Design of geometric molecular bonds, à la Reed-Solomon

Workshop on coding techniques for synthetic biology

University of Illinois, Urbana-Champaign

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Department of Computer Science
University of California, Davis

Experimental background: Structural DNA nanotechnology

a.k.a. DNA carpentry

DNA origami

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

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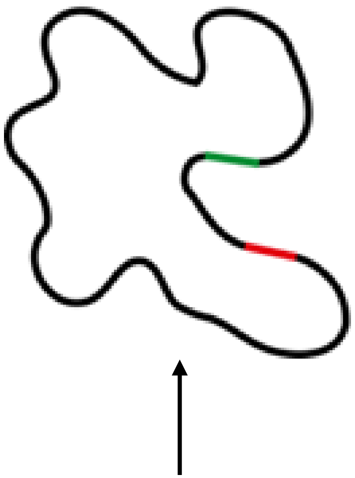

scaffold DNA strand

(M13mp18 bacteriophage virus)

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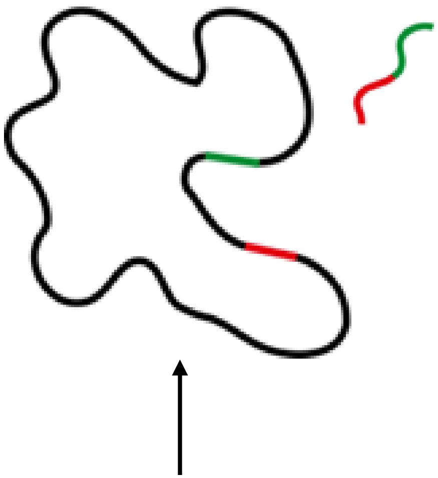

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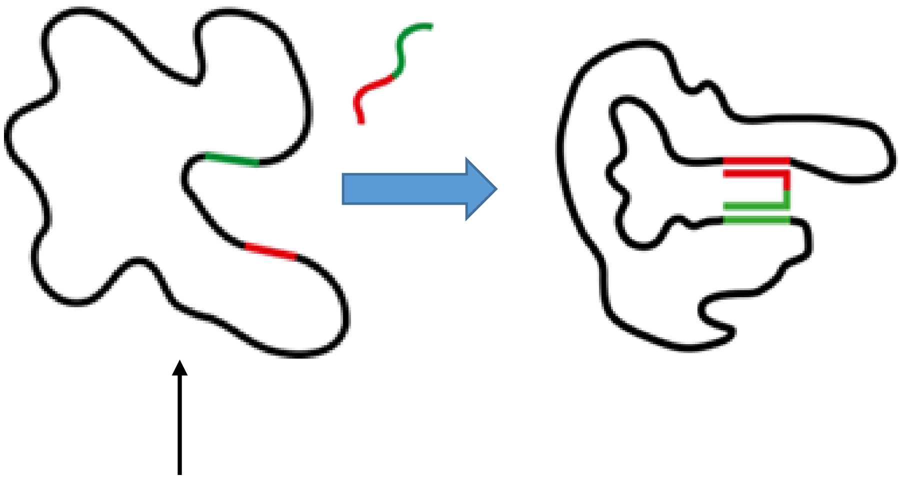

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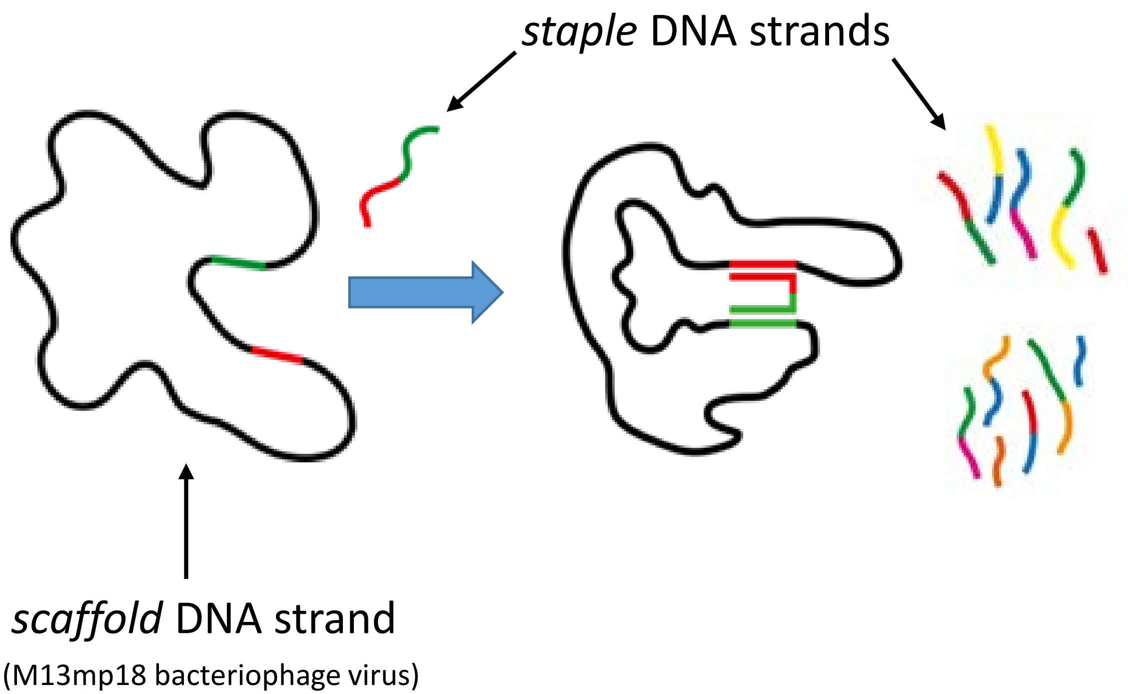

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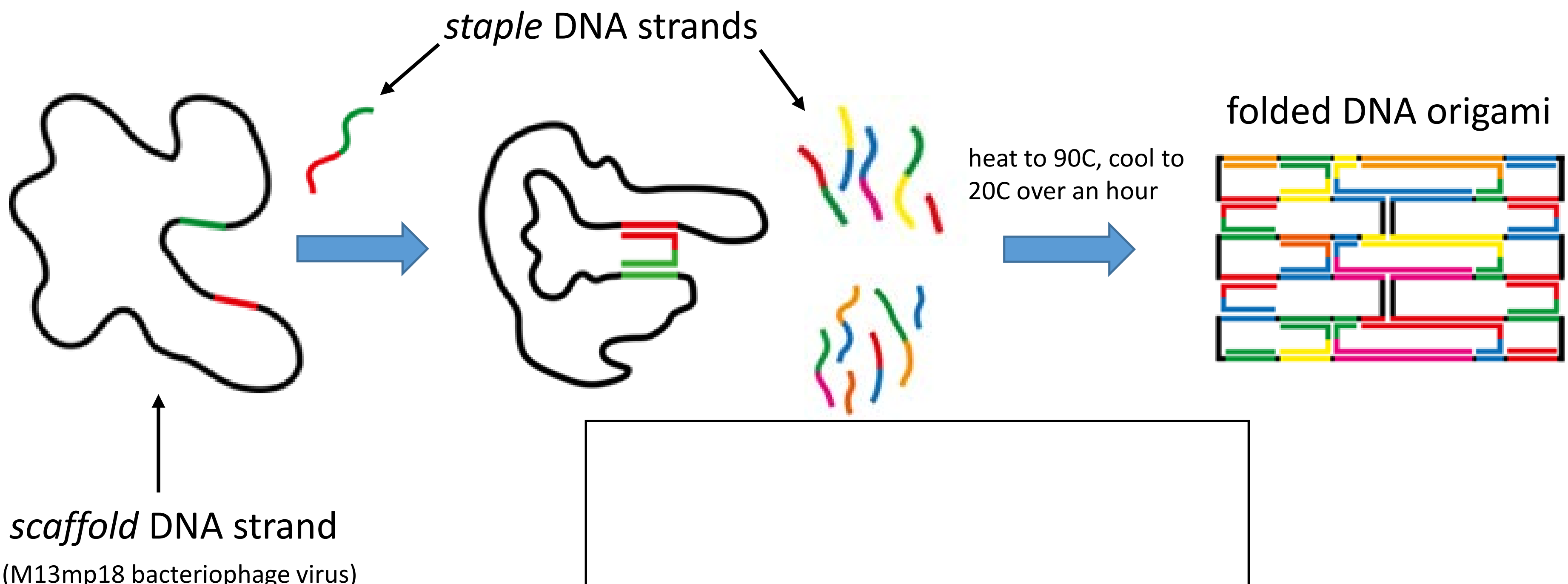

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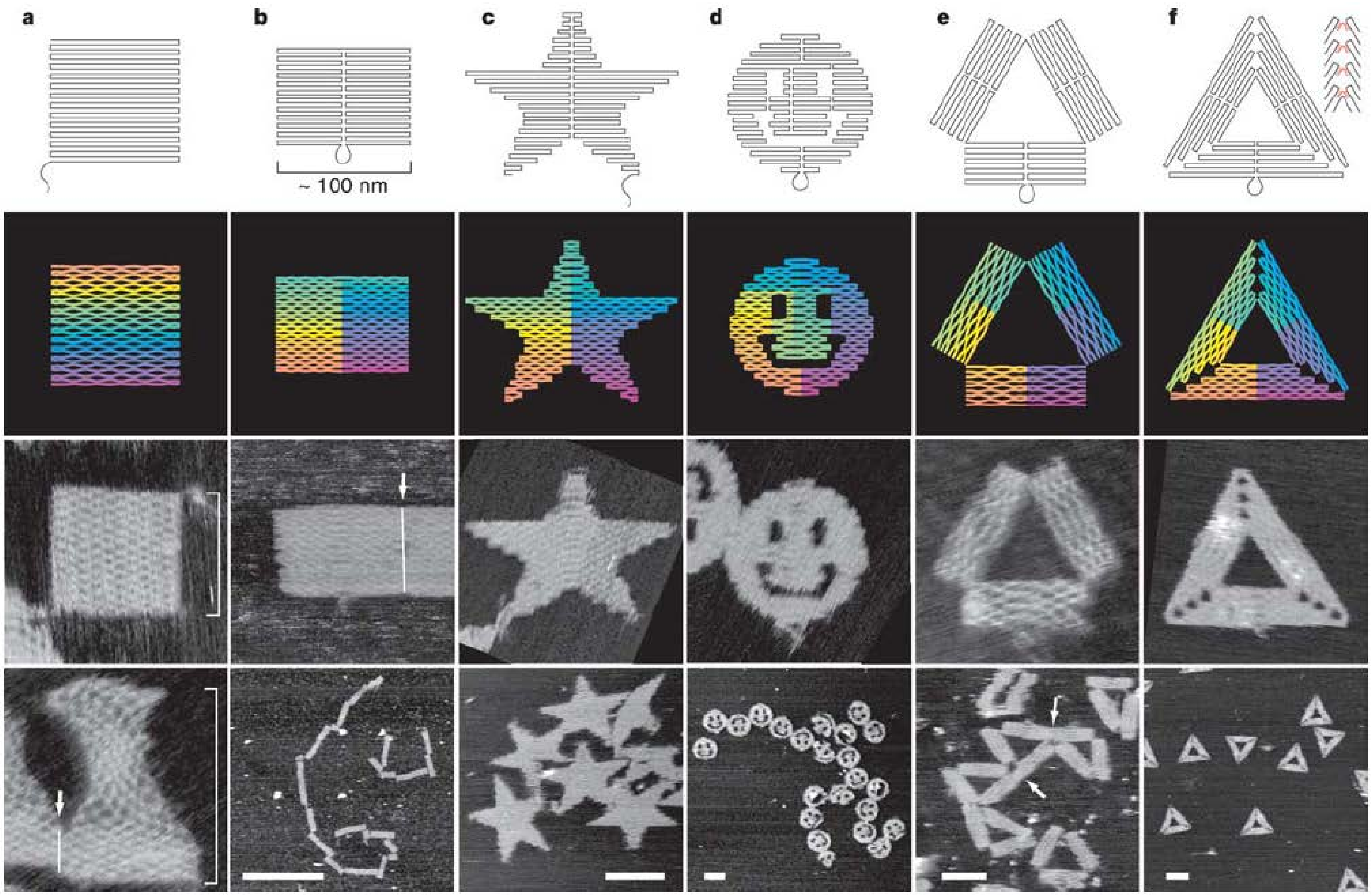
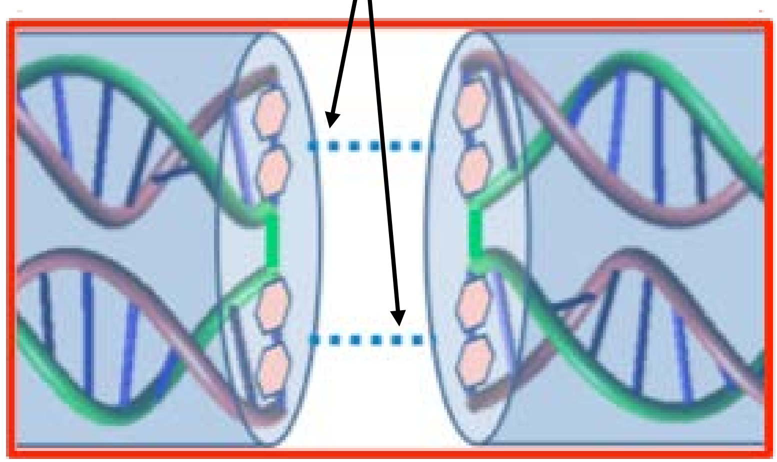


