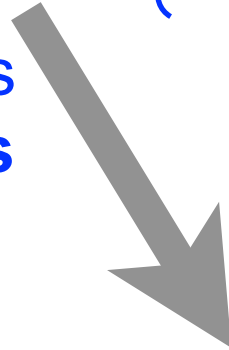
tiles &
seed

An example experiment: SORTING

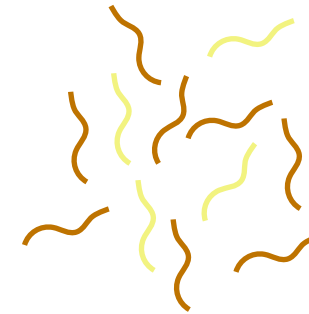
355 tiles that
implement **any**
6-bit circuit



programmer: chooses
100 bubble sort tiles

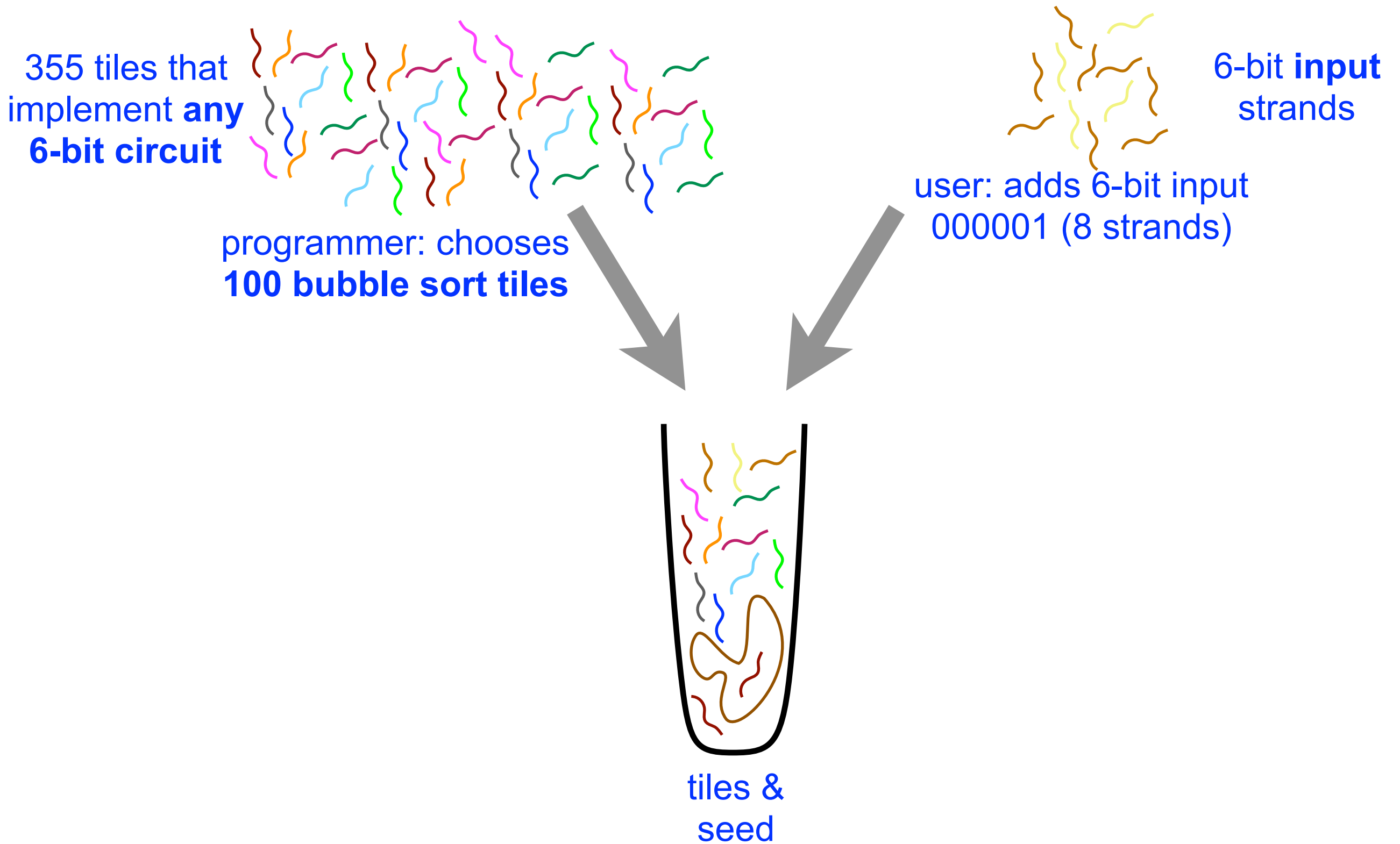


tiles &
seed



6-bit input
strands

An example experiment: SORTING



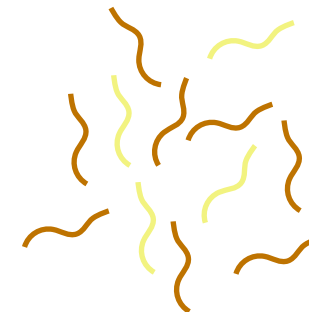
An example experiment: SORTING

355 tiles that implement **any 6-bit circuit**

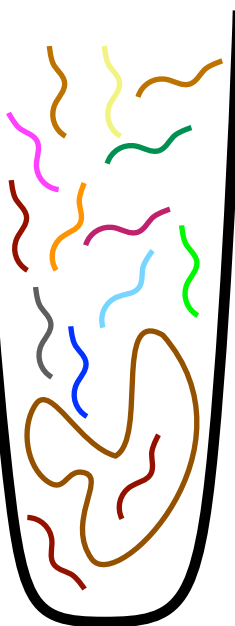
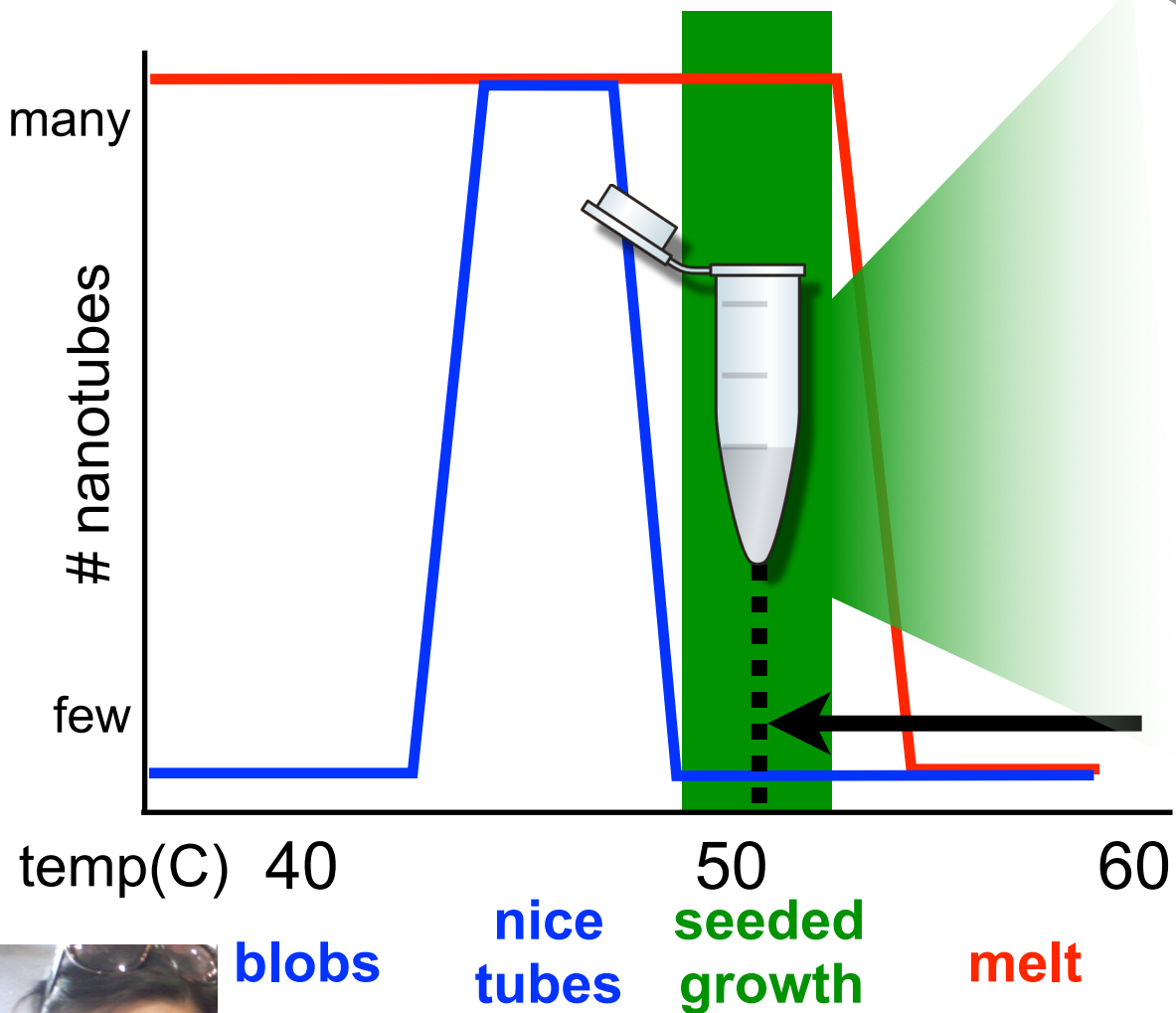


programmer: chooses **100 bubble sort tiles**

6-bit input strands



user: adds 6-bit input
000001 (8 strands)

