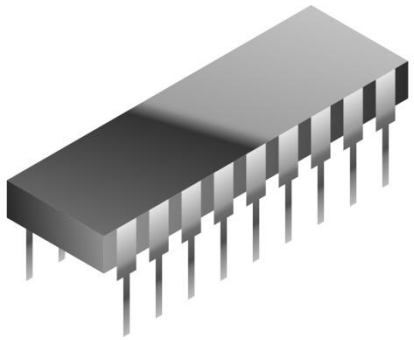
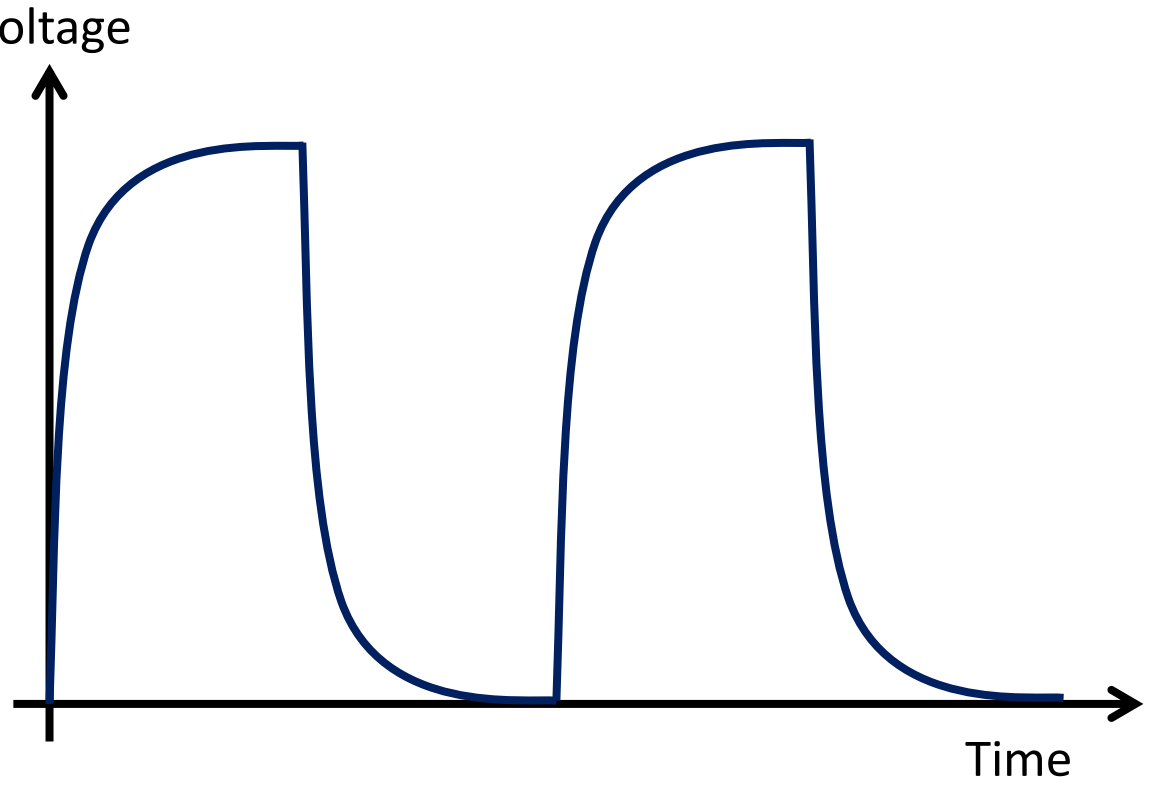
Thermodynamic binding networks

slides © 2021, David Haley and David Doty

ECS 232: Theory of Molecular Computation, UC Davis

Representing Information with Molecules





In an electronic circuit,

voltage can represent Boolean input

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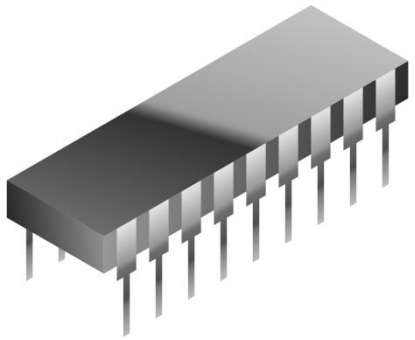