Atomic force microscope images

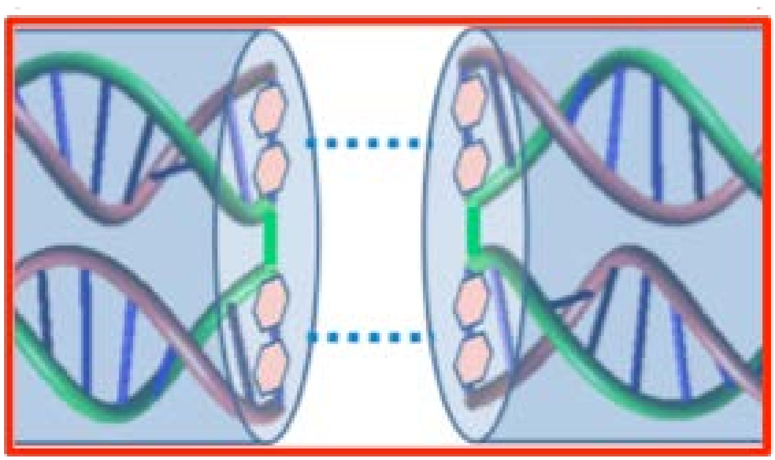
100 nm

DNA stacking interactions between blunt ends

nonspecific attractive interactions



Stacking at edges of DNA origami



Sungwook Woo, Paul Rothemund
Programmable molecular recognition based on the geometry of DNA nanostructures
Nature Chemistry 2011

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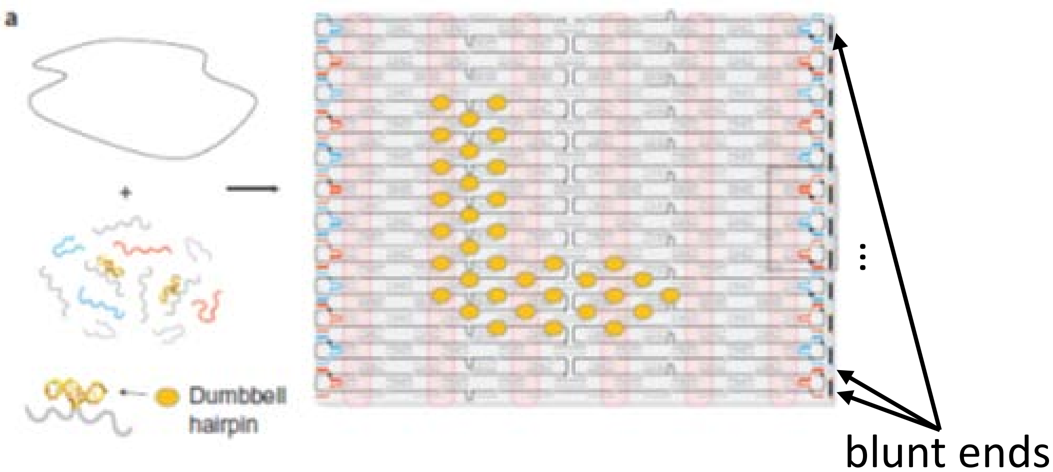

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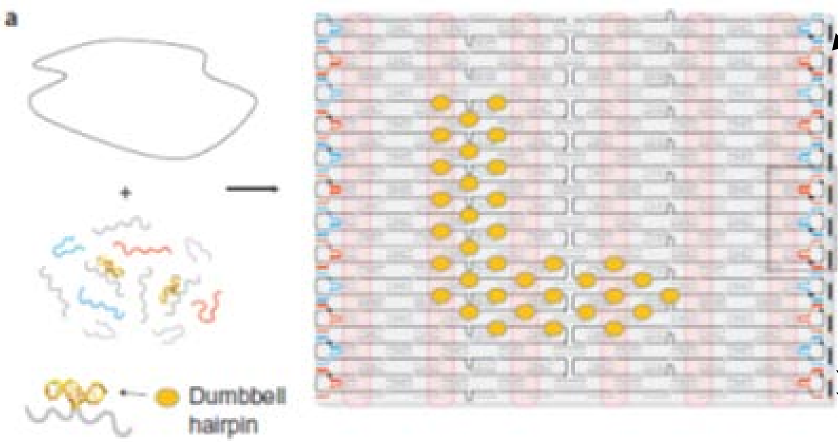
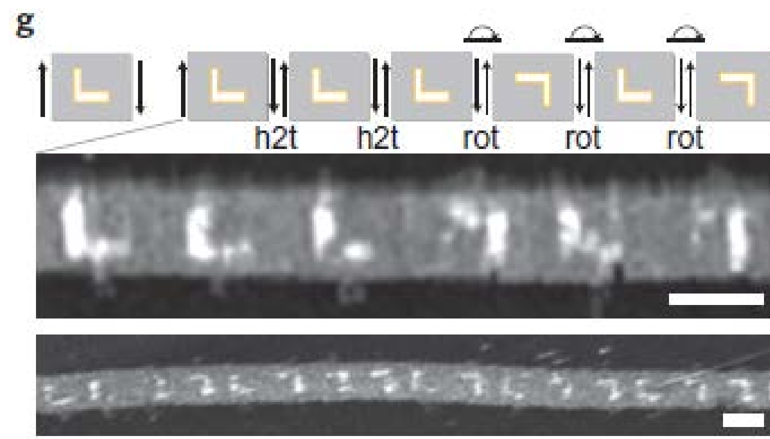


blunt ends



scale bars: 100nm

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Programming <u>specific</u> macrobonds through geometric arrangement of <u>nonspecific</u> bonds (“patches”)

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staple left out to
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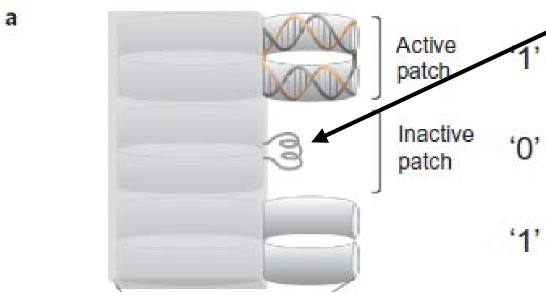

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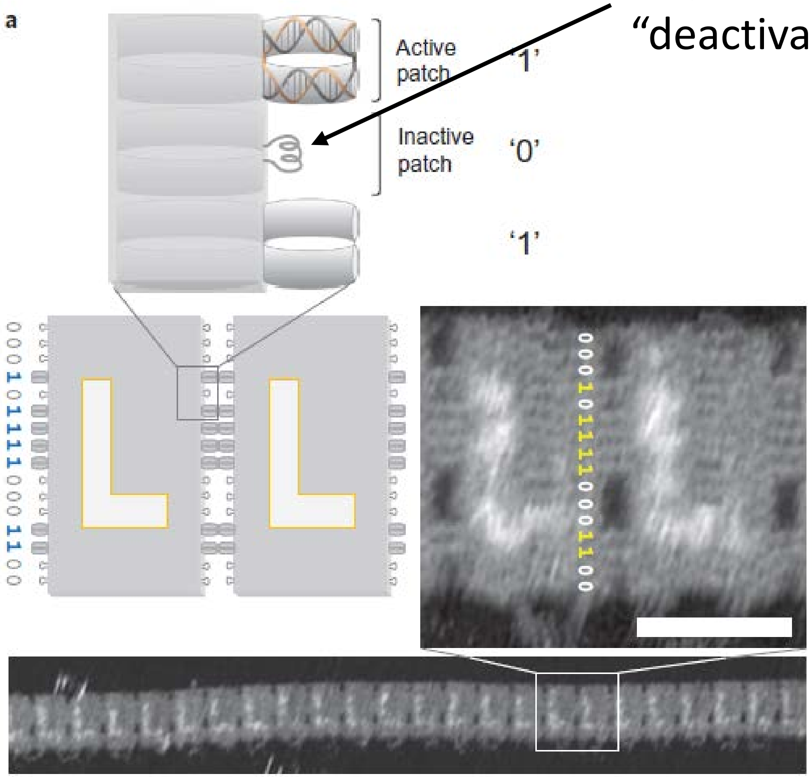

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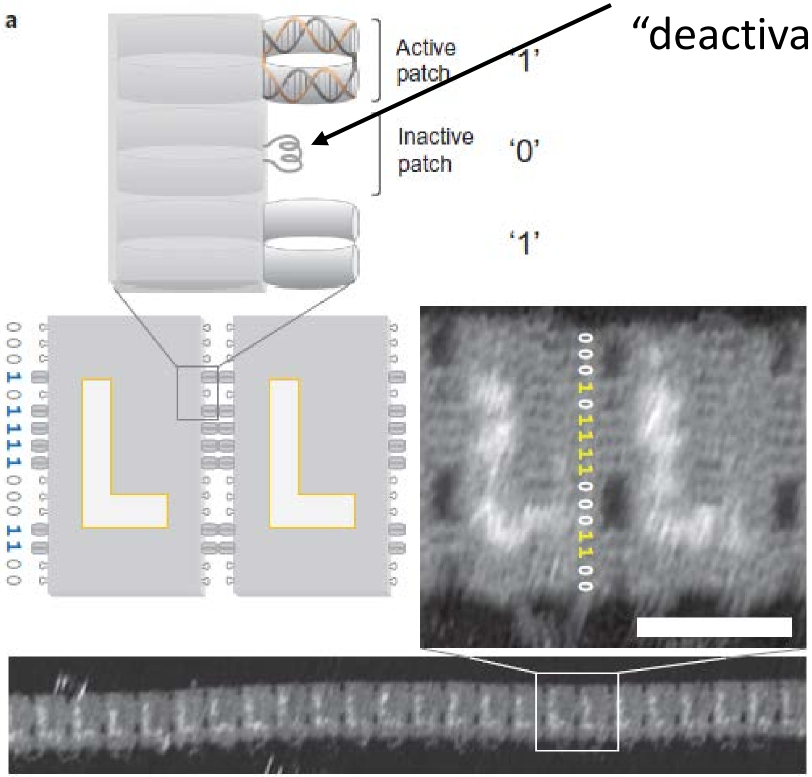
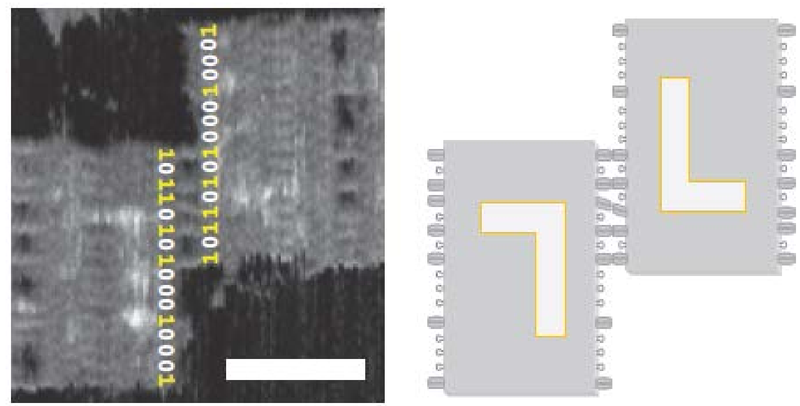


unintended translations can result in overlap between large subset of patches



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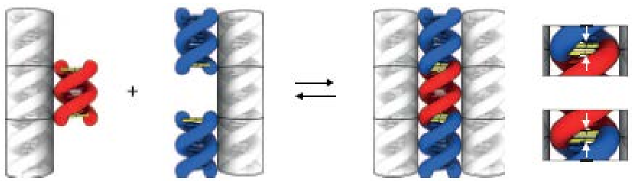
Extending from 1D to 2D bonds

