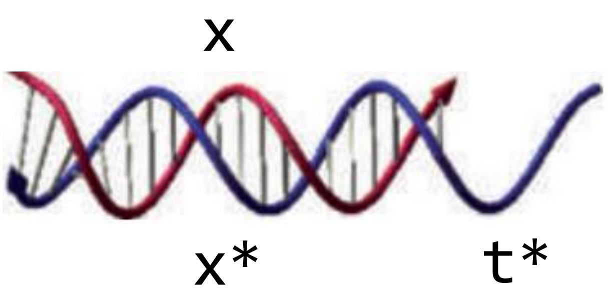
DNA strand displacement

DNA reconfiguring itself without enzymes

ECS 232: Theory of Molecular Computation, UC Davis

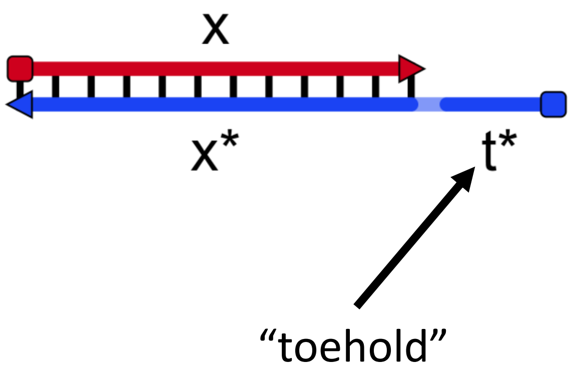
DNA strands with “long” and “short” (toehold) binding domains

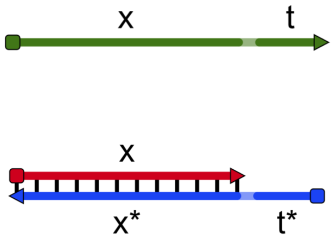


=

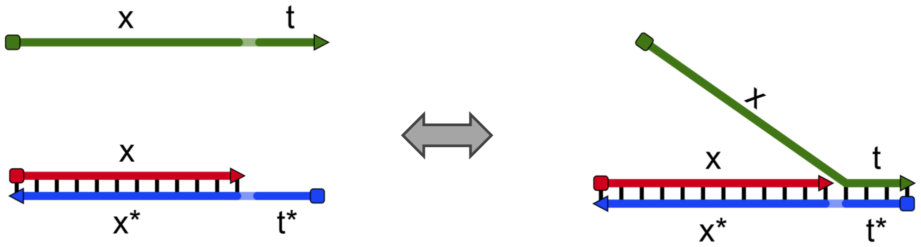
```
     x
TGTACCTGTCGA
||||||||||||
ACATGGACAGCTATAC
     x*     t*
```

=





DNA strand displacement example



DNA strand displacement example

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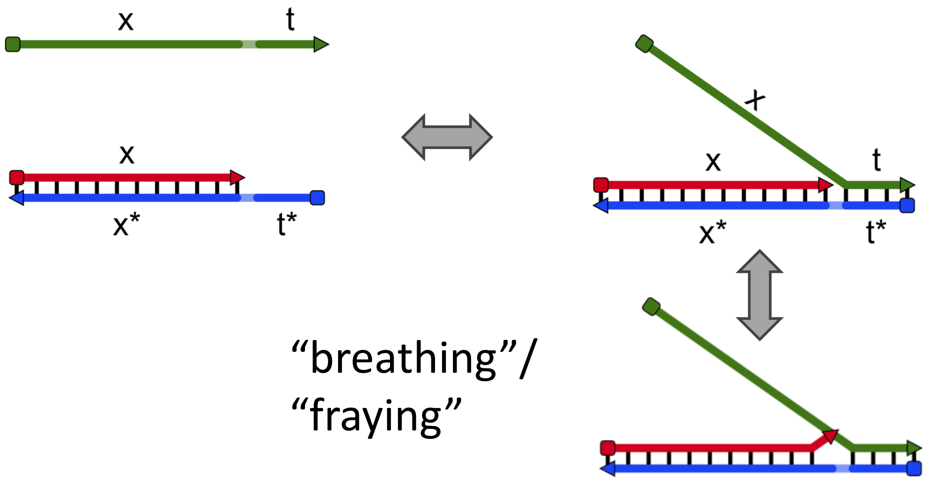
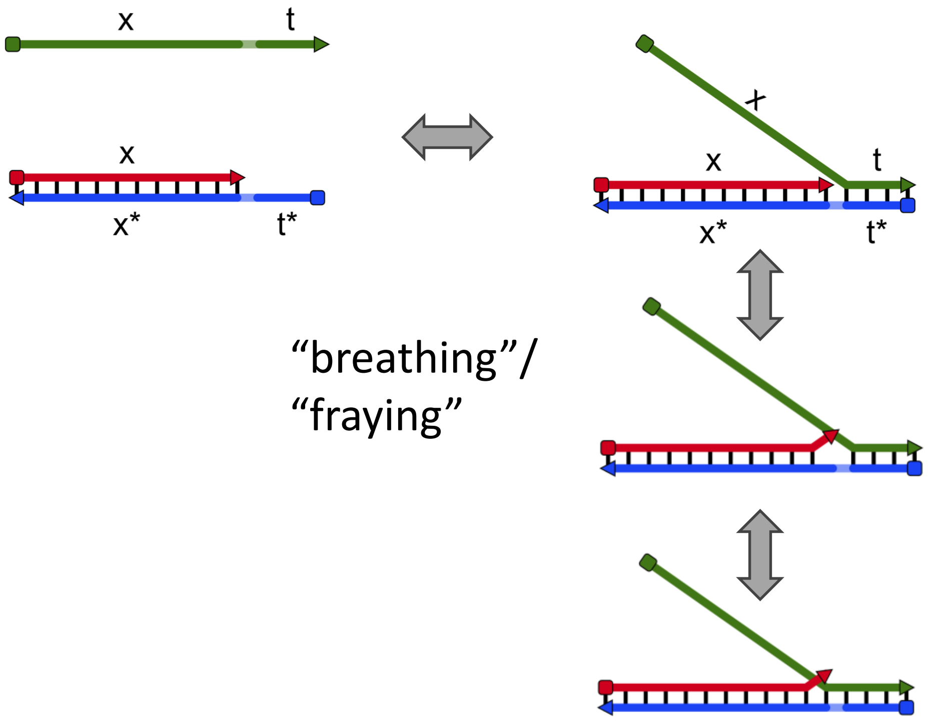


“breathing”/
“fraying”

DNA strand displacement example



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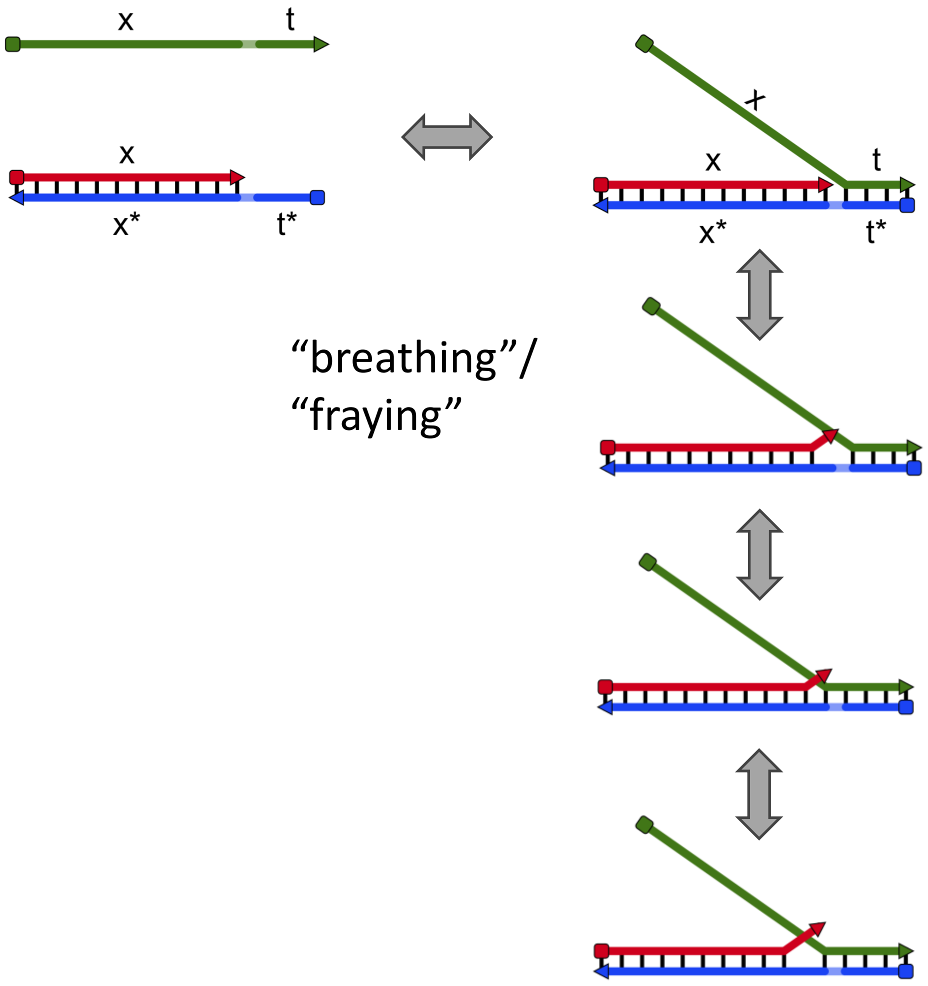

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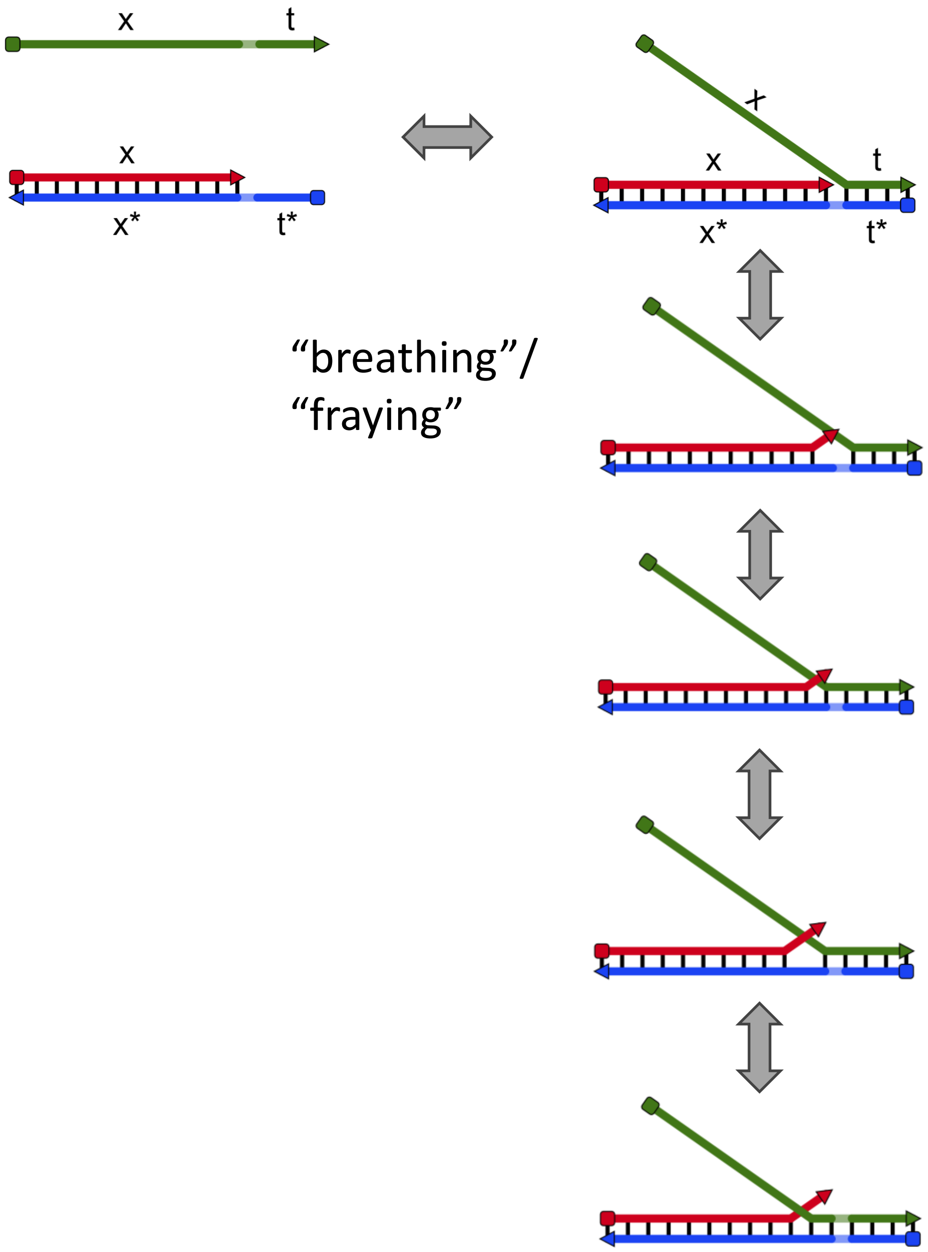
DNA strand displacement example



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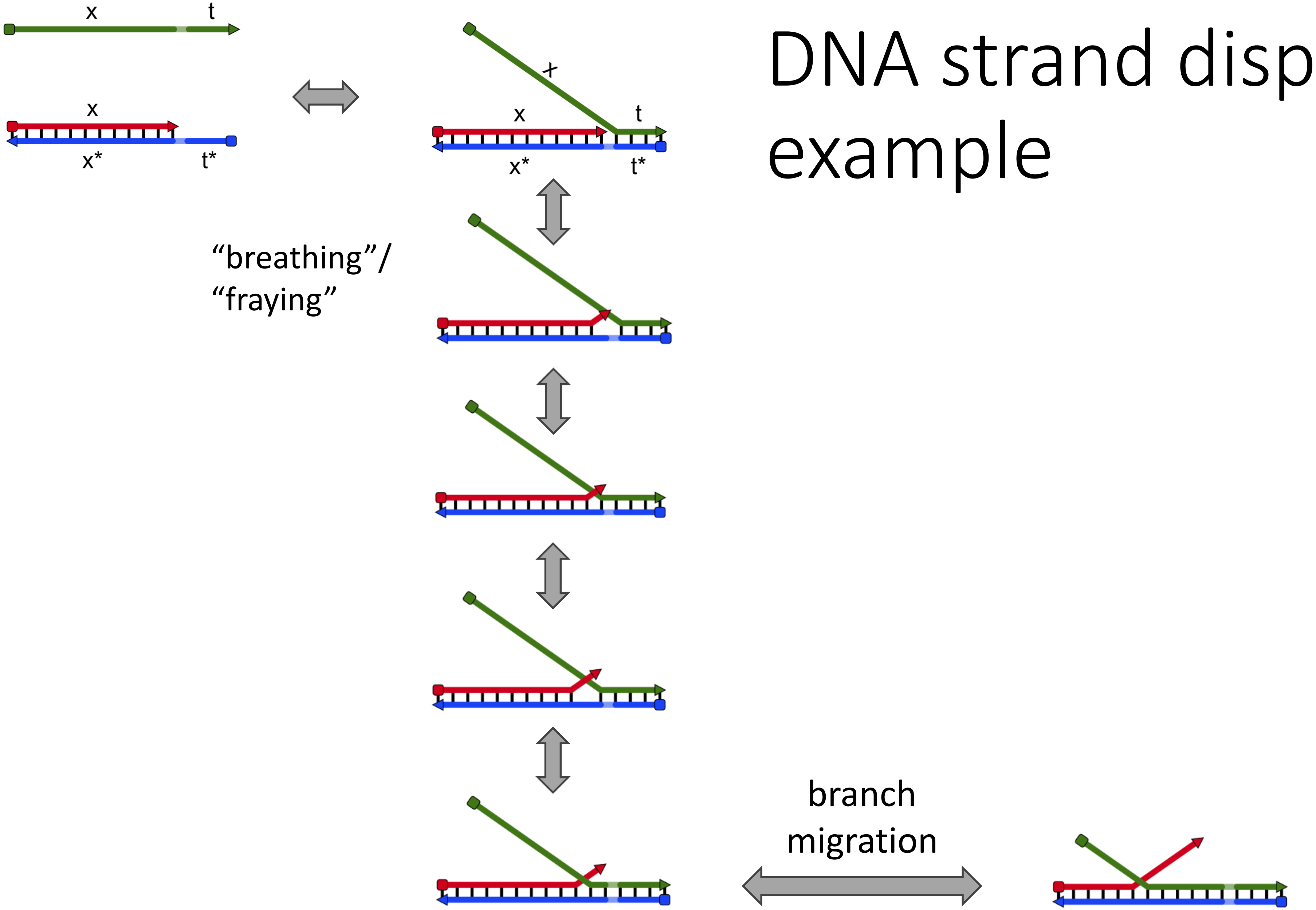

“breathing”/
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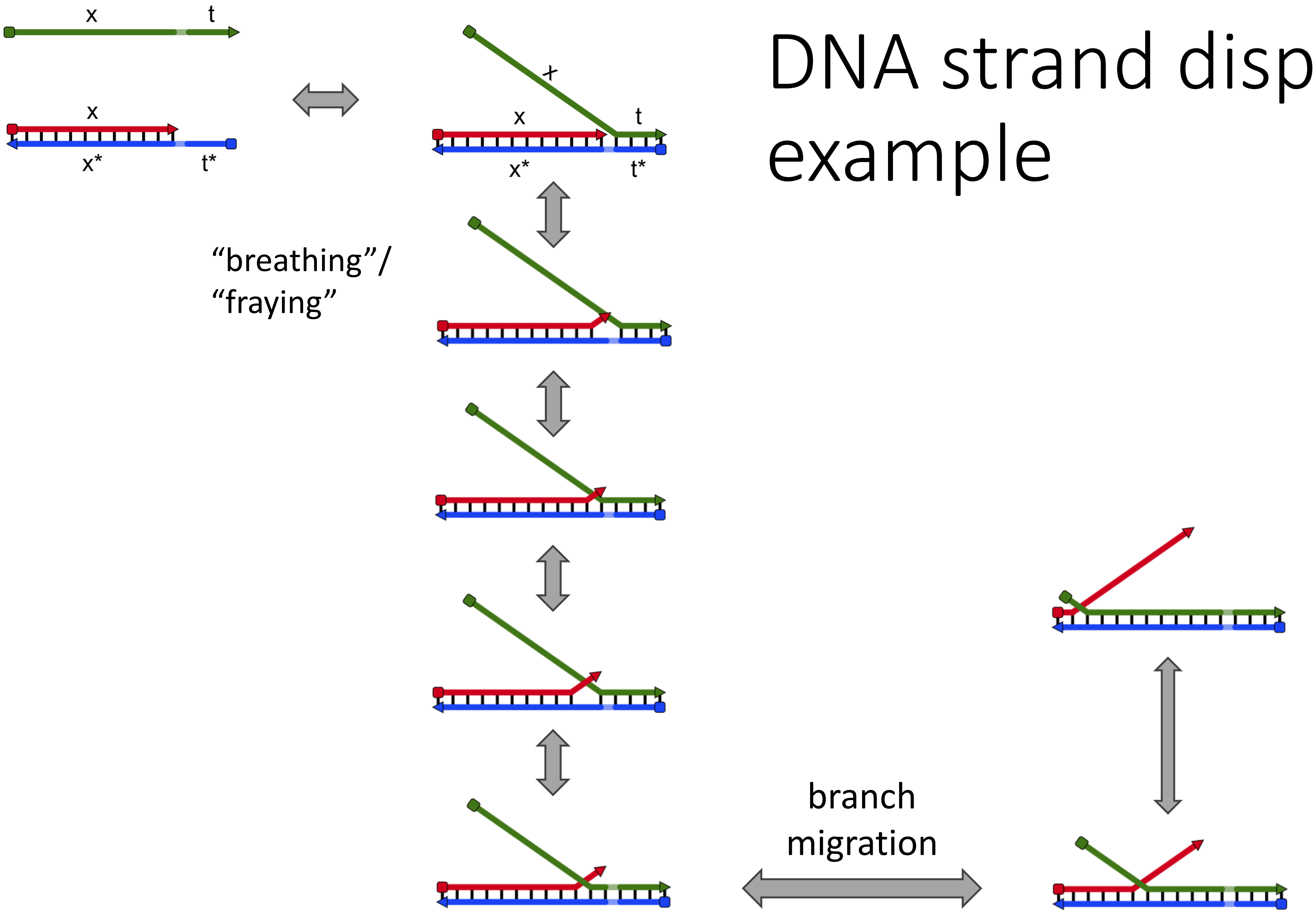
branch
migration