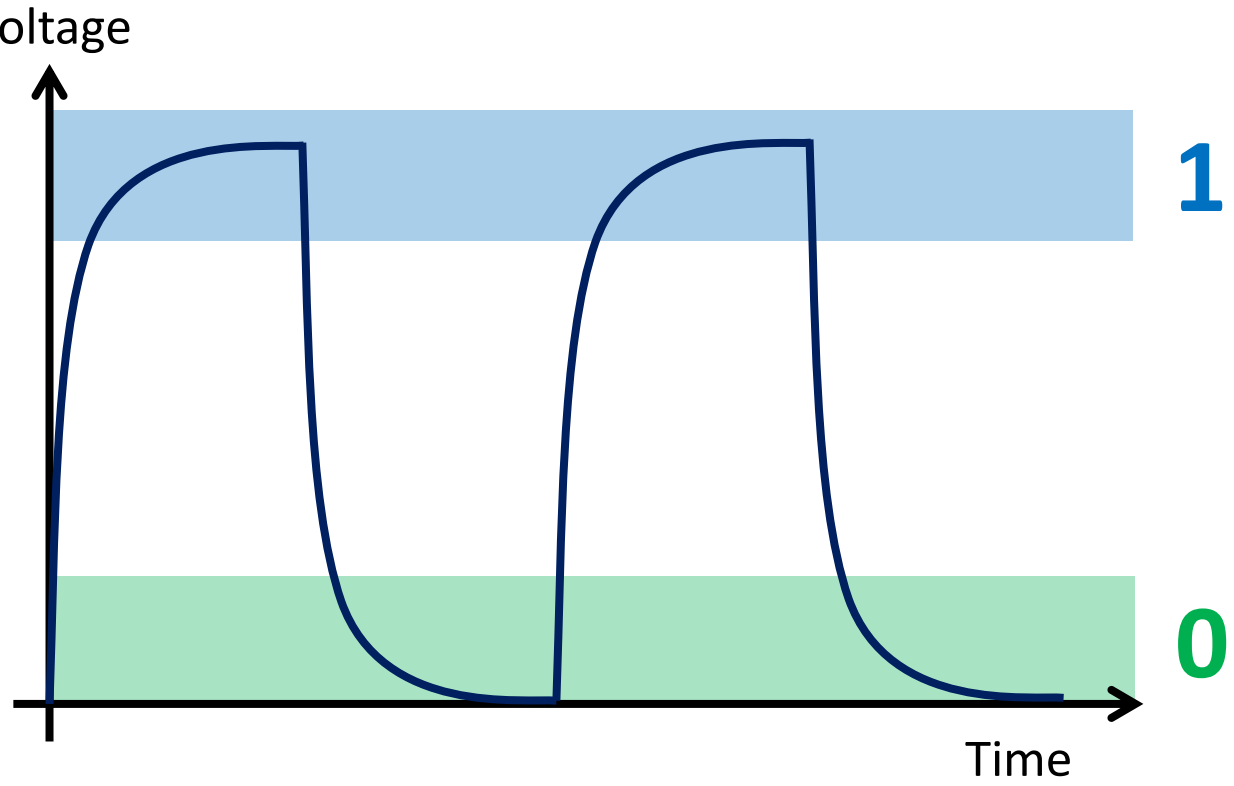

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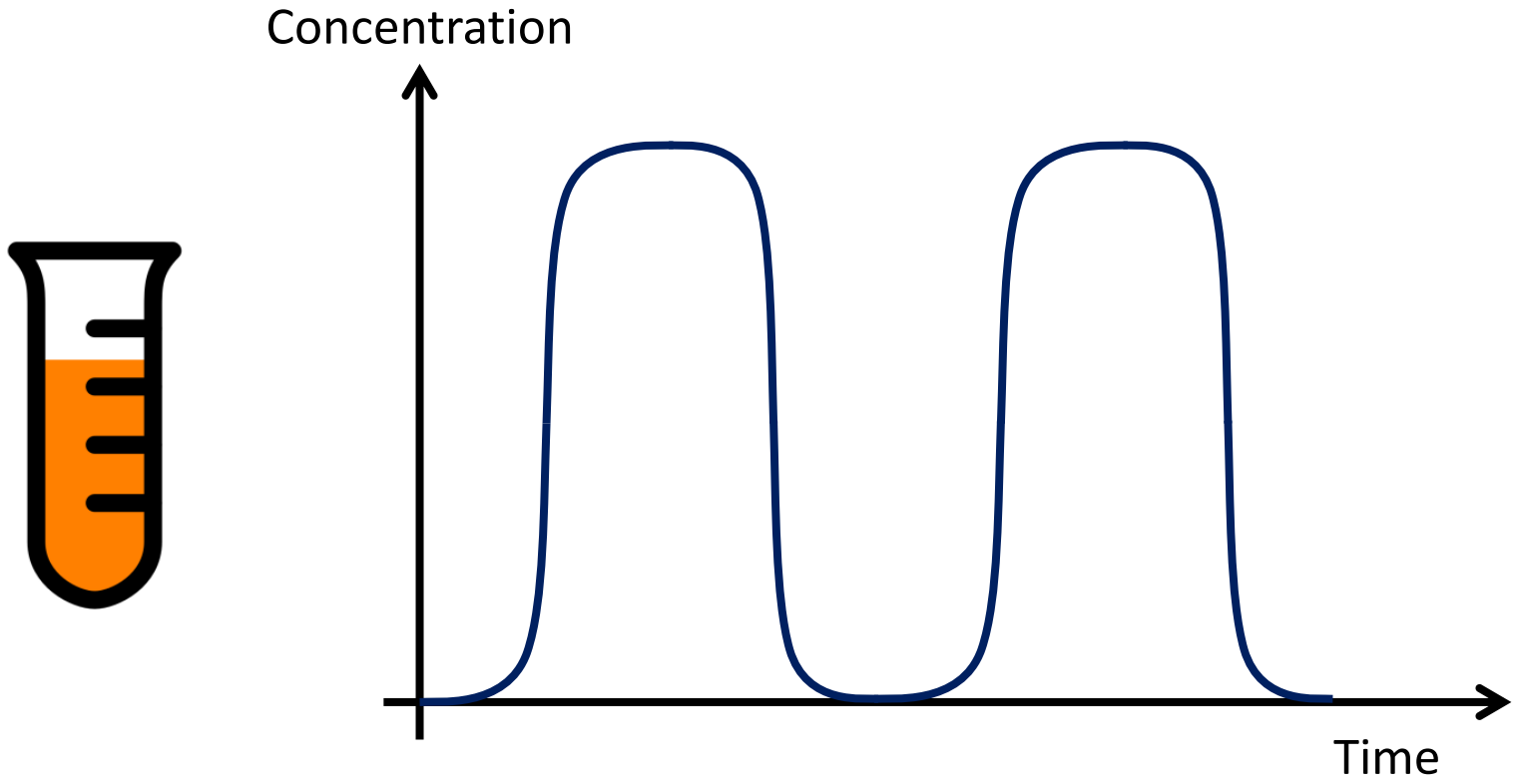