Thomas Gerling, Klaus F. Wagenbauer, Andrea M. Neuner, Hendrik Dietz
Dynamic DNA devices and assemblies formed by shape-complementary, non–base pairing 3D components
Science 2015

Extending from 1D to 2D bonds



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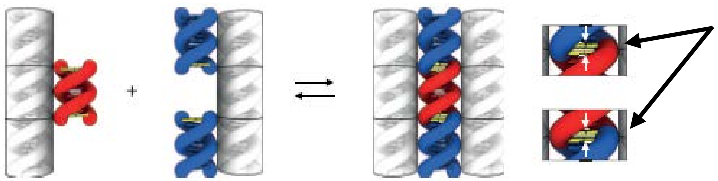

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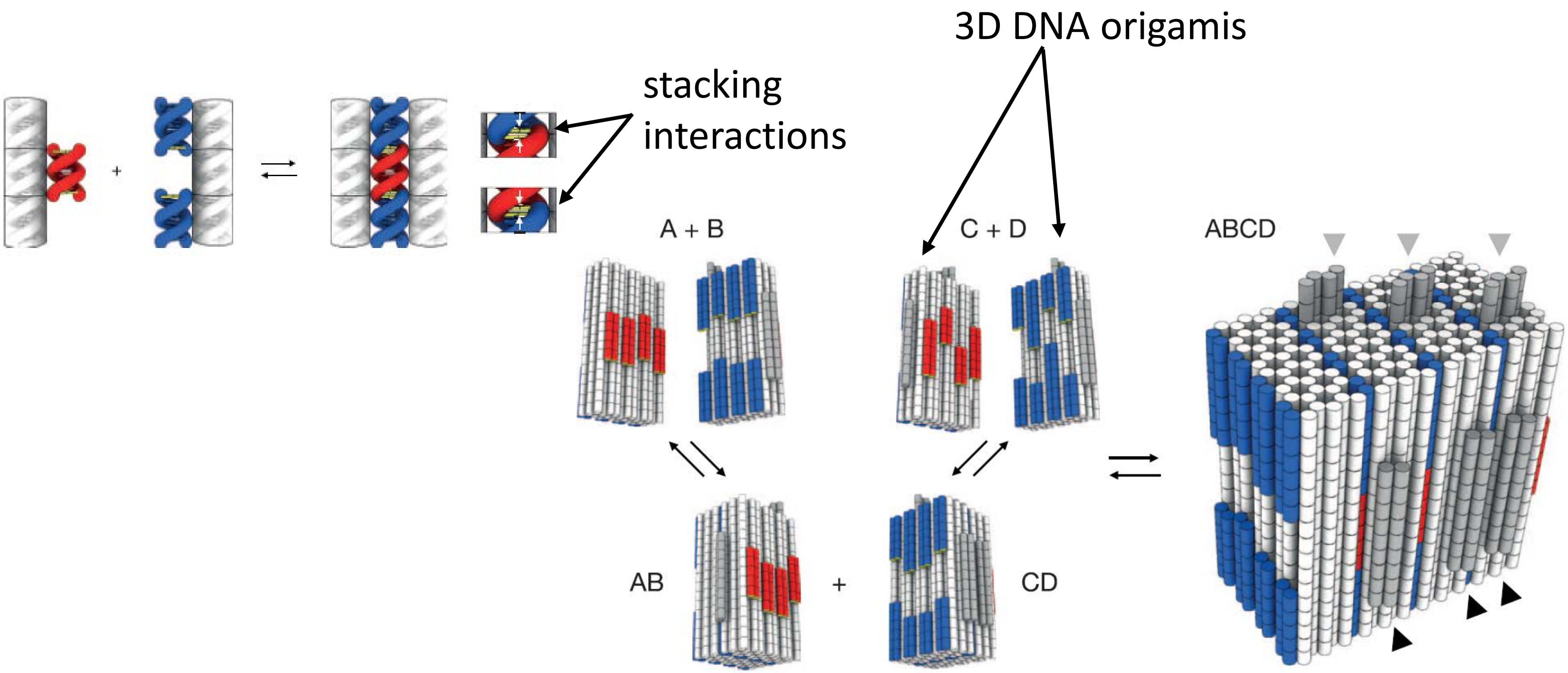

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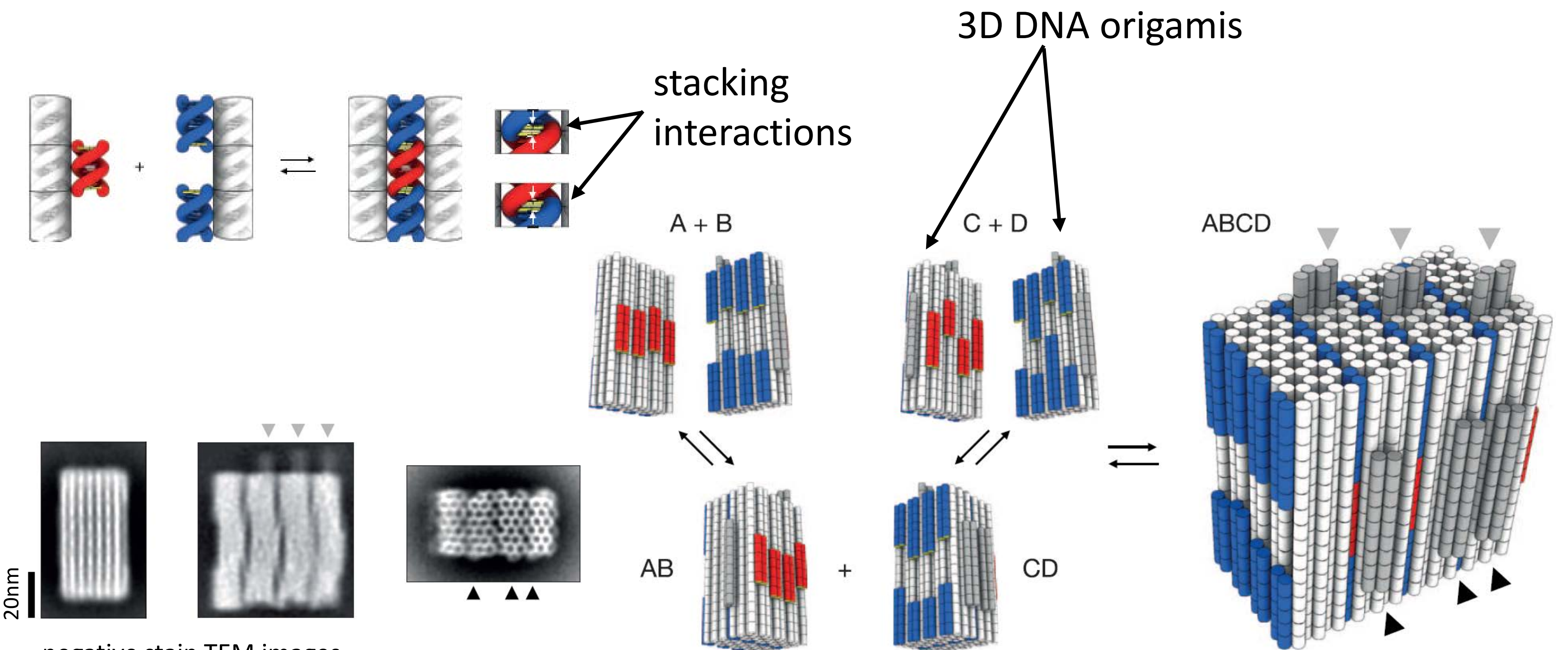

negative stain TEM images

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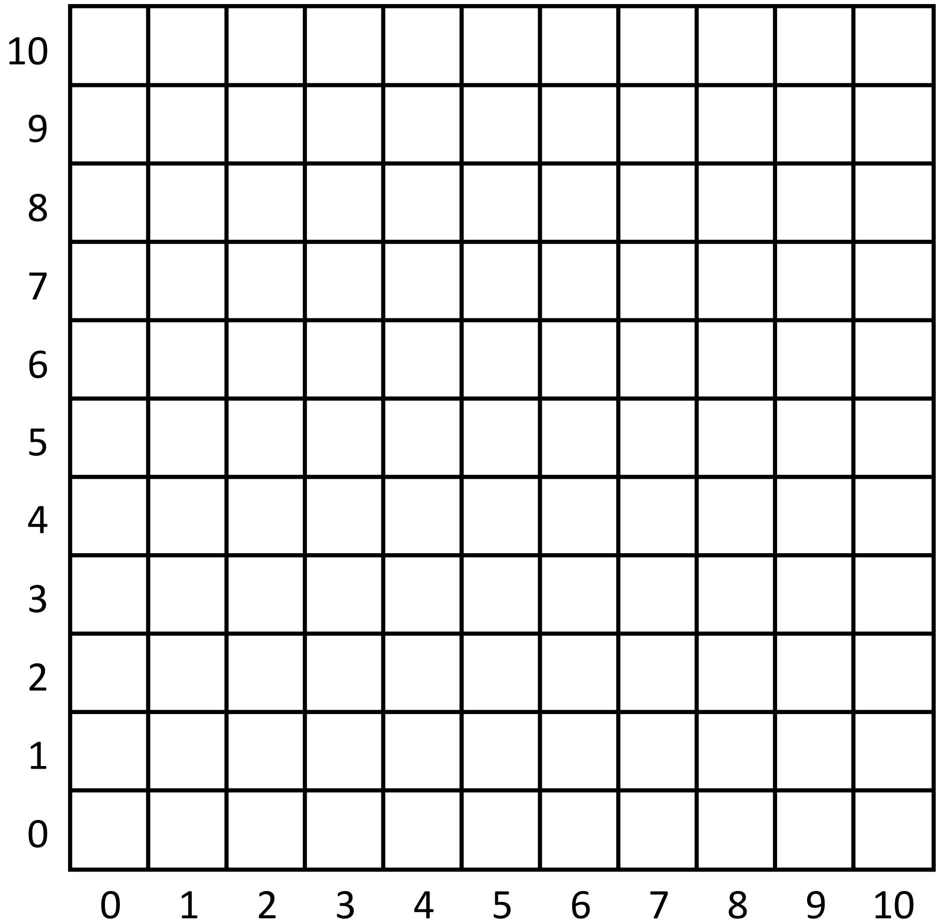
Science 2015

Design of geometric molecular bonds, à la Reed-Solomon

How to engineer large sets of specific molecular bonds that do not bind (strongly) in unintended ways