DNA strand displacement example



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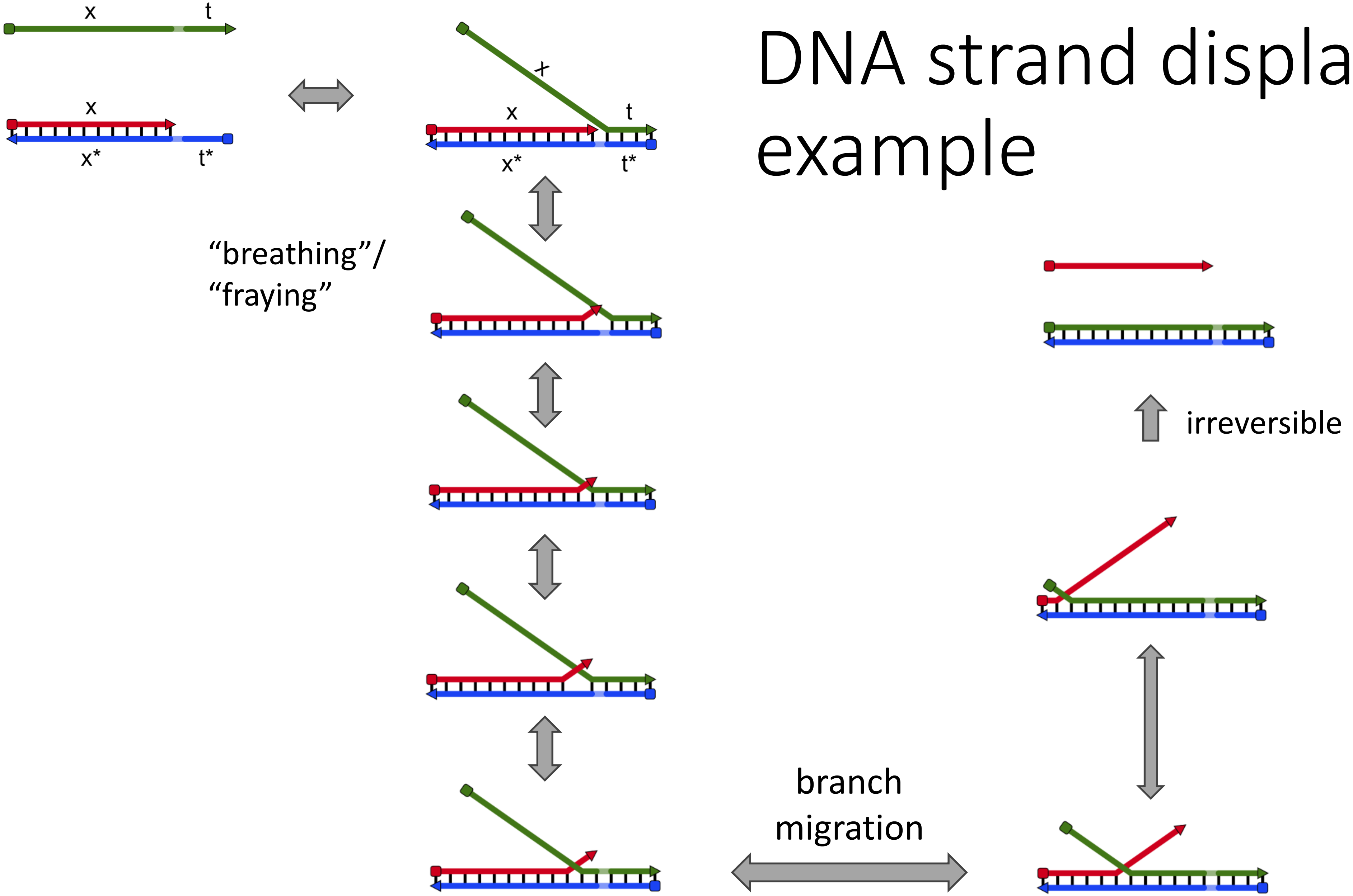
DNA strand displacement example



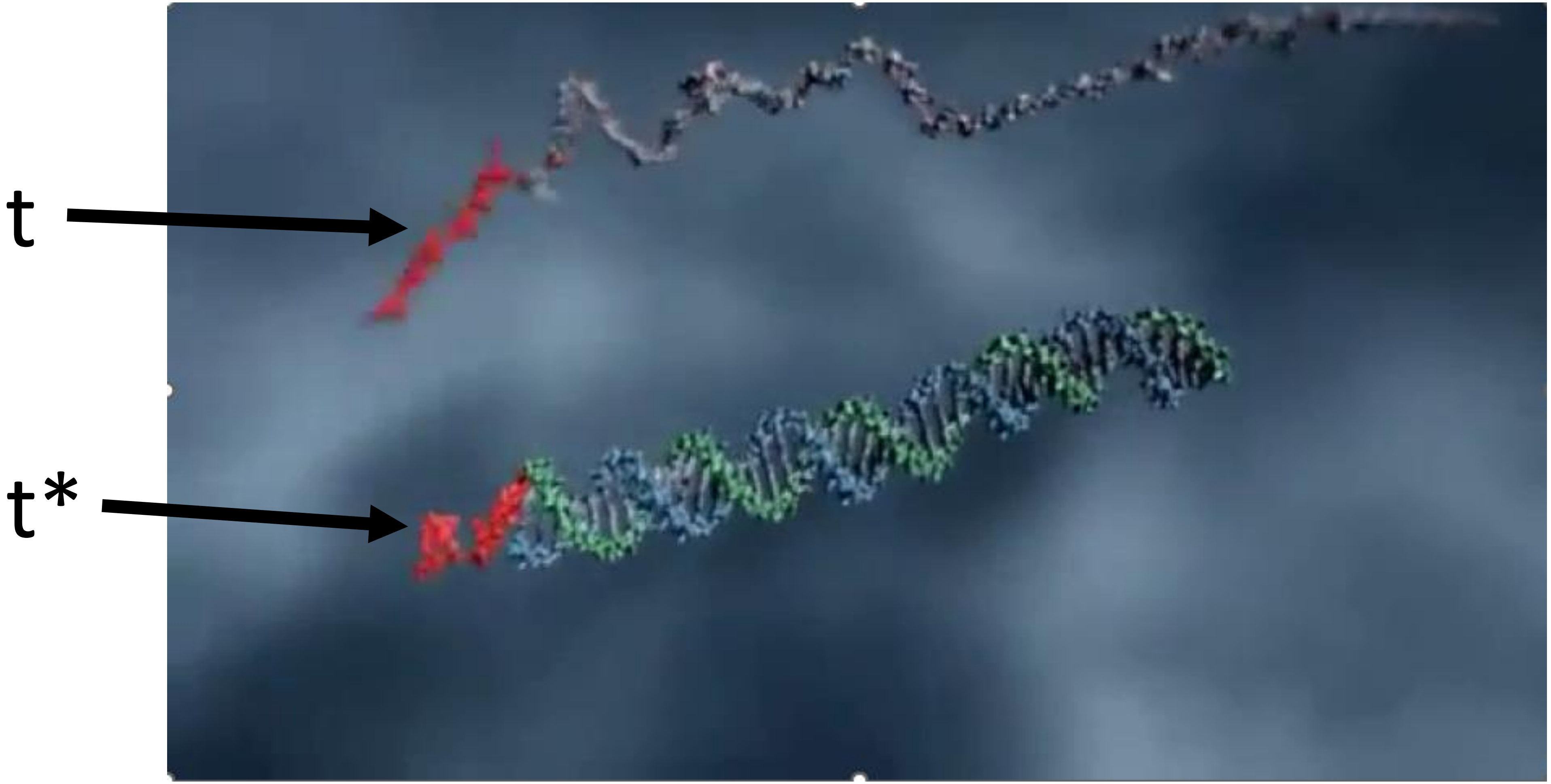
“breathing”/ “fraying”

branch migration

irreversible

DNA strand displacement

https://www.microsoft.com/en-us/research/video/dna-strand-displacement/



DNA strand displacement

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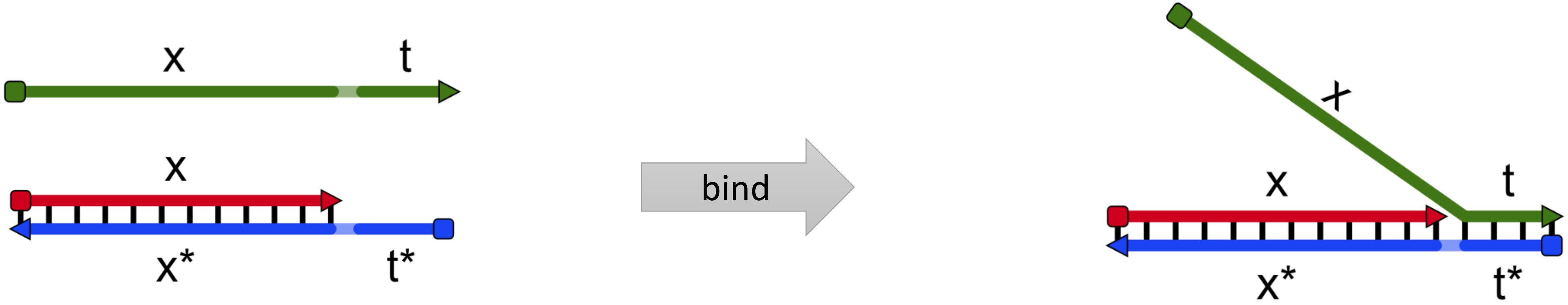
DNA strand displacement model

3 rules:

1. bind
2. release
3. displace

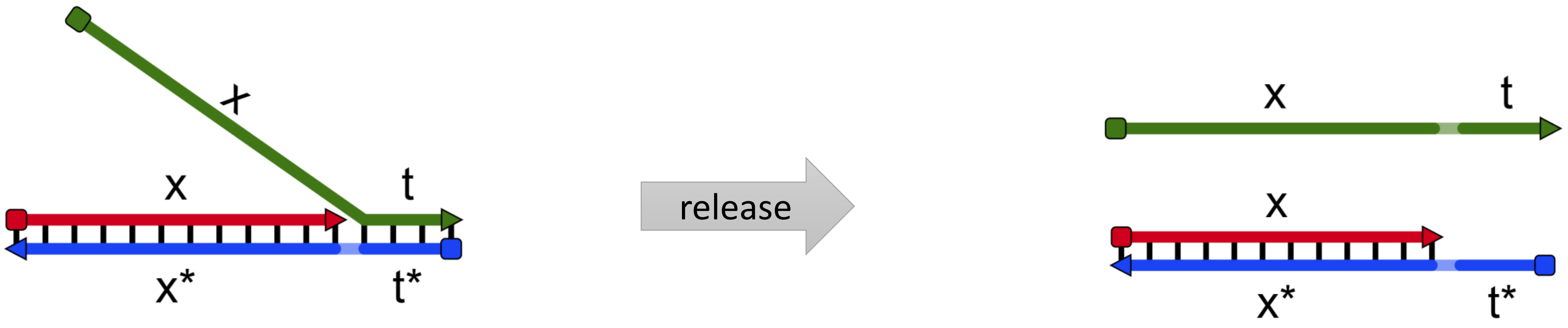
Bind rule

single-stranded complementary domains can bind



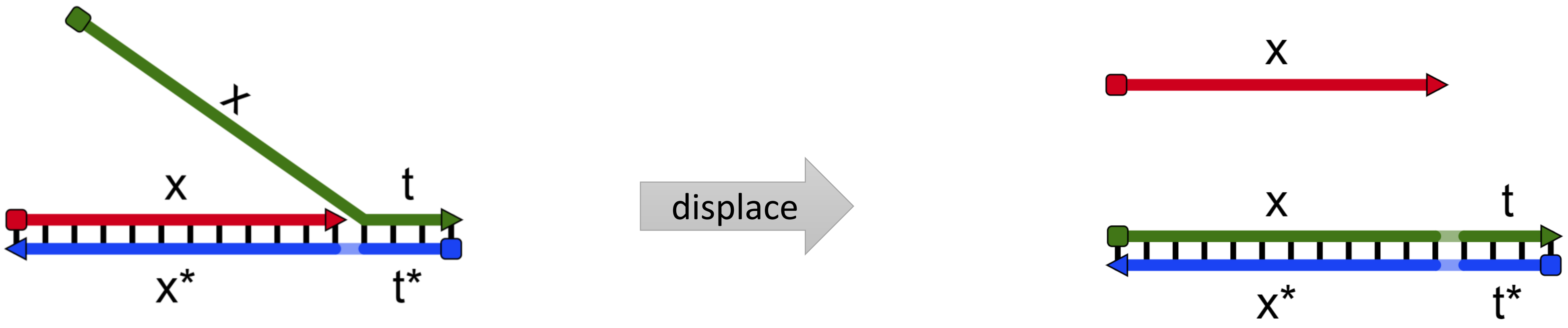
Release rule

double-stranded complementary domains can unbind
IF they are toehold-length (short, < 8 nt)



Displace rule

A domain (invader) can displace an identical domain (incumbent) of another strand,
IF neighboring domains are already bound



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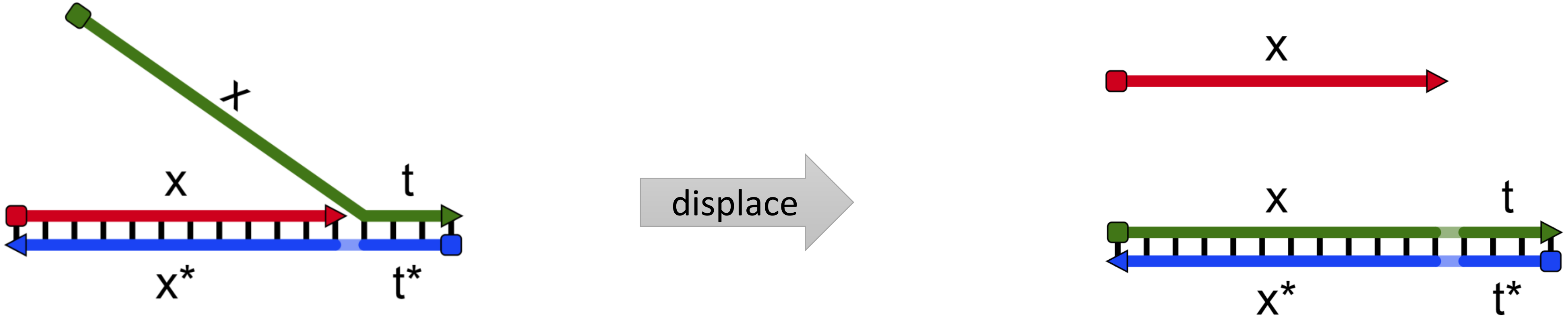
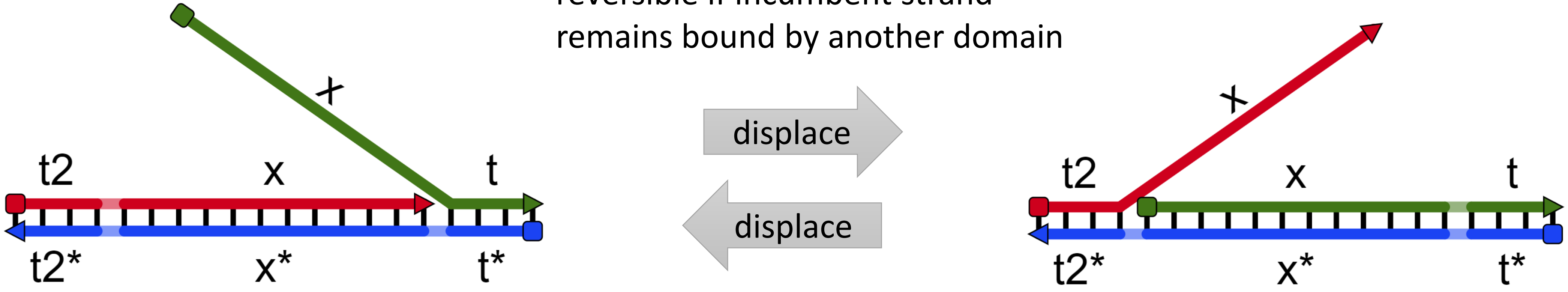
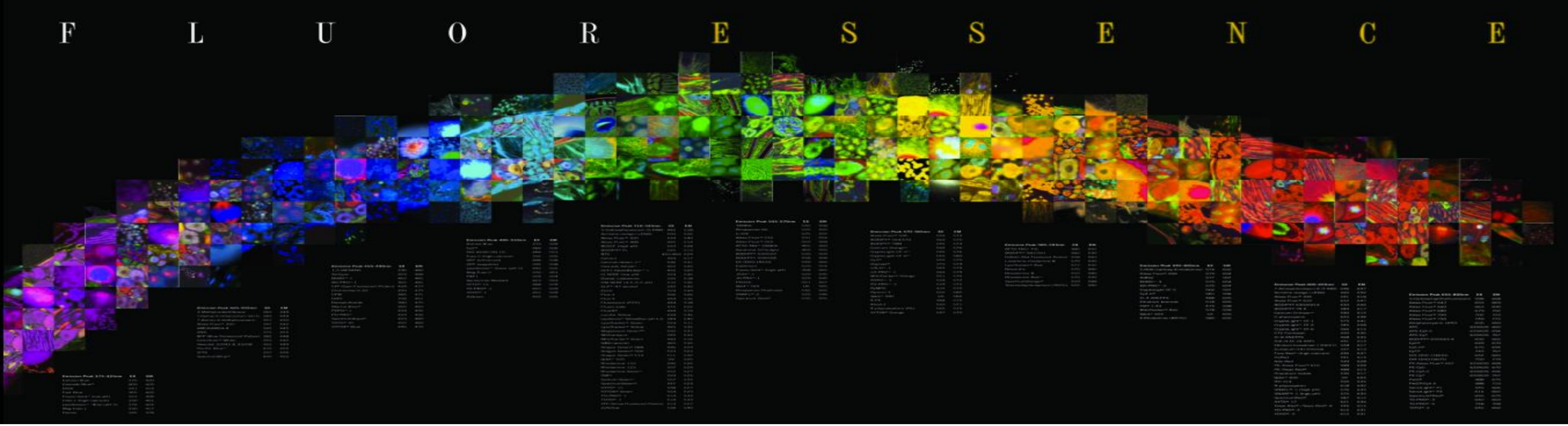


reversible if incumbent strand
remains bound by another domain

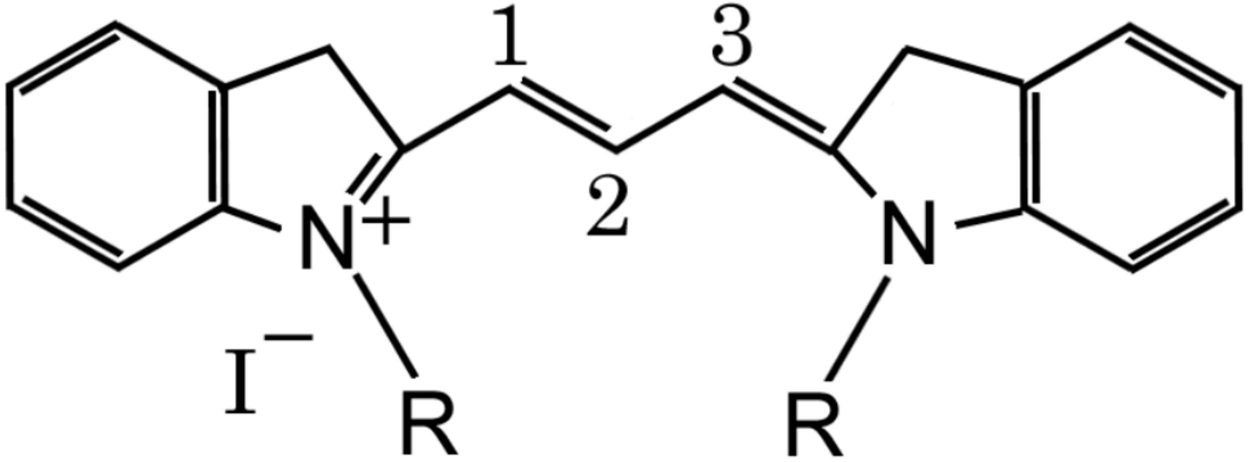


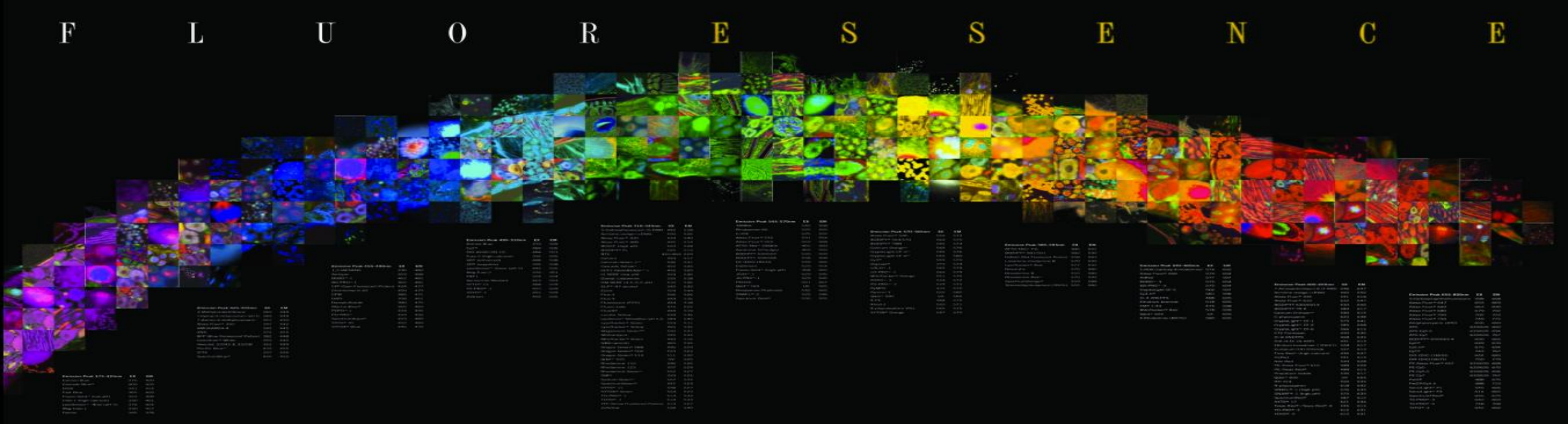
Readout

How do we read a “signal” in a DNA strand displacement system?