In a well-mixed solution,

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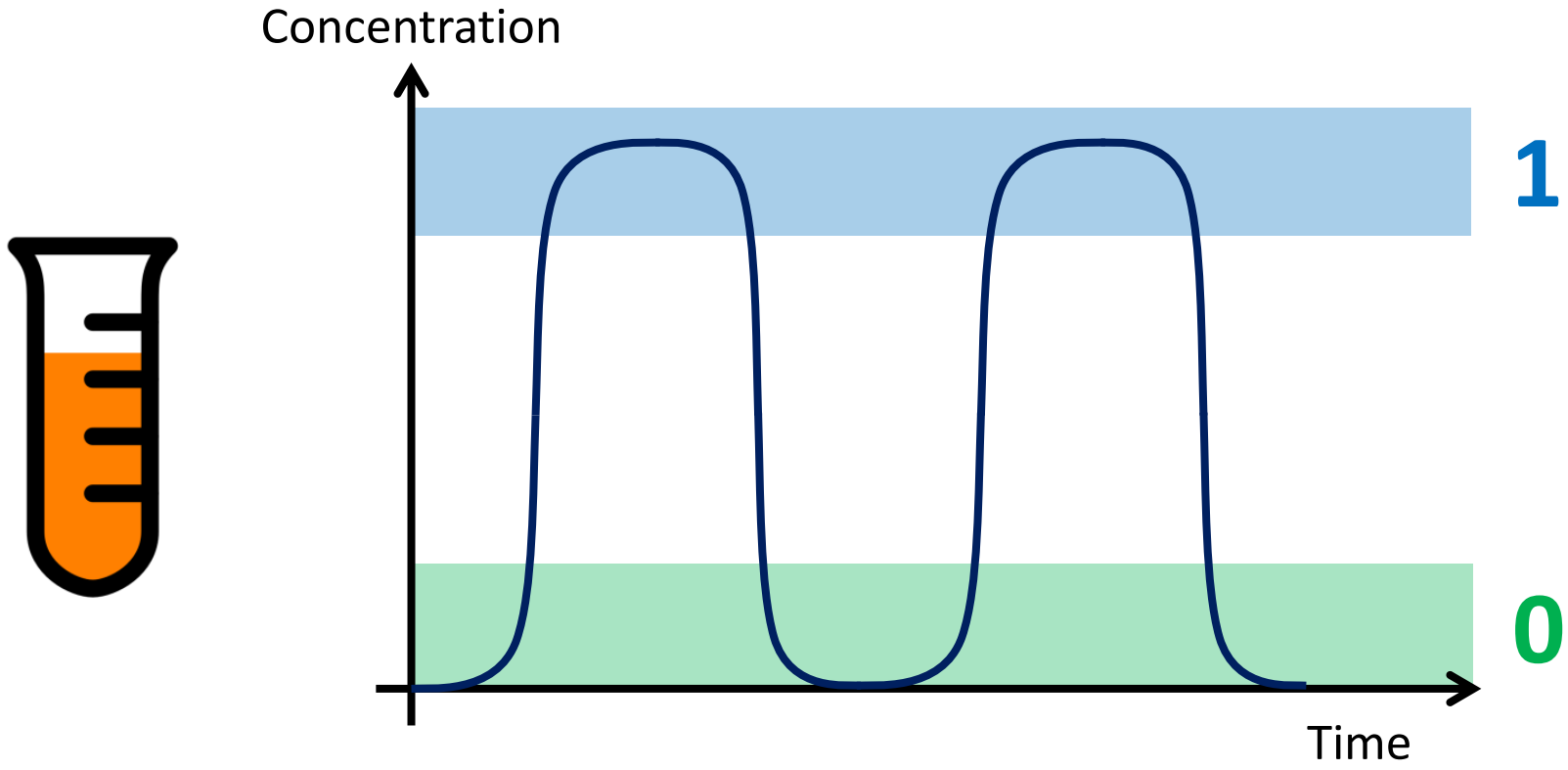

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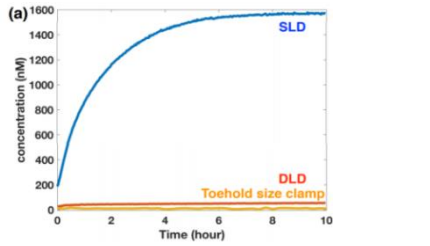
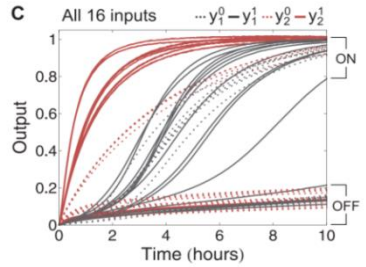
Chemical Identity Gate: Idealized vs. Actual Behavior

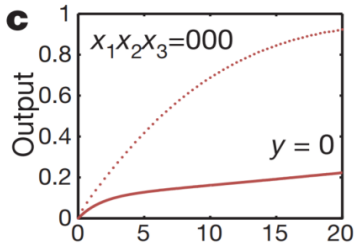
Experimental Implementation of Chemical Logic



Wang et al. ***DNA*** 23, 2017



Qian et al. ***Science*** 332, 2011



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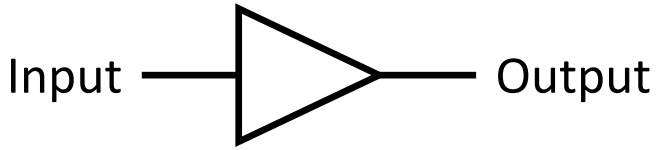
(Don't worry about the details in the pictures above)



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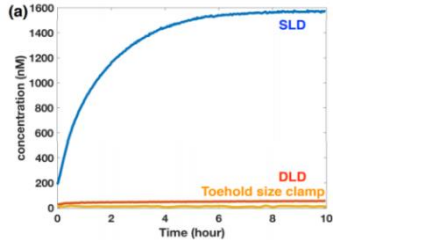

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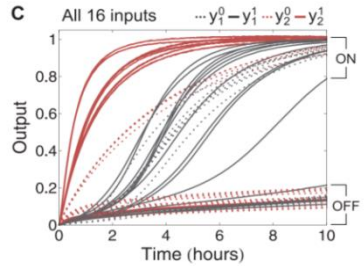

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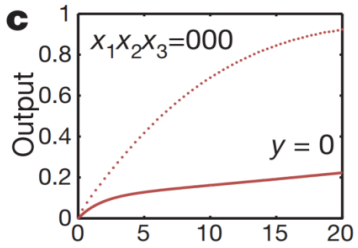

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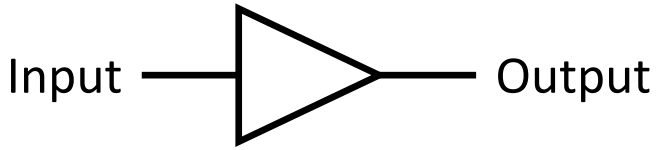