Mathematical model

macrobond:
subset of
n x *n* square



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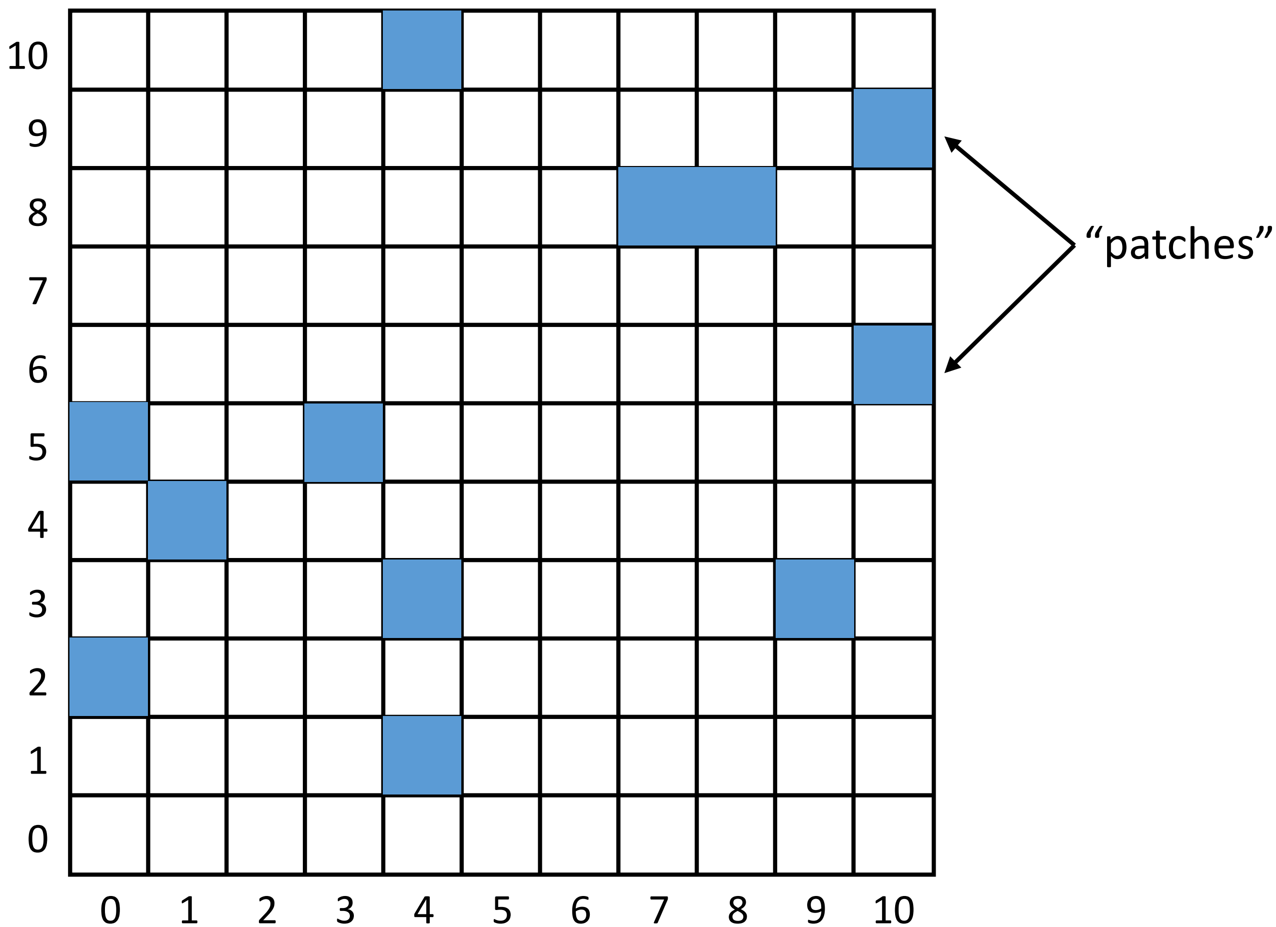
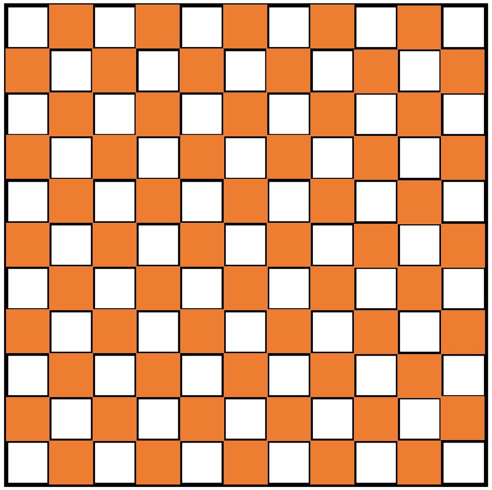


Desired outcomes

1) any **nonzero** translation of macrobond has “small” overlap with untranslated original



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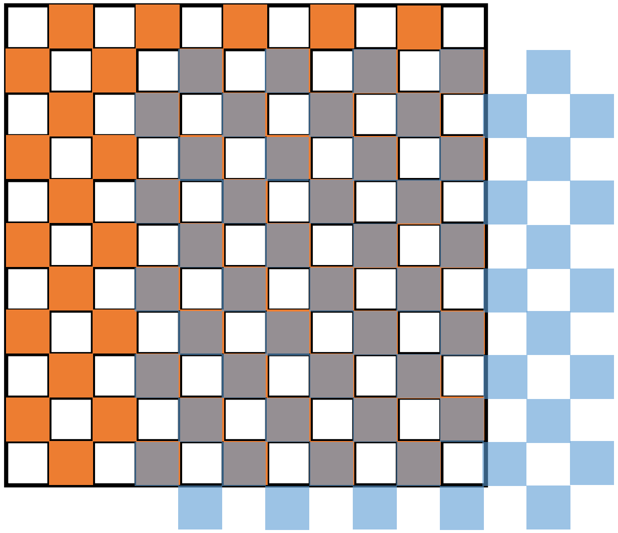

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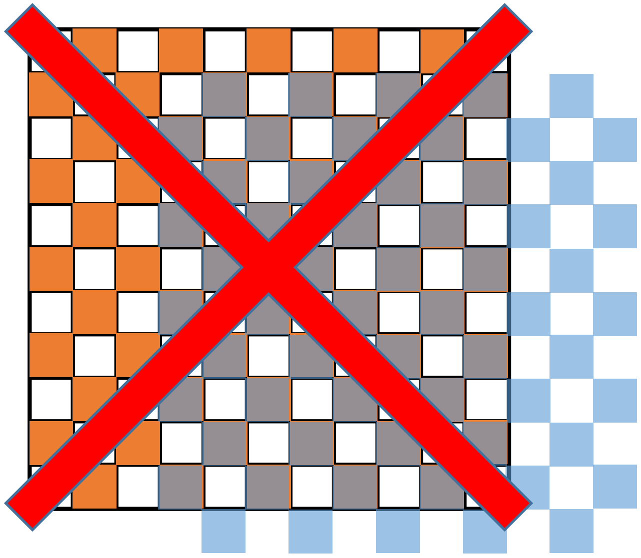

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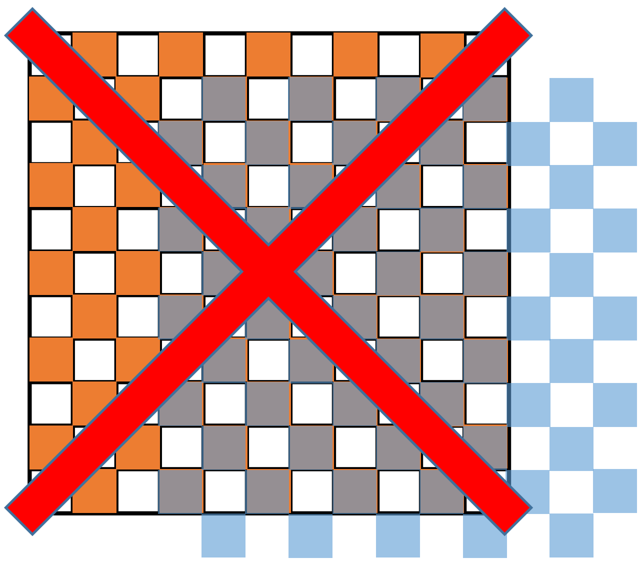
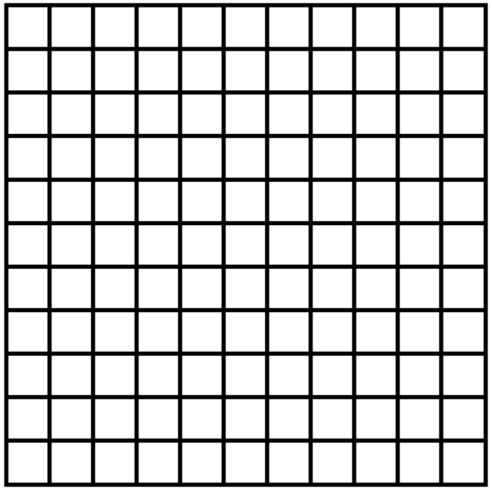


2) **any** translation of macrobond has "small" overlap with **other** macrobonds



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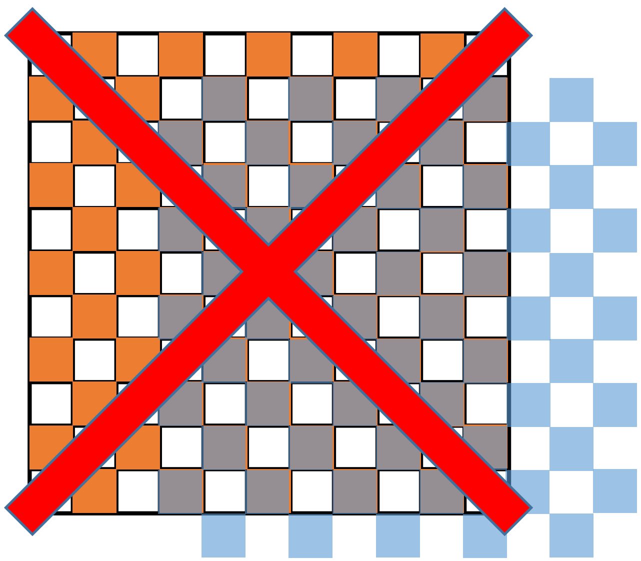

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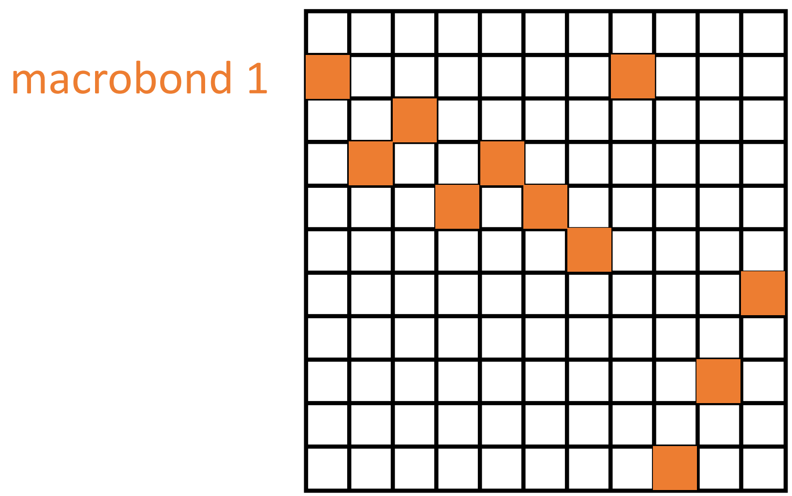

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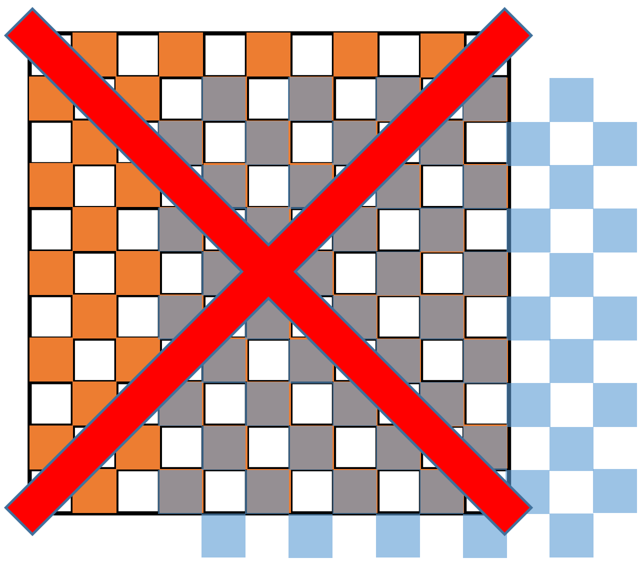

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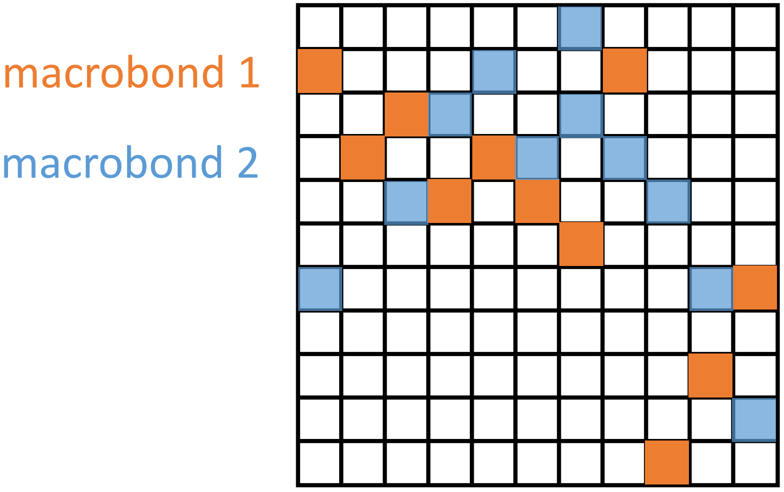