Fluorophores, when “excited” by light at one wavelength, emit light at a longer wavelength.





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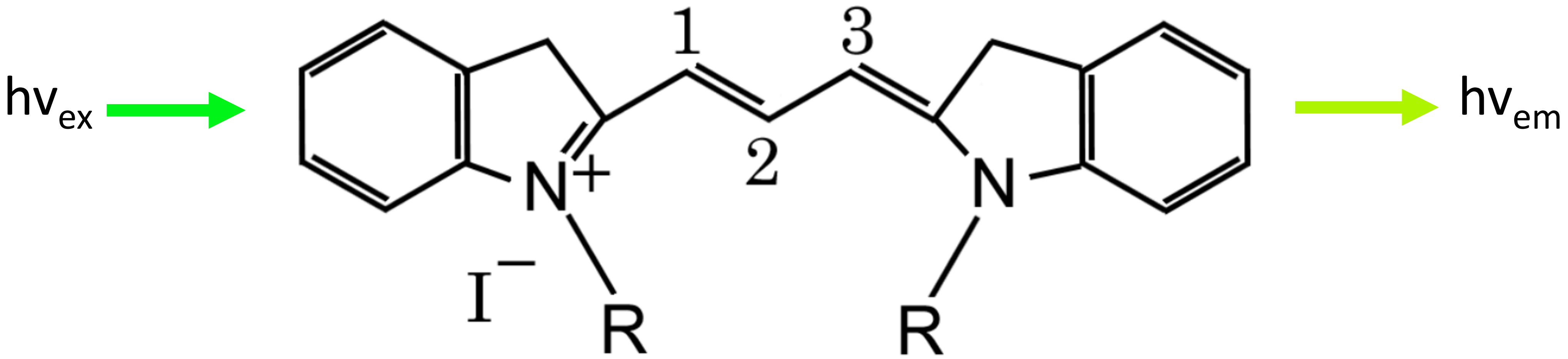
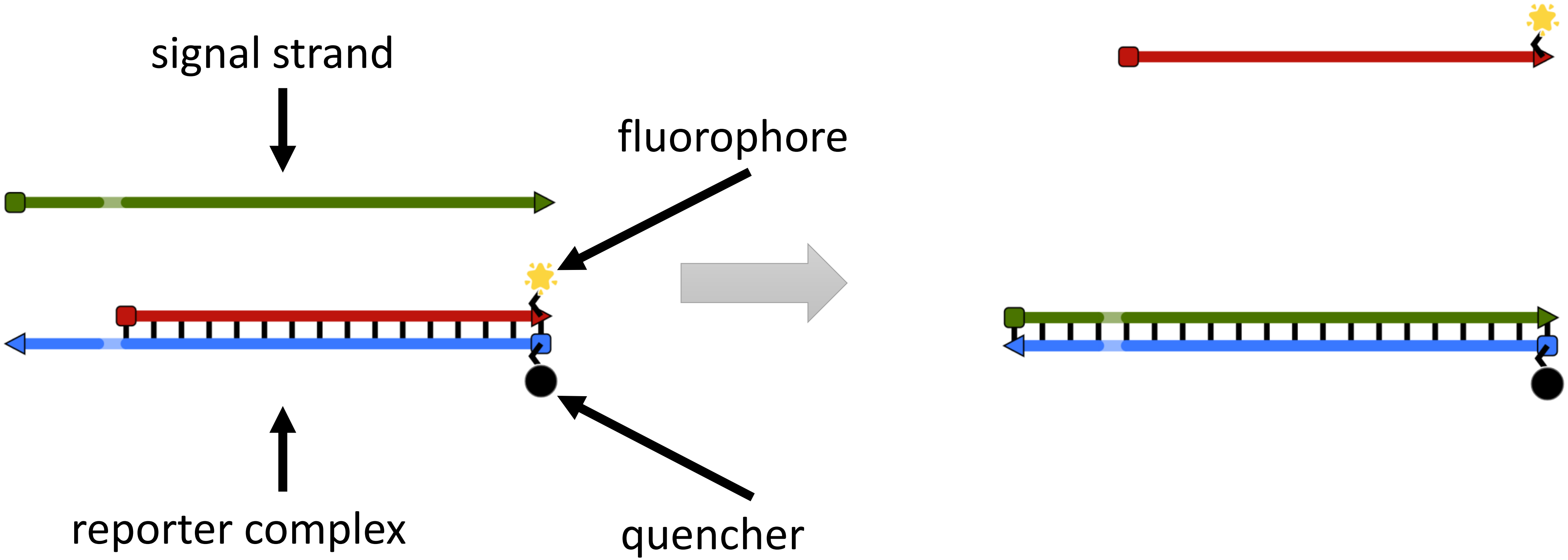
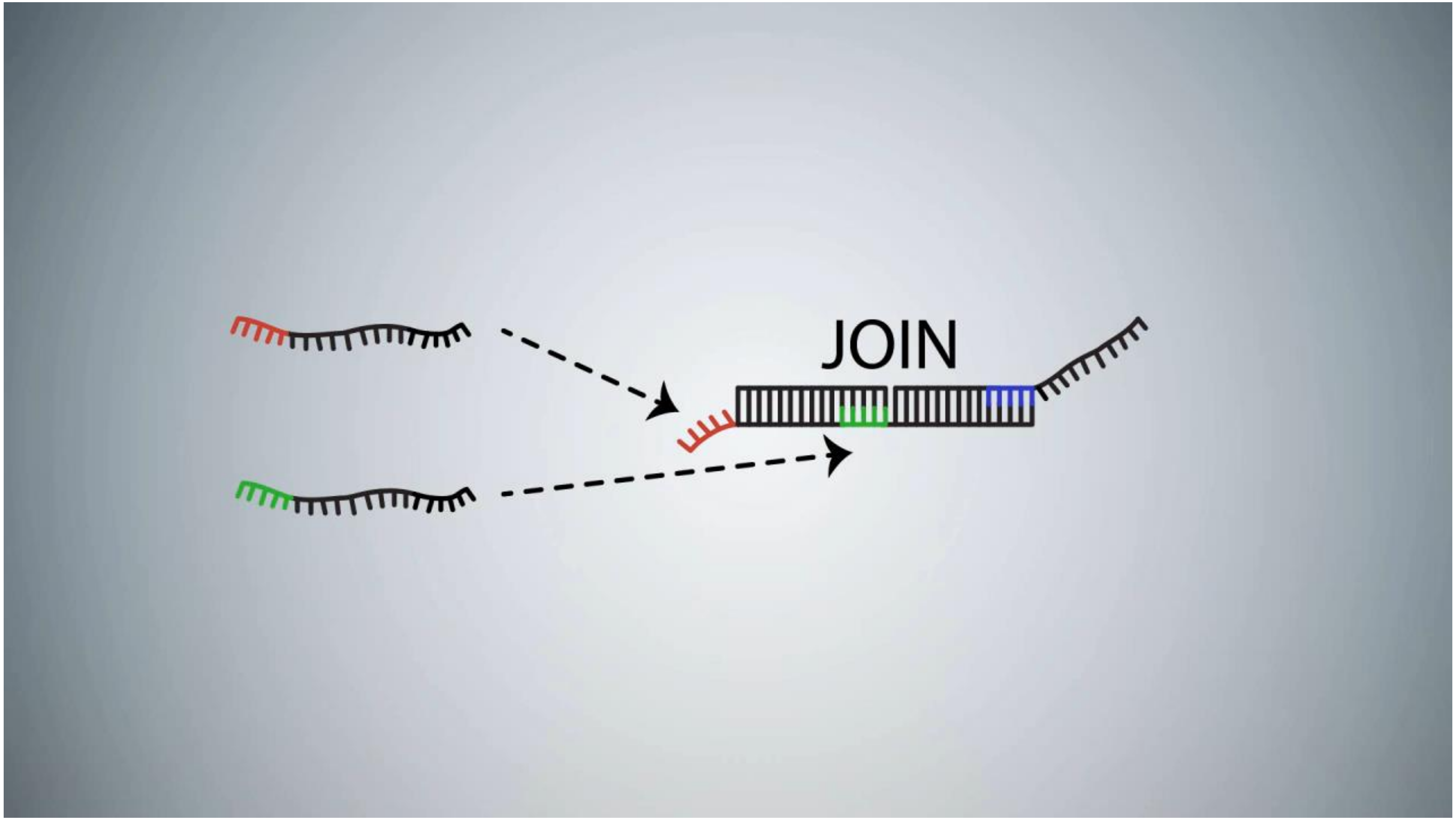


Reporter complexes

How do we read a “signal”?
“signal” = single strand is freed from a double-stranded complex.



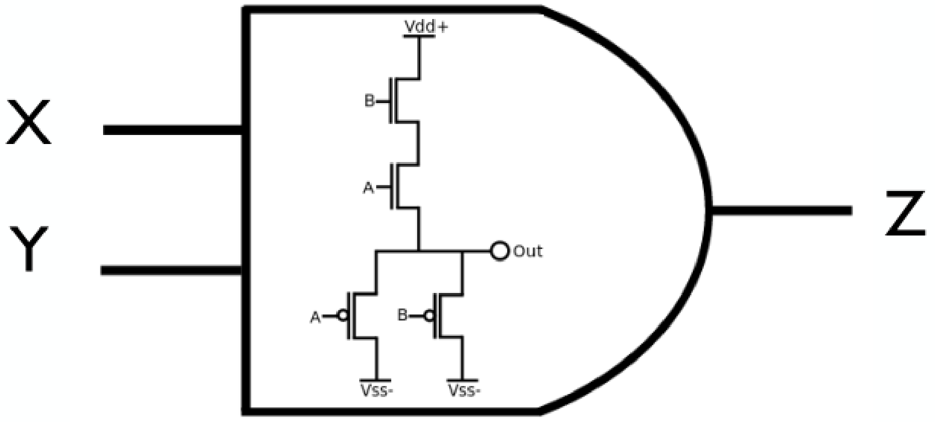
Reporter complex depiction



Boolean logic with DNA strand displacement

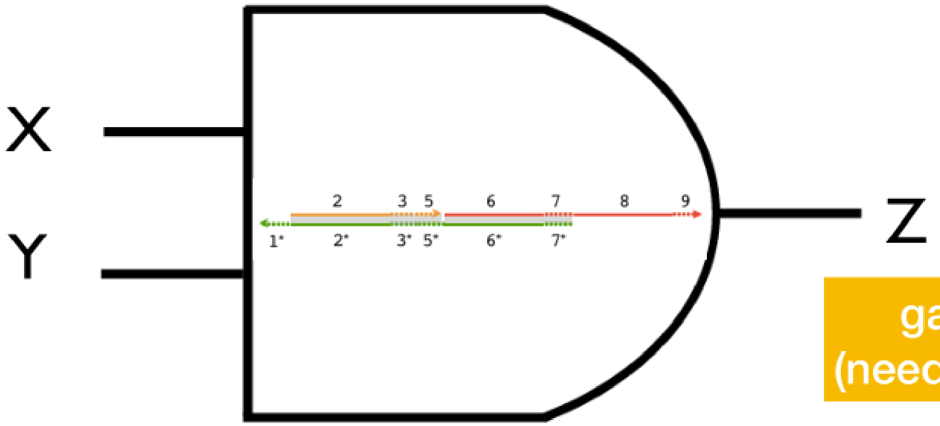
AND gate

voltages



release Z if and only if X and Y are present

strands

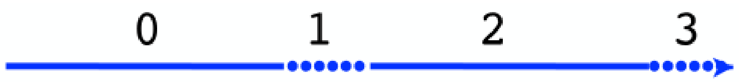


gates get consumed!
(need to have many copies)

gate=complex

[slides credit: Chris Thachuk]

Strand displacement cascade example: AND gate



input X

release Z if and only
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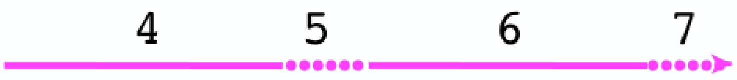
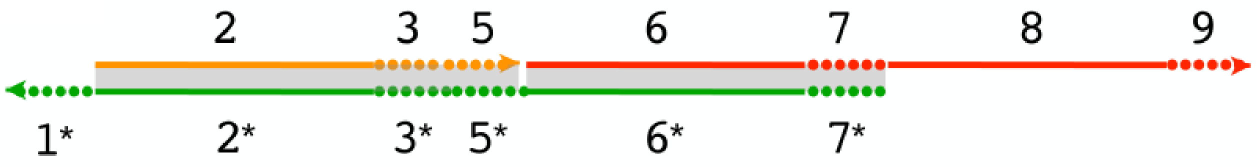


input Y



AND gate

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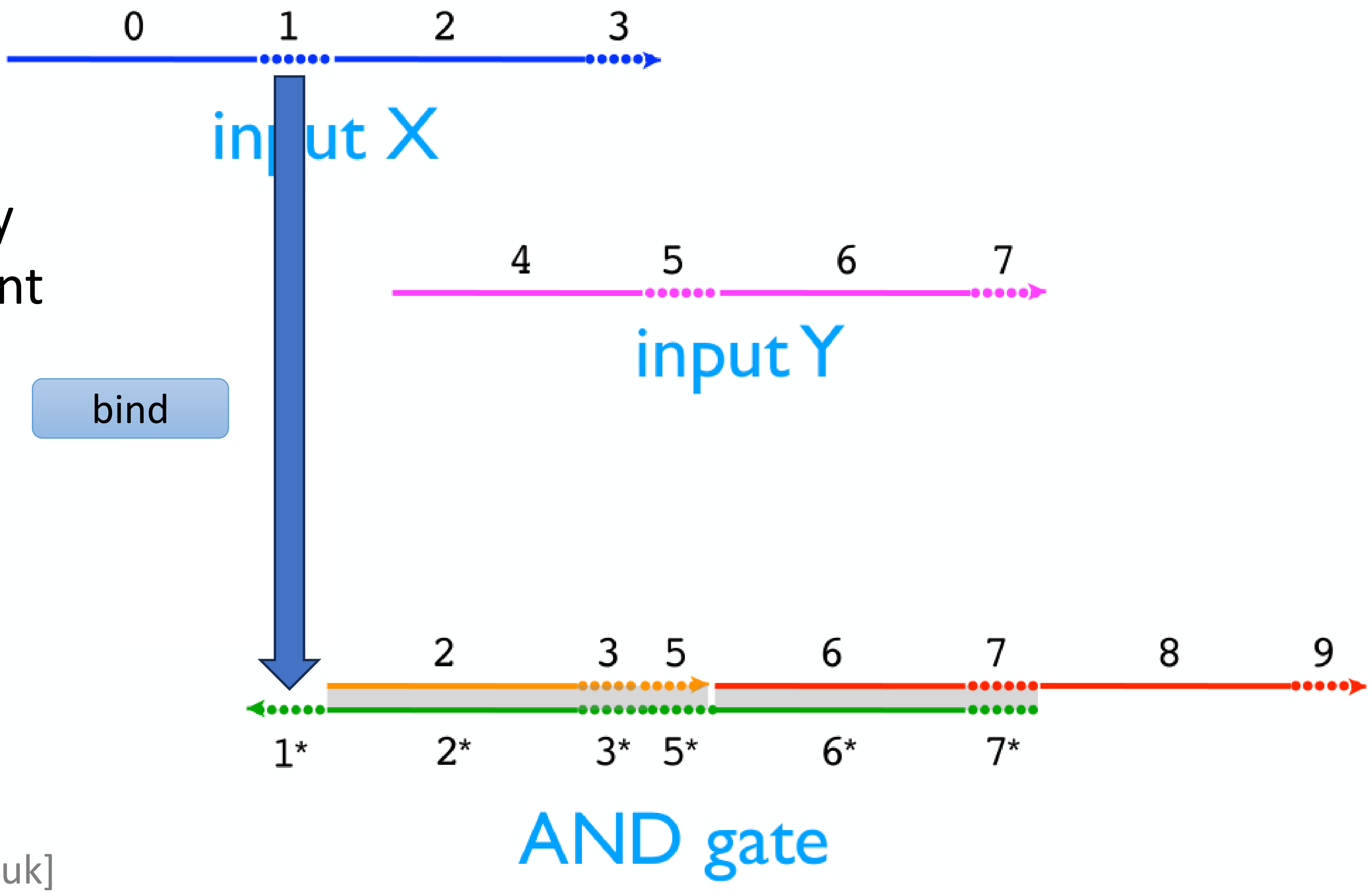