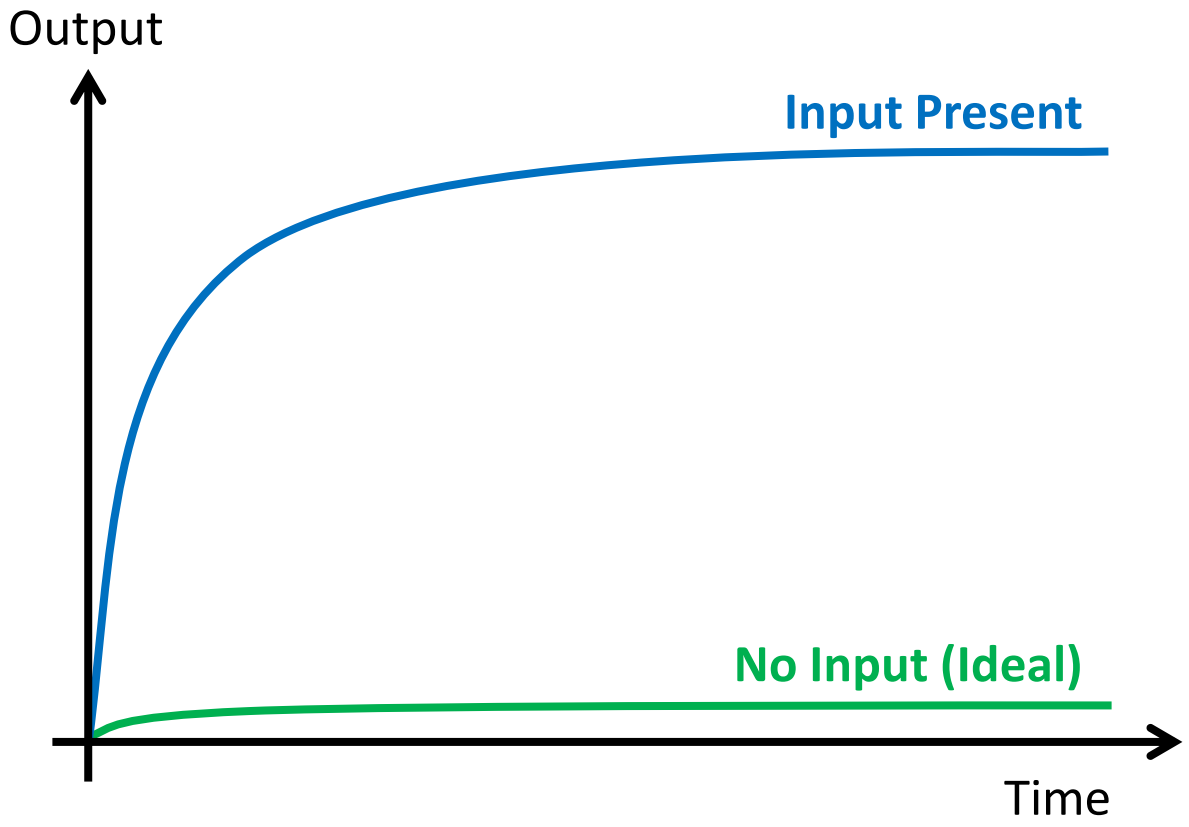

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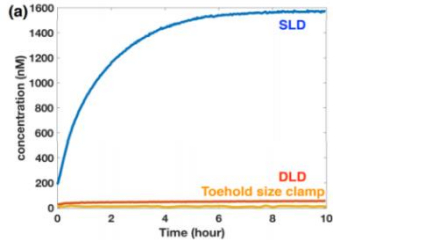

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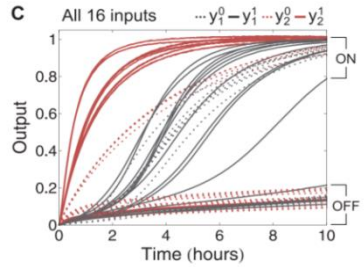

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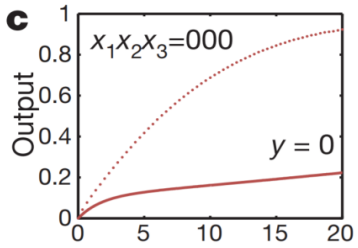

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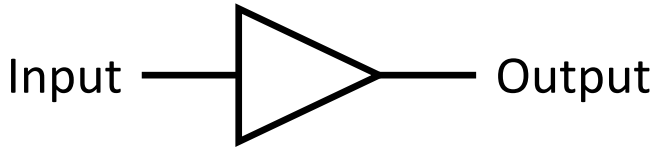