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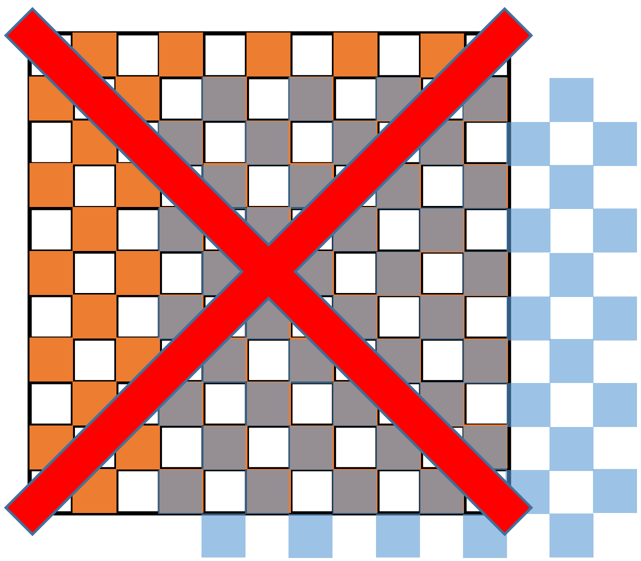

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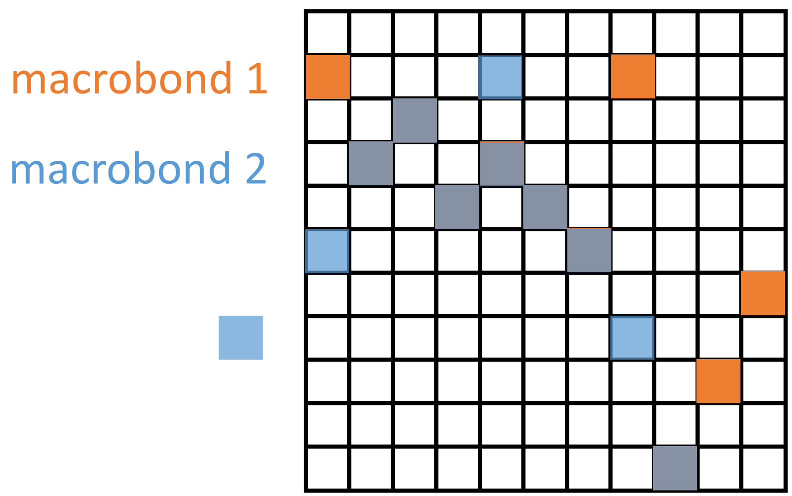

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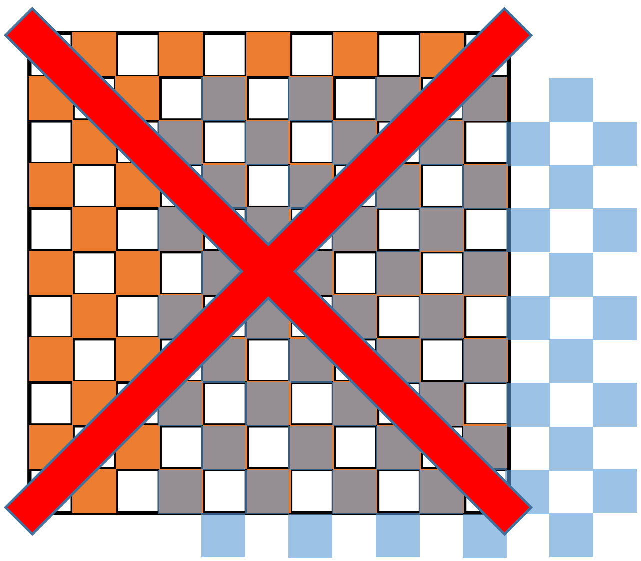
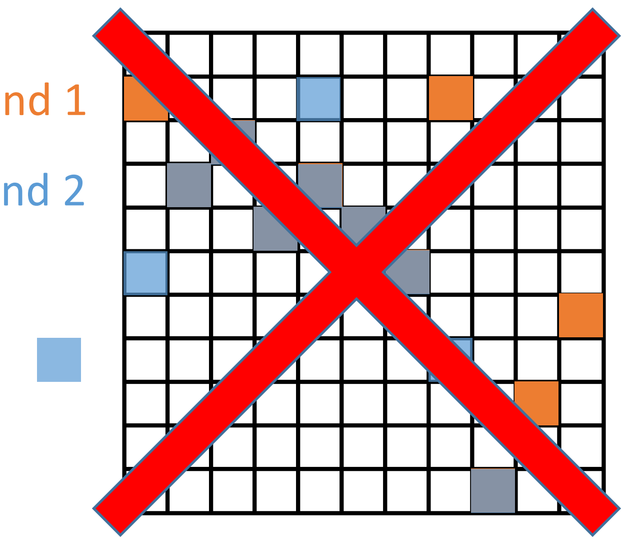
1) any **nonzero** translation of macrobond has “small” overlap with untranslated original



2) **any** translation of macrobond has “small” overlap with **other** macrobonds

macrobond 1

macrobond 2

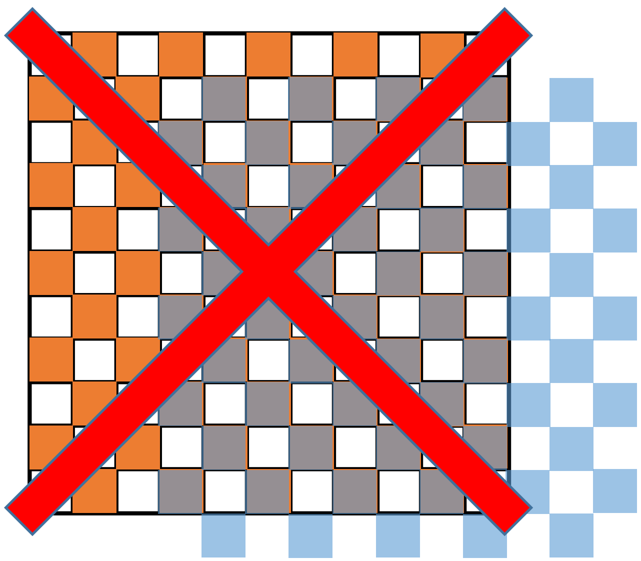


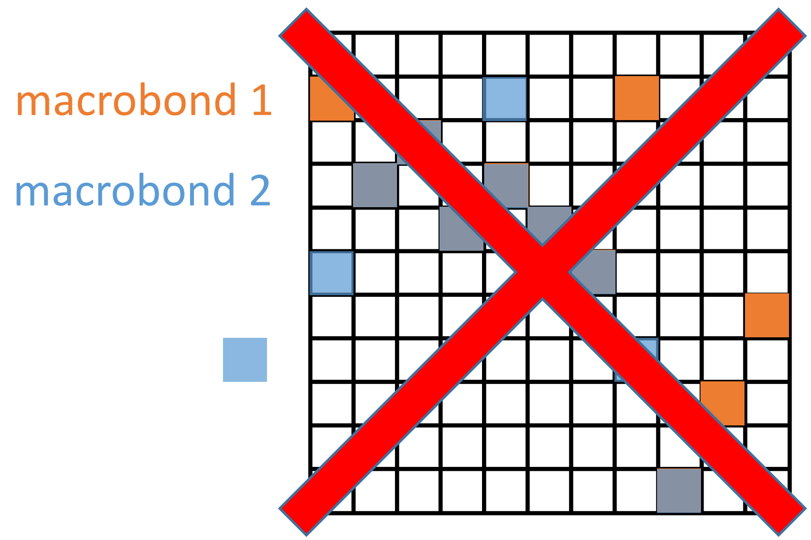
Desired outcomes

1) any **nonzero** translation of macrobond has "small" overlap with untranslated original

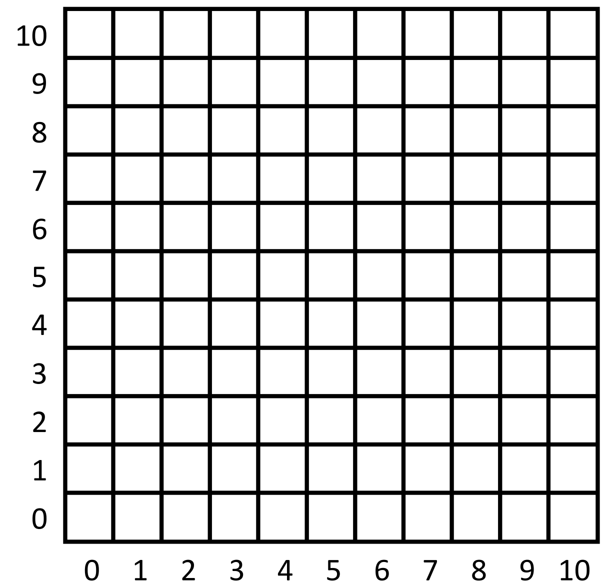
3) lots of macrobonds!

2) **any** translation of macrobond has "small" overlap with **other** macrobonds





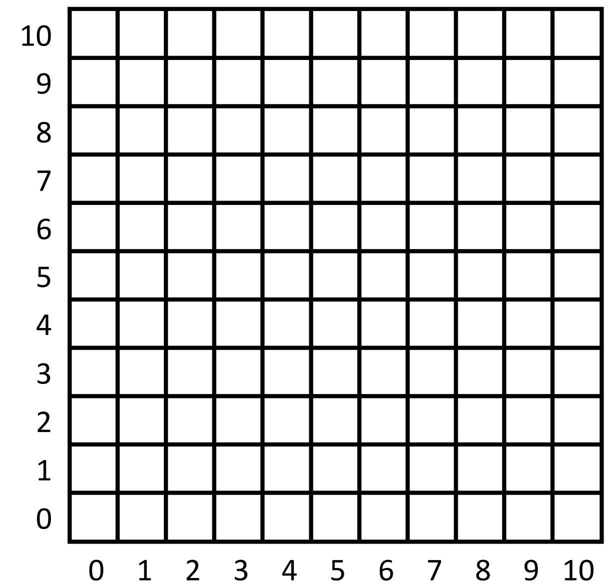
Orthogonal macrobond design problem



- *n* x *n* square such that:
  - $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$

Orthogonal macrobond design problem

n = 11



- n = width of square

- n x n square such that:
  - $\neq \mathbf{0}$: $|S_i \cap (S_i + \mathbf{v})| \leq d$
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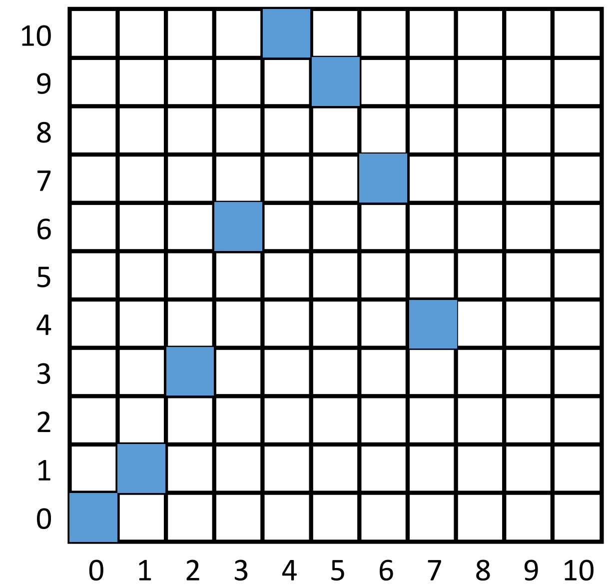
Orthogonal macrobond design problem