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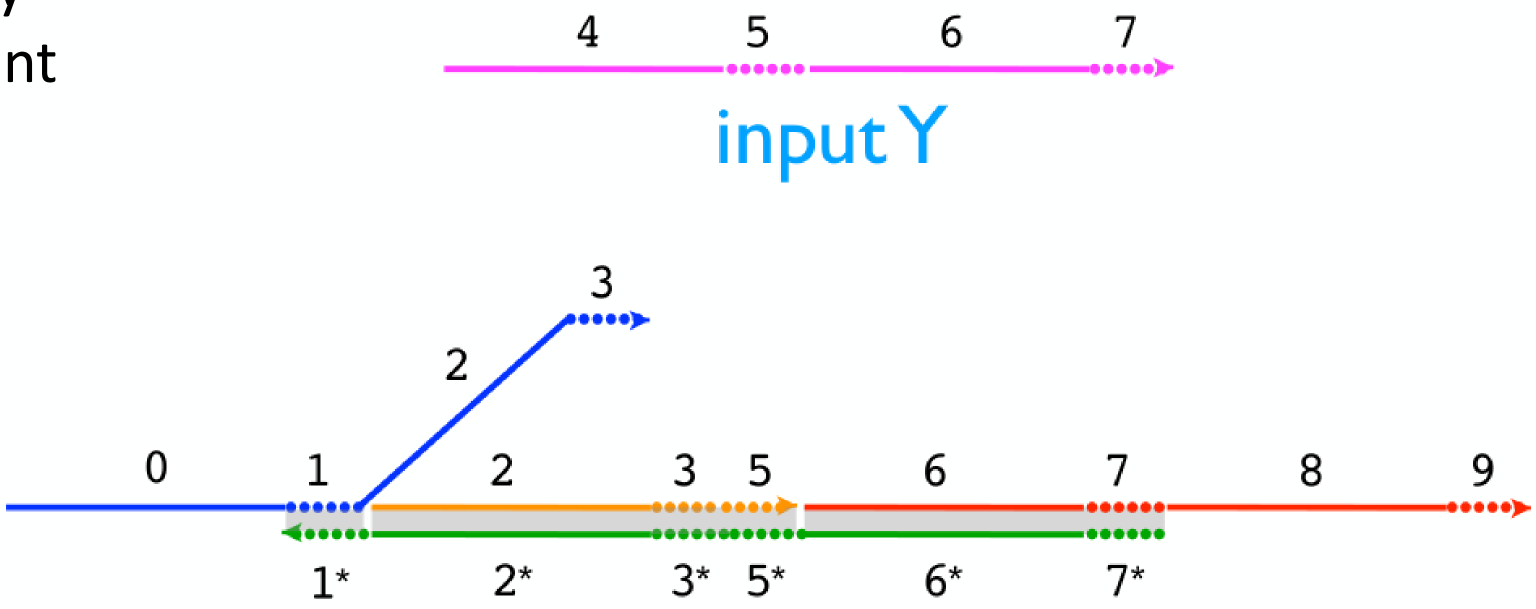

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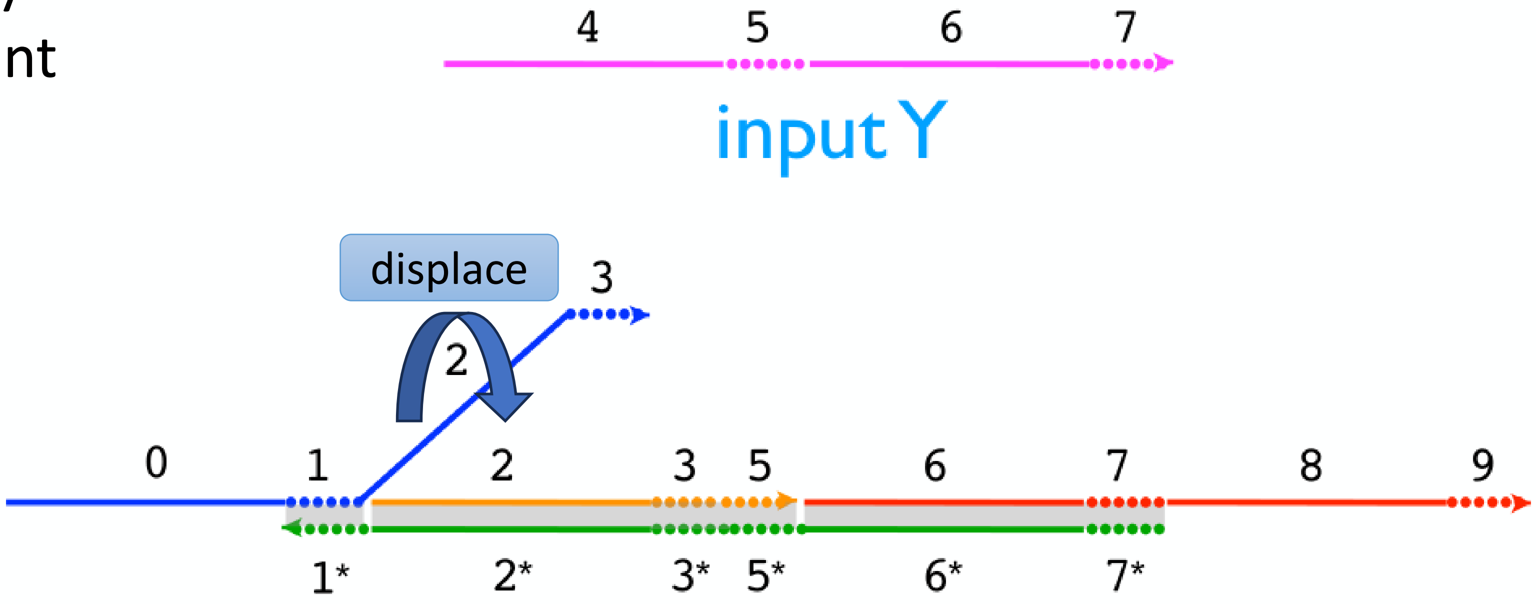

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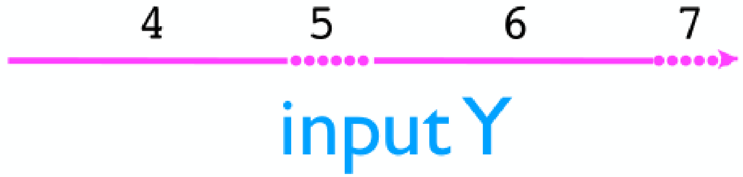

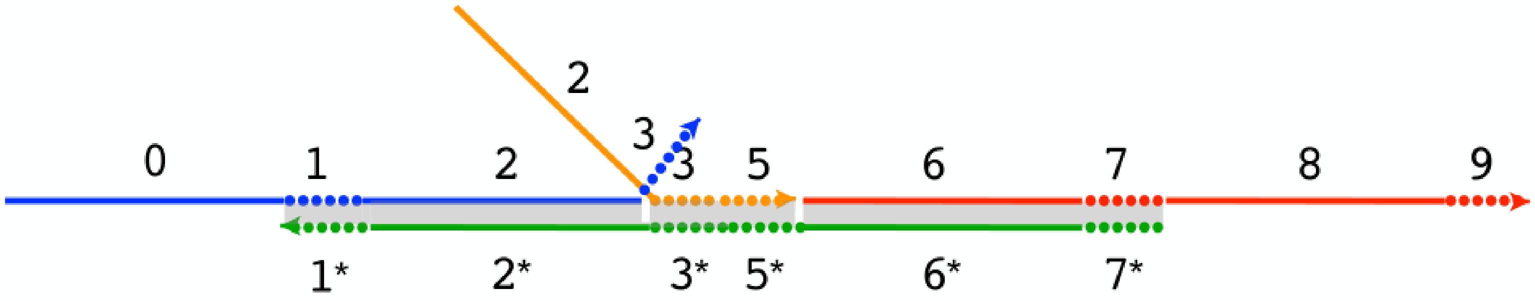

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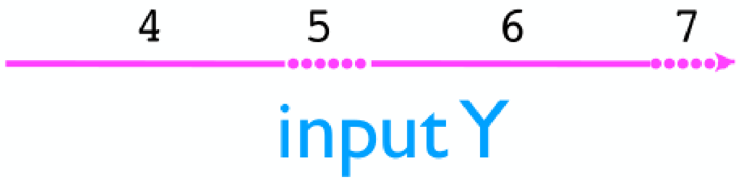

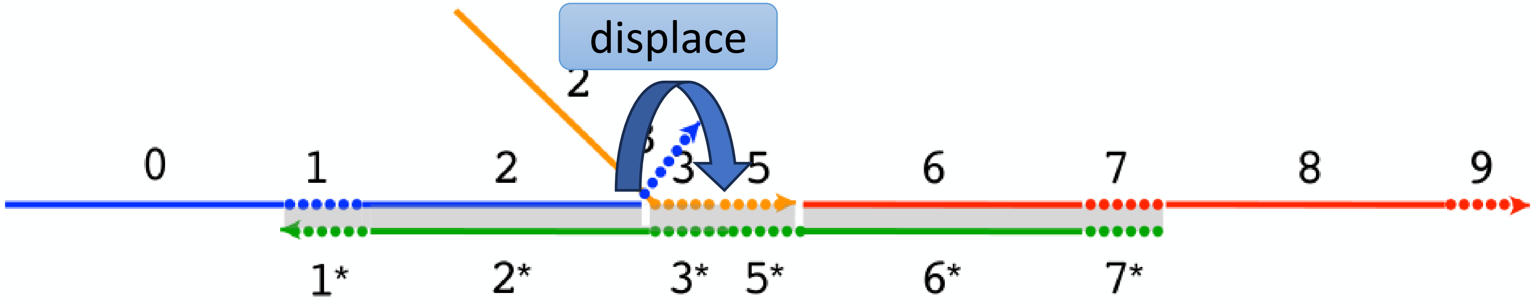

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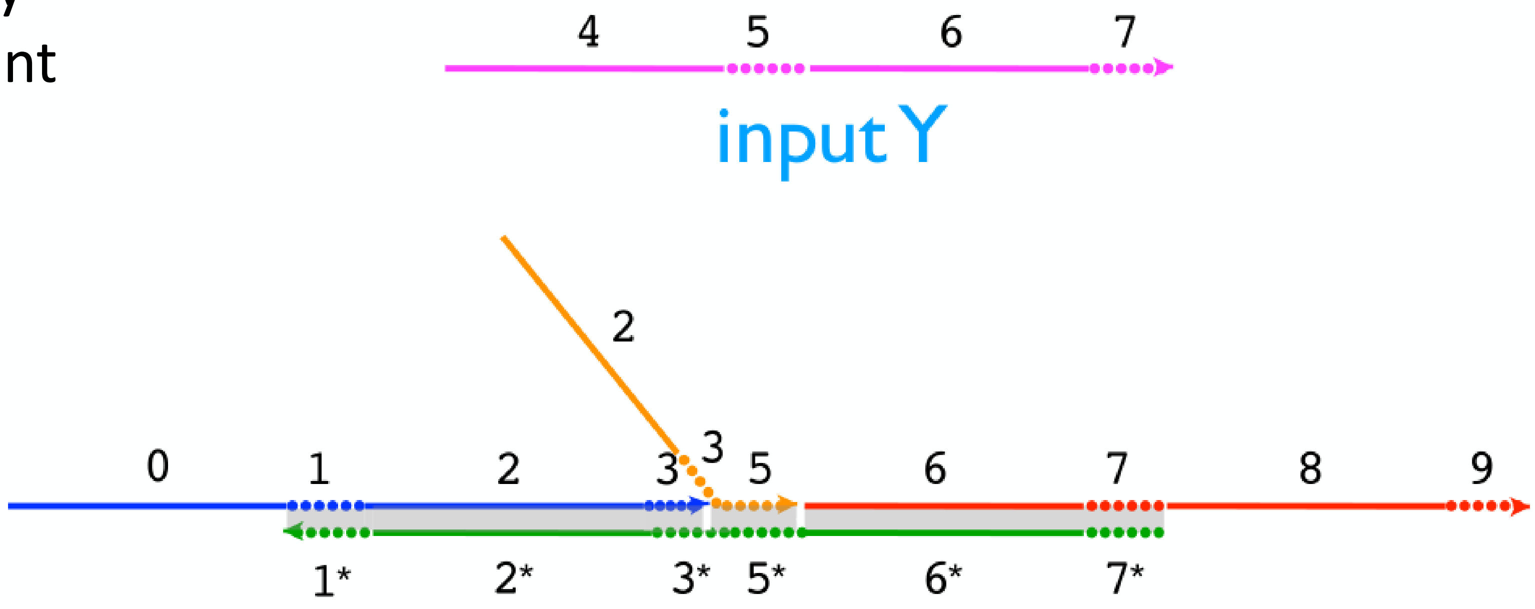

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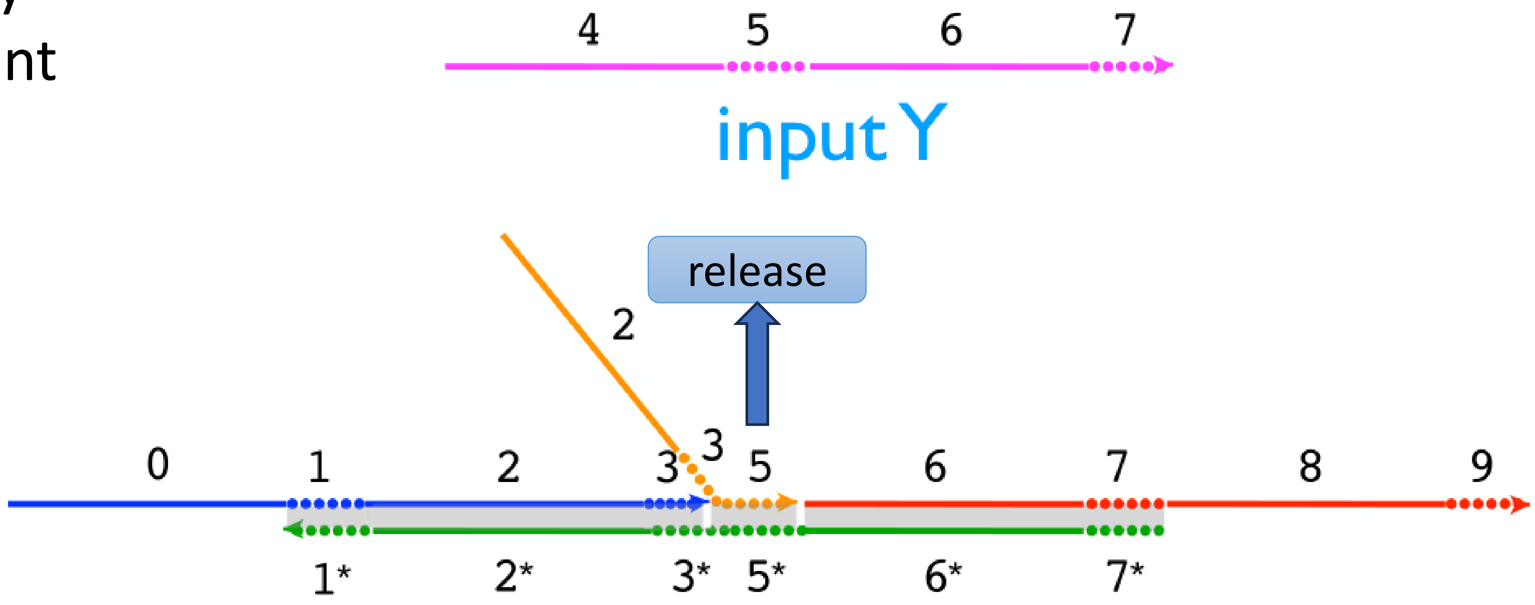

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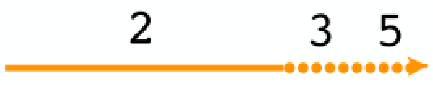
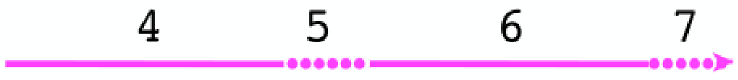
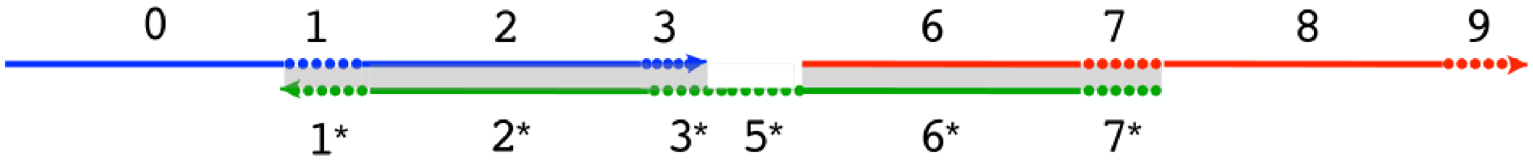


waste

release Z if and only
if X and Y are present



input Y



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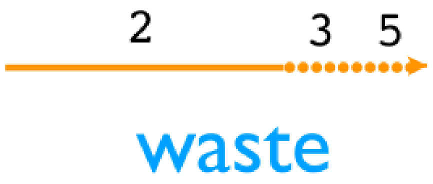

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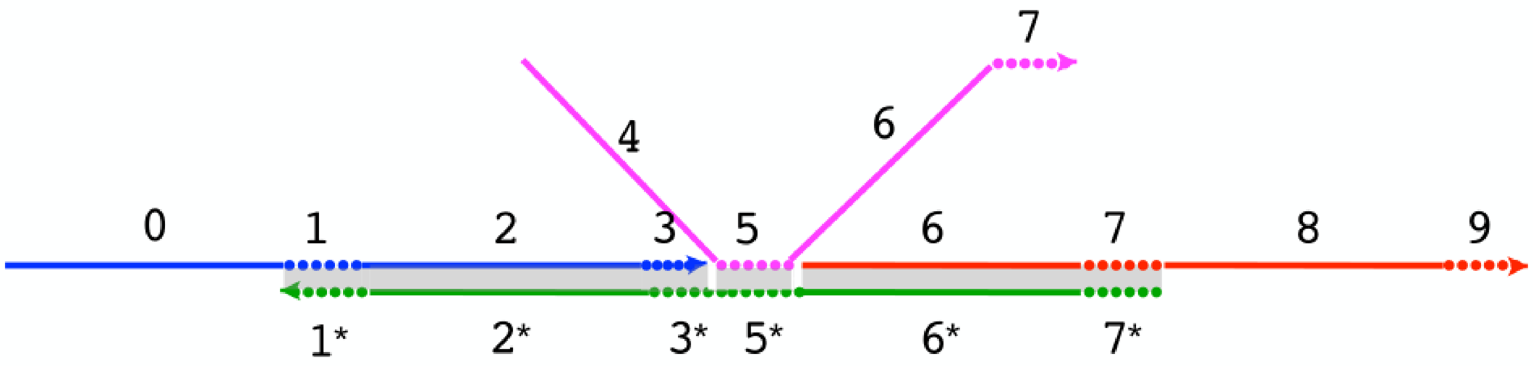

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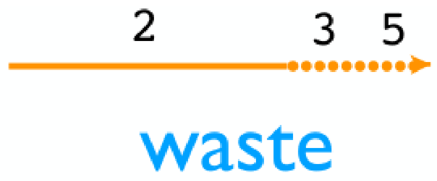

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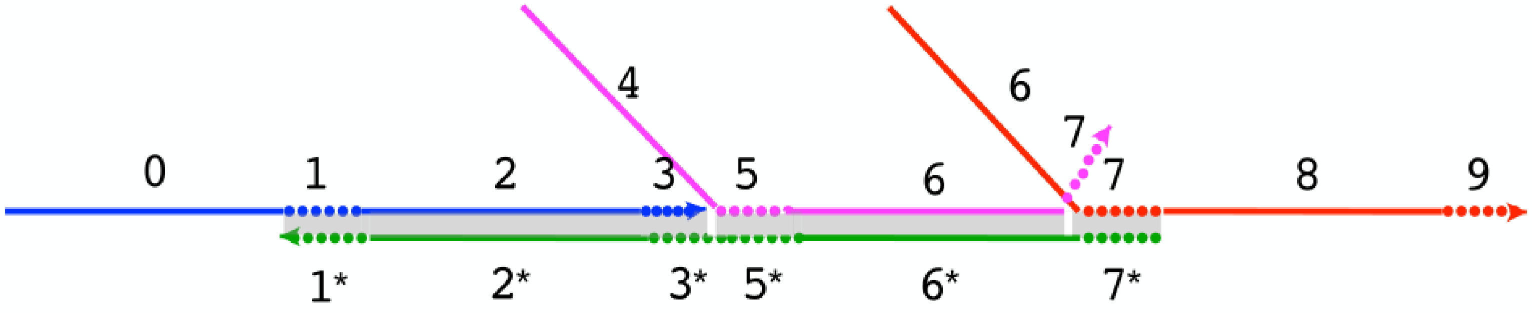

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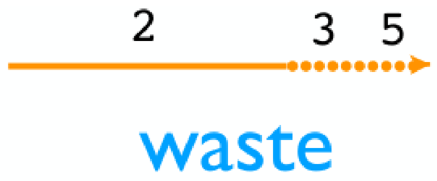