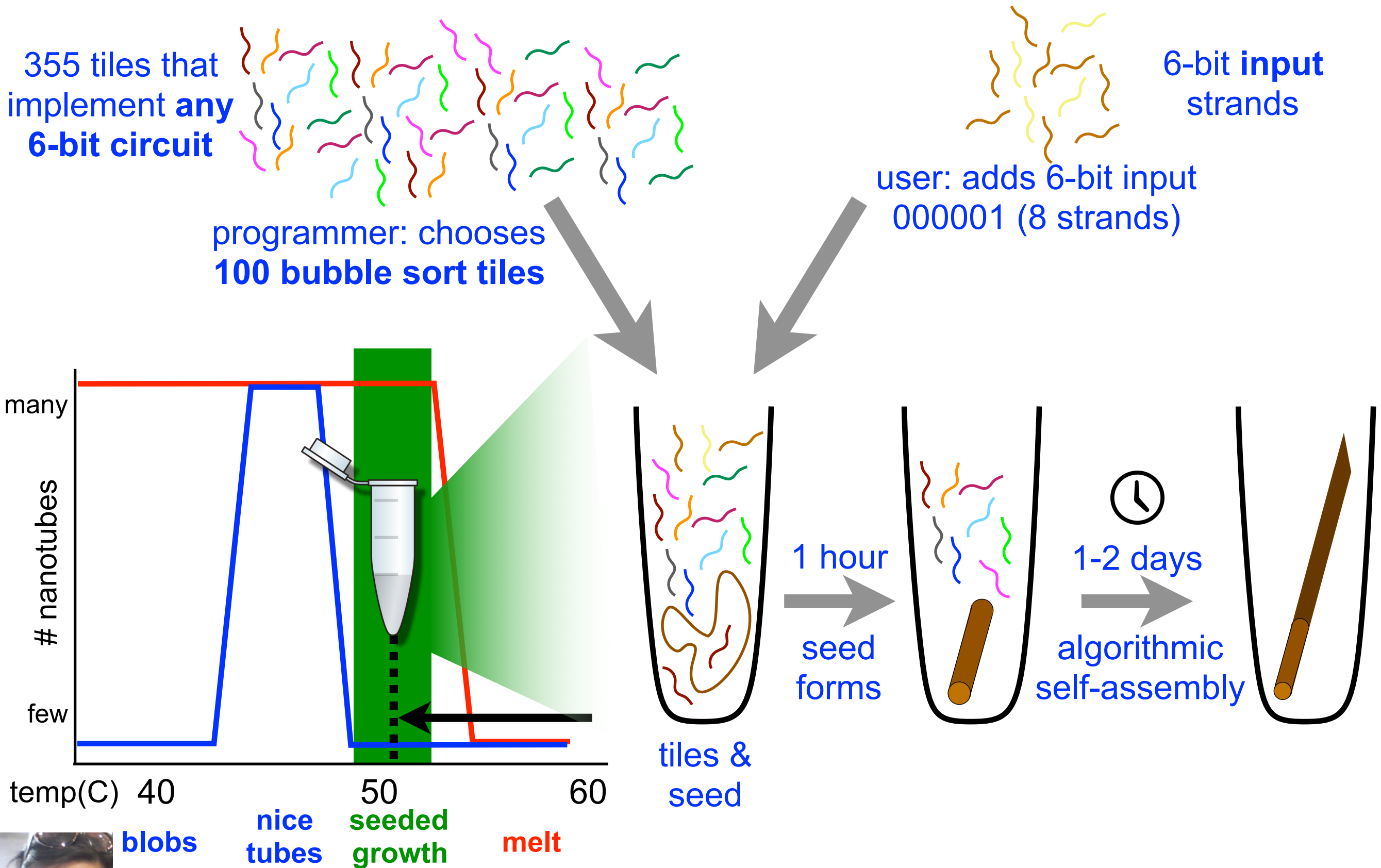


tiles & seed



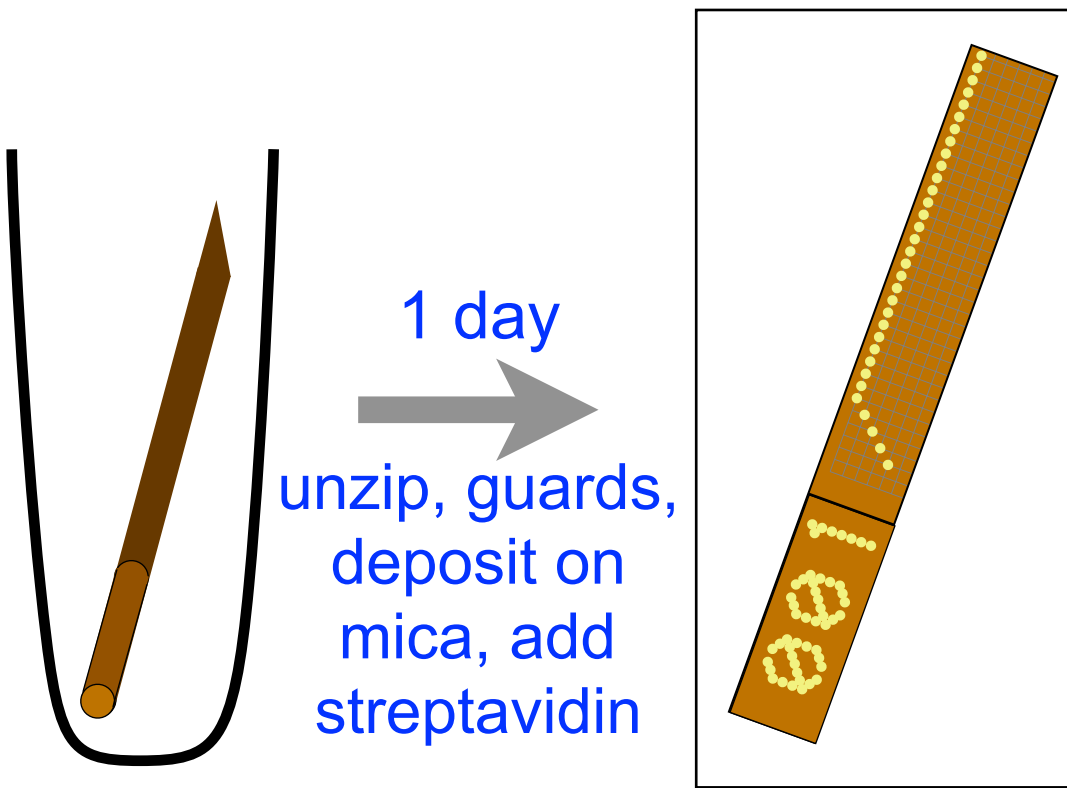
Joy Hui

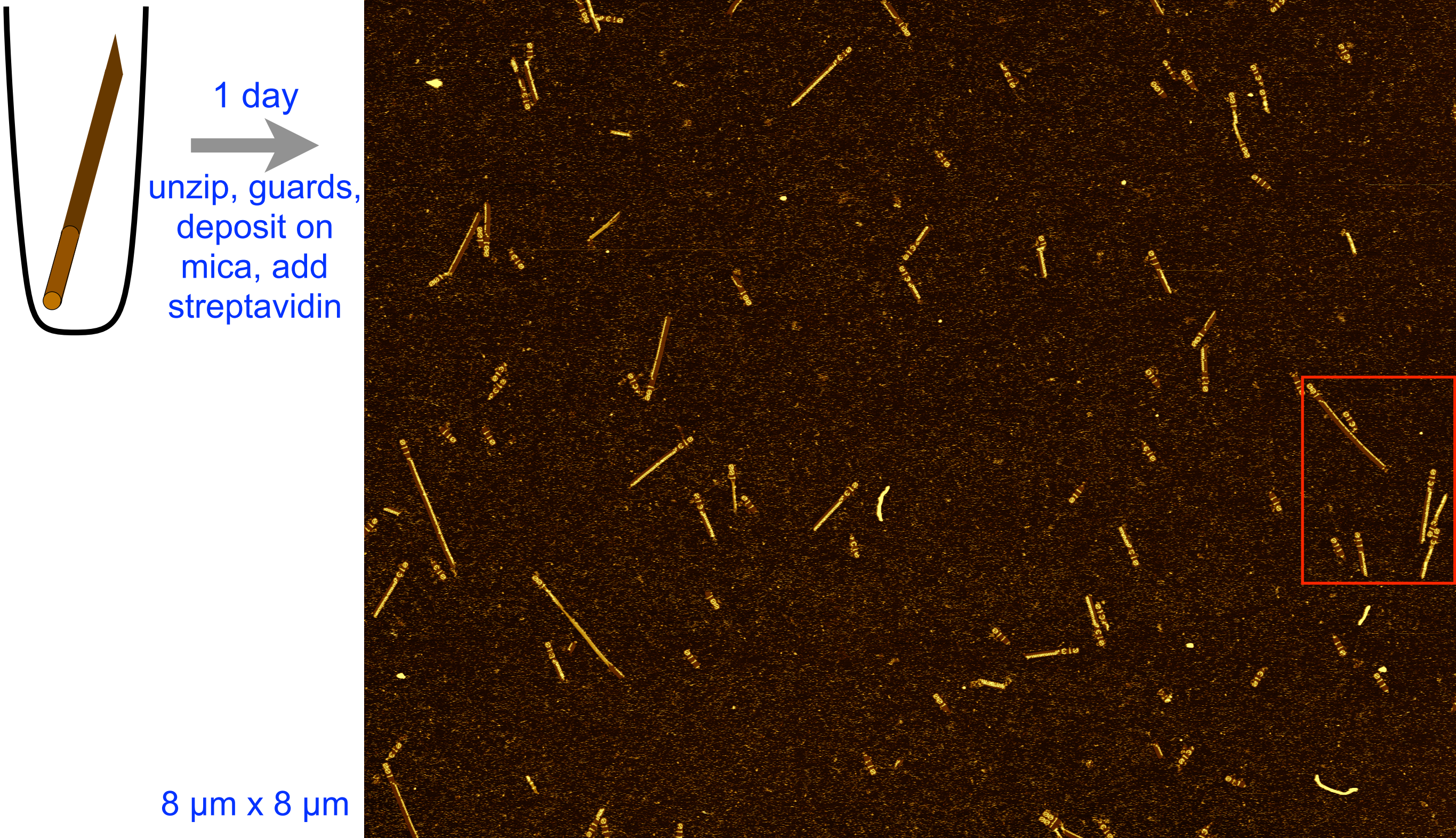
An example experiment: SORTING



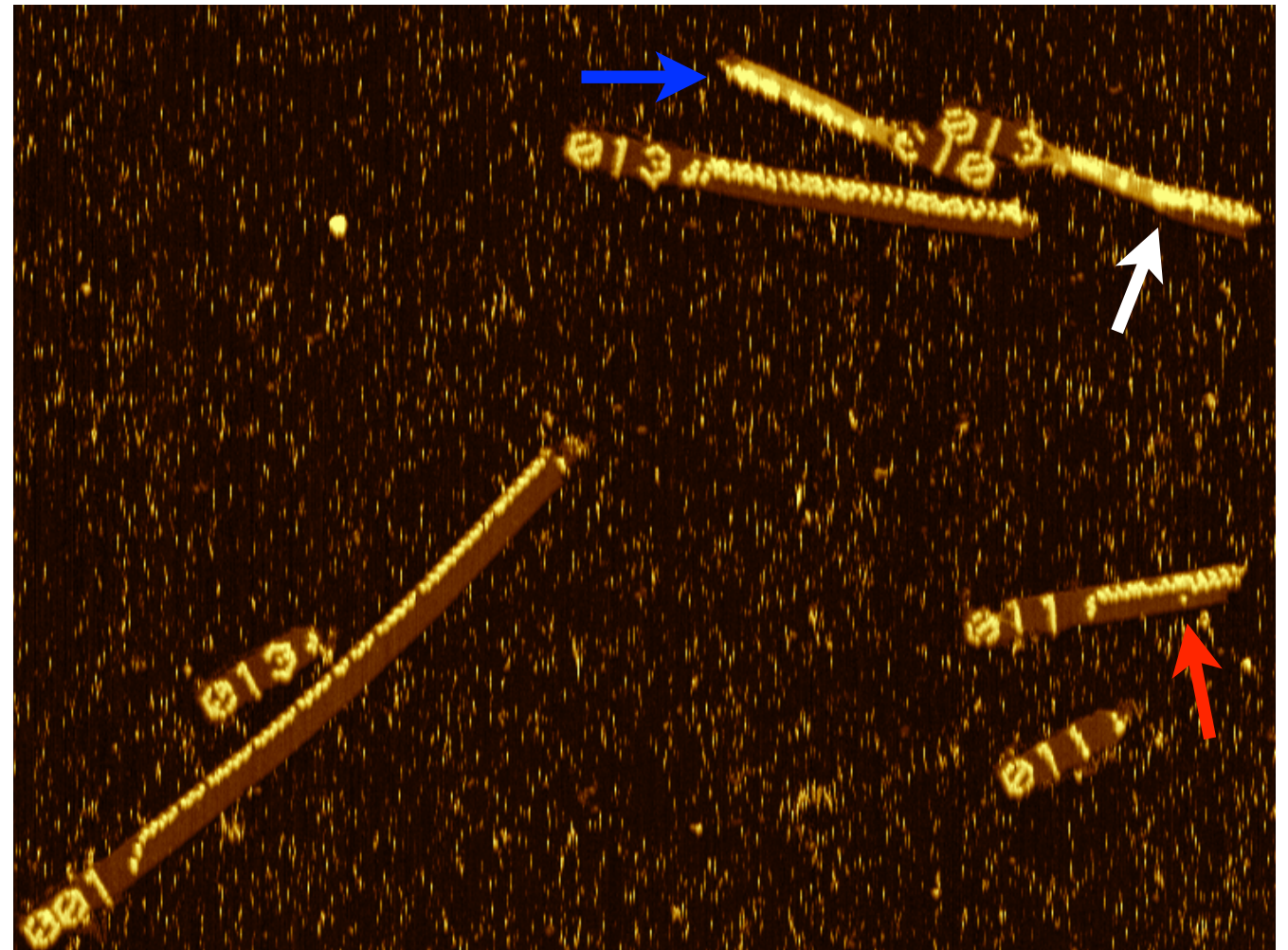
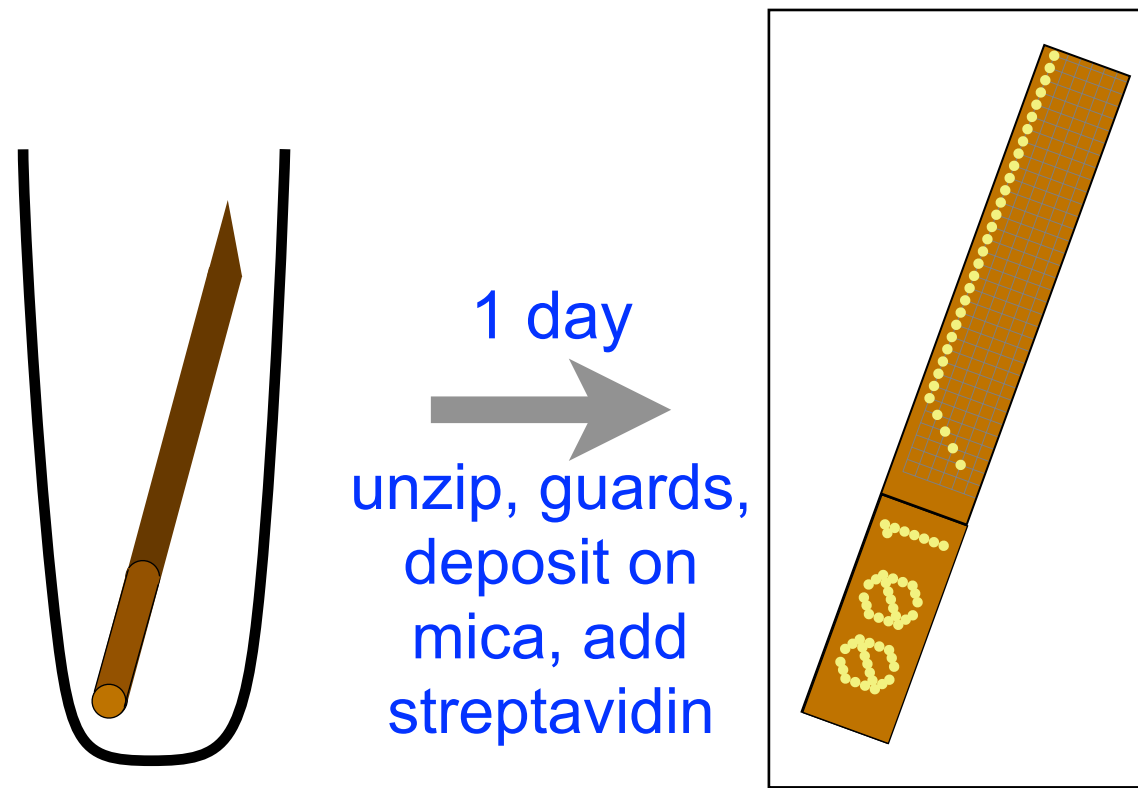
Joy Hui

An example experiment: SORTING

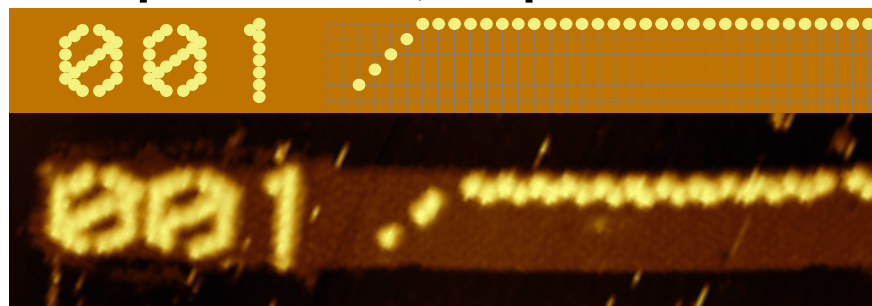




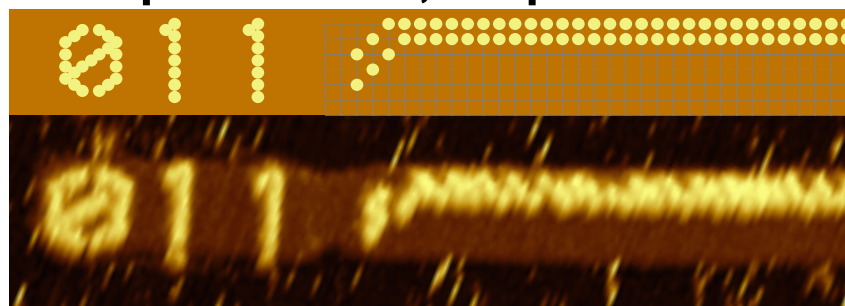
An example experiment: SORTING



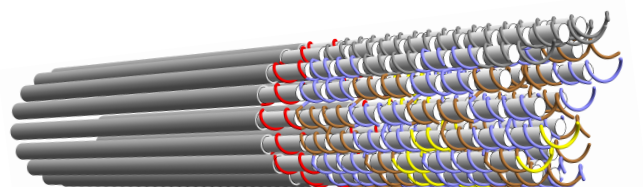
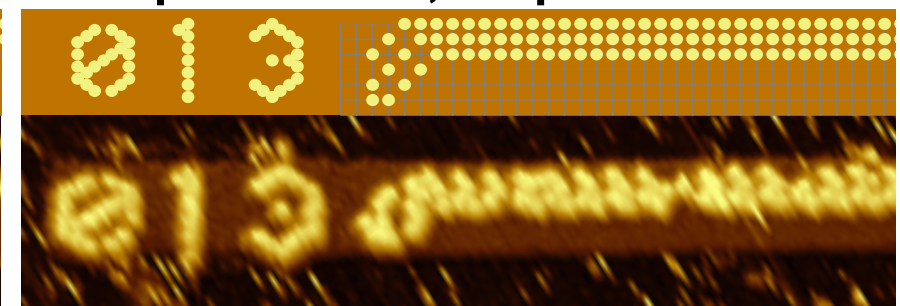
input: 000001, output: 100000



input: 000101, output: 110000

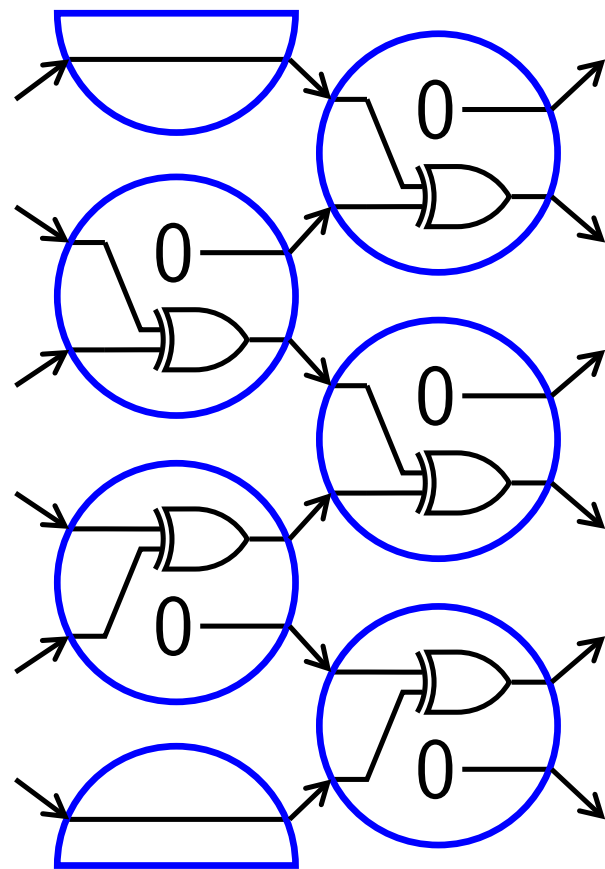


input: 000111, output: 111000

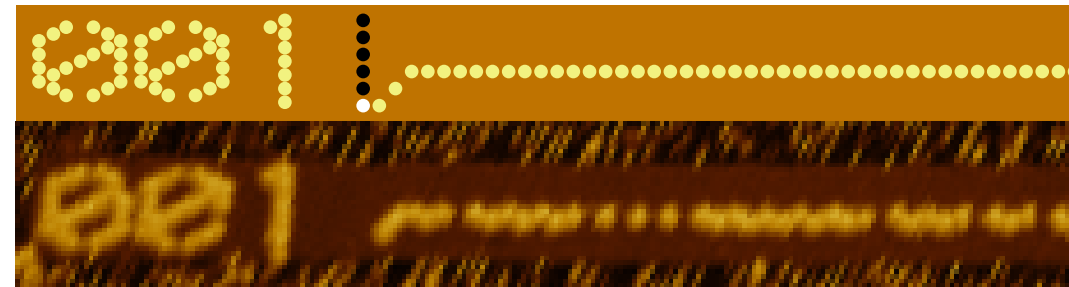


100nm

PARITY: is the number of 1s odd?