$n = 11$

$k = 8$



- n = width of square
- k = # of patches in macrobond

- n x n square such that:
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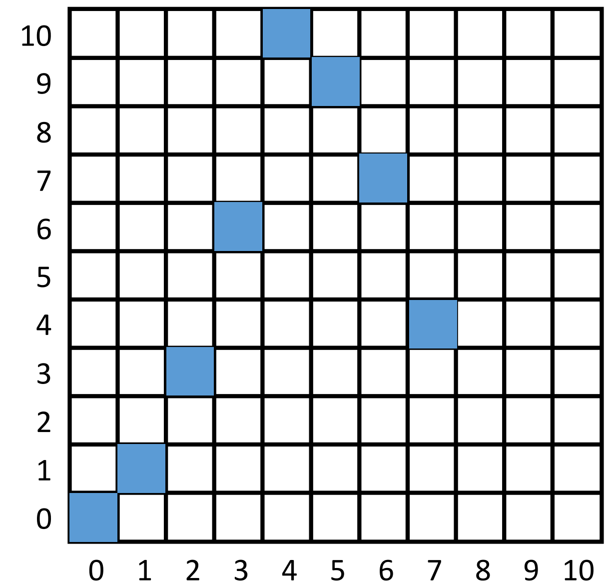

- n = width of square
- k = # of patches in macrobond
- d = maximum overlap between macrobonds
- n x n square such that:
  - $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$

Orthogonal macrobond design problem

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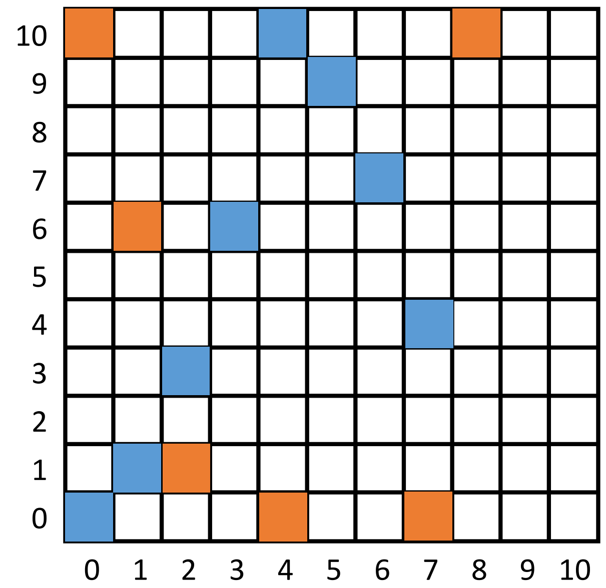

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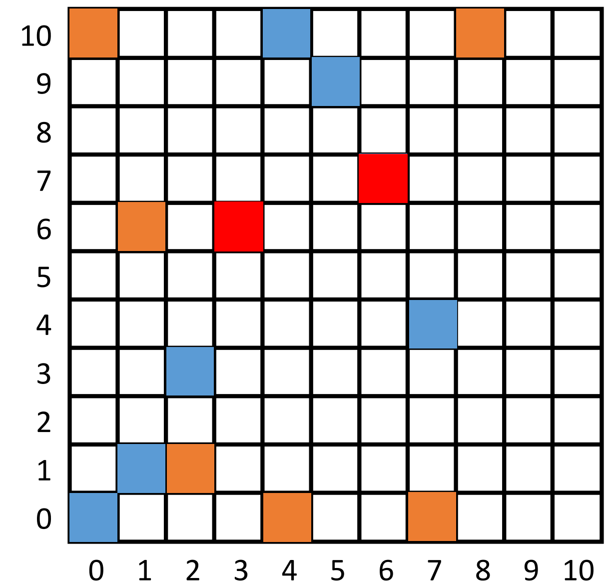
- d = maximum overlap between macrobonds
- n x n square such that:
  - $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$

Orthogonal macrobond design problem

n = 11

k = 8

d = 2



- n = width of square
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- d = maximum overlap between macrobonds
- n x n square such that:
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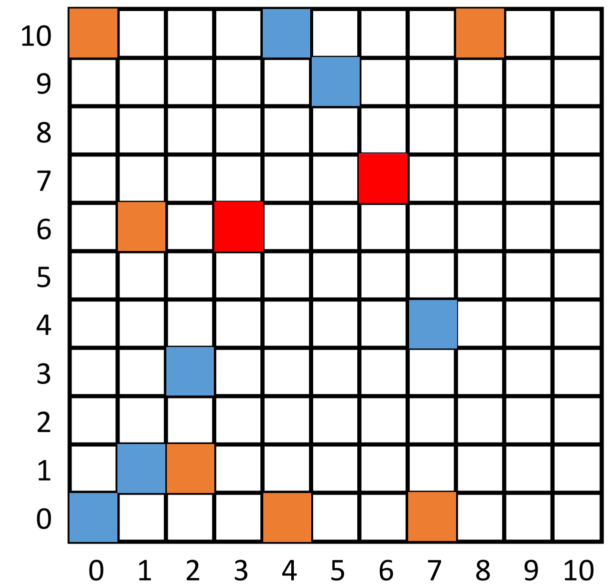

- n x n square such that:
- n = width of square
- k = # of patches in macrobond
- d = maximum overlap between macrobonds
- find macrobonds $S_1,\ldots,S_m \subseteq n$ x n square such that:
  - $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$

Orthogonal macrobond design problem

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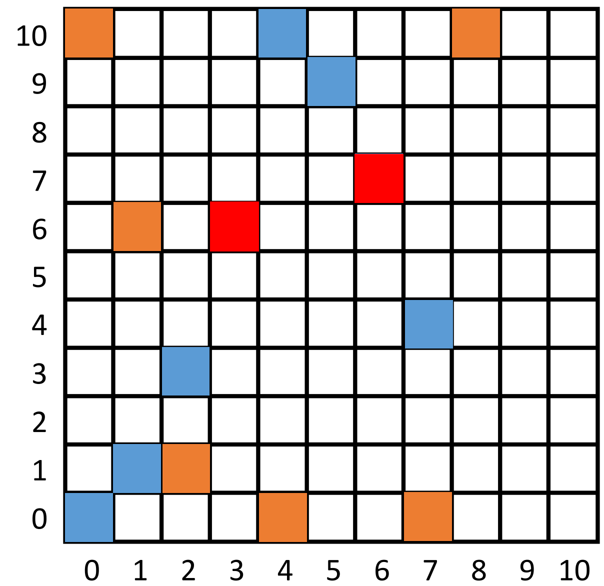

- *n* x *n* square such that:
- n = width of square
- *k* = # of patches in macrobond
- *d* = maximum overlap between macrobonds
  - for all i: $|S_i| = k$
  - $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$

Orthogonal macrobond design problem

$n = 11$

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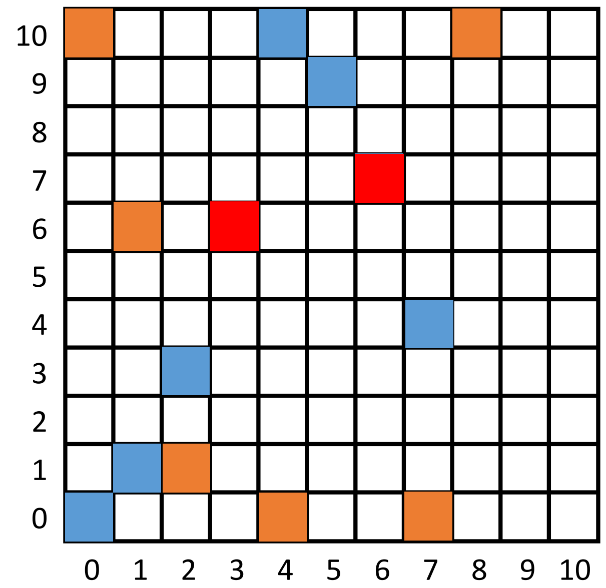


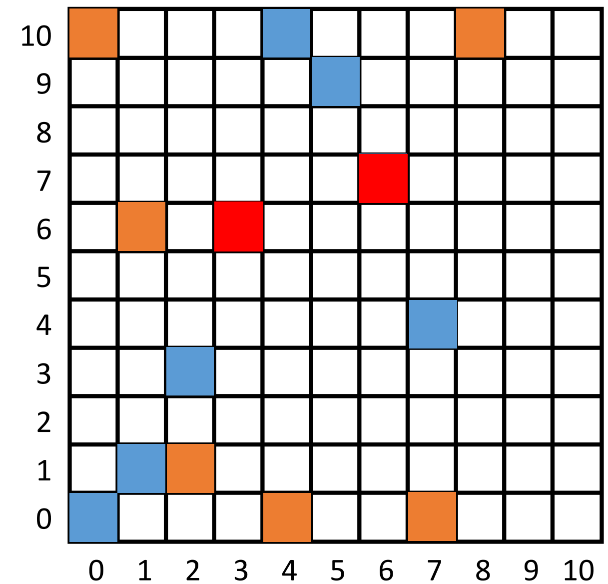
- *≠ 0: |Si ∩ (Si+v)| ≤ d*
- n x n square such that:
- n = width of square
- k = # of patches in macrobond
- d = maximum overlap between macrobonds
  - for all i: $|S_i| = k$
  - for all i and all translations $\mathbf{v} \neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$

Orthogonal macrobond design problem

$n = 11$

$k = 8$

$d = 2$



- *$\neq j$ and all translations v: $|Si \cap (Sj+v)| \leq d$*
- *$\neq 0$: $|Si \cap (Si+v)| \leq d$*
- n x n square such that:
- n = width of square
- k = # of patches in macrobond
- d = maximum overlap between macrobonds
  - for all i: $|S_i| = k$
  - for all $i \neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$
  - $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
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Orthogonal macrobond design problem

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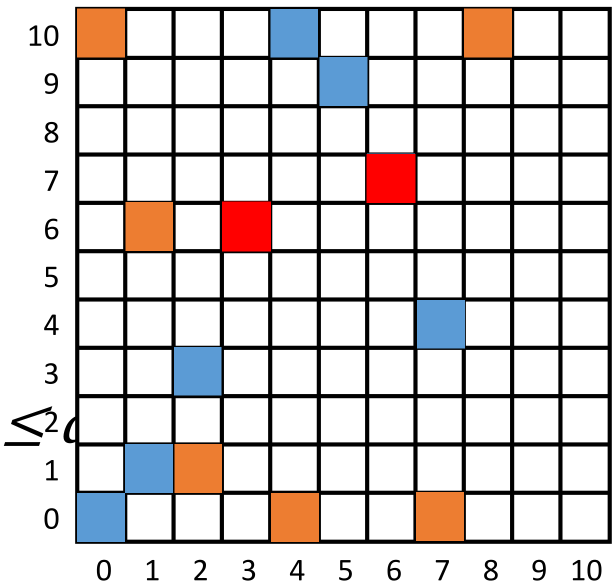

- $\neq j$ *and all translations v:* $|Si \cap (Sj+v)| \leq d$
- $\neq 0$: $|Si \cap (Si+v)| \leq d$
- n x n square such that:
- n = width of square
- k = # of patches in macrobond
- d = maximum overlap between macrobonds
  - for all i: $|S_i| = k$
  - m is "large" $\neq \mathbf{0}$: $|S_i \cap (S_i+\mathbf{v})| \leq d$
  - $\neq j$ and all translations $\mathbf{v}$: $|S_i \cap (S_j+\mathbf{v})| \leq d$

… à la Reed-Solomon

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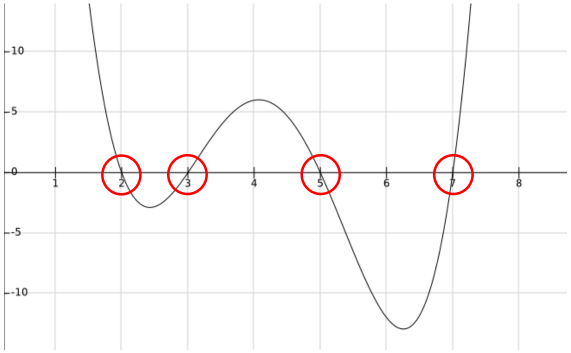
- **Fundamental theorem of algebra**: any degree d polynomial $p(x) = c_d x^d + c_{d-1} x^{d-1} + \ldots + c_1 x + c_0$ over field $\mathbb{F}$ has at most d roots (values x where $p(x) = 0$) unless all $c_i = 0$