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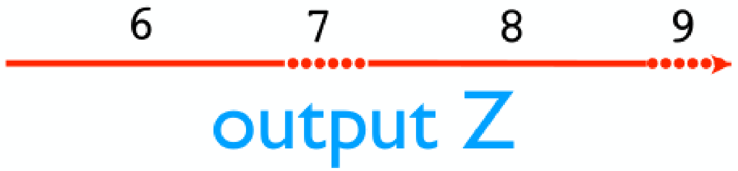

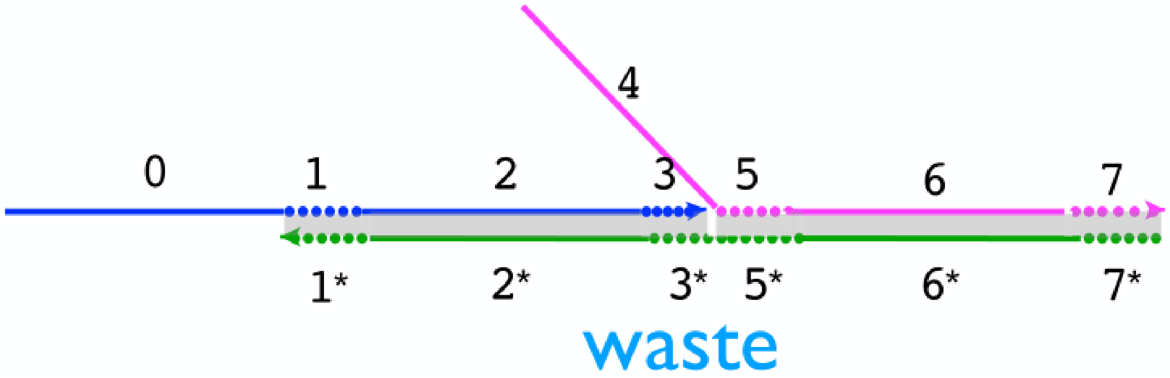

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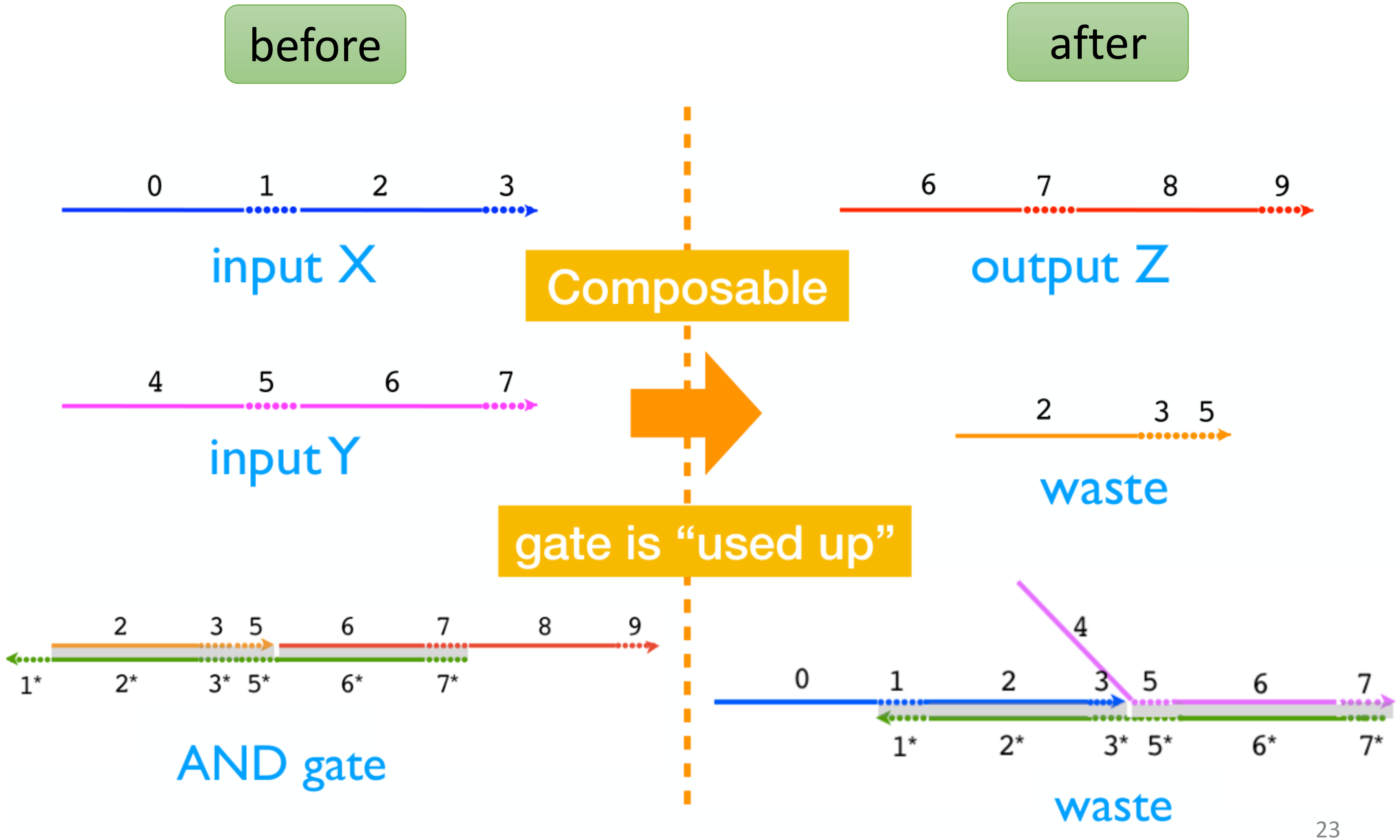

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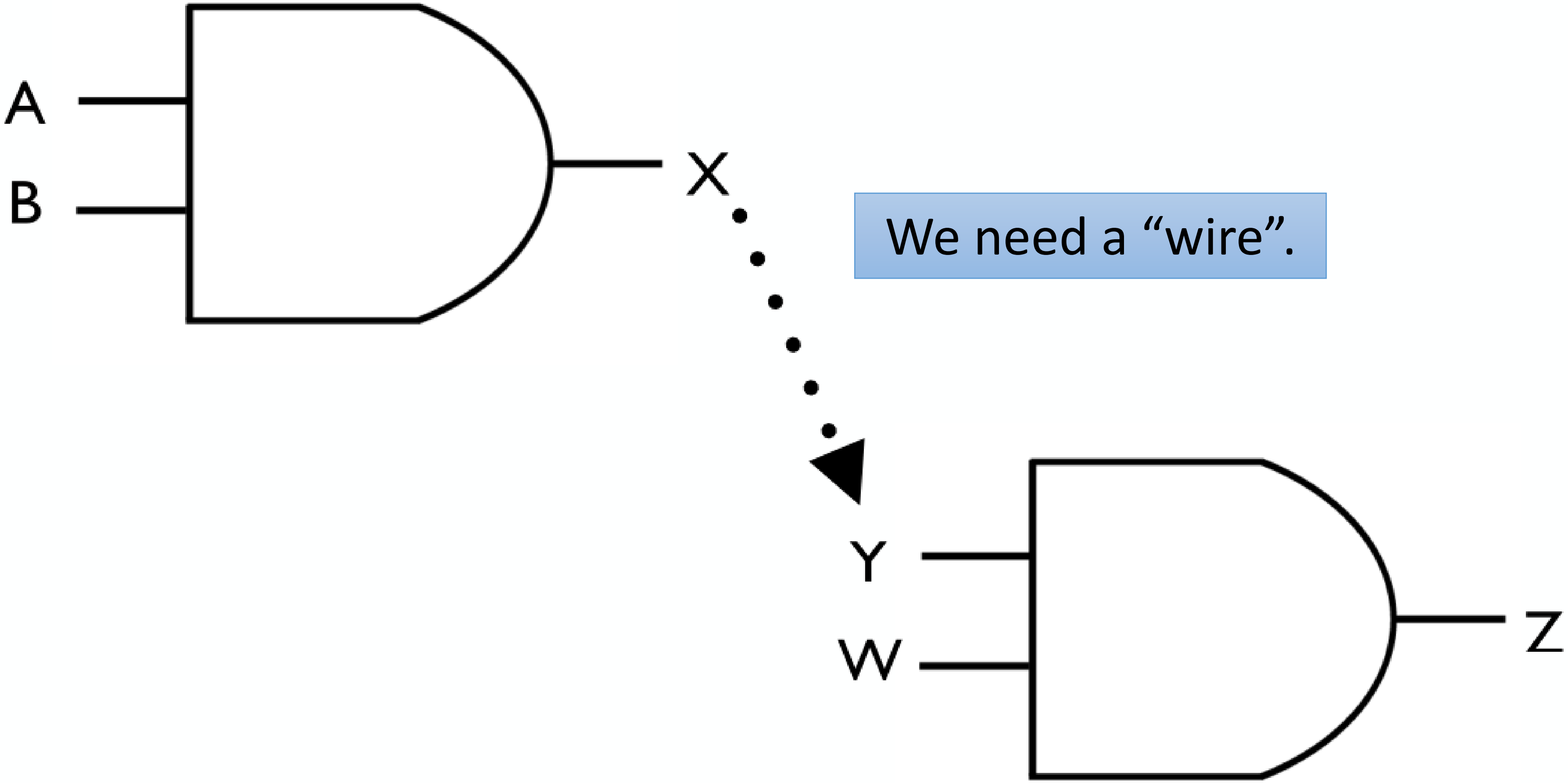
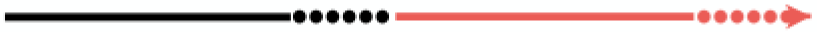
Composing AND gates



We need a “wire”.

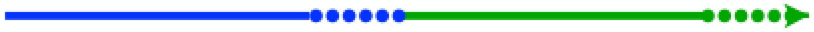
Translator gate ("wire")

input X

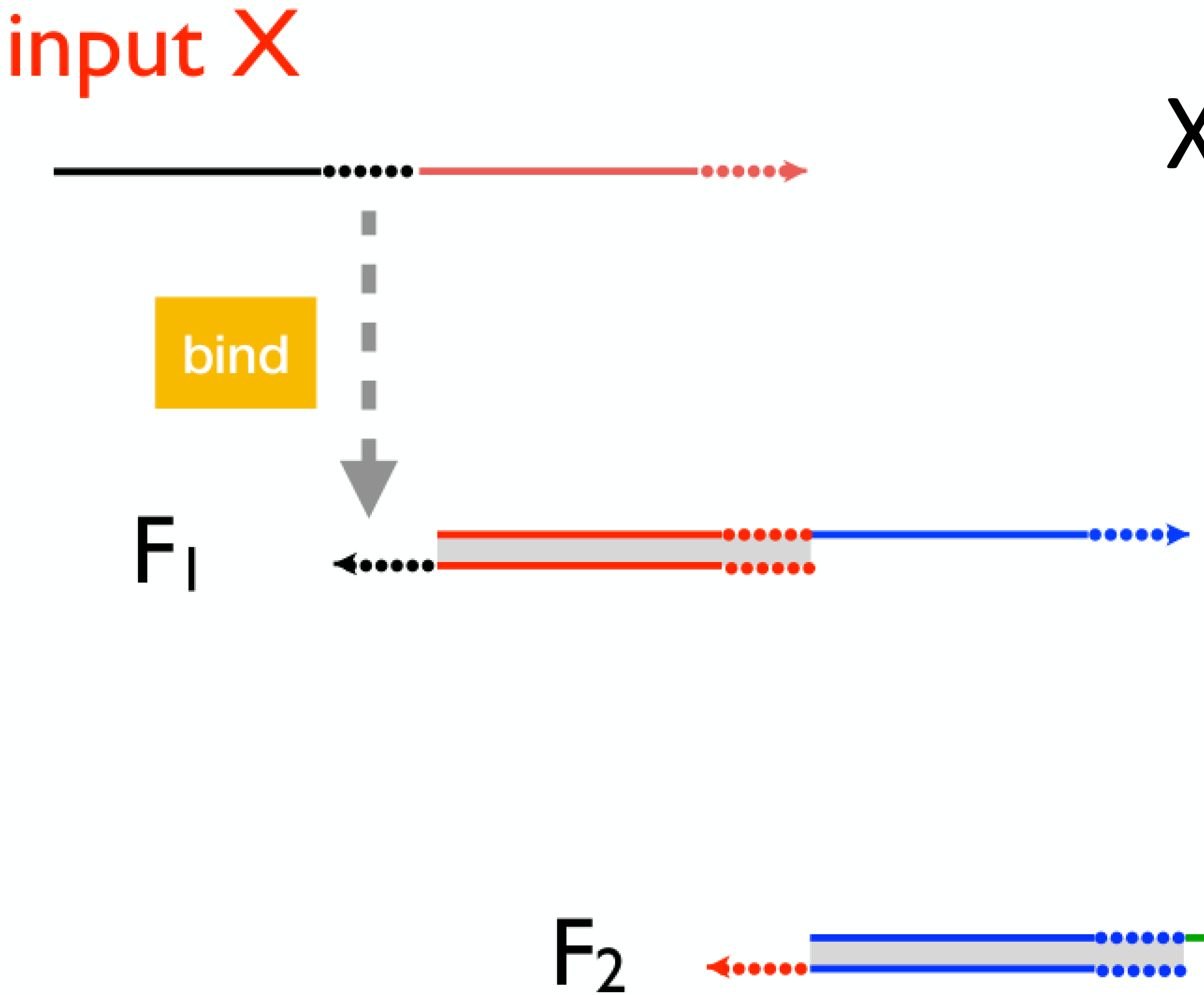


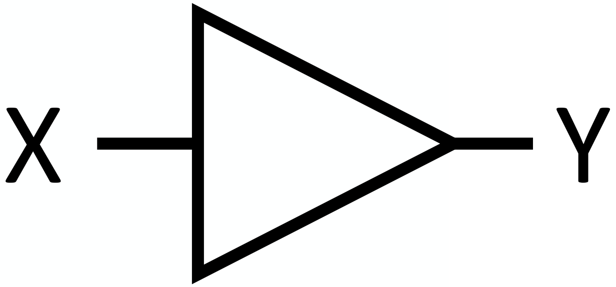
We need a "wire" to translate the signal:
X → Y
(with no shared DNA sequences between X and Y)

output Y



Translator gate (a "wire")





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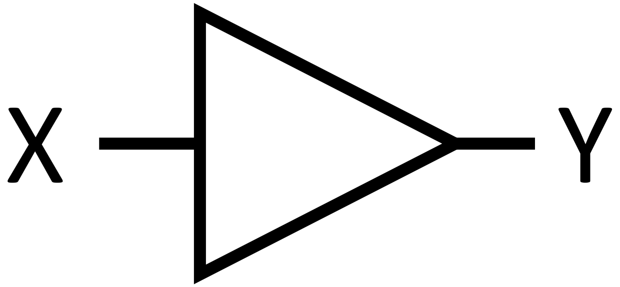

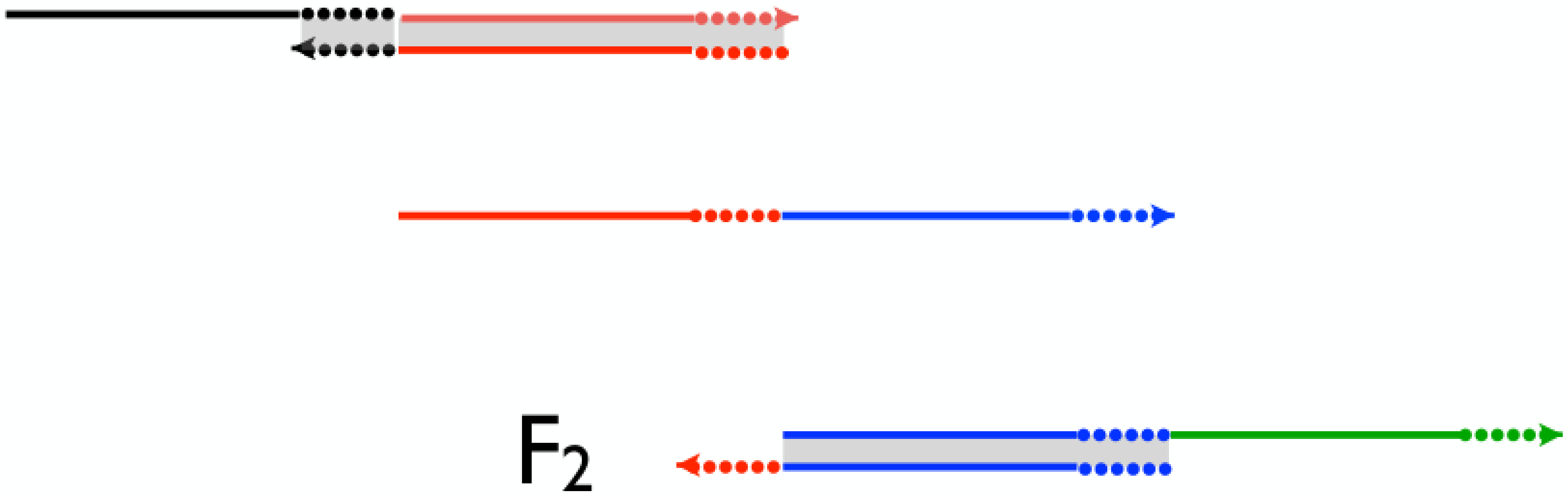

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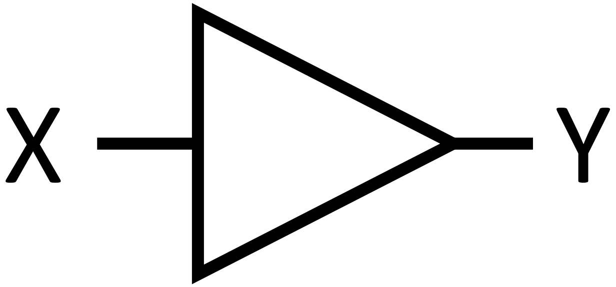
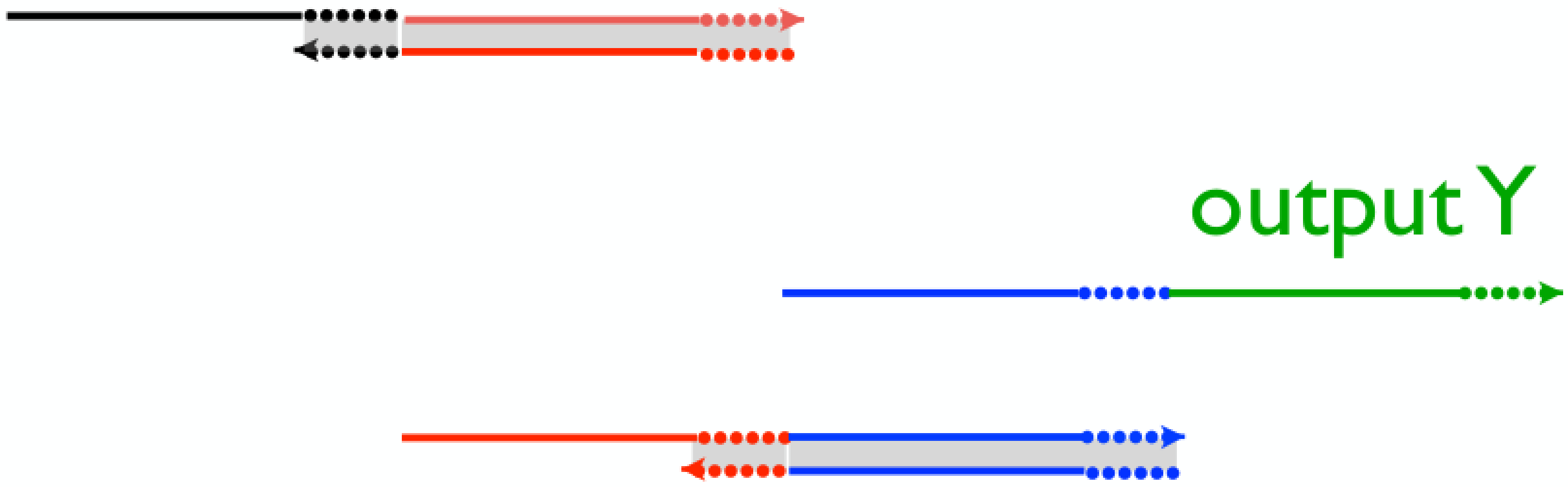
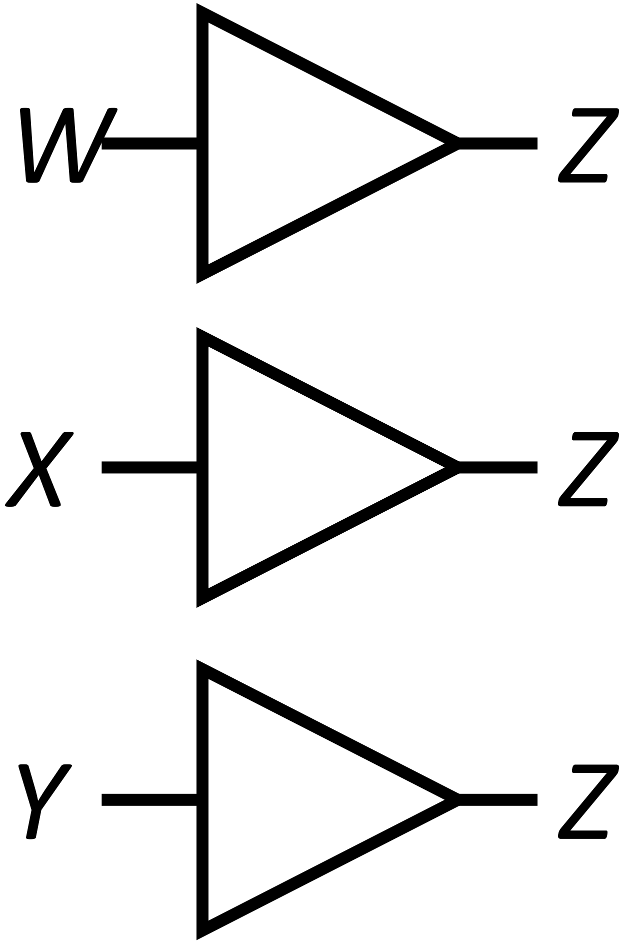




Strand displacement cascade example: OR gate

An OR gate can be implemented by multiple translators:

$Z \leftarrow W\ \mathbf{OR}\ X\ \mathbf{OR}\ Y$



Strand displacement cascade example: Avoiding the need for NOT gates using dual-rail logic

NOT gates are tricky with molecular circuits:

How to make a molecule Y present
if and only if X is not present??