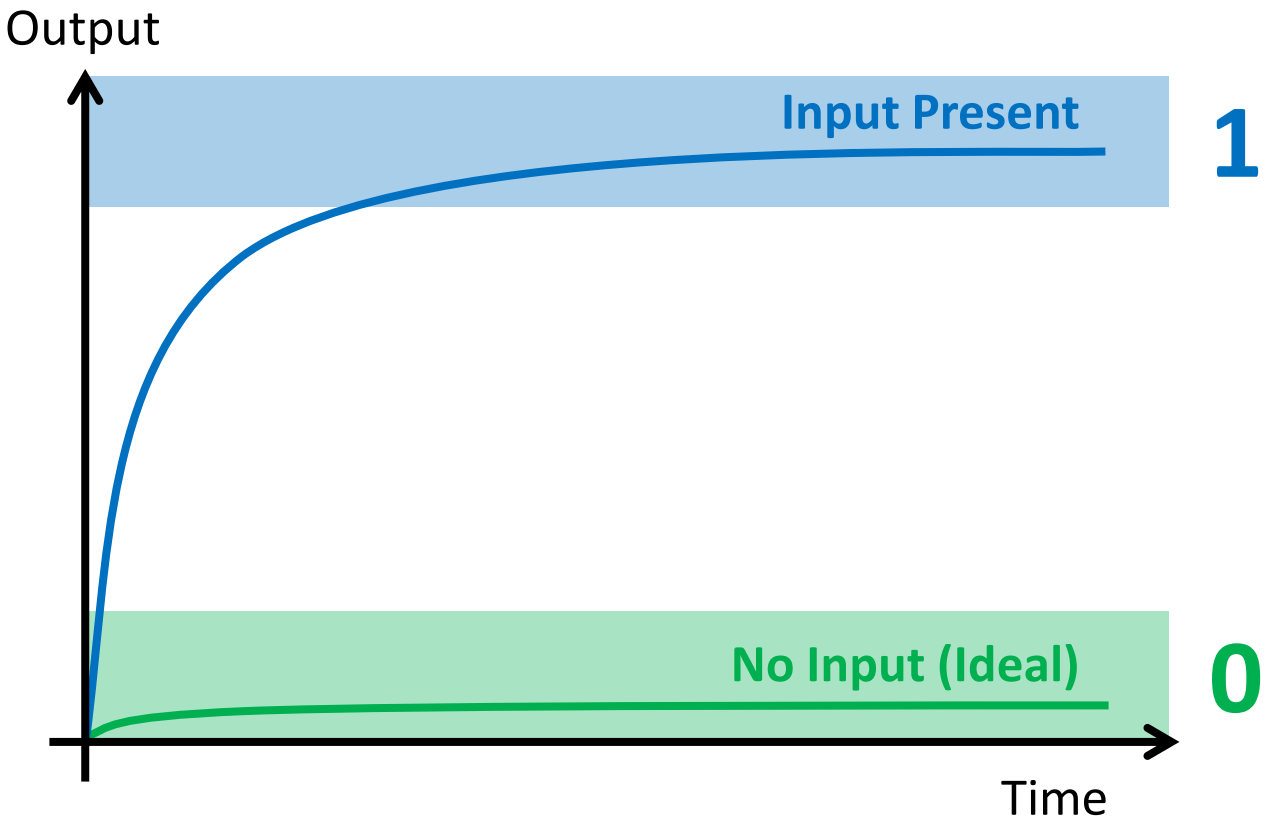

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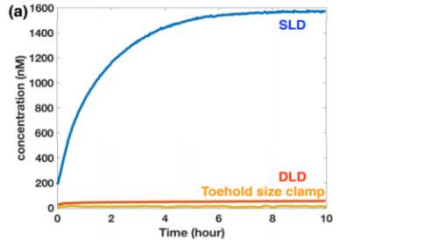

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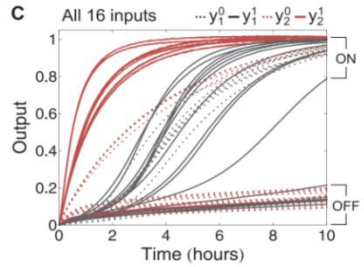

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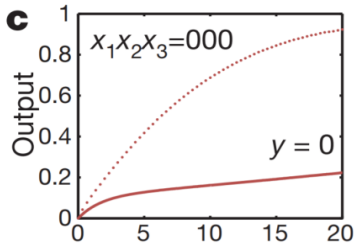

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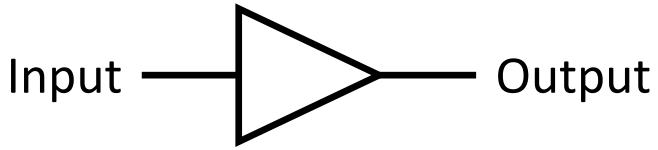