$d = 4$

… à la Reed-Solomon

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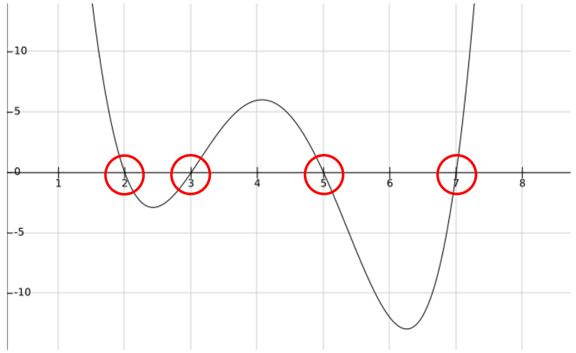
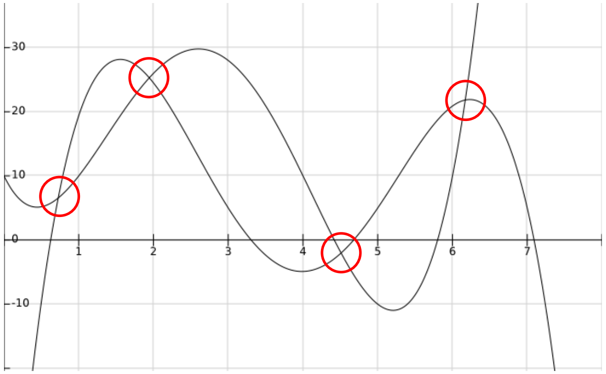


$d = 4$

- **Consequence**: since the difference $p(x)$-$q(x)$ of two different degree d polynomials is a degree d polynomial, $p(x) = q(x)$ on at most d values of x



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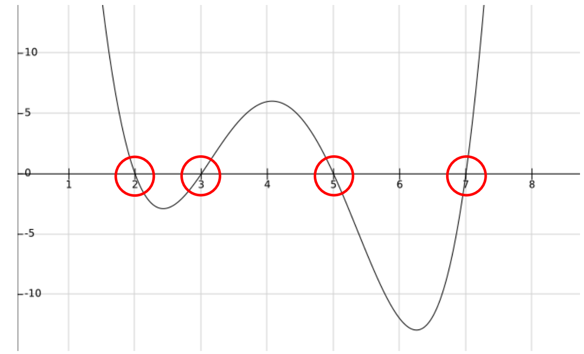

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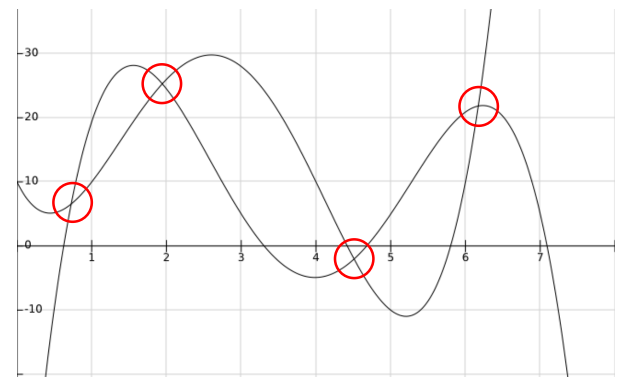
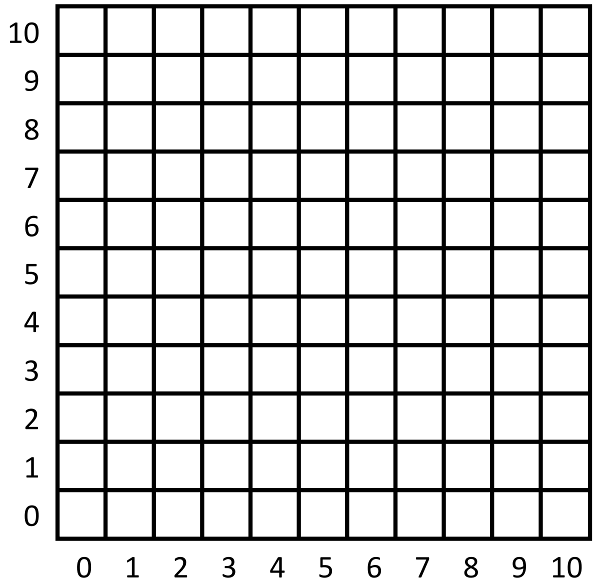


- If n is prime, addition and multiplication of integers modulo n defines a field $\mathbb{F}$

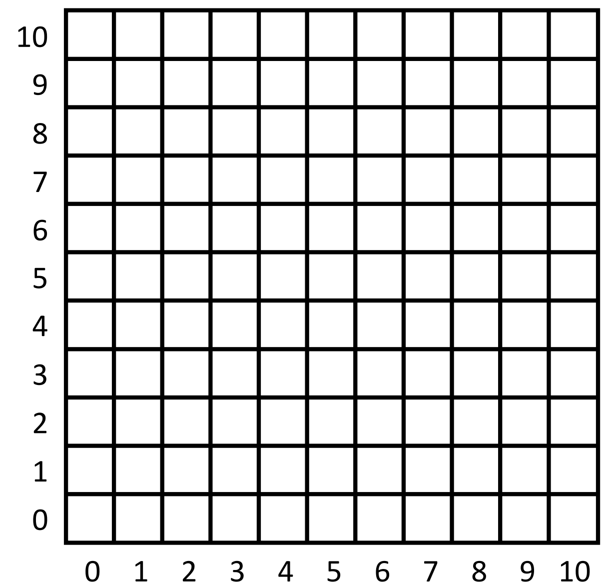
Algorithm for generating macrobonds



Algorithm for generating macrobonds

- Works for $k = n$

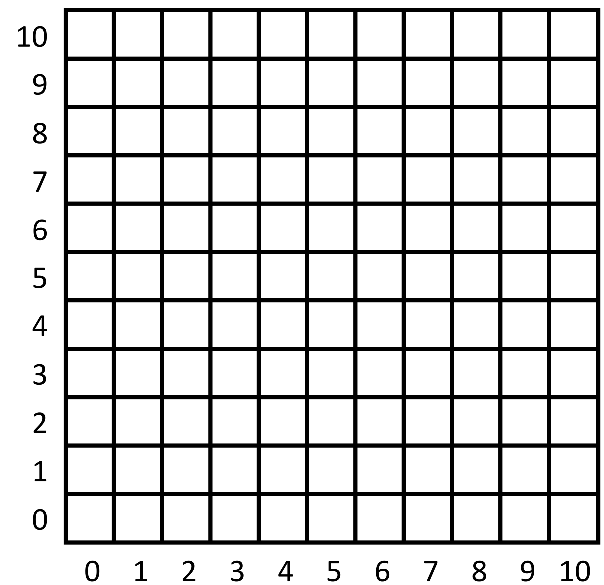
$n = k = 11 \qquad d = 3$



Algorithm for generating macrobonds

$n = k = 11 \qquad d = 3$

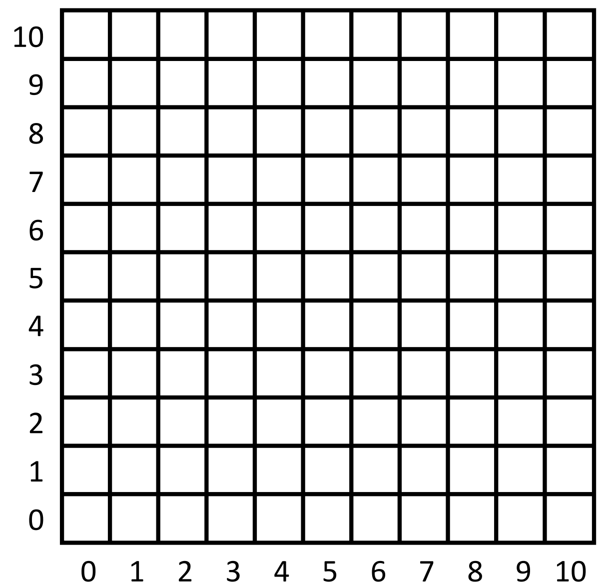
- Works for $k = n$
- Let $p(x) = c_d x^d + c_{d-1} x^{d-1} + \ldots + c_1 x + c_0$,



Algorithm for generating macrobonds

$n = k = 11 \qquad d = 3$

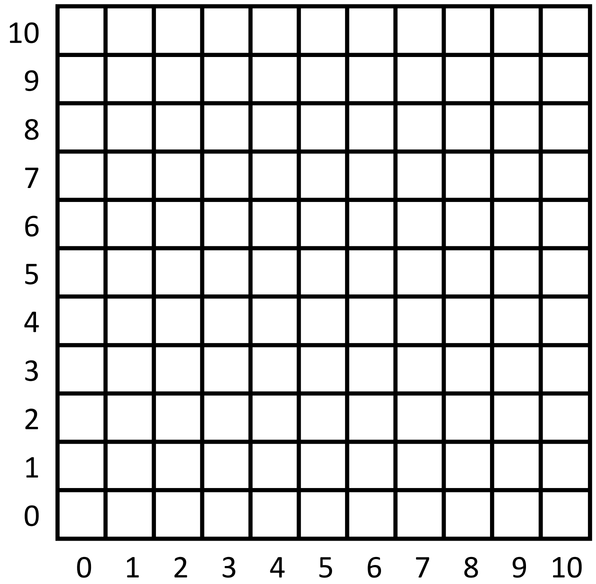
- {0,1,…,n-1}
- Works for $k = n$
- Let $p(x) = c_d x^d + c_{d-1} x^{d-1} + \ldots + c_1 x + c_0$,
    - each $c_i \in \{0,1,\ldots,n-1\}$



Algorithm for generating macrobonds

- 0
- {0,1,…,n-1}
- Works for $k = n$
- Let $p(x) = c_d x^d + c_{d-1} x^{d-1} + \ldots + c_1 x + c_0$,
  - $c_d \neq 0$

$n = k = 11$ $d = 3$



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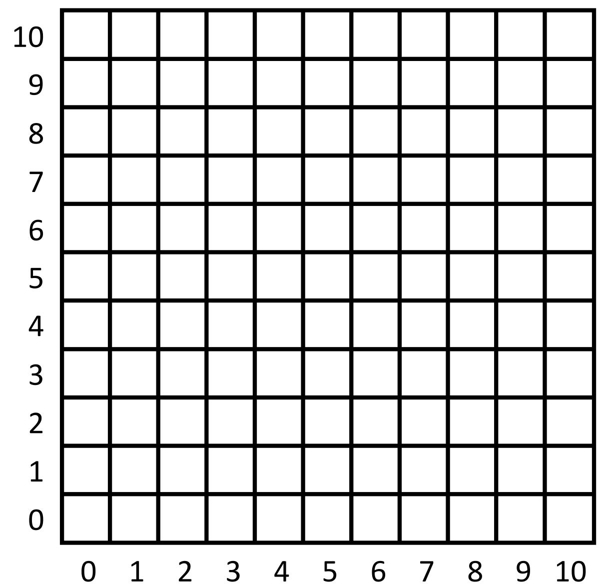

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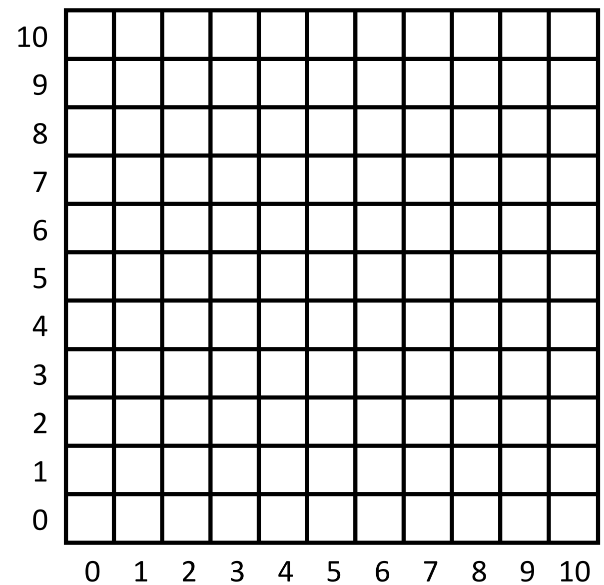