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Instead we use dual-rail logic, using de Morgan’s Laws to push all the NOT gates to the input.

(Then we can “manually” specify FALSE input values by the presence of a “negated” strand.)

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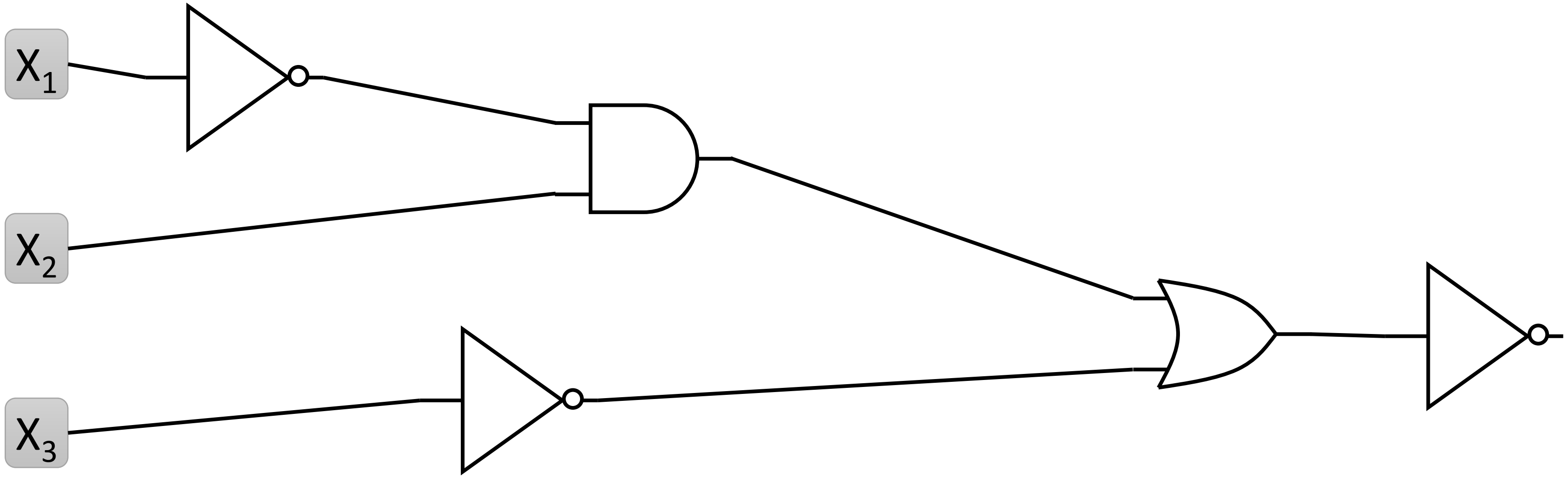

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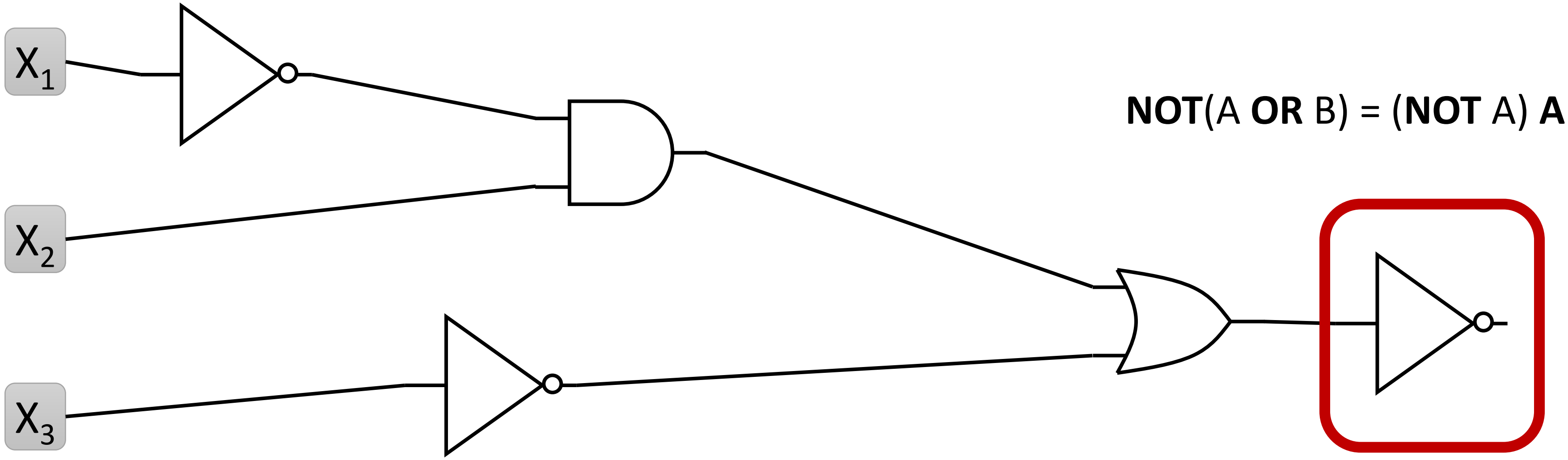
NOT(A **OR** B) = (**NOT** A) **AND** (**NOT** B)



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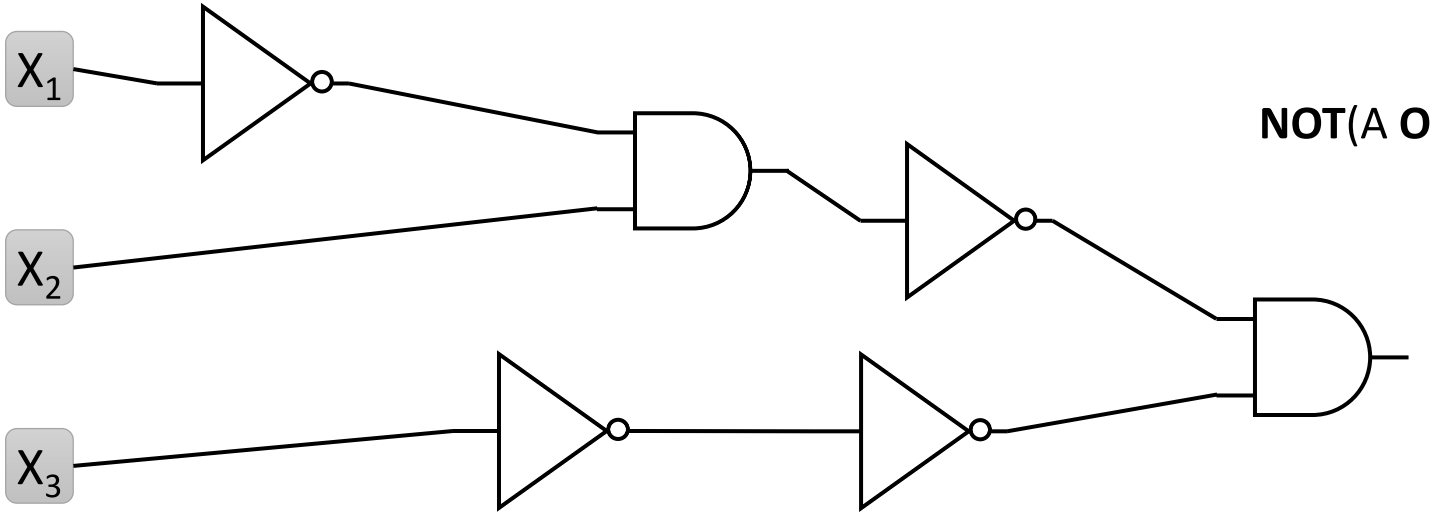

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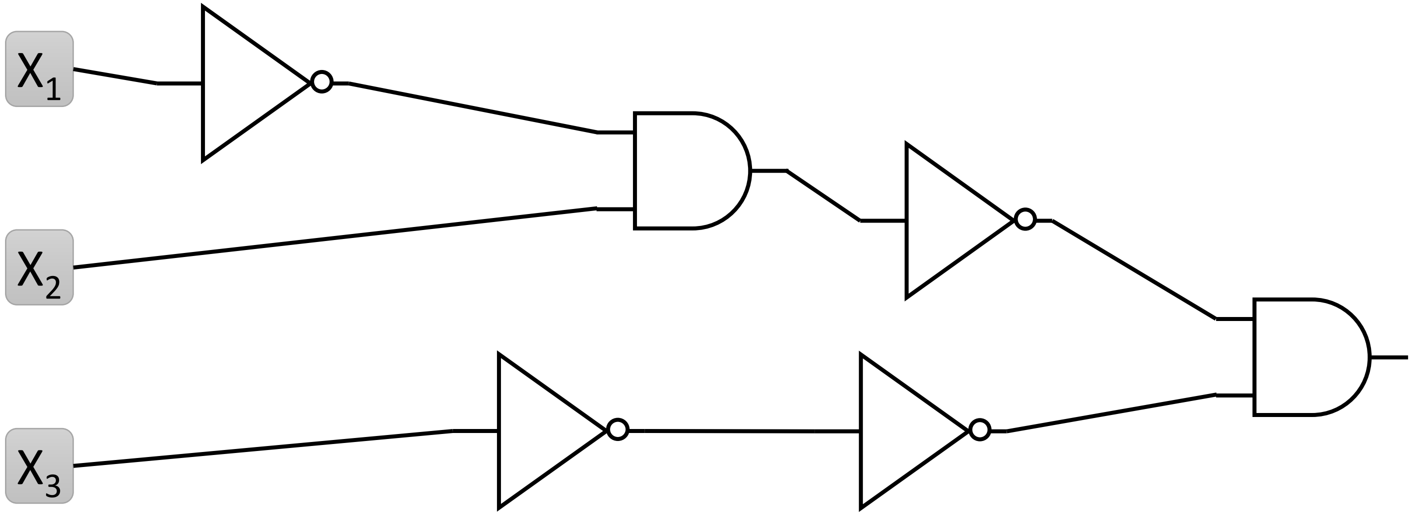

Strand displacement cascade example: Avoiding the need for NOT gates using dual-rail logic

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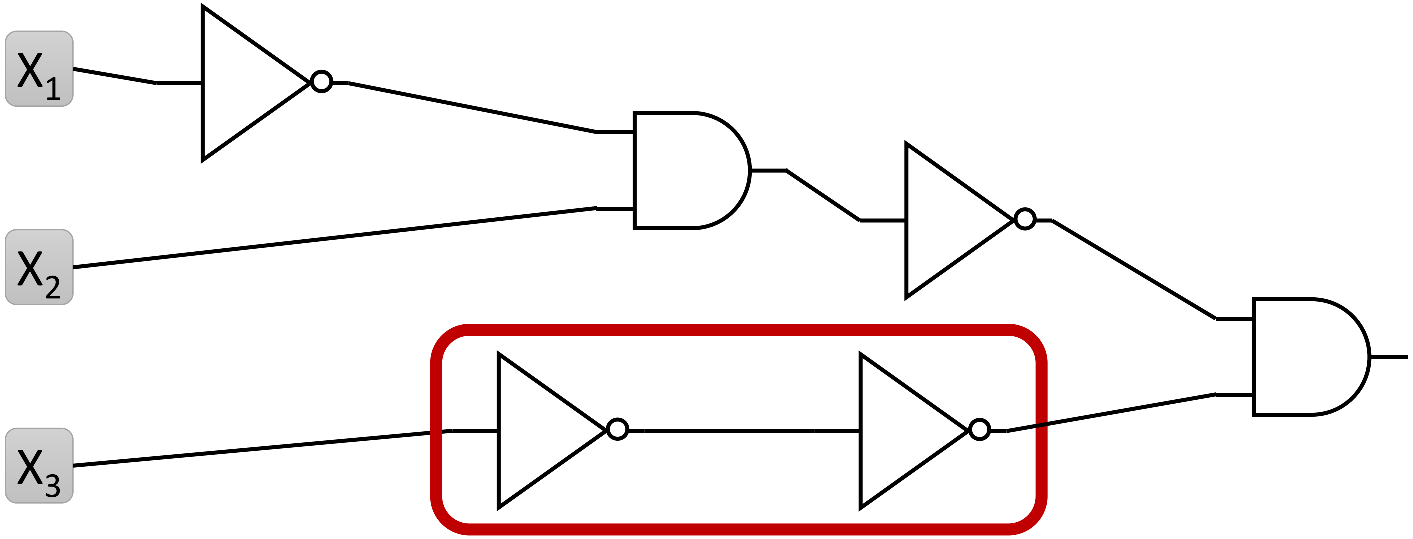

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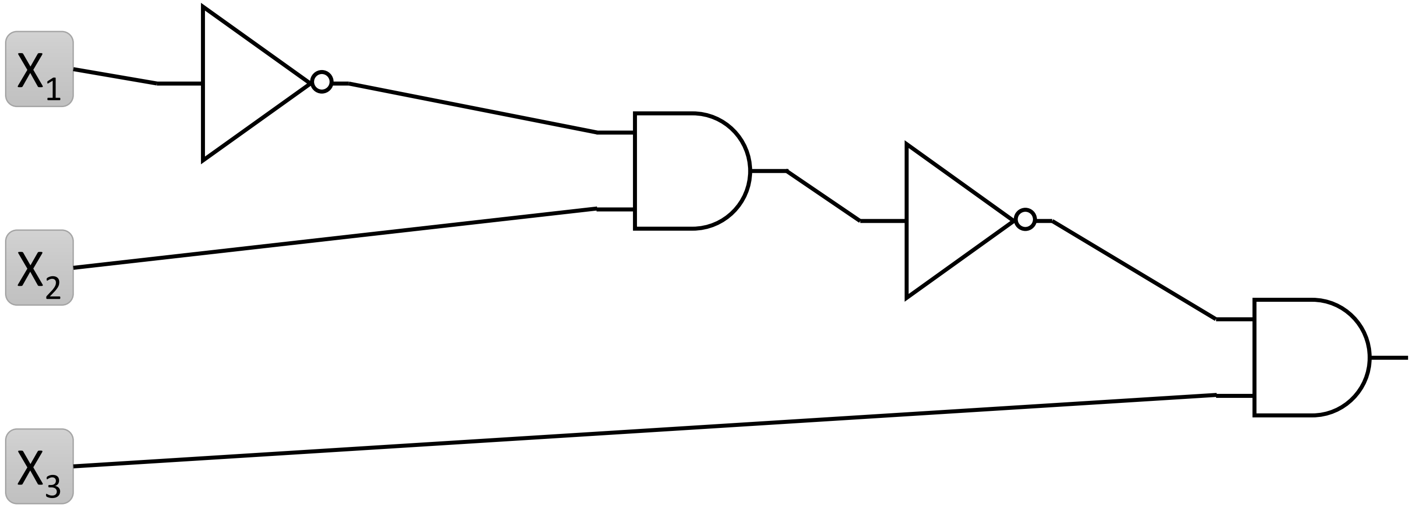

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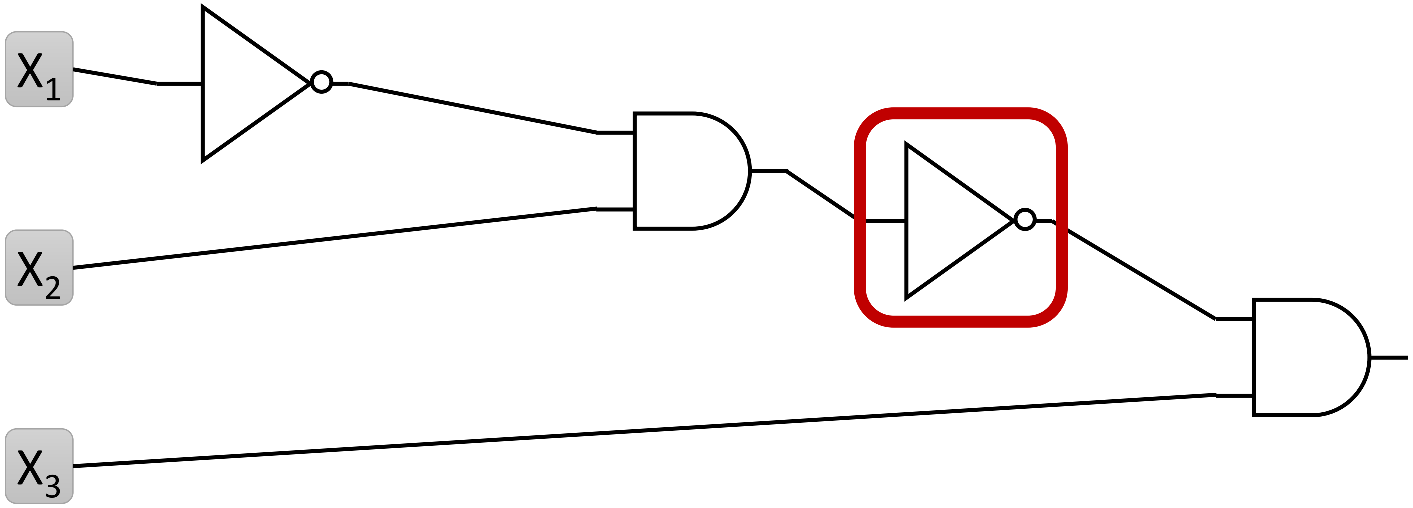