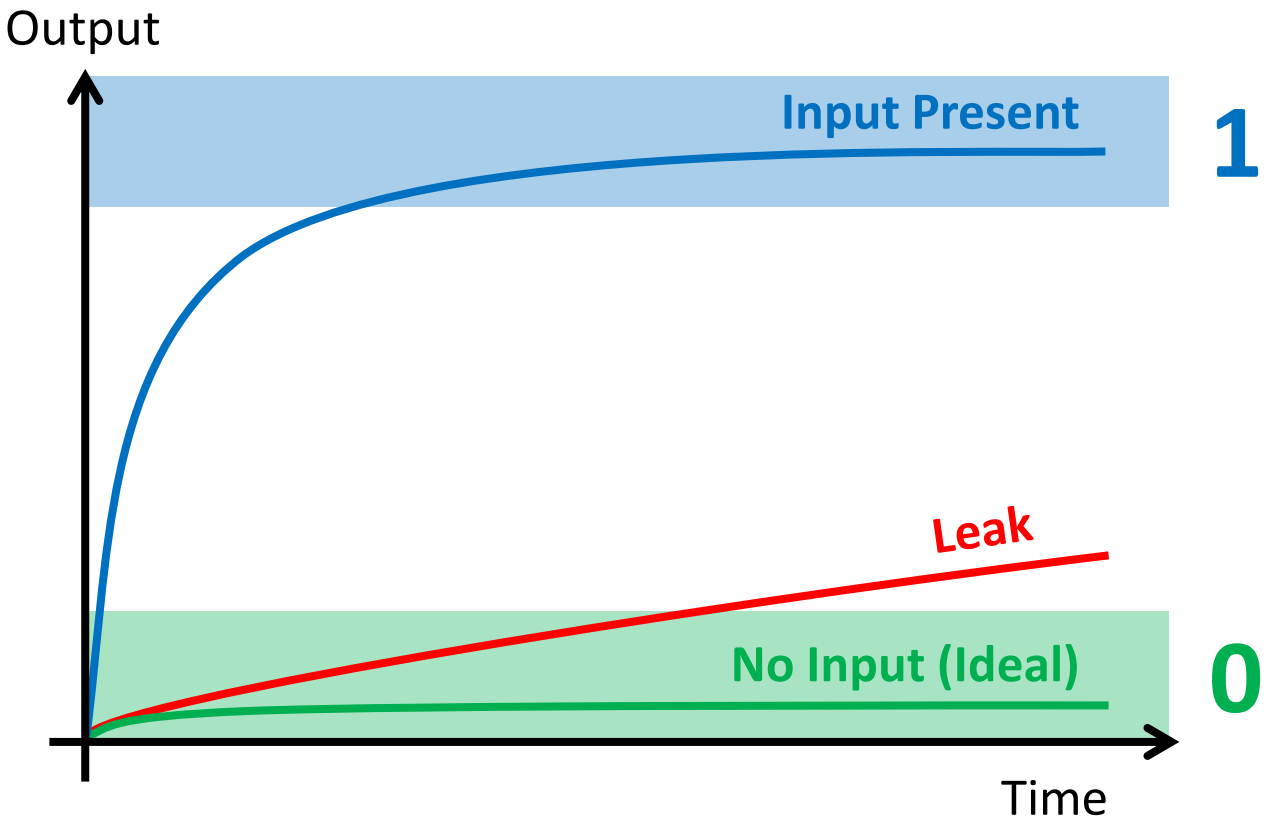

Levels of Abstraction

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DNA

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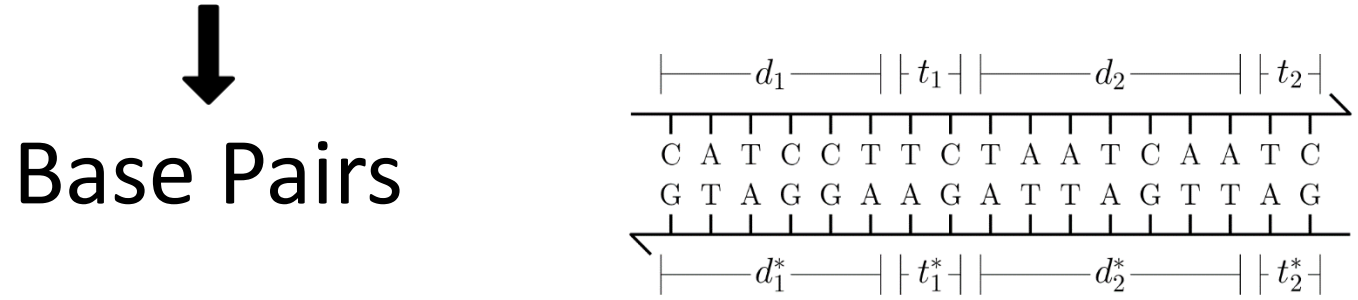
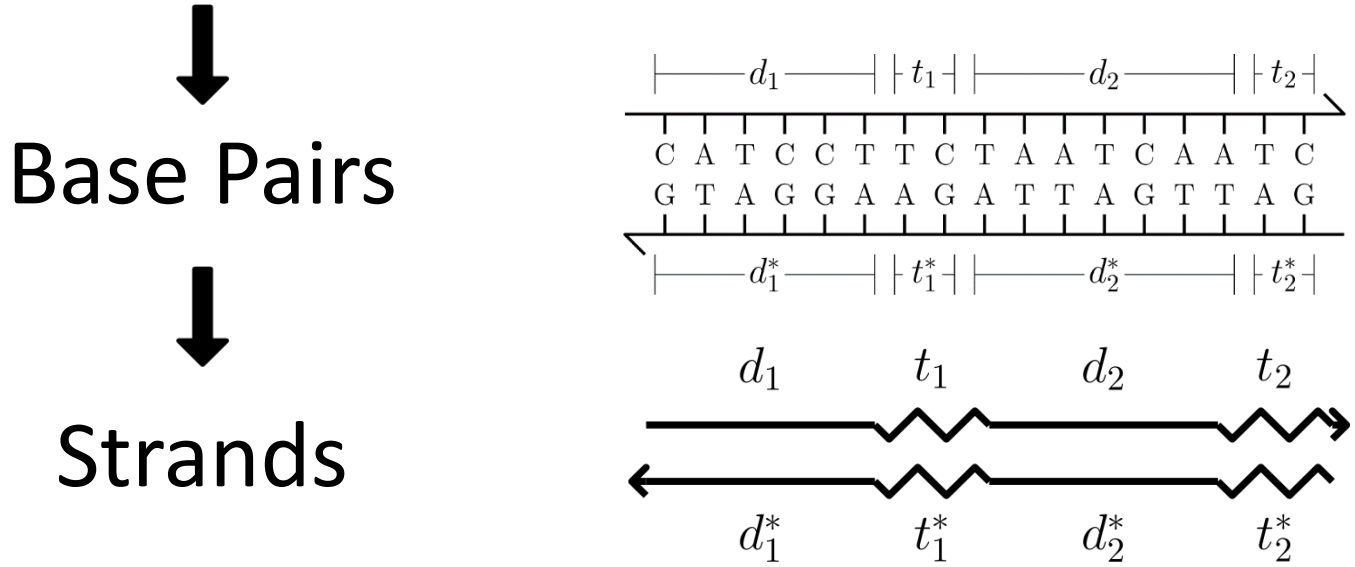


Base Pairs

Levels of Abstraction

DNA



Base Pairs

Strands

Levels of Abstraction

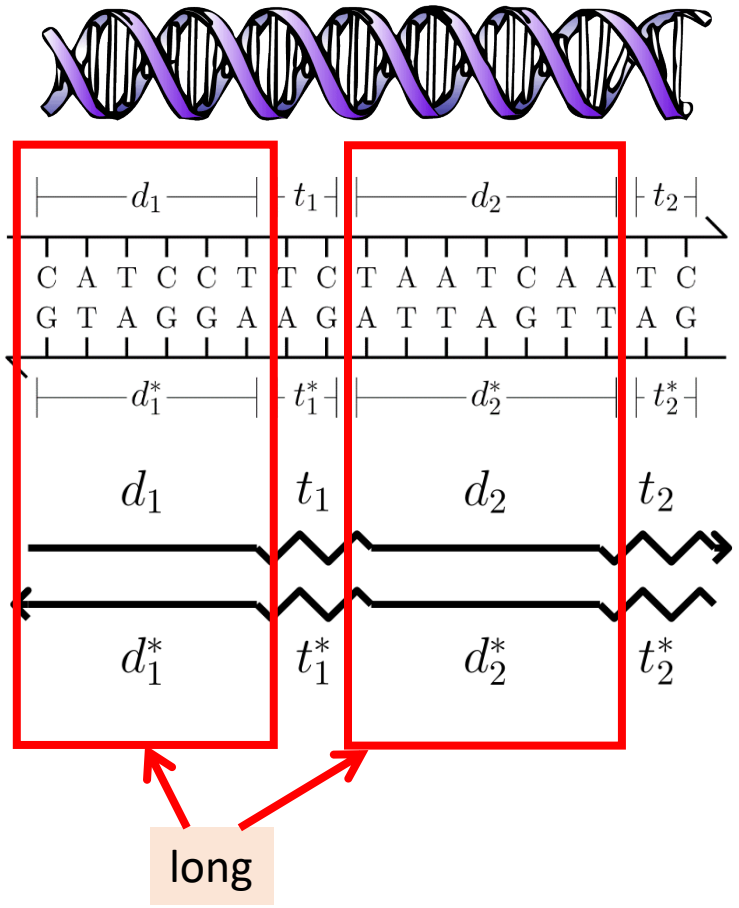
DNA

⬇

Base Pairs

⬇

Strands

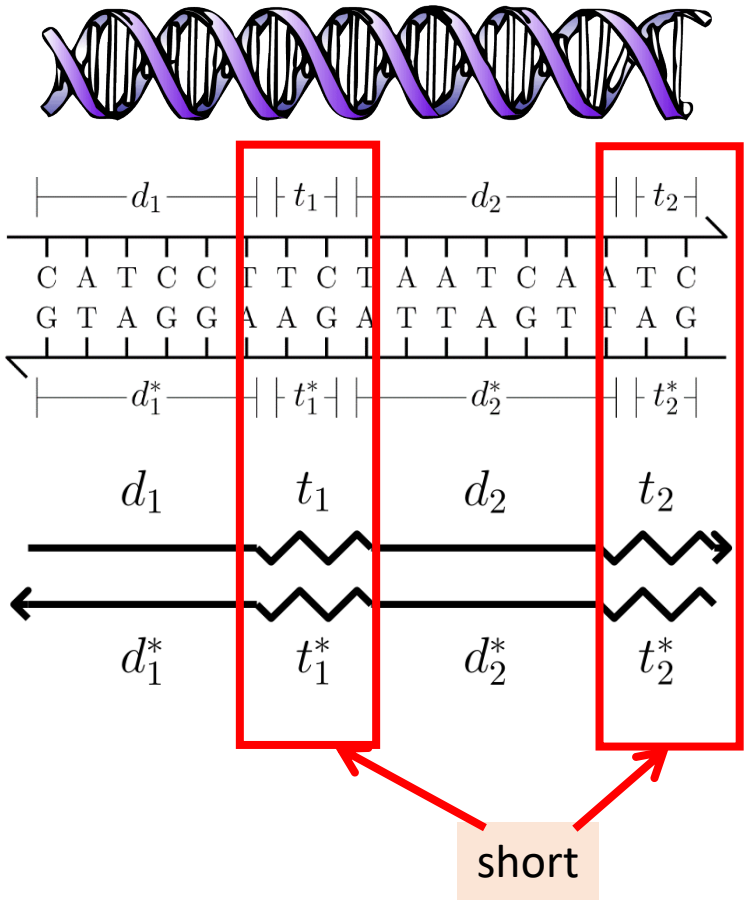


Levels of Abstraction

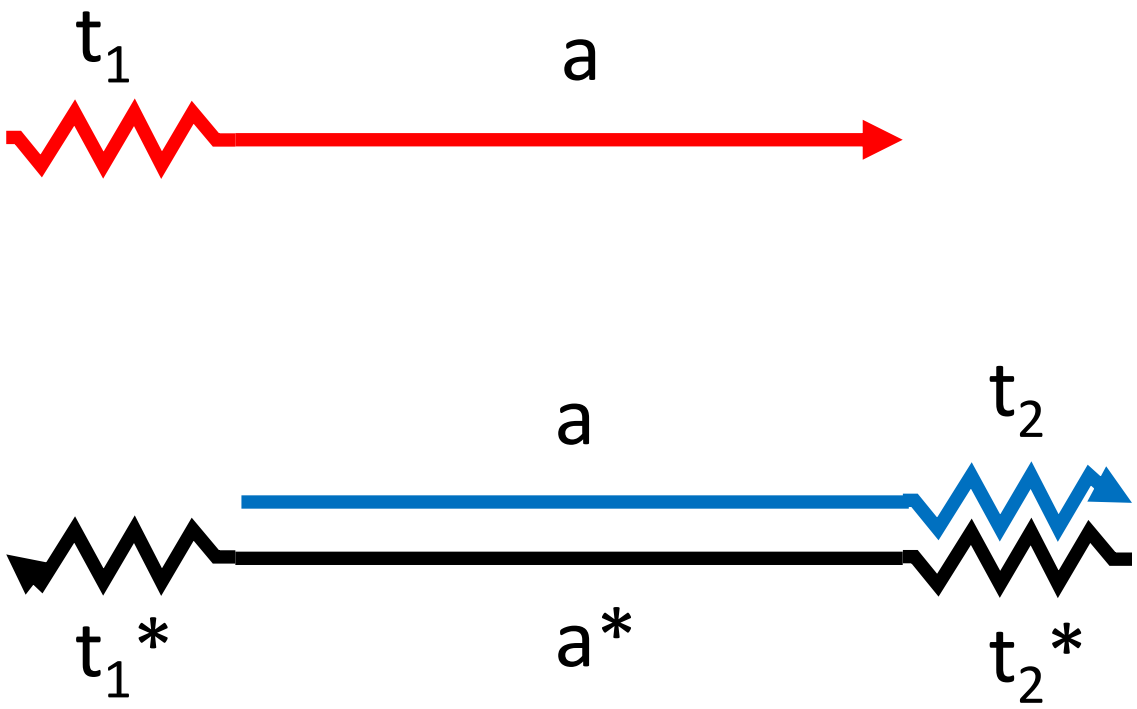
DNA

Base Pairs

Strands

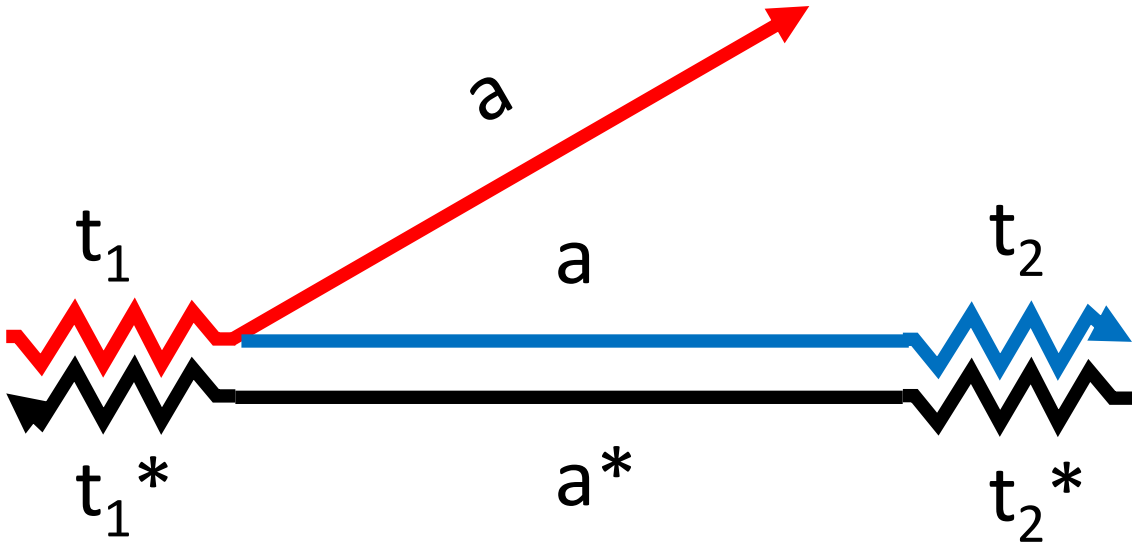