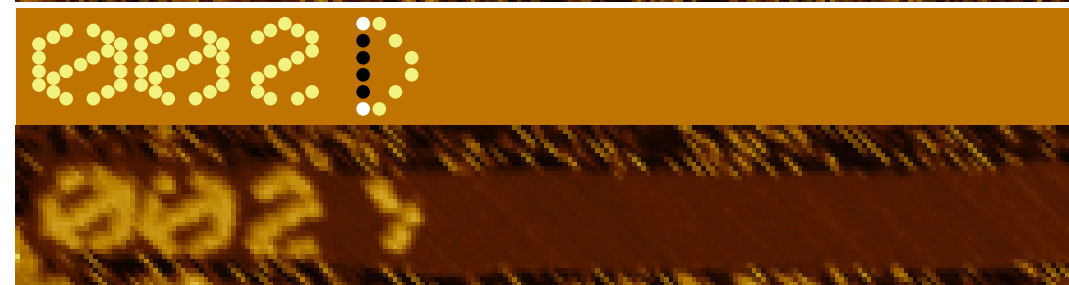


000001



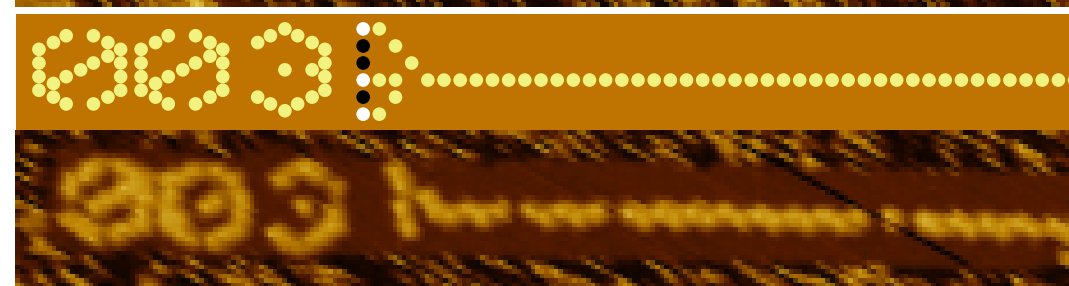
yes

100001



no

100101



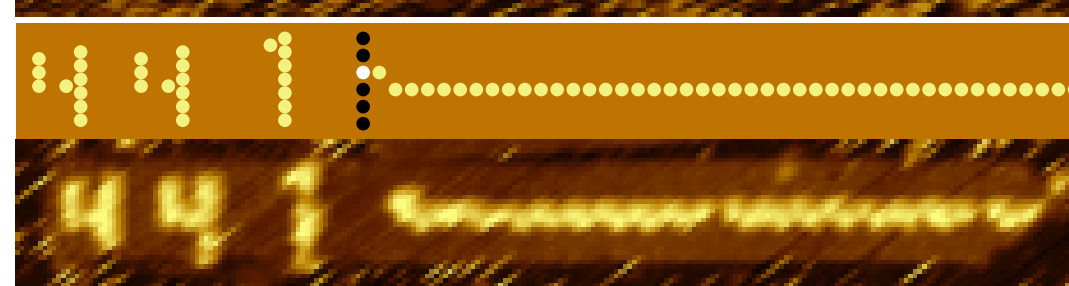
yes

110101



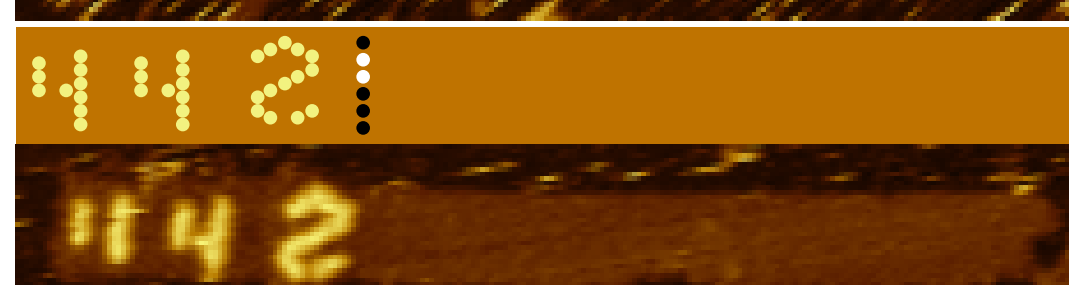
no

001000



yes

011000




no

Testing of tile set: Parity on all 64 inputs

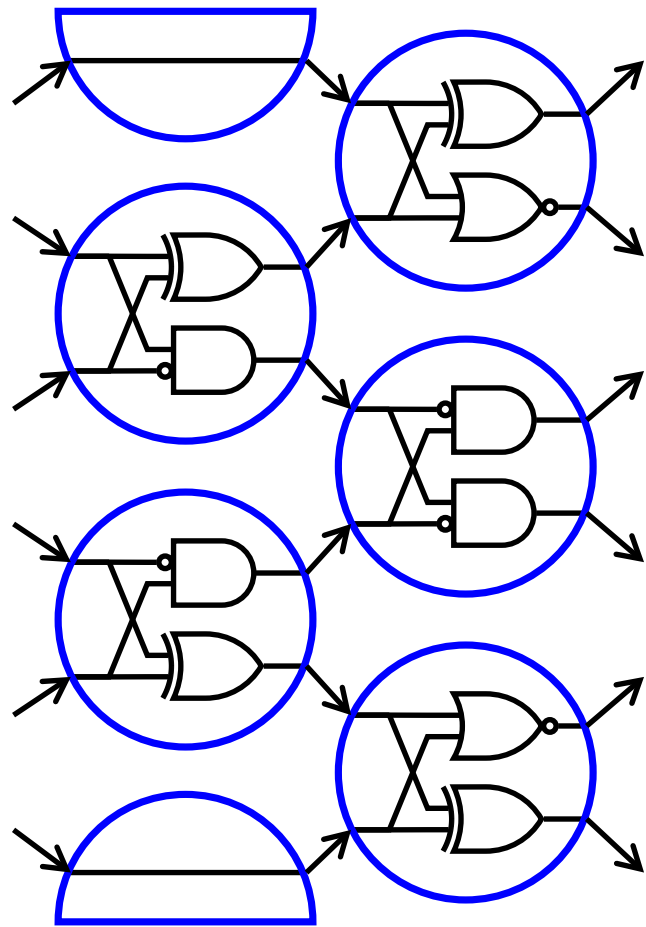
32 x No

$\sigma(000000) = 000$		$\sigma(100001) = 002$	
$\sigma(000011) = 013$		$\sigma(100010) = 212$	
$\sigma(000101) = 021$		$\sigma(100100) = 221$	
$\sigma(000110) = 022$		$\sigma(100111) = 223$	
$\sigma(001001) = 024$		$\sigma(101000) = 230$	
$\sigma(001010) = 030$		$\sigma(101011) = 233$	
$\sigma(001100) = 101$		$\sigma(101101) = 300$	
$\sigma(001111) = 110$		$\sigma(101110) = 301$	
$\sigma(010001) = 112$		$\sigma(110000) = 303$	
$\sigma(010010) = 113$		$\sigma(110011) = 333$	
$\sigma(010100) = 121$		$\sigma(110101) = 004$	
$\sigma(010111) = 130$		$\sigma(111001) = 404$	
$\sigma(011000) = 442$		$\sigma(111010) = 410$	
$\sigma(011011) = 133$		$\sigma(111100) = 420$	
$\sigma(011101) = 200$		$\sigma(111110) = 431$	
$\sigma(011110) = 201$			

32 x Yes

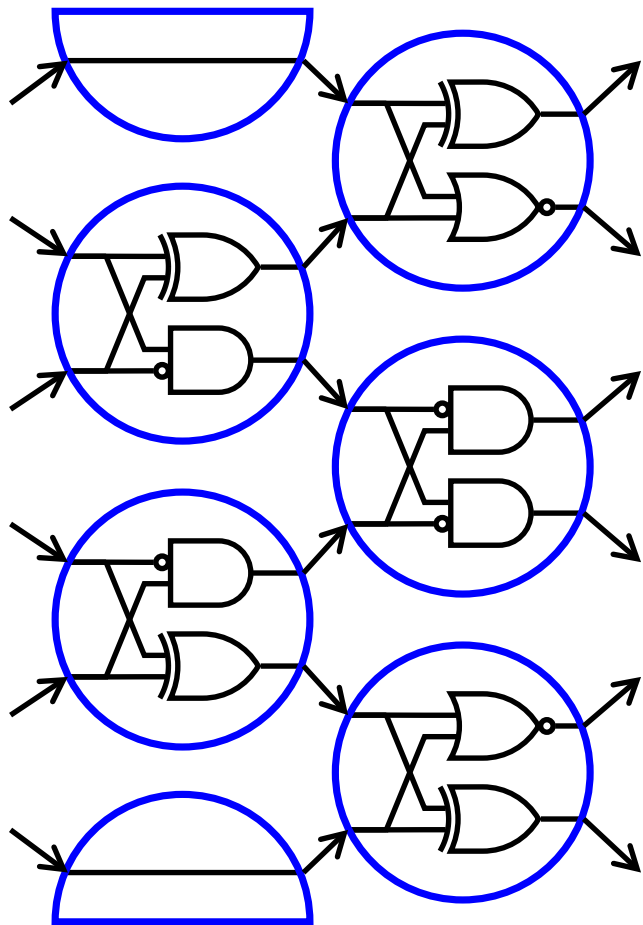
$\sigma(000001) = 001$		$\sigma(100000) = 211$	
$\sigma(000010) = 011$		$\sigma(100011) = 213$	
$\sigma(000100) = 020$		$\sigma(100101) = 003$	
$\sigma(000111) = 023$		$\sigma(100110) = 222$	
$\sigma(001000) = 441$		$\sigma(101001) = 231$	
$\sigma(001011) = 100$		$\sigma(101010) = 232$	
$\sigma(001101) = 102$		$\sigma(101100) = 234$	
$\sigma(001110) = 103$		$\sigma(101111) = 302$	
$\sigma(010000) = 111$		$\sigma(110001) = 310$	
$\sigma(010011) = 114$		$\sigma(110010) = 320$	
$\sigma(010101) = 122$		$\sigma(110100) = 330$	
$\sigma(010110) = 123$		$\sigma(110111) = 400$	
$\sigma(011001) = 131$		$\sigma(111000) = 401$	
$\sigma(011010) = 132$		$\sigma(111011) = 411$	
$\sigma(011100) = 134$		$\sigma(111101) = 421$	
$\sigma(011111) = 210$		$\sigma(111110) = 430$	

Is the input a multiple of 3?

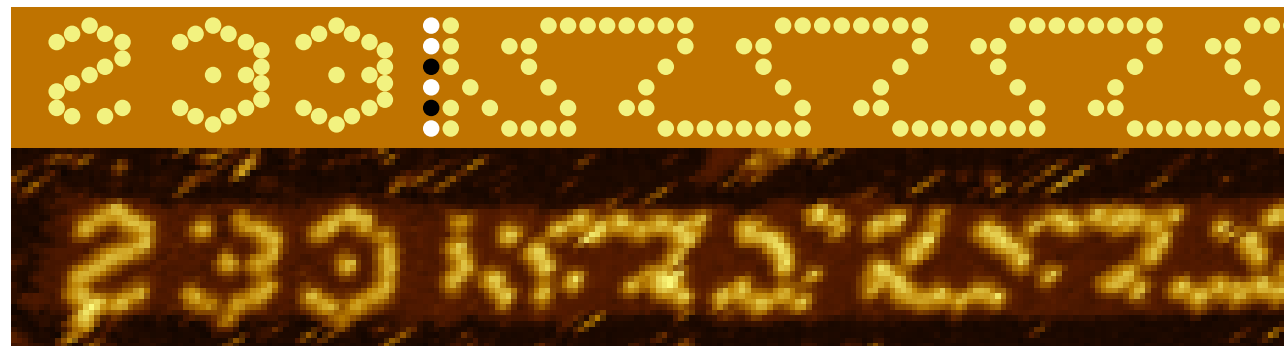


110101

Is the input a multiple of 3?

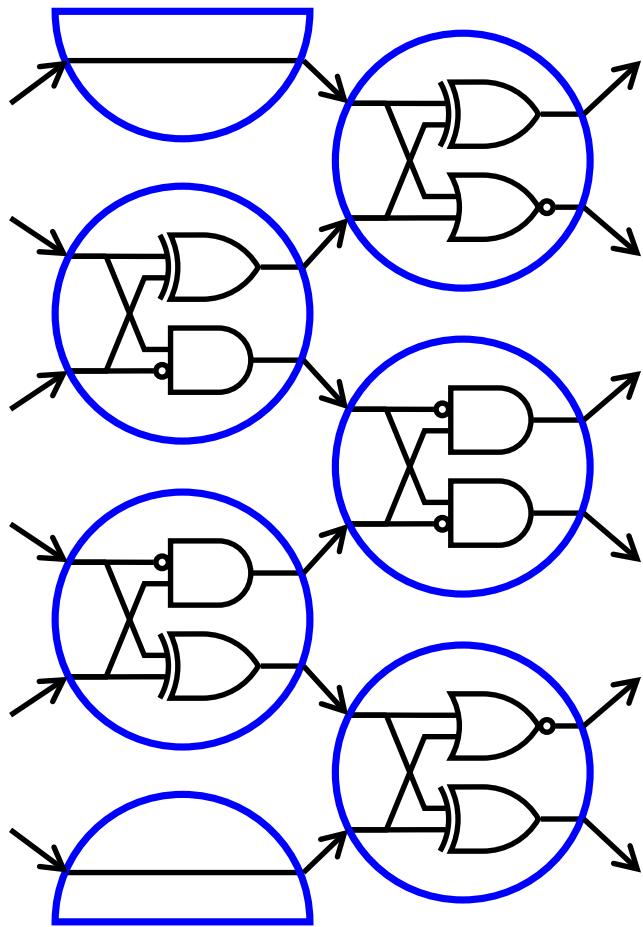


110101
=53

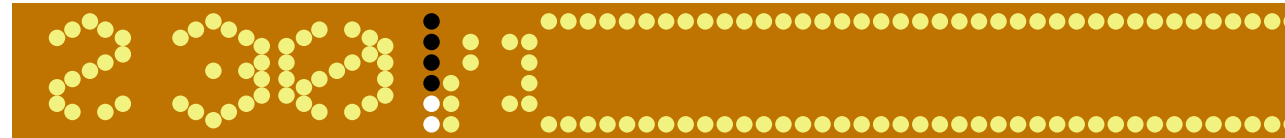


no

Is the input a multiple of 3?

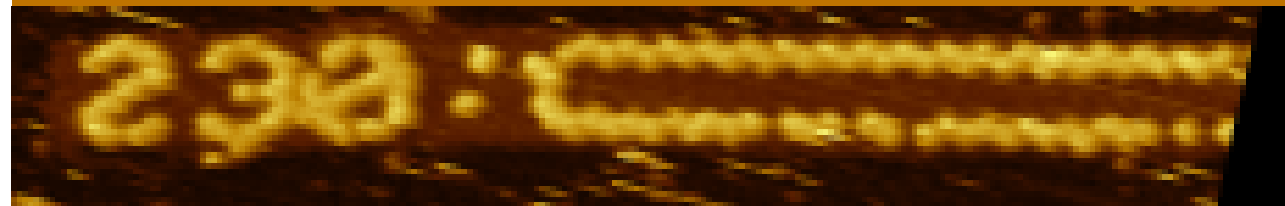


000011
=3



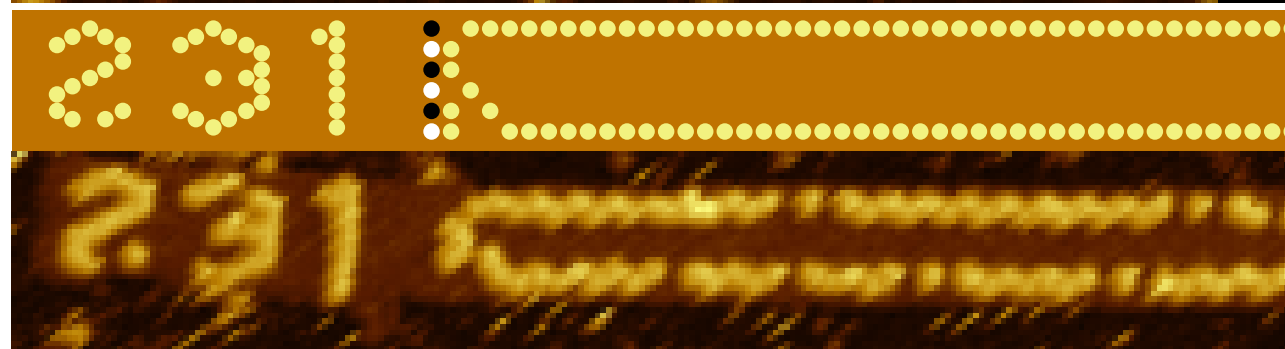
yes

010101
=21



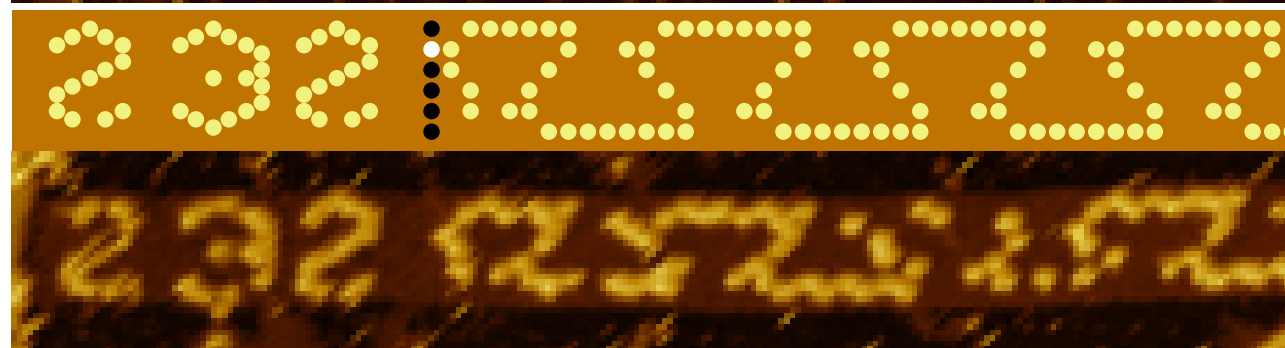
yes

010000
=16

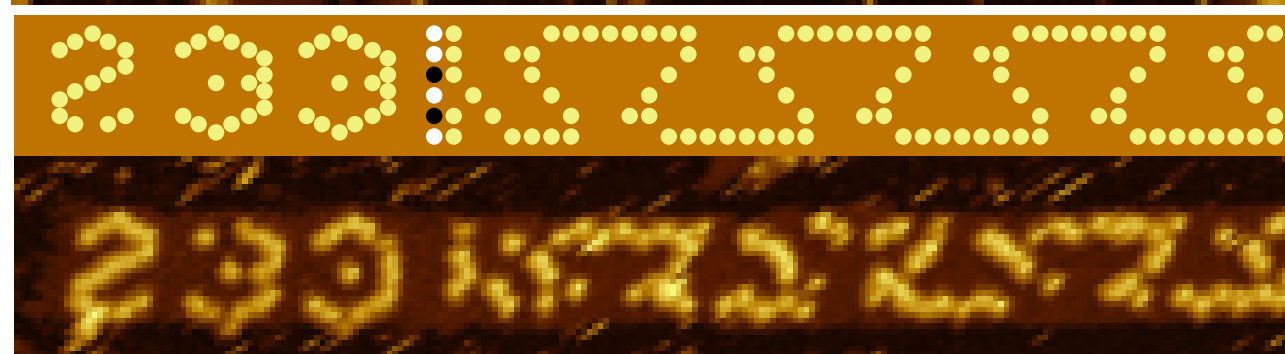


no

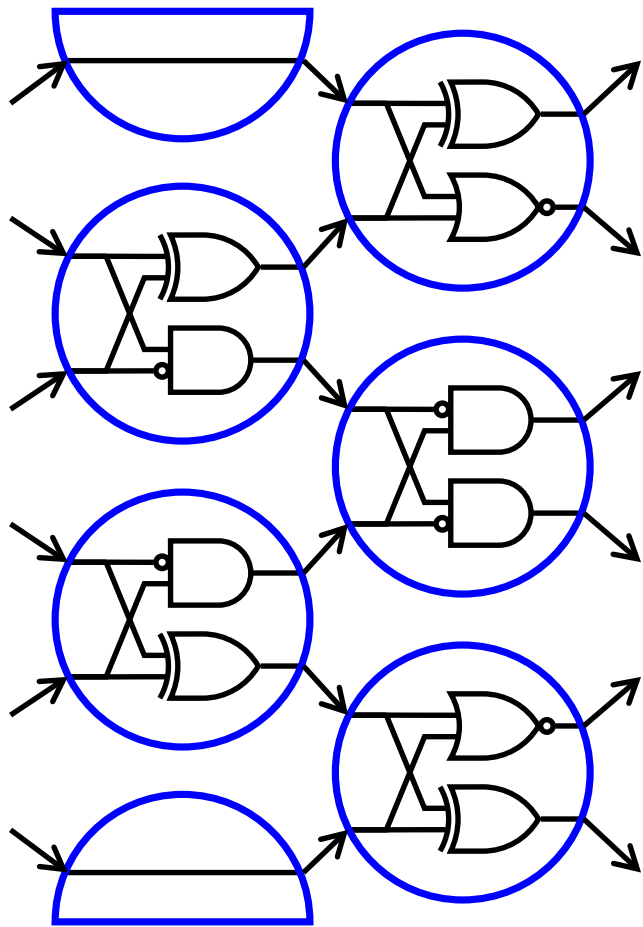
110101
=53



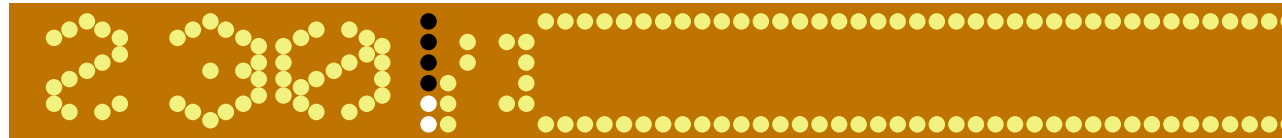
no



Is the input a multiple of 3?

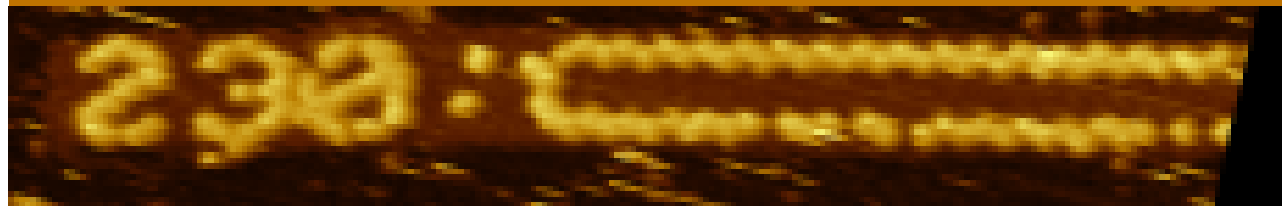


000011
=3



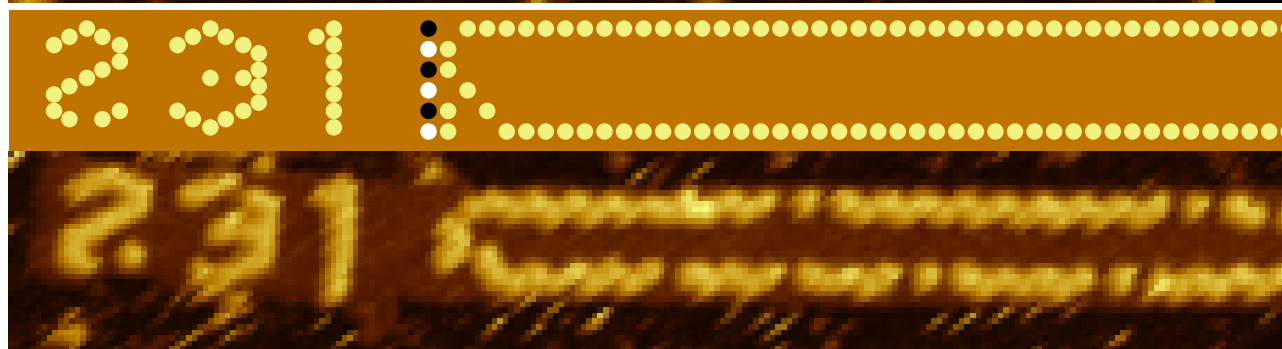
yes

010101
=21



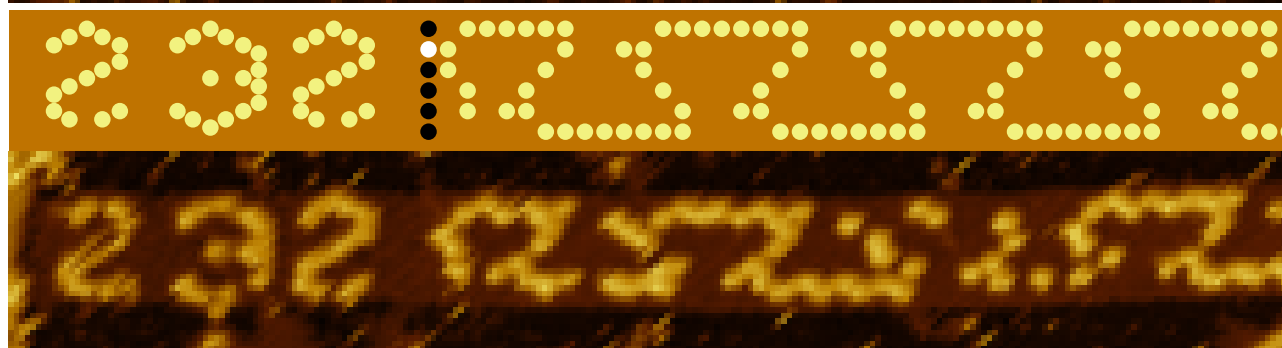
yes

010000
=16

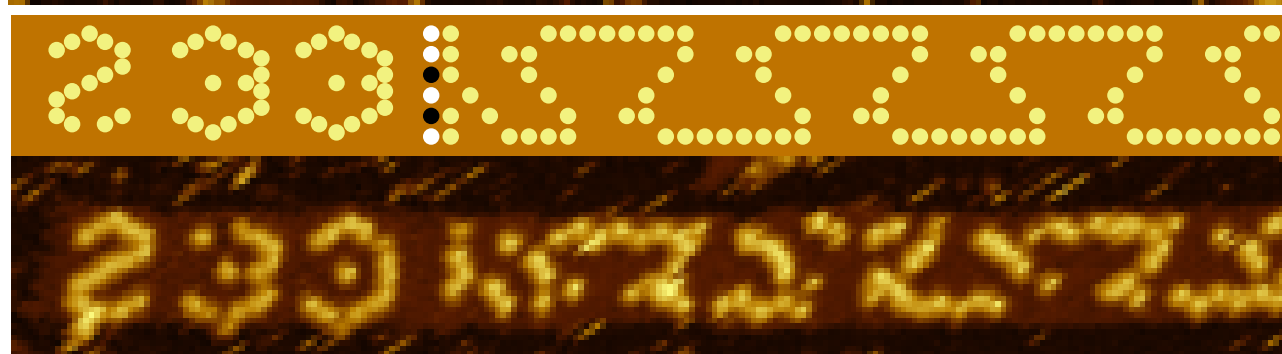


no

110101
=53



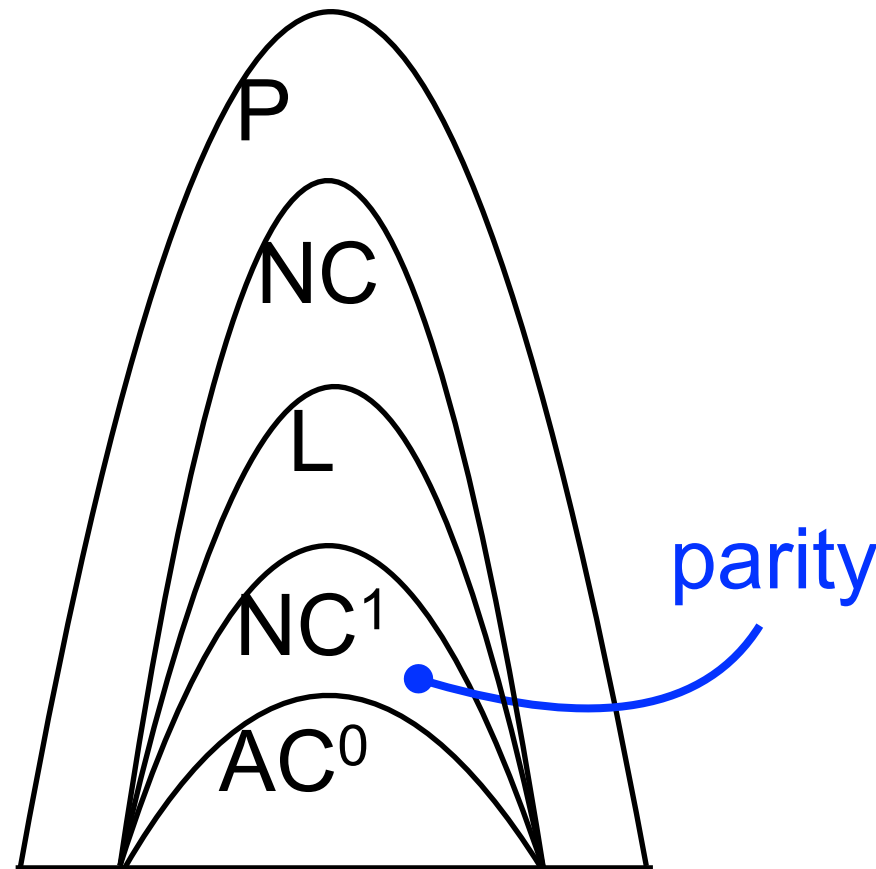
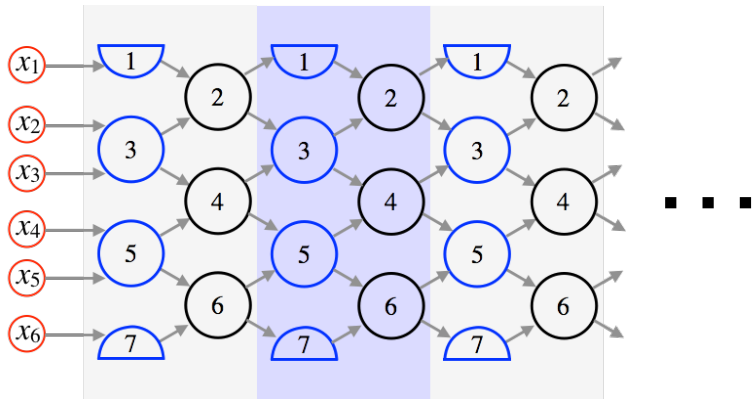
no



Erik Winfree

Computational power of this model?

The model is a rather restricted circuit model: “depth 2 layer”, restricted wiring within layer, repeated-layer, 0/1 signals on the wires. What can it compute?



Something outside AC⁰ (parity), no more than P (via explicit simulation for t layers)

Classes of problems:

AC⁰: constant depth, poly size, Boolean circuits with arbitrary fanin gates

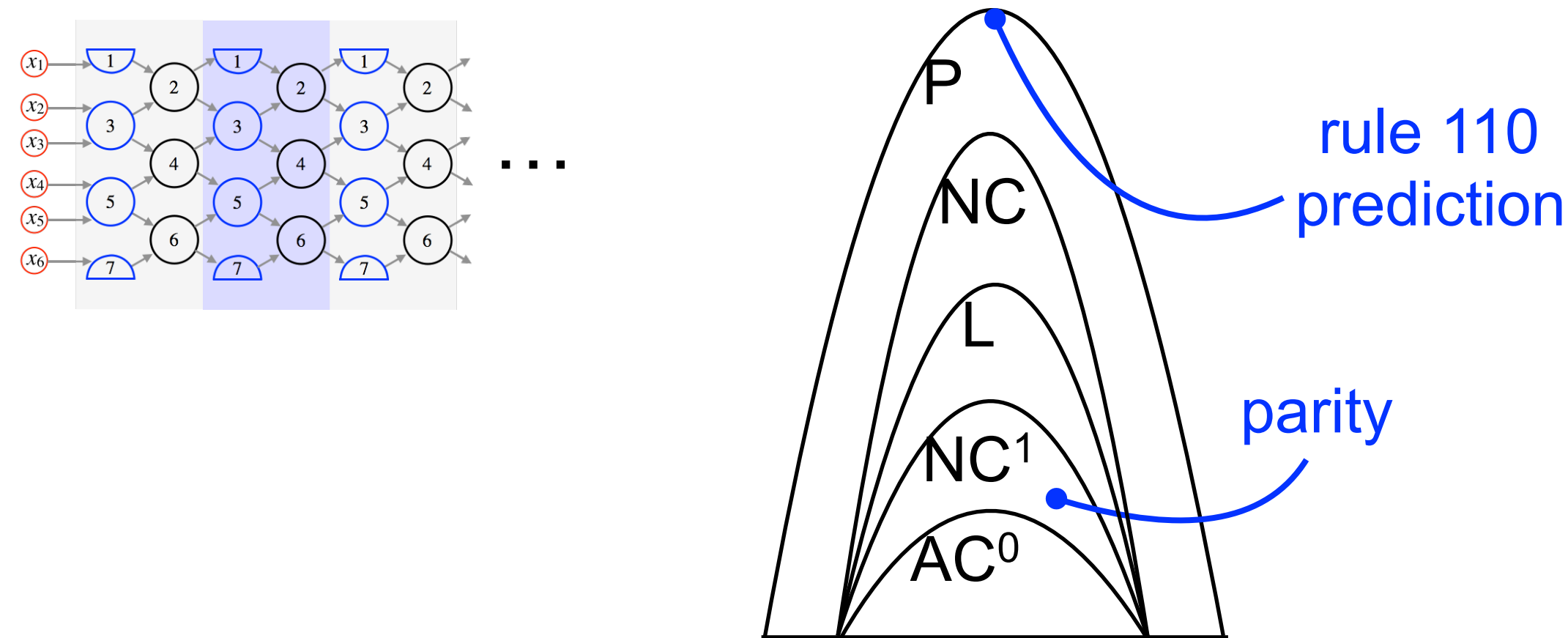
NC¹: log depth, poly size, Boolean circuits with fanin ≤ 2 gates

L: deterministic log space Turing machines

P: deterministic polynomial time Turing machines

Computational power of this model?

The model is a rather restricted circuit model: “depth 2 layer”, restricted wiring within layer, repeated-layer, 0/1 signals on the wires. What can it compute?



Something outside AC^0 (parity), no more than P (via explicit simulation for t layers)

Classes of problems:

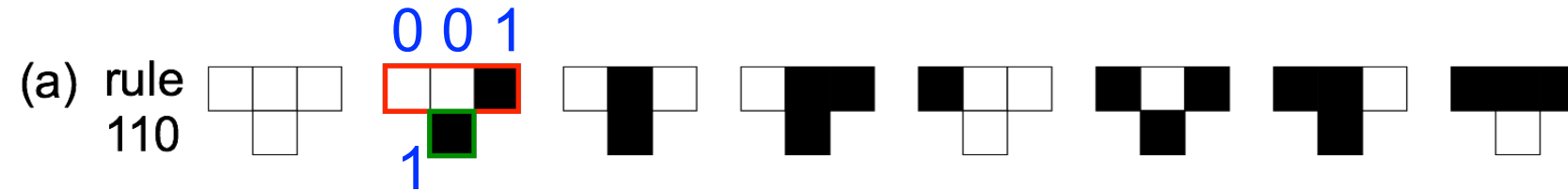
AC^0 : constant depth, poly size, Boolean circuits with arbitrary fanin gates

NC^1 : log depth, poly size, Boolean circuits with fanin ≤ 2 gates

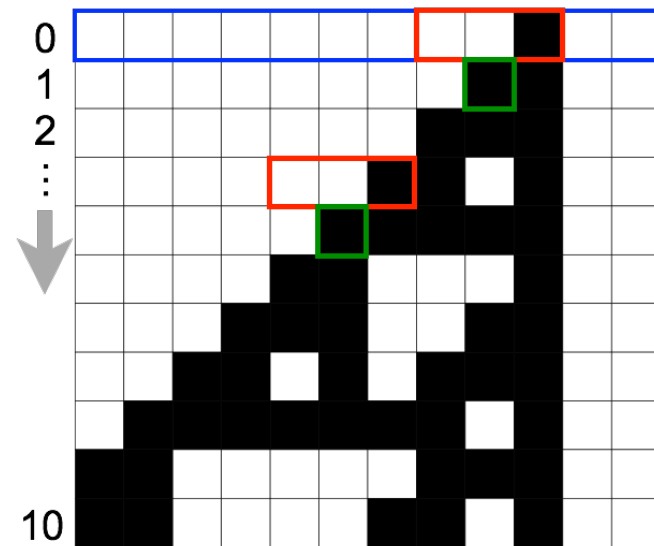
L : deterministic log space Turing machines

P : deterministic polynomial time Turing machines

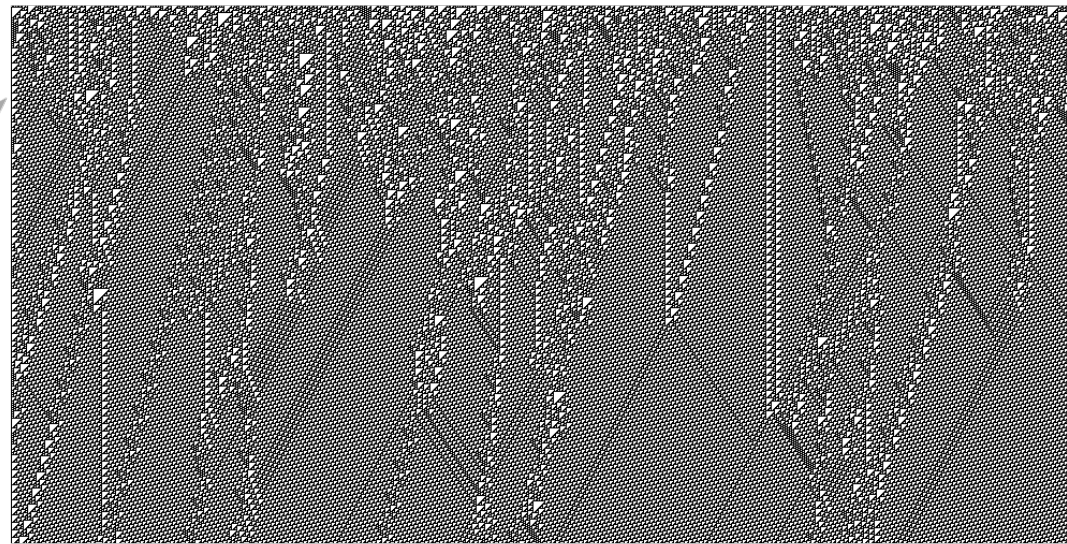
Rule 110



(b) 12-bit input, 10 time steps



(c) 1,000-bit input, 500 time steps



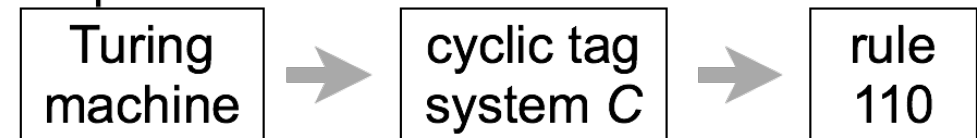
Theorem: Let M be a Turing machine that runs in time t , rule 110 simulates M in $O(t^2 \log t)$ steps

[Cook 2004]

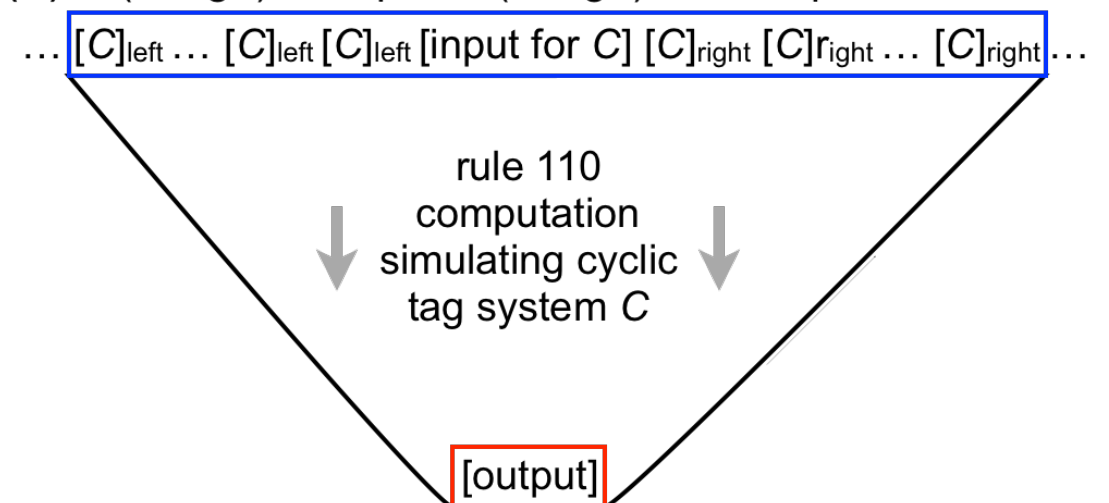
[Neary, Woods, 2006]

[Neary, PhD thesis]

(d) sequence of simulations



(e) $O(t^2 \log t)$ -bit input, $O(t^2 \log t)$ time steps



Simulation of rule 110

$x\ y\ z$
 $F(0,0,0) = 0$
 $F(0,0,1) = 1$
 $F(0,1,0) = 1$
 $F(0,1,1) = 1$

$x\ y\ z$
 $F(1,0,0) = 0$
 $F(1,0,1) = 1$
 $F(1,1,0) = 1$
 $F(1,1,1) = 0$

rule 110
truth table

x

y

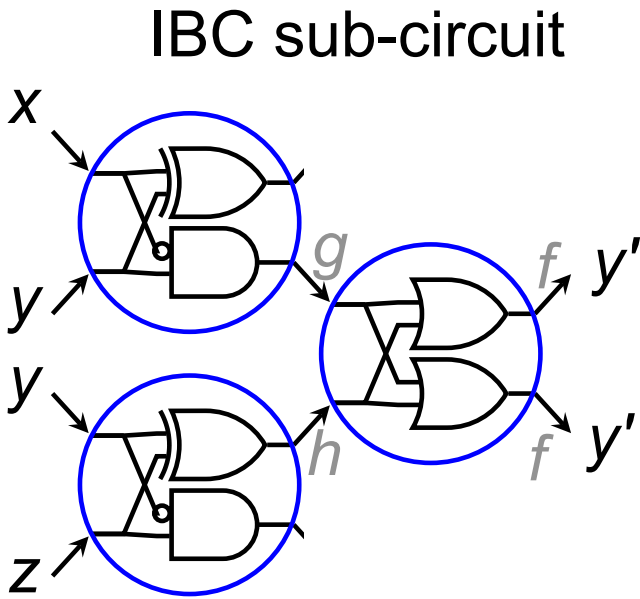
z

Express the rule as $f(g(x,y),h(y,z))$

y

y'

$$y' = (\neg x \wedge y) \vee (y \otimes z)$$



Simulation of rule 110

$x\ y\ z$
 $F(0,0,0) = 0$
 $F(0,0,1) = 1$
 $F(0,1,0) = 1$
 $F(0,1,1) = 1$

$x\ y\ z$
 $F(1,0,0) = 0$
 $F(1,0,1) = 1$
 $F(1,1,0) = 1$
 $F(1,1,1) = 0$

rule 110
truth table

x

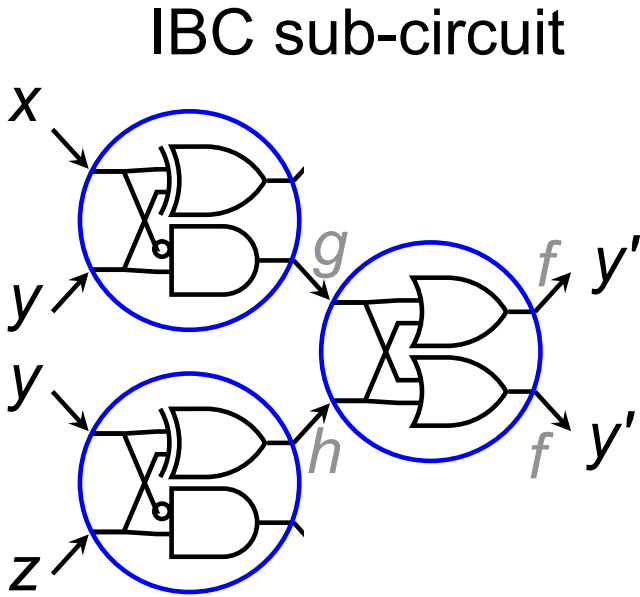
y

z

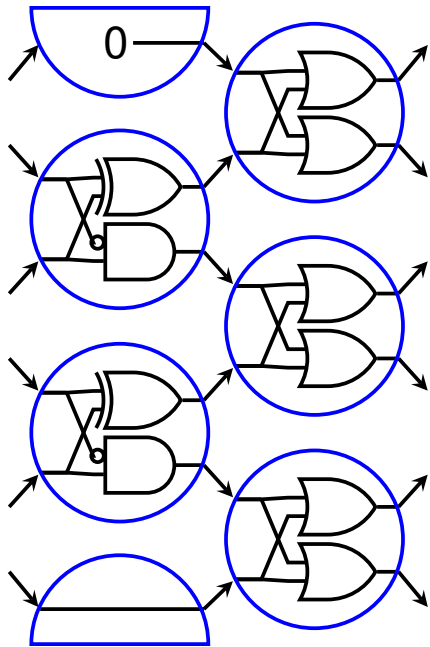
y'

Express the rule as $f(g(x,y),h(y,z))$

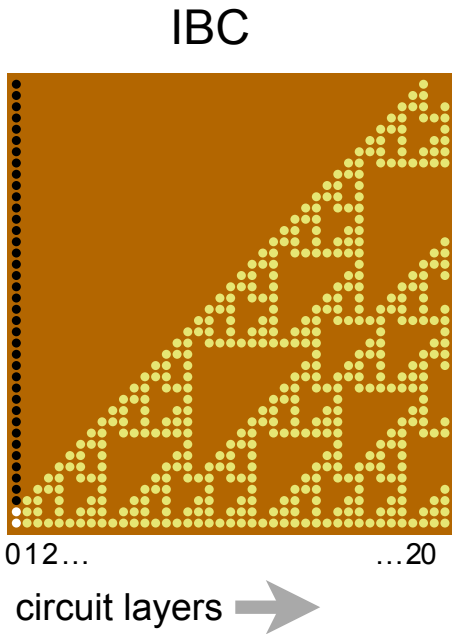
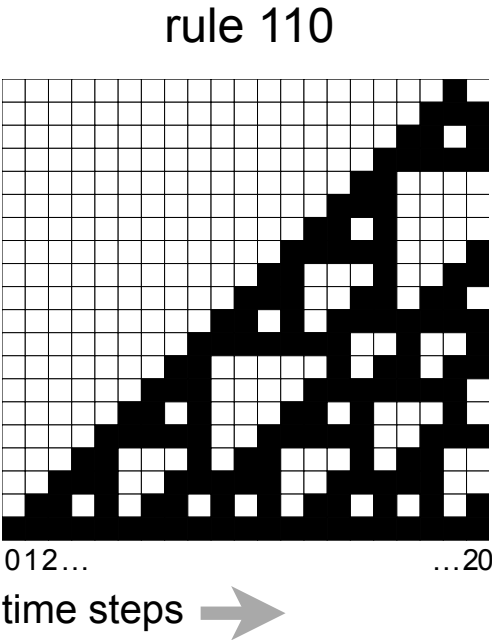
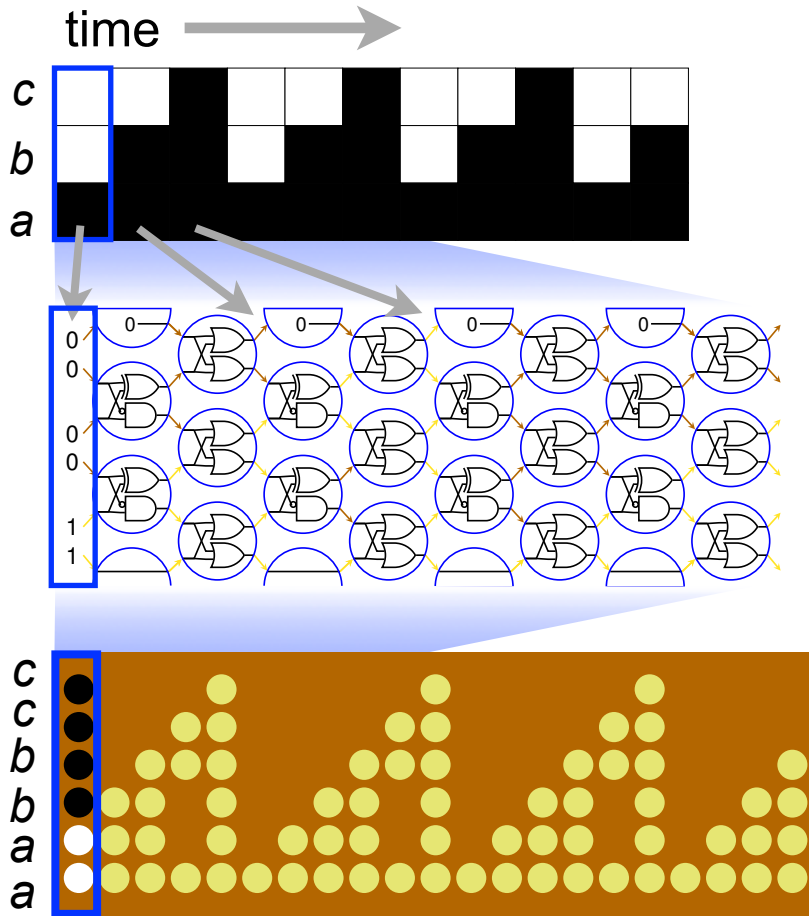
$$y' = (\neg x \wedge y) \vee (y \otimes z)$$



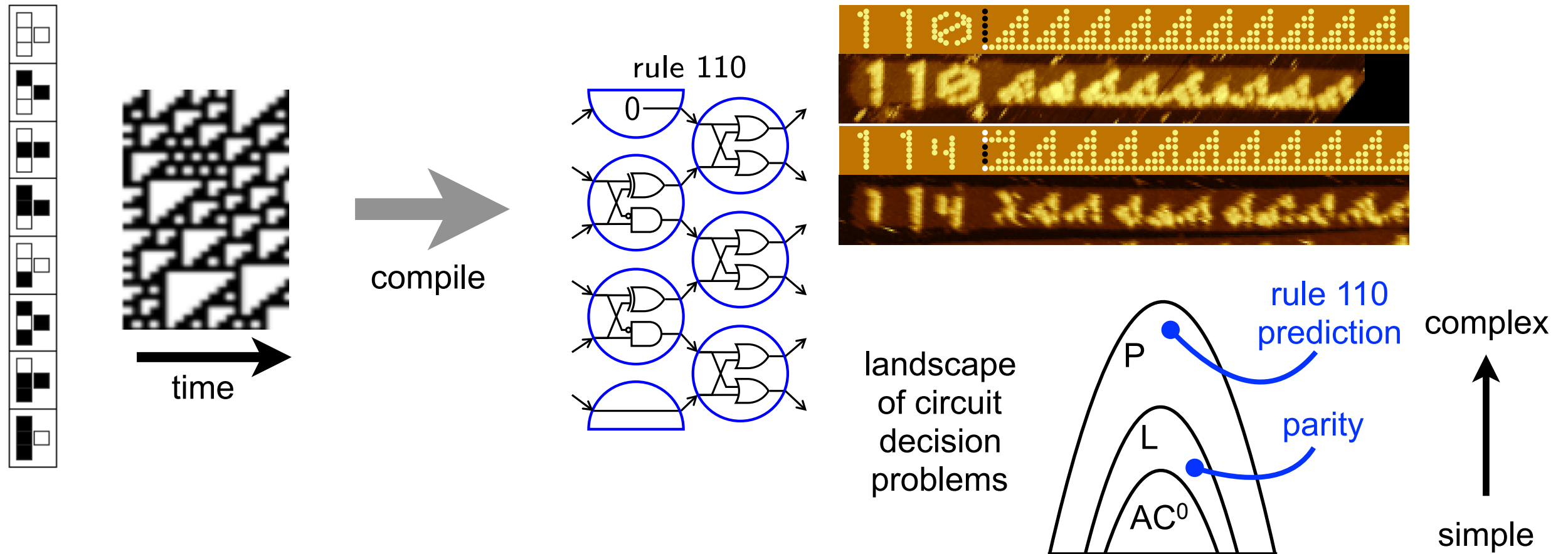
6-bit IBC to simulate
3 bits of rule 110



IBC simulation on 3 bits



RULE110 circuit: simulation of cellular automata



Theorem: Let M be a single-tape Turing machine that runs in time t , then $O(t^2 \log t)$ -bit 1-layer circuits (IBCs) simulate M

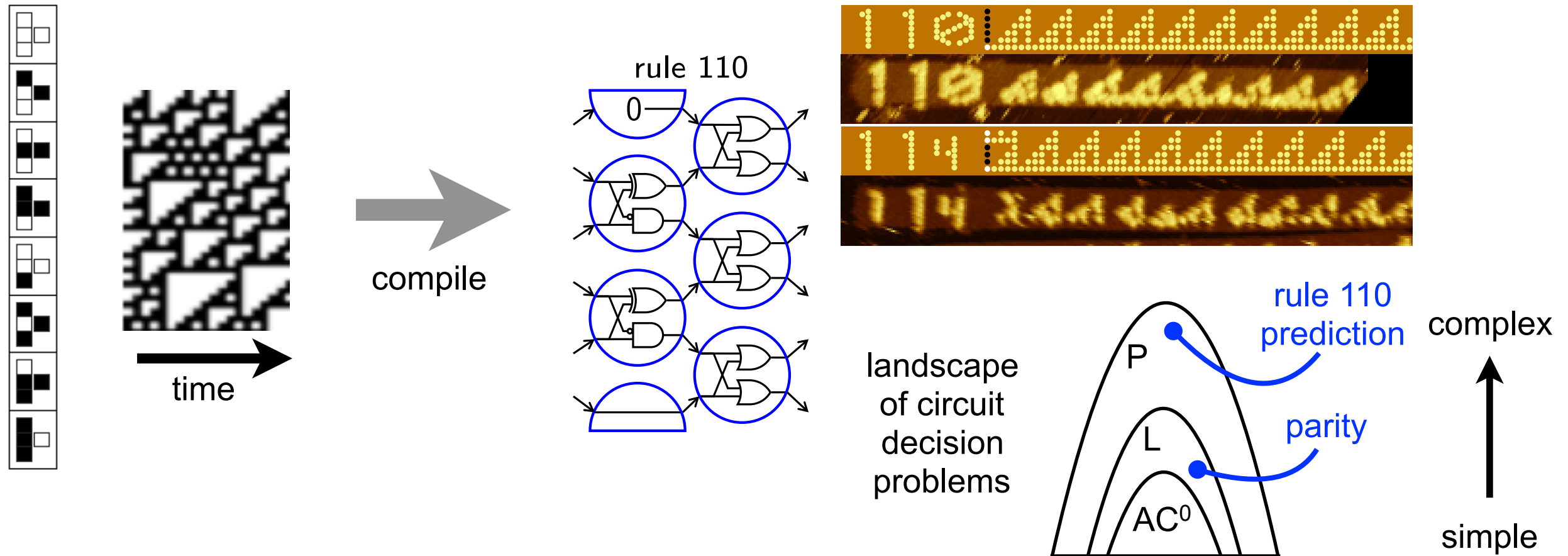
IBCs efficiently simulate any algorithm

[Cook 2004]

[Neary, Woods, 2006]

[Neary, PhD thesis]

RULE110 circuit: simulation of cellular automata



Theorem: Let M be a single-tape Turing machine that runs in time t , then $O(t^2 \log t)$ -bit 1-layer circuits (IBCs) simulate M

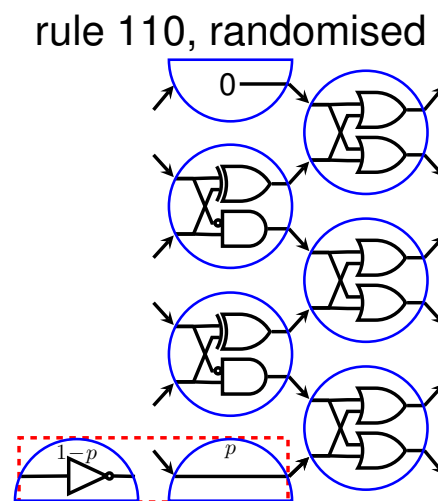
IBCs efficiently simulate any algorithm

[Cook 2004]

[Neary, Woods, 2006]

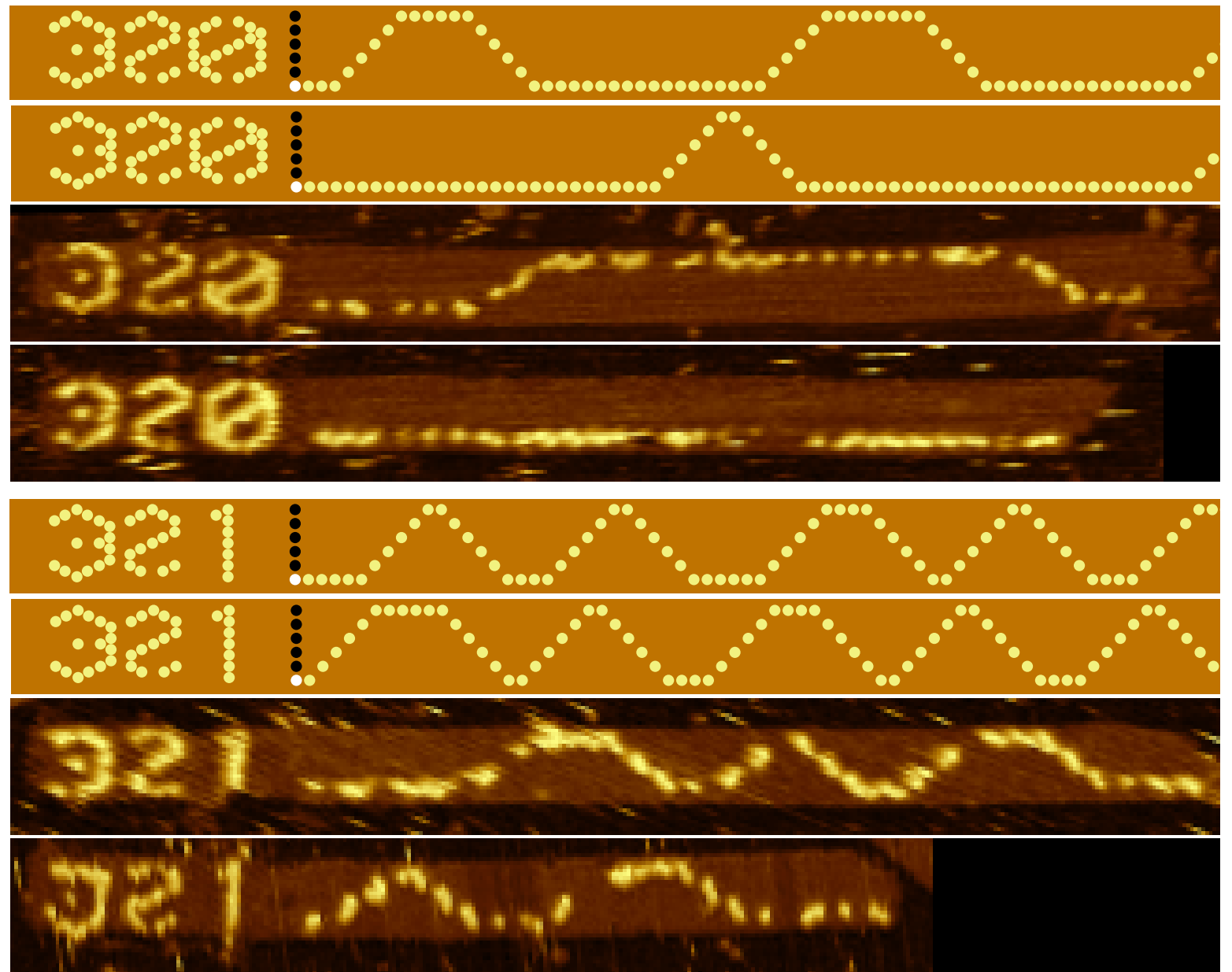
[Neary, PhD thesis]

Open: characterise power of randomised model

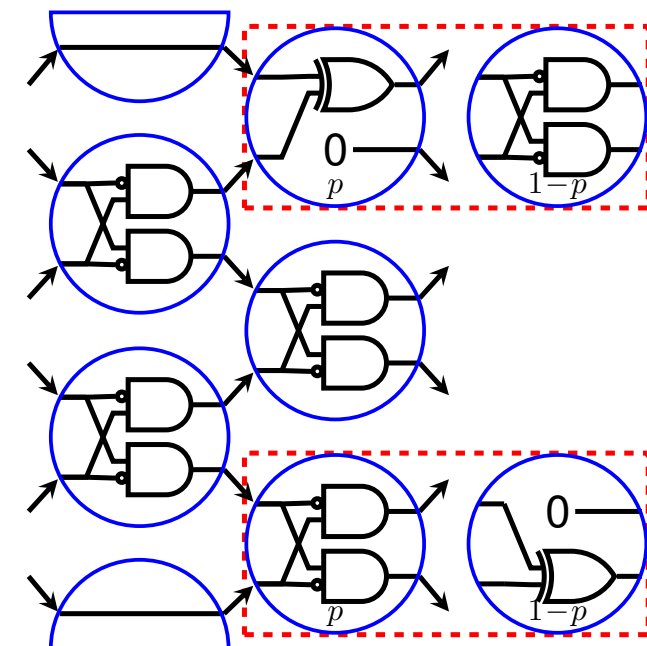


California surf: WAVES

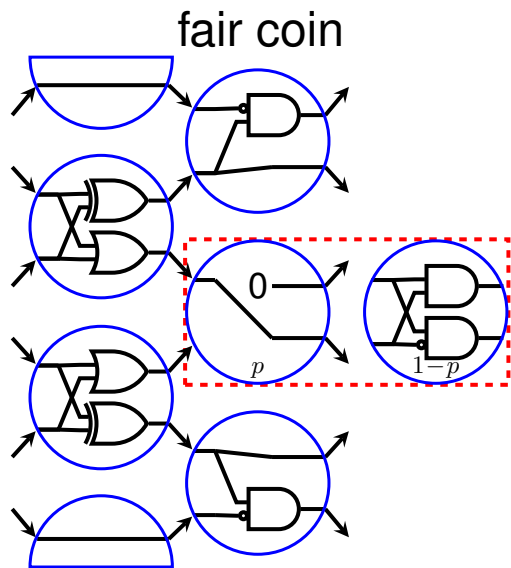
$\Pr[\text{create wave}] = 0.1$
 $\Pr[\text{crash wave}] = 0.5$



$\Pr[\text{create wave}] = 0.5$
 $\Pr[\text{crash wave}] = 0.5$



FAIRCOIN: Unbiased bit from biased coin

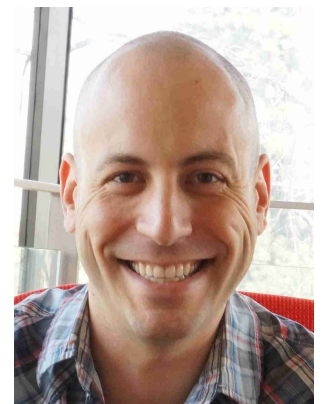
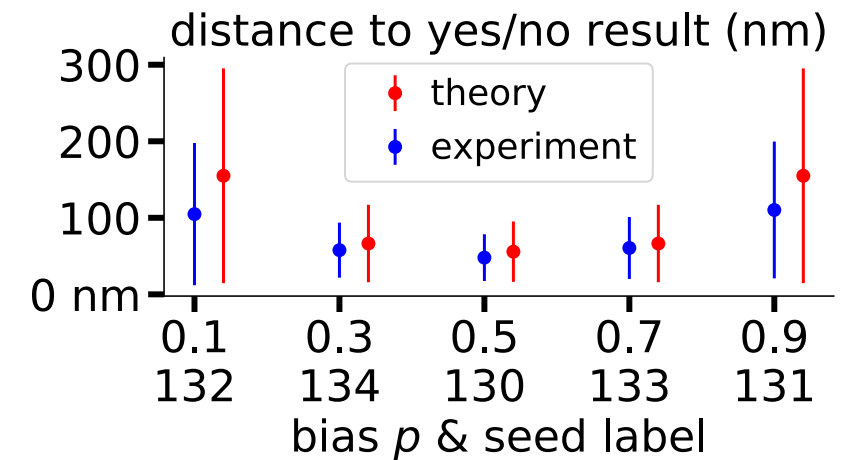
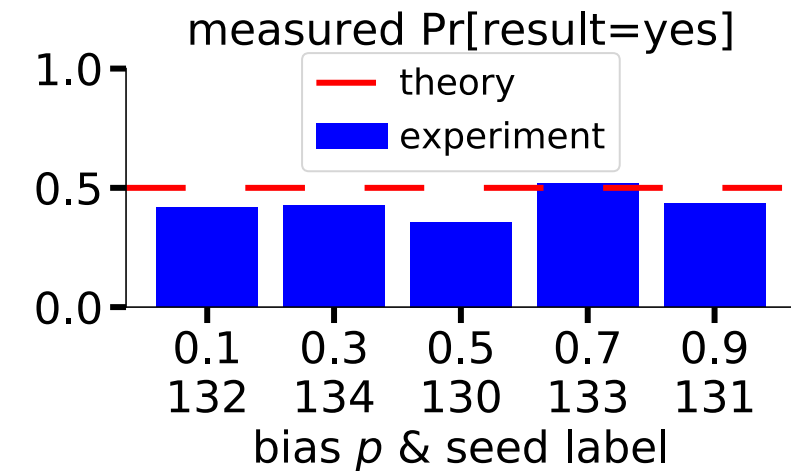
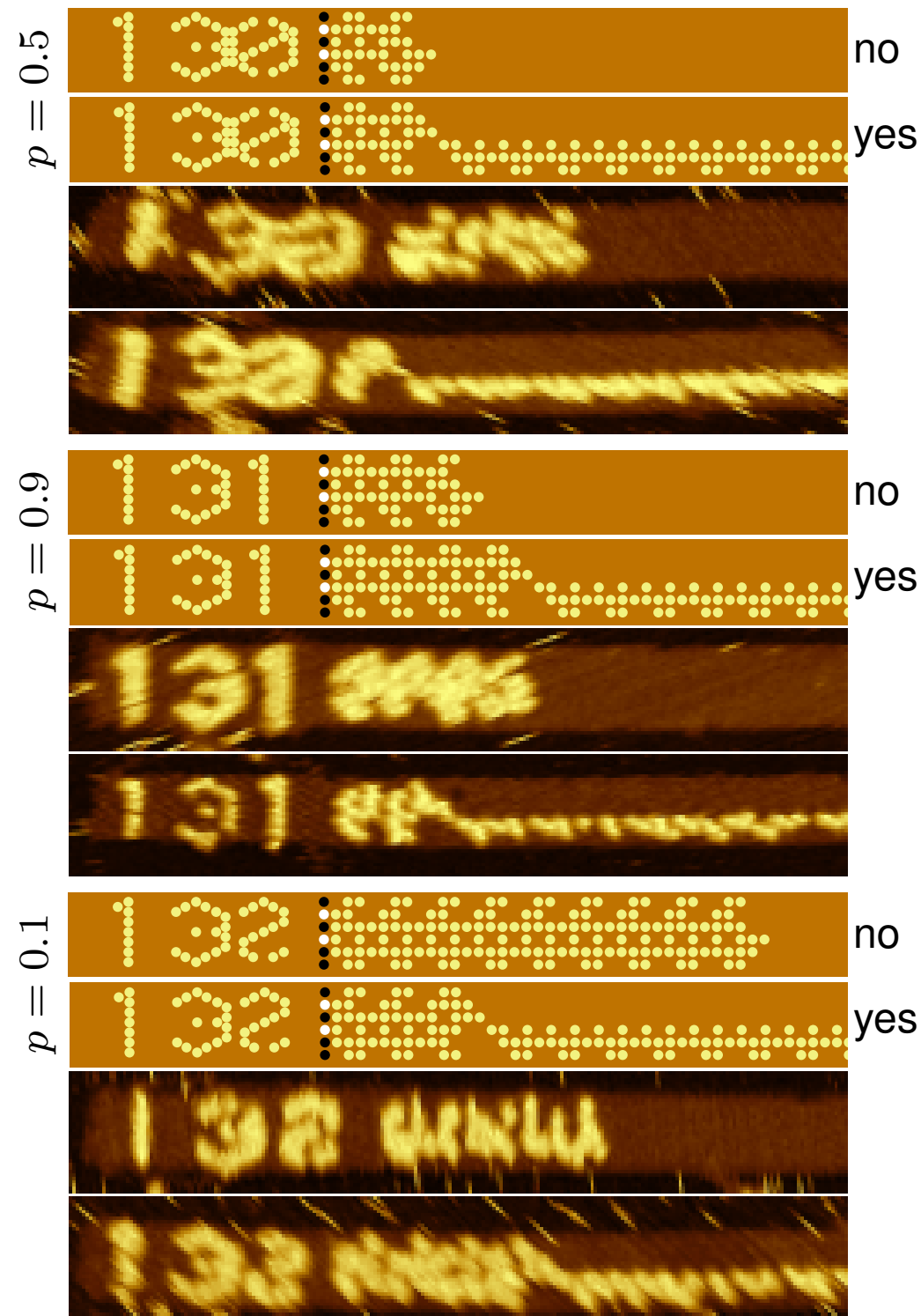


1:1

9:1

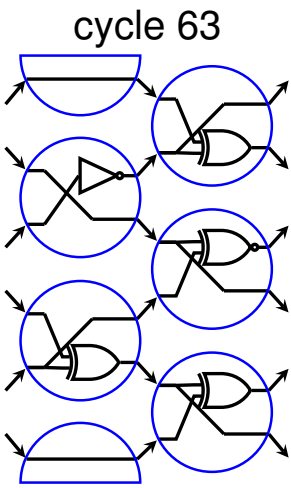
1:9

heads:tails



Dave Doty

Counting to 63



Circuit with 63 distinct strings

1 2 3 ...
↓ ↓ ↓

...62 63 1 2 ...
↓



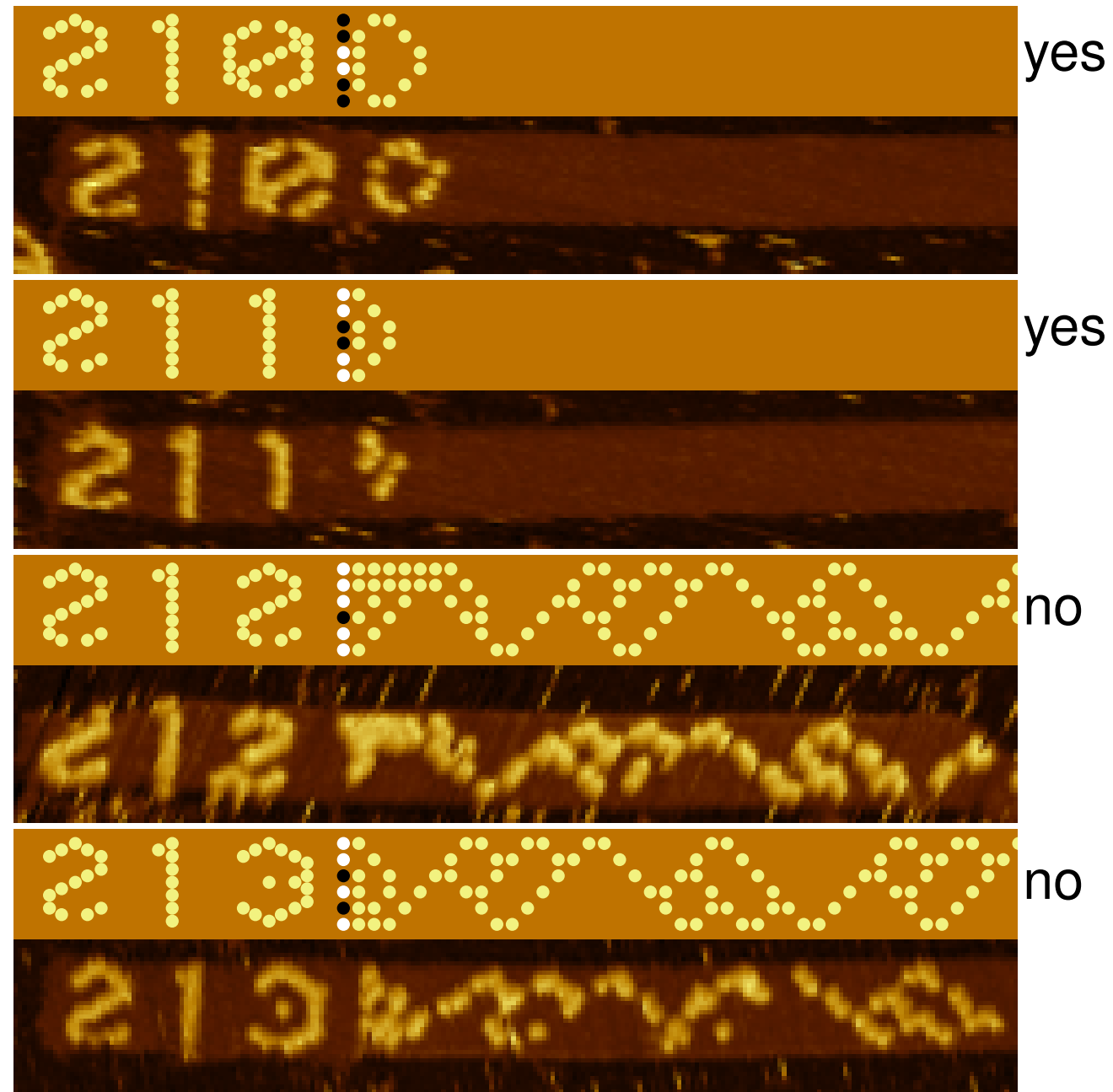
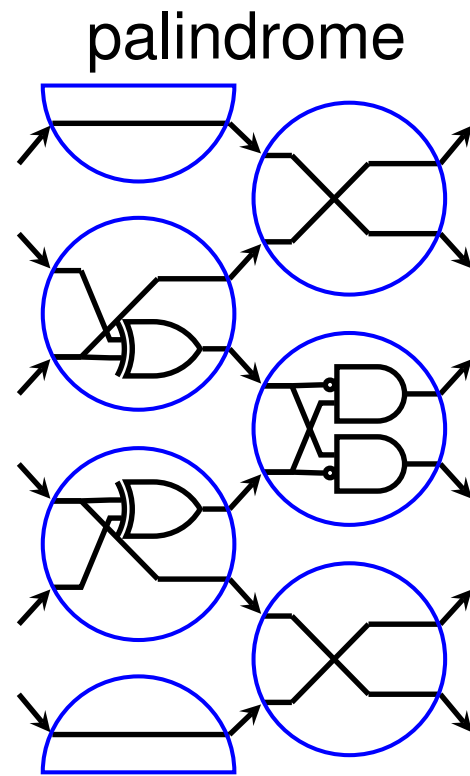
Is there a 64-counter?

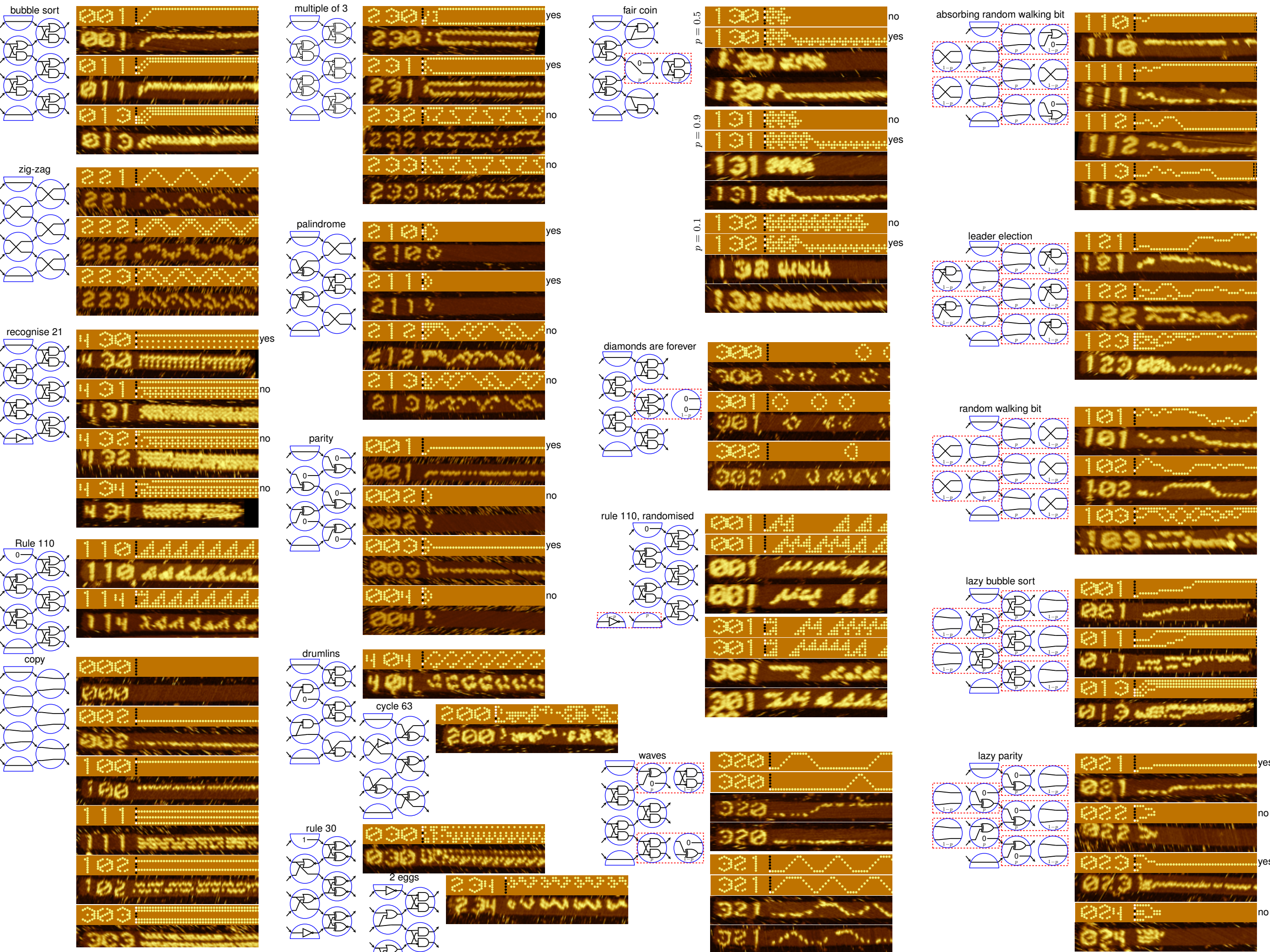
No!

Proof by Tristan Stérin, Maynooth University



Palindromes: high communication complexity



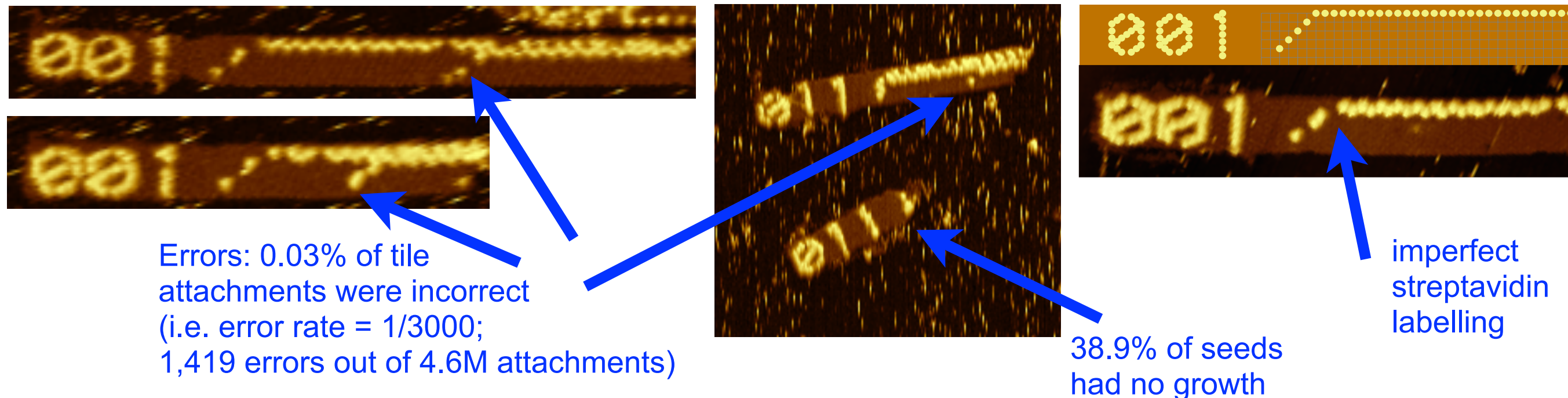


How well did the 21 circuits work?

Extensive testing of all 355 tiles:

- **every tile type** was used in some circuit
- for many circuits **tested all tile types for that circuit**
- ran one circuit on **all 64 inputs**

Analysed ~12k nanotubes with ~5M tile attachments:



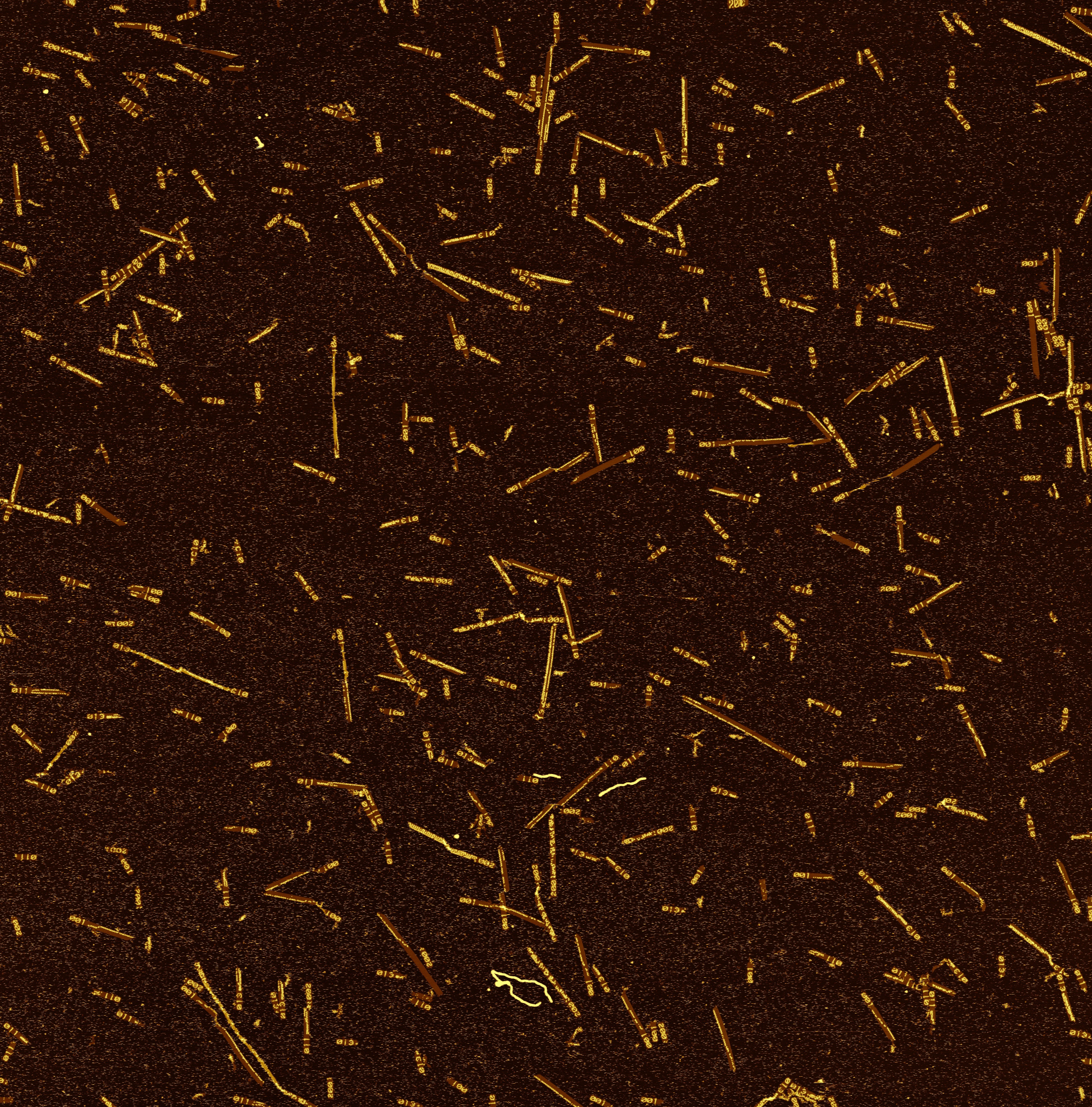
Reprogrammable: demonstrated many new self-assembly programs

Scaling up: 15x more tile types than previous algorithmic self-assembly systems

Low error: Careful sequence design; Proofreading

Good structure: Nanotube lattice & hardcoded rows

Lots of tile types: Long SST domains



raw data
8 μ m x 8 μ m

Acknowledgements



Dave Doty
UC Davis



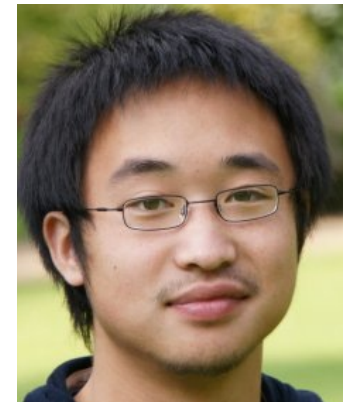
Erik Winfree
Caltech



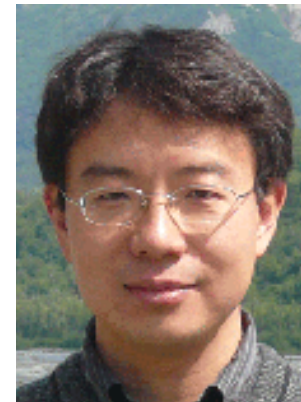
C Myhrvold
Harvard



Joy Hui
Harvard



Felix Zhou
Oxford



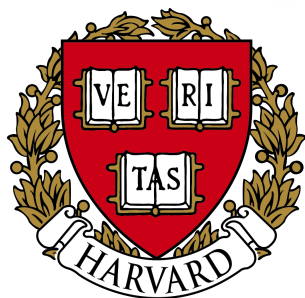
Peng Yin
Harvard



Woods, Doty, Myhrvold, Hui, Zhou, Yin, Winfree.
*Diverse and robust molecular algorithms using
reprogrammable DNA self-assembly.*
Nature. 567 (7748), 366 2019



UC Davis

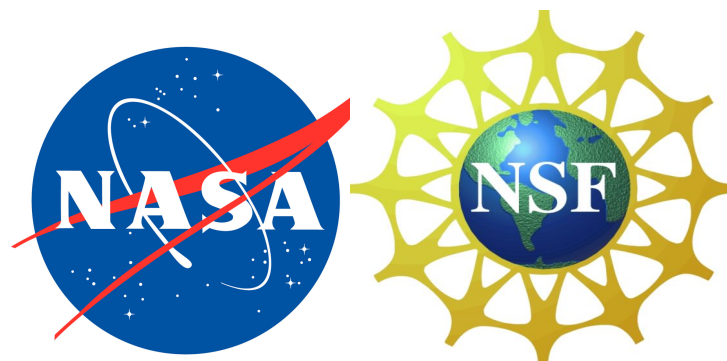


Harvard



**Maynooth
University**
National University
of Ireland Maynooth

Special thanks to: Constantine Evans, Ashwin Gopinath, Paul
Rothmund, Sungwook Woo, Cody Geary, Cris Moore, Chris
Thachuk, Rizal Hariadi, Rebecca Schulman



- 1219274 Doty, Woods
- 1162589 Winfree Yin Doty Woods
- 0832824 & 1317694 Molecular Programming Project. Winfree et al.
- NASA #NNX13AJ56G. Woods.

Fin?

Ongoing and future work:

- Self-assembly
- Molecular robotics
- Self-replication

We are looking for postdocs and PhD students!

damien.woods@mu.ie



**Maynooth
University**
National University
of Ireland Maynooth