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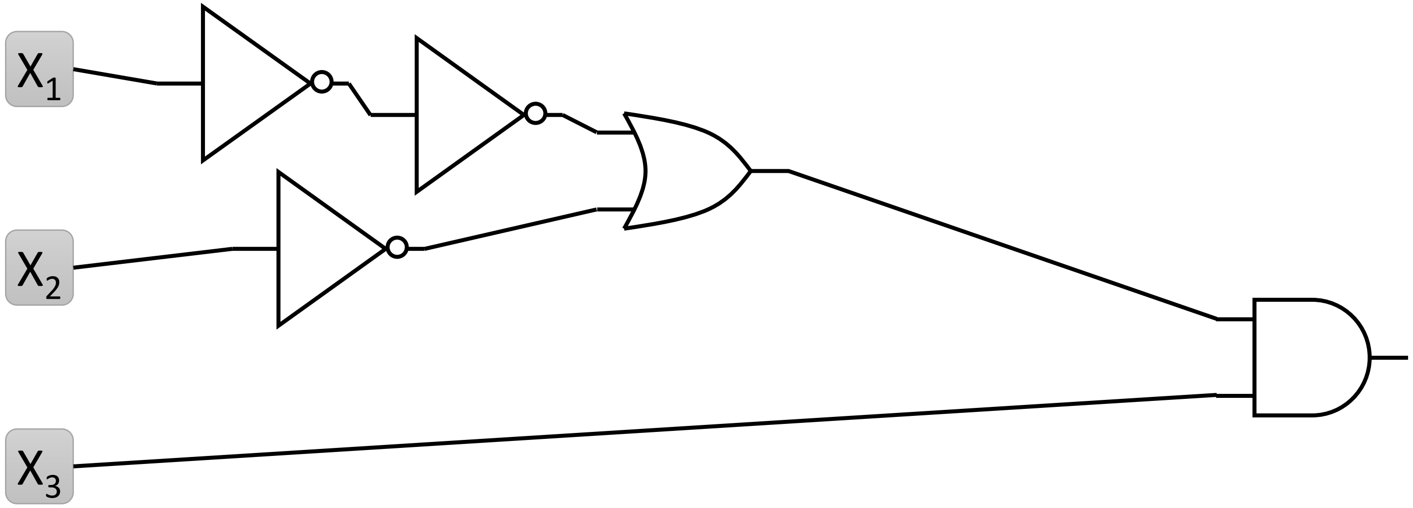

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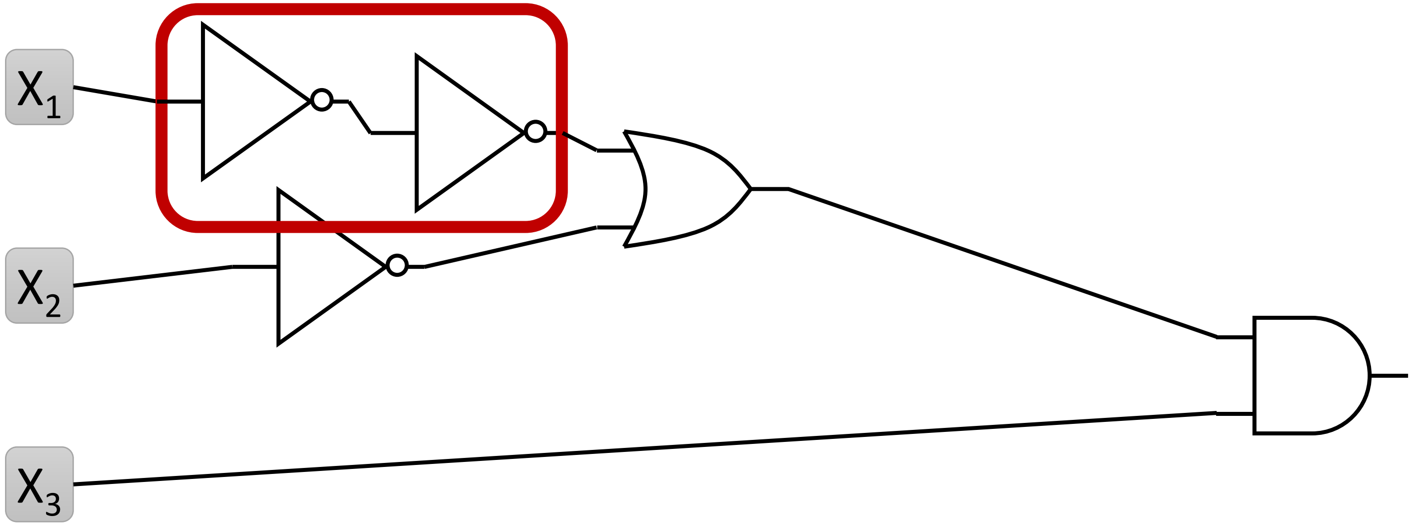

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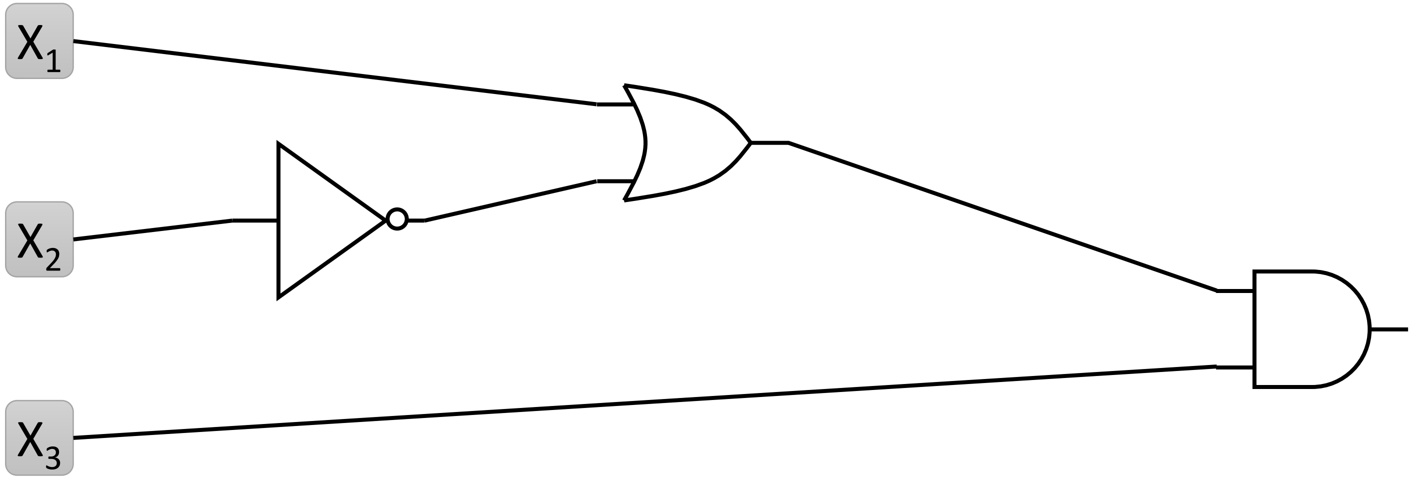
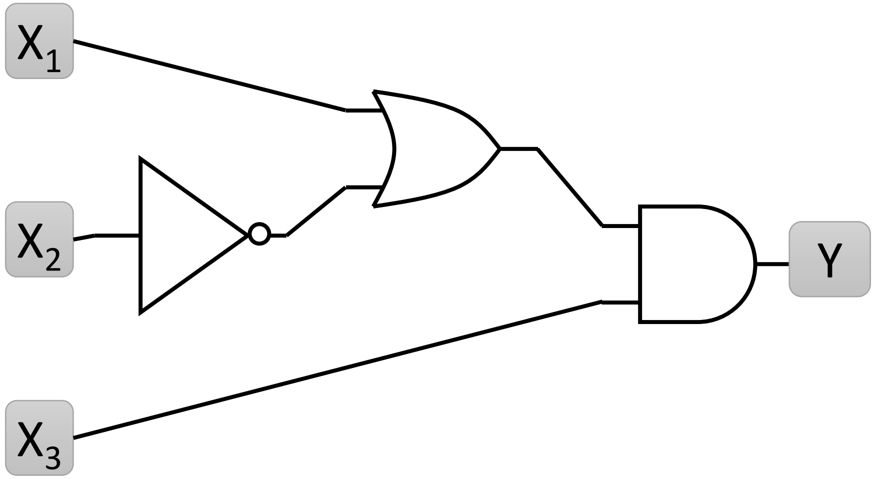


Strand displacement cascade example: Avoiding the need for NOT gates using dual-rail logic

For each input X_i, there are two species X_i^T and X_i^F:
Give species X_i^F to specify that Boolean input X_i = *False*
Give species X_i^T to specify that Boolean input X_i = *True*.



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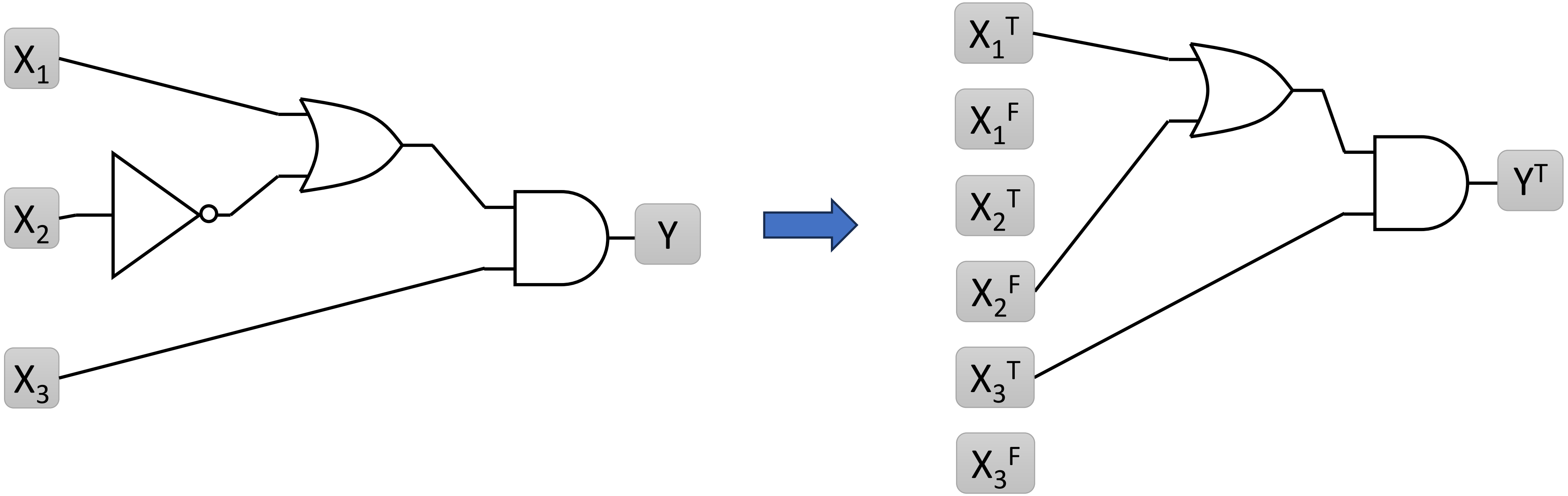

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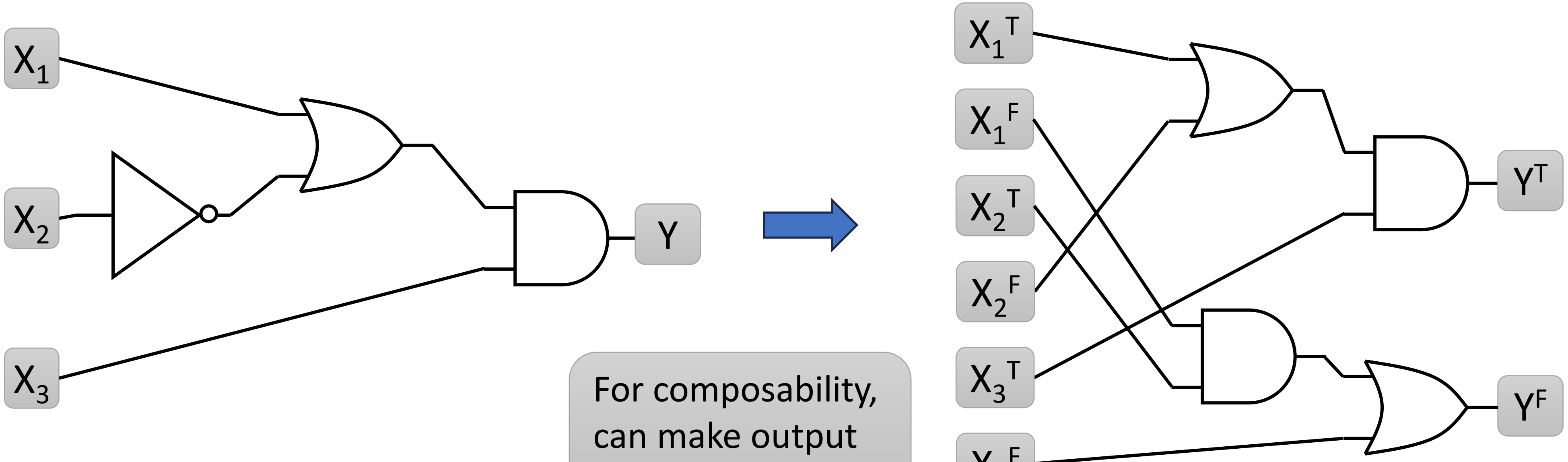
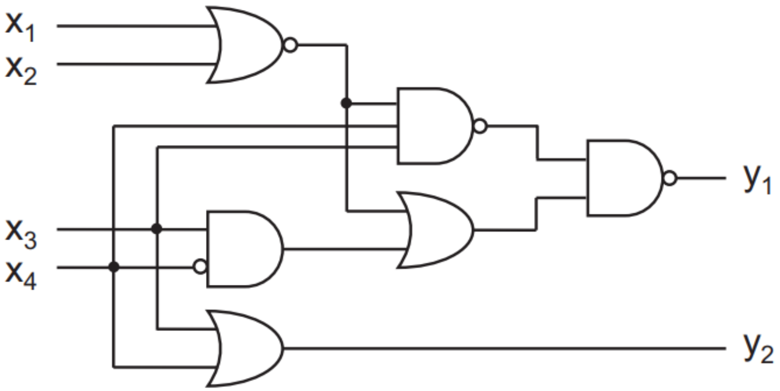
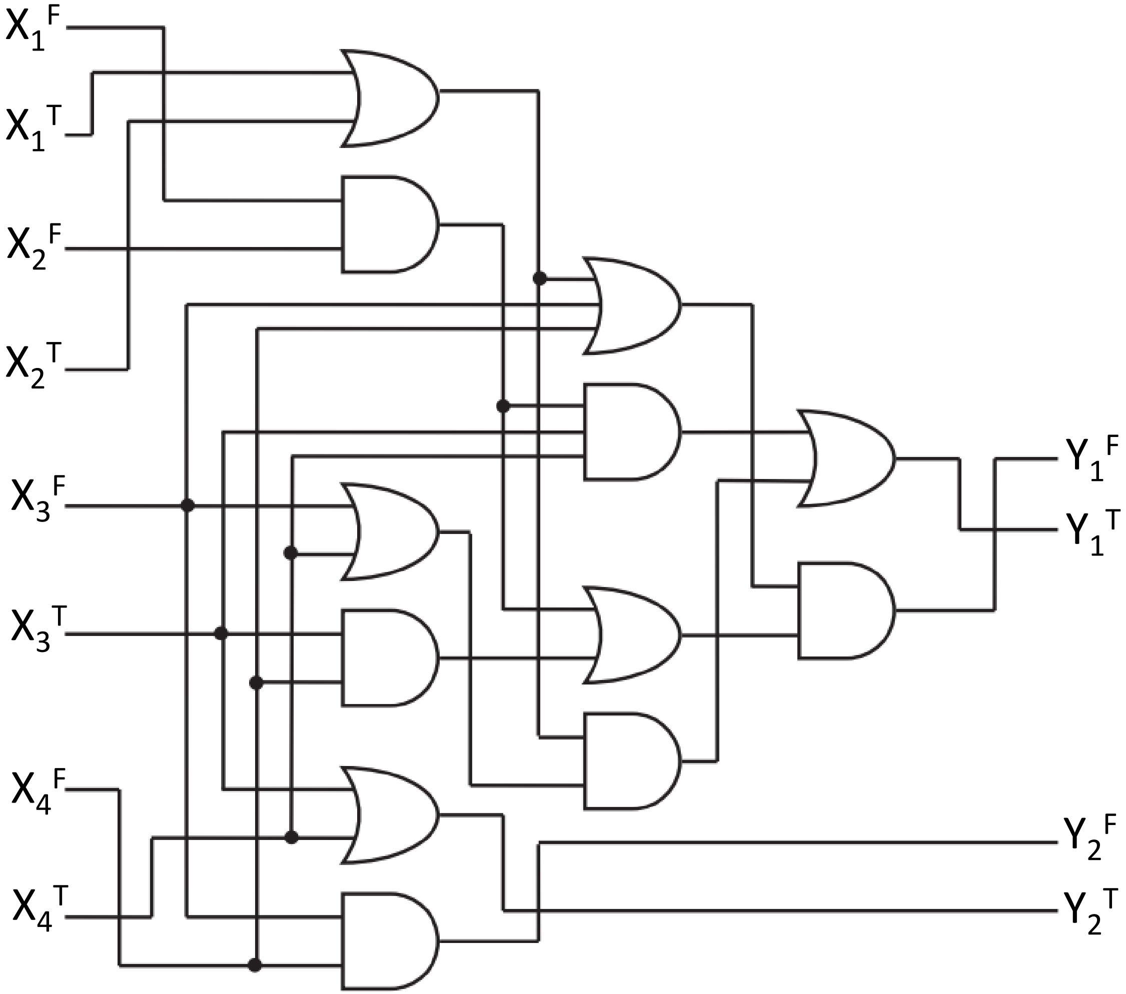


For composability, can make output dual-rail as well.