DNA strand displacement



DNA strand displacement

Bind



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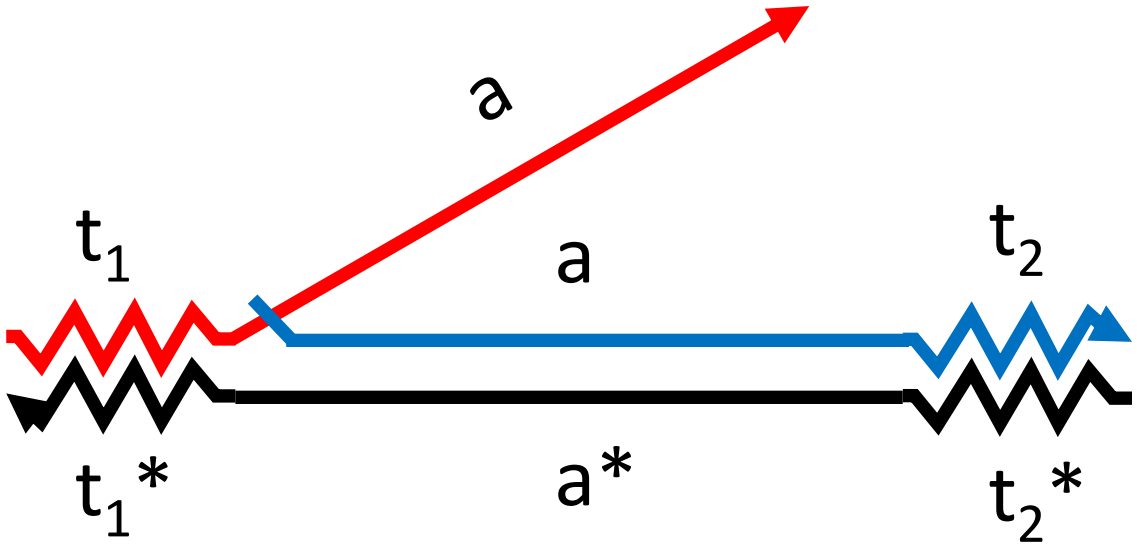

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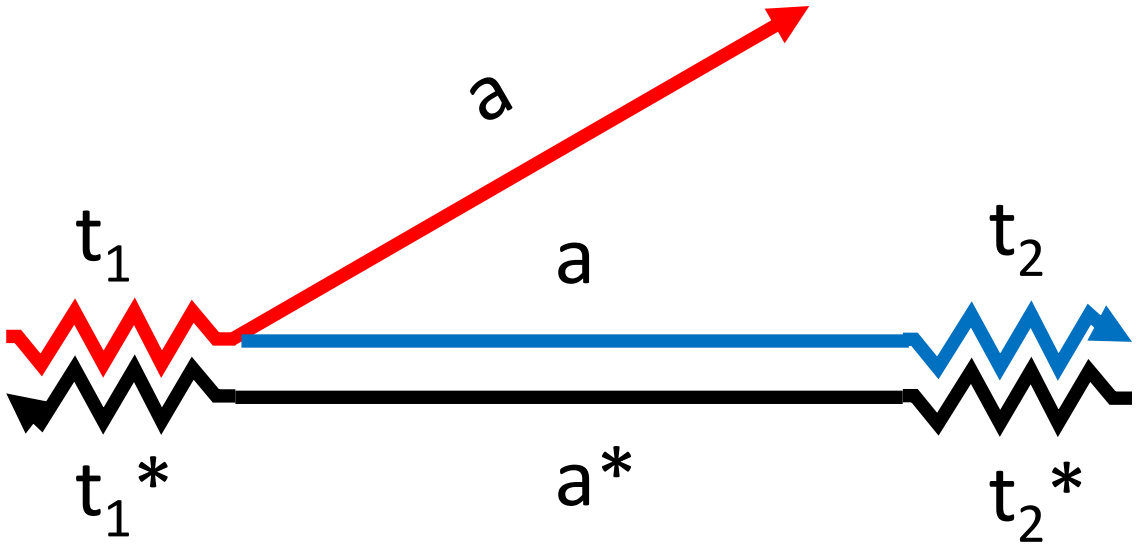

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