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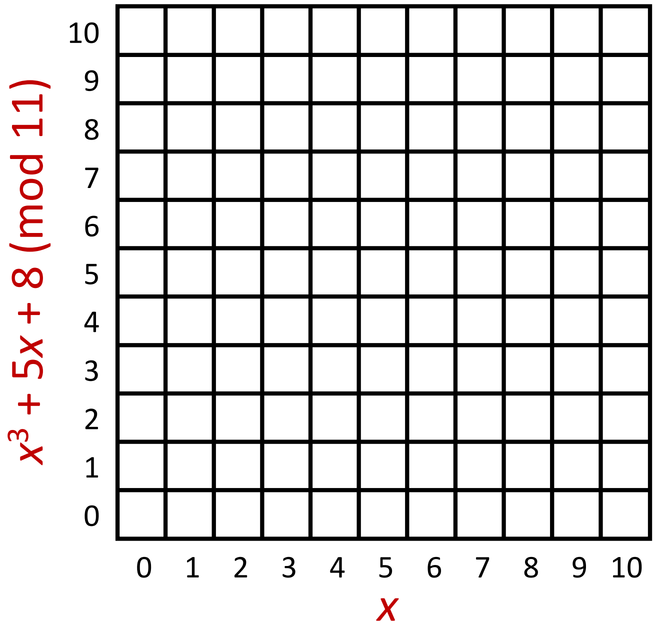

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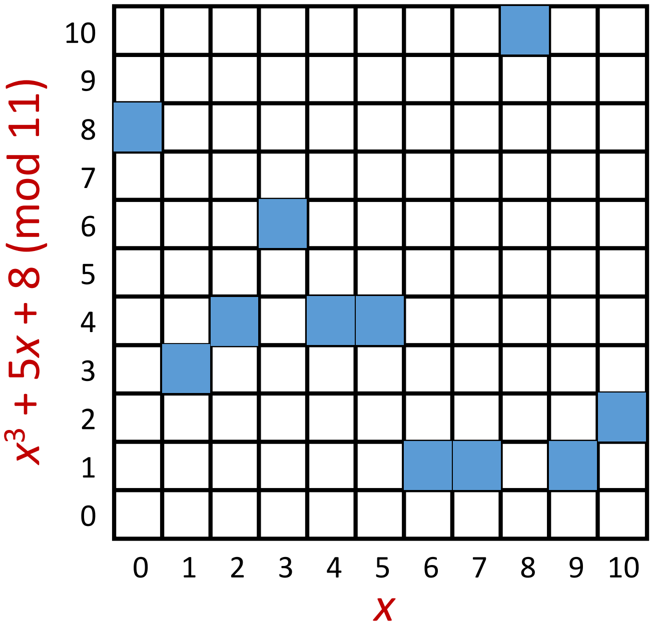

Algorithm for generating macrobonds

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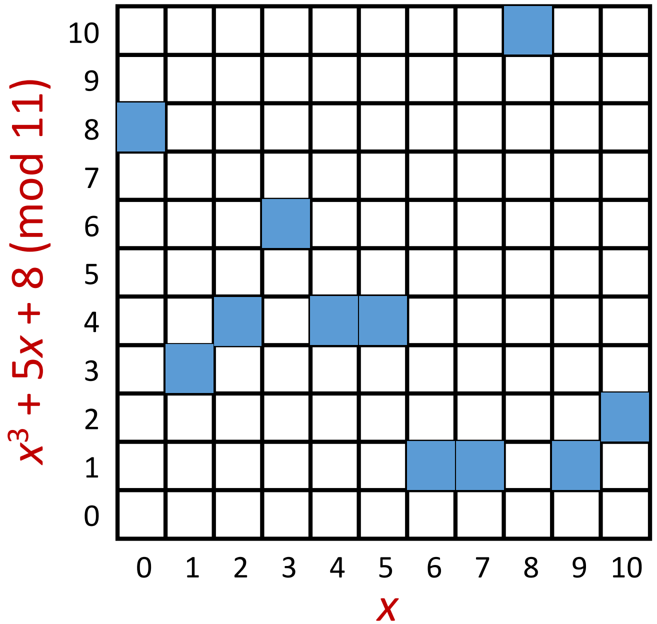
$n = k = 11$ $d = 3$

example macrobond:



Algorithm for generating macrobonds

- nd-1
- {0,1,…,n-1}
- 0
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- Let $p(x) = c_d x^d + c_{d-1} x^{d-1} + \ldots + c_1 x + c_0$,
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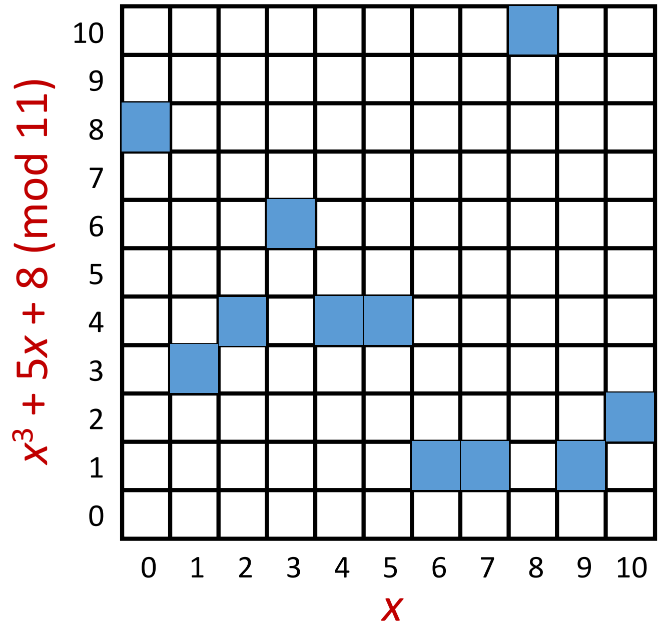

Algorithm for generating macrobonds

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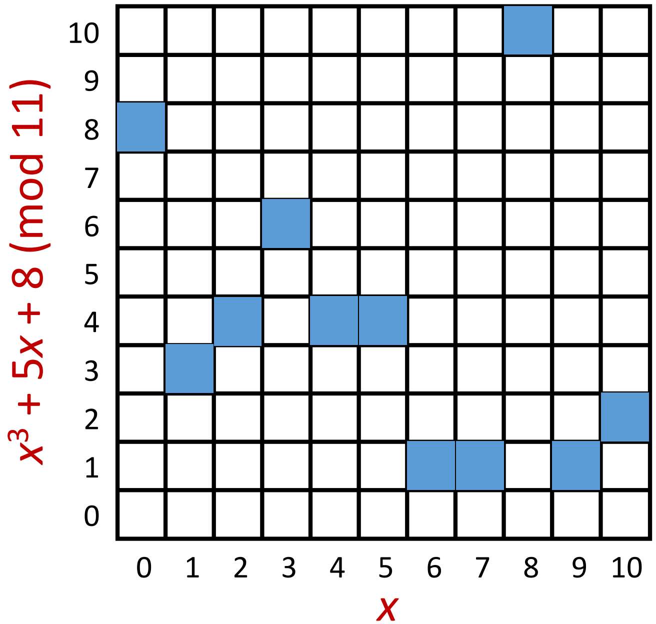

Why is overlap at most *d*?

Why is overlap at most *d*?

- $p(x) = a_d x^d + a_{d\text{-}1} x^{d\text{-}1} + \ldots + a_1 x + a_0 \qquad q(x) = b_d x^d + b_{d\text{-}1} x^{d\text{-}1} + \ldots + b_1 x + b_0$

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$\neq 0 \qquad\qquad = 0 \qquad\qquad\qquad\qquad \neq 0 \qquad\qquad = 0$

- $p(x) = a_d x^d + a_{d-1} x^{d-1} + \ldots + a_1 x + a_0 \qquad q(x) = b_d x^d + b_{d-1} x^{d-1} + \ldots + b_1 x + b_0$

Why is overlap at most *d*?

- $p(x) = \overset{\neq 0}{a_d} x^d + \overset{= 0}{a_{d-1}} x^{d-1} + \dots + a_1 x + \overset{= 0}{a_0}$ $\qquad q(x) = \overset{\neq 0}{b_d} x^d + \overset{= 0}{b_{d-1}} x^{d-1} + \dots + b_1 x + \overset{= 0}{b_0}$
- Translate macrobond derived from p by vector $\mathbf{v}=(-\delta_x,\delta_y)$ (both $< n$): gives polynomial $p'(x) = p(x + \delta_x) + \delta_y$.

Why is overlap at most *d*?

$\neq 0$ $= 0$ $\neq 0$ $= 0$

- q, then $p'(x) = q(x)$ on at most d values of x, and we are done.
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- Translate macrobond derived from p by vector $\mathbf{v}=(-\delta_x,\delta_y)$ (both $< n$): gives polynomial $p'(x) = p(x + \delta_x) + \delta_y$.
- If $p' \neq q$, then $p'(x) = q(x)$ on at most d values of x, and we are done.

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- $p(x) = a_d x^d + a_{d-1} x^{d-1} + \ldots + a_1 x + a_0$ $\qquad q(x) = b_d x^d + b_{d-1} x^{d-1} + \ldots + b_1 x + b_0$
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$= 0$

Why is overlap at most *d*?

≠ 0 = 0 ≠ 0 = 0

- *0 mod n, so (dδxad ≡ 0 mod n) ⇒ (δx = 0)*
- q, then $p'(x) = q(x)$ on at most d values of x, and we are done.
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  - binomial theorem says x^{d-1} coefficient (i.e., b_{d-1}) is $a_{d-1} + d\delta_x a_d$ $\quad = 0$
  - But $d, a_d \not\equiv 0 \bmod n$, so $(d\delta_x a_d \equiv 0 \bmod n) \Rightarrow (\delta_x = 0)$

Why is overlap at most *d*?

$\neq 0$ $= 0$ $\neq 0$ $= 0$

- *b0 mod n*
- *0 mod n, so (dδxad ≡ 0 mod n) ⇒ (δx = 0)*
- q, then $p'(x) = q(x)$ on at most d values of x, and we are done.
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  - Also, binomial theorem says constant coefficient (i.e., b_0) is $a_d\delta_x^{\,d} + a_{d-1}\delta_x^{\,d-1} + \ldots + a_1\delta_x^{\,1} + a_0 + \delta_y \equiv b_0 \bmod n$

Why is overlap at most d?

$\neq 0$ $= 0$ $\neq 0$ $= 0$

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- *0 mod n, so ($d\delta xad \equiv 0$ mod n) $\Rightarrow$ ($\delta x = 0$)*
- q, then $p'(x) = q(x)$ on at most d values of x, and we are done.
- $p(x) = a_d x^d + a_{d-1}x^{d-1} + \ldots + a_1 x + a_0$ $q(x) = b_d x^d + b_{d-1}x^{d-1} + \ldots + b_1 x + b_0$
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$= 0$ … $= 0$

Why is overlap at most *d*?

$\neq 0$ $= 0$ $\neq 0$ $= 0$

- *0 mod n, i.e., δy = 0*
- *b0 mod n*
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  - So $\delta_y \equiv 0 \bmod n$, i.e., $\delta_y = 0$

= 0 = 0

Why is overlap at most *d*?

$\neq 0$ $= 0$ $\neq 0$ $= 0$

- *q, then their translations are unequal also*
- *0 mod n, i.e., δy = 0*
- *b0 mod n*
- *0 mod n, so (dδxad ≡ 0 mod n) ⇒ (δx = 0)*
- q, then $p'(x) = q(x)$ on at most d values of x, and we are done.
- $p(x) = a_d x^d + a_{d-1} x^{d-1} + \dots + a_1 x + a_0$ $q(x) = b_d x^d + b_{d-1} x^{d-1} + \dots + b_1 x + b_0$
- Translate macrobond derived from p by vector $\mathbf{v}=(-\delta_x,\delta_y)$ (both < n): gives polynomial $p'(x) = p(x + \delta_x) + \delta_y$.
- Otherwise coefficients of p' and q are the same:
  - $p'(x) = [a_d(x + \delta_x)^d + a_{d-1}(x + \delta_x)^{d-1} + \dots a_1(x + \delta_x) + a_0] + \delta_y$
  - binomial theorem says x^{d-1} coefficient (i.e., b_{d-1}) is $a_{d-1} + d\delta_x a_d$
  - Also, binomial theorem says constant coefficient (i.e., b_0) is $\delta_y \equiv b_0 \bmod n$
- So $p = q$, *i.e.*, if $p \neq q$, then their translations are unequal also

$\equiv b_{d-1} \bmod n$

$= 0$

$a_d\delta_x^d + a_{d-1}\delta_x^{d-1} + \dots + a_1\delta_x^1 + a_0 +$

$\neq 0$ … $= 0$

Why is overlap at most d?

$\neq 0$ $= 0$ $\neq 0$ $= 0$

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$= 0$ $= 0$

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- Rotations
  - may be moot with particular DNA origami examples
- Allow smooth transition from initial misaligned binding to intended alignment
- Lower bounds

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