Dual-rail logic computing square root of 4-bit number

$$y_2 y_1 = \left\lfloor \sqrt{x_4 x_3 x_2 x_1} \right\rfloor$$





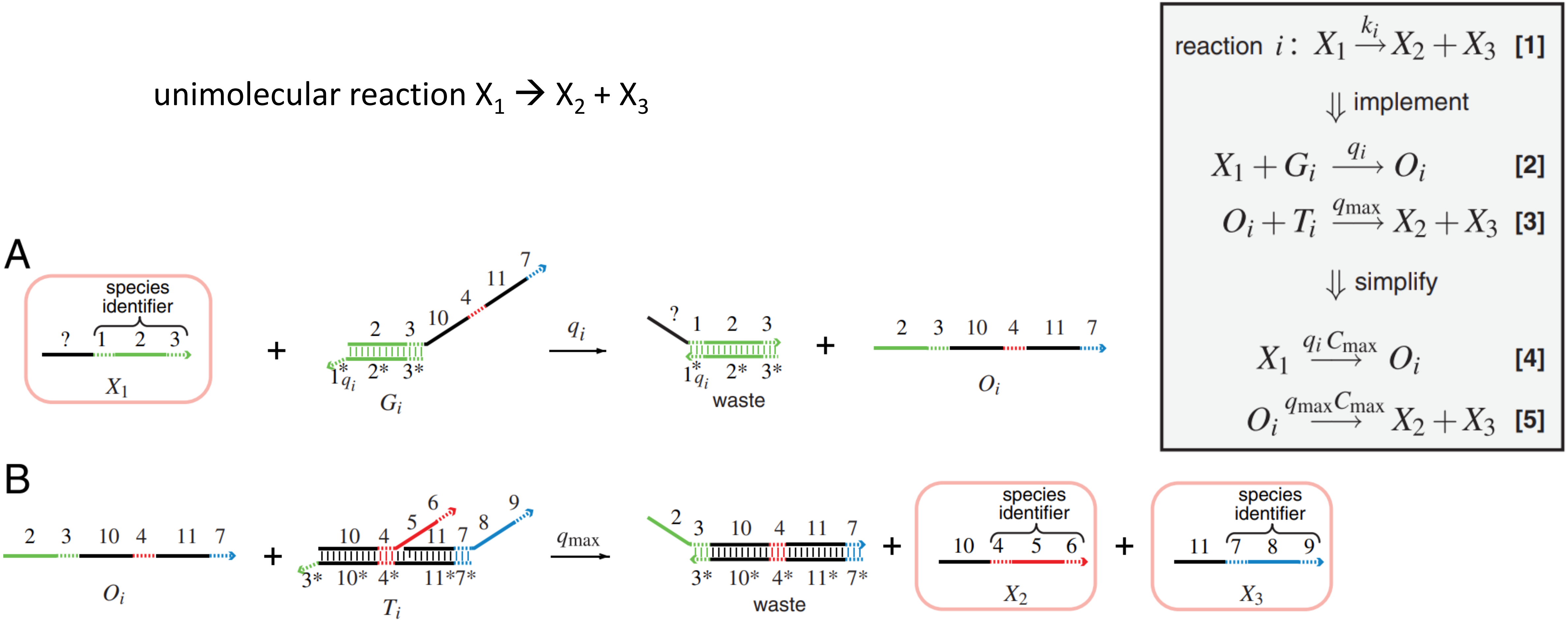
[Scaling up digital circuit computation with DNA strand displacement cascades. Lulu Qian and Erik Winfree, *Science* 2011]

Implementing CRNs with DNA

“Compiling” arbitrary chemical reaction networks into DNA strands that implement the reactions using DNA strand displacement

DNA strand displacement can implement any CRN

unimolecular reaction $X_1 \rightarrow X_2 + X_3$



reaction $i: X_1 \xrightarrow{k_i} X_2 + X_3$ [1]

$\Downarrow$ implement

$$X_1 + G_i \xrightarrow{q_i} O_i \quad [2]$$

$$O_i + T_i \xrightarrow{q_{\max}} X_2 + X_3 \quad [3]$$

$\Downarrow$ simplify

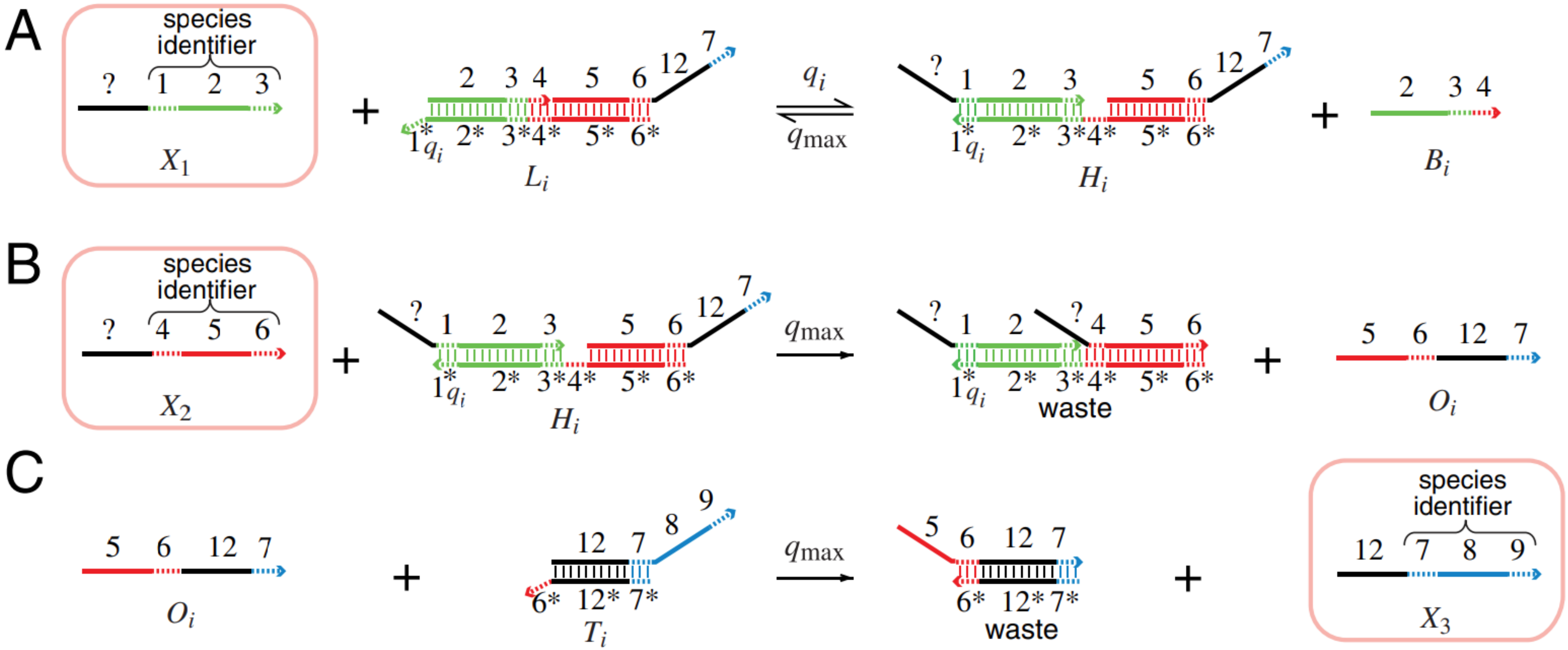
$$X_1 \xrightarrow{q_i C_{\max}} O_i \quad [4]$$

$$O_i \xrightarrow{q_{\max} C_{\max}} X_2 + X_3 \quad [5]$$

[DNA as a universal substrate for chemical kinetics, David Soloveichik, Georg Seelig, and Erik Winfree, *PNAS* 2010]

DNA strand displacement can implement any CRN

bimolecular reaction $X_1 + X_2 \rightarrow X_3$



reaction i: $X_1 + X_2 \xrightarrow{k_i} X_3$ [6]

⇓ implement

$X_1 + L_i \underset{q_{\max}}{\overset{q_i}{\rightleftharpoons}} H_i + B_i$ [7]

$X_2 + H_i \xrightarrow{q_{\max}} O_i$ [8]

$O_i + T_i \xrightarrow{q_{\max}} X_3$ [9]

⇓ simplify

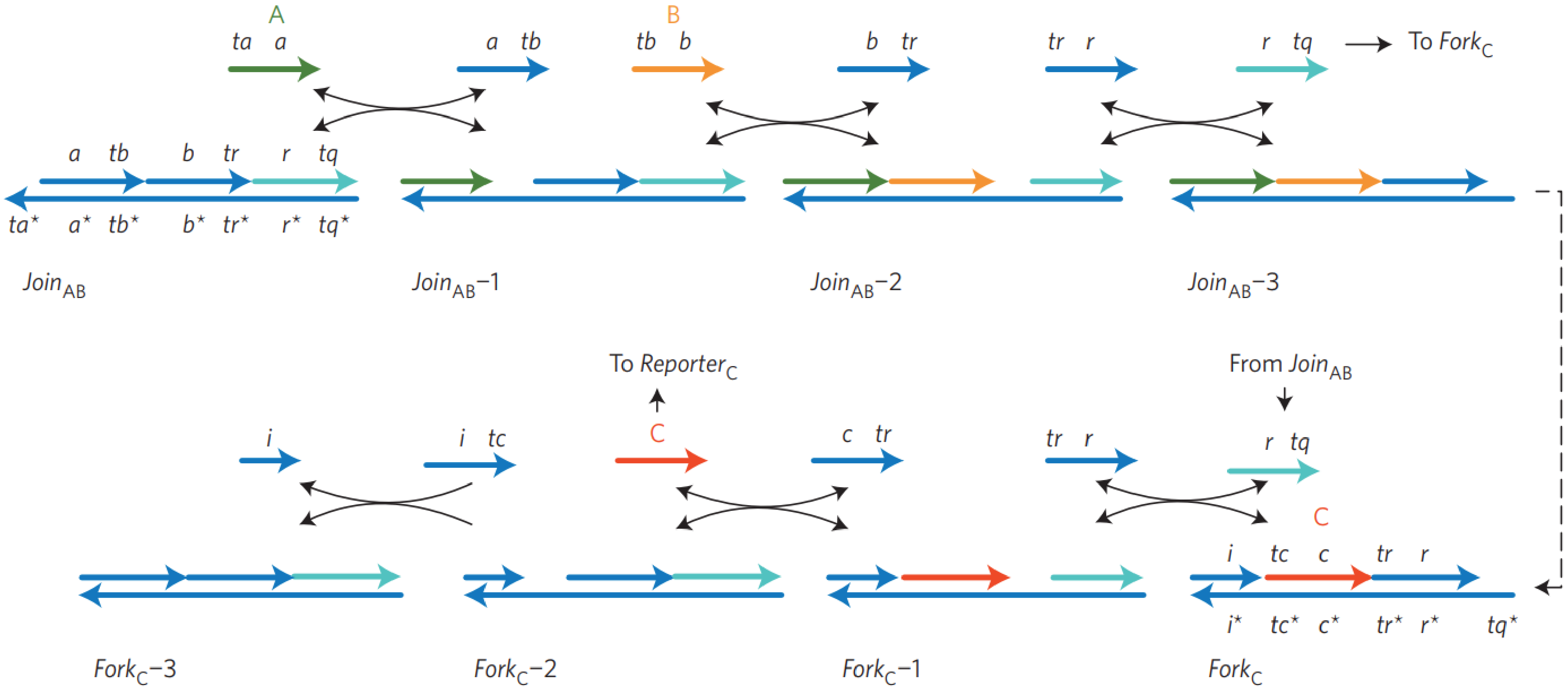
$X_1 \underset{q_{\max} C_{\max}}{\overset{q_i C_{\max}}{\rightleftharpoons}} H_i$ [10]

$X_2 + H_i \xrightarrow{q_{\max}} X_3$ [11]

[DNA as a universal substrate for chemical kinetics, David Soloveichik, Georg Seelig, and Erik Winfree, *PNAS* 2010]

“Two-domain” scheme for compiling CRN to DSD

reaction A+B → C

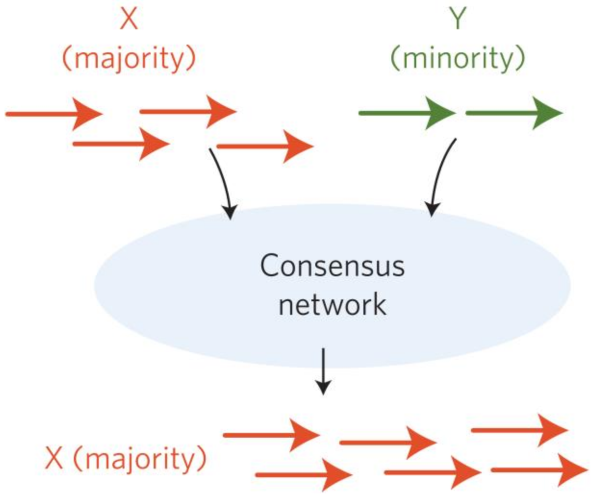


[Programmable chemical controllers made from DNA. Yuan-Jyue Chen, Neil Dalchau, Niranjan Srinivas, Andrew Phillips, Luca Cardelli, David Soloveichik, and Georg Seelig. *Nature Nanotechnology* 2013.]

Experimental implementations of CRN-to-DSD schemes

DSD computing approximate majority

Goal:



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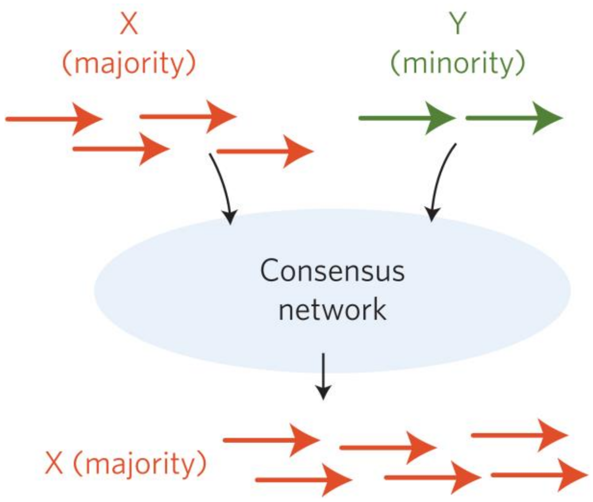

CRN:

$X+Y \rightarrow 2B$

$X+B \rightarrow 2X$

$Y+B \rightarrow 2Y$

[Programmable chemical controllers made from DNA. Yuan-Jyue Chen, Neil Dalchau, Niranjan Srinivas, Andrew Phillips, Luca Cardelli, David Soloveichik, and Georg Seelig. *Nature Nanotechnology* 2013.]

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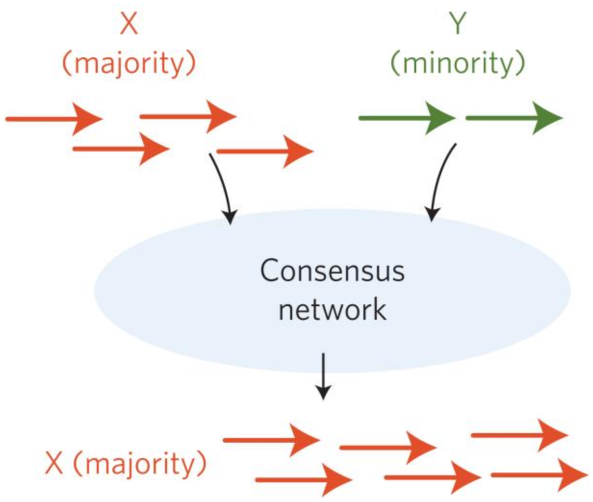

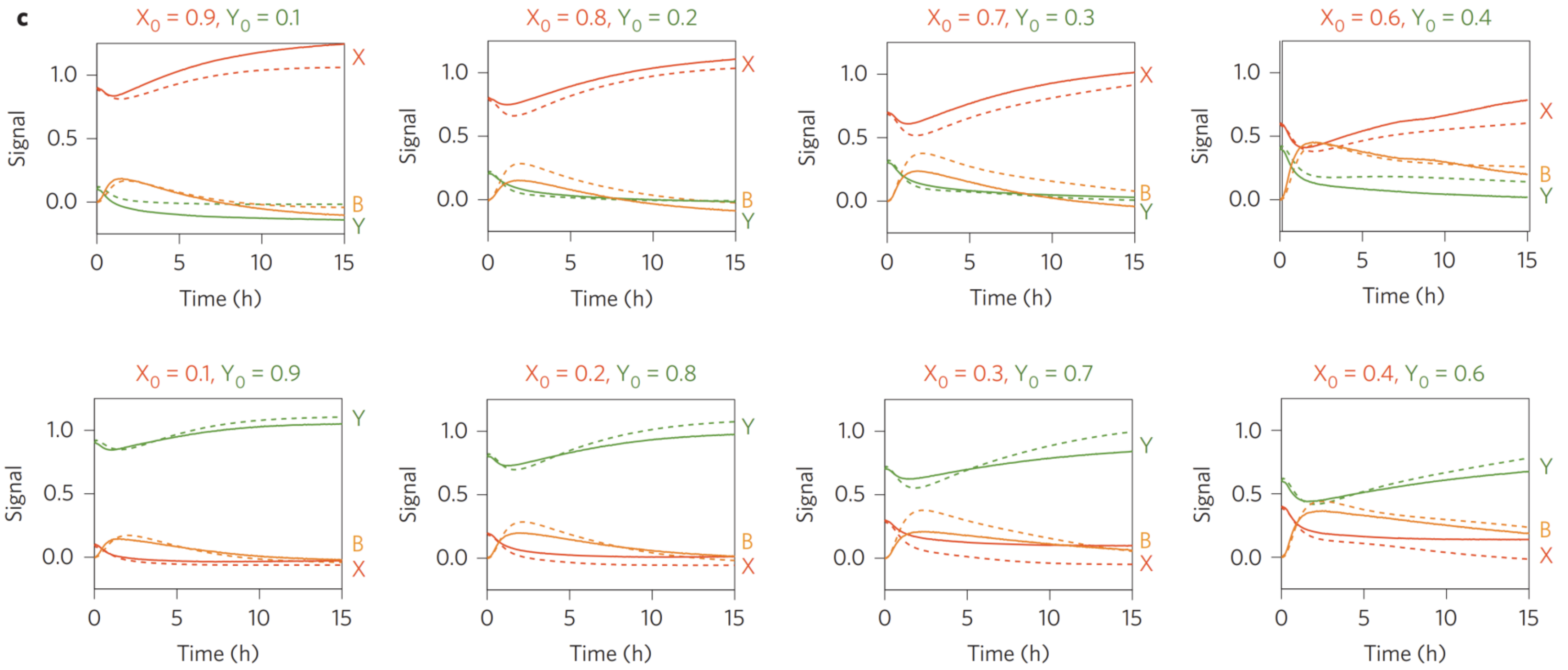

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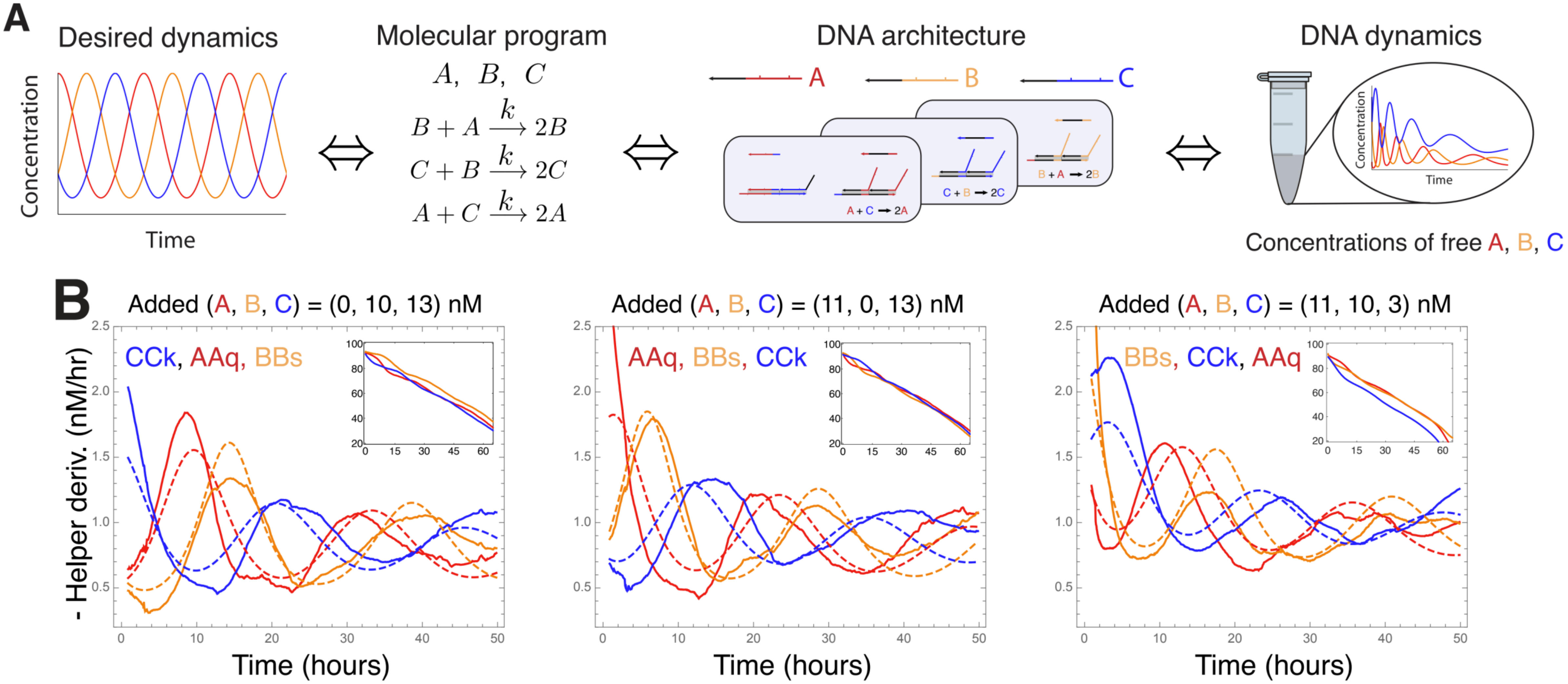
[Programmable chemical controllers made from DNA. Yuan-Jyue Chen, Neil Dalchau, Niranjan Srinivas, Andrew Phillips, Luca Cardelli, David Soloveichik, and Georg Seelig. *Nature Nanotechnology* 2013.]

DSD implementing chemical “rock-paper-scissors” oscillator



$$A,\ B,\ C$$

$$B + A \xrightarrow{k} 2B$$

$$C + B \xrightarrow{k} 2C$$

$$A + C \xrightarrow{k} 2A$$

[Enzyme-free nucleic acid dynamical systems. Niranjan Srinivas, James Parkin, Georg Seelig, Erik Winfree, David Soloveichik, *Science* 2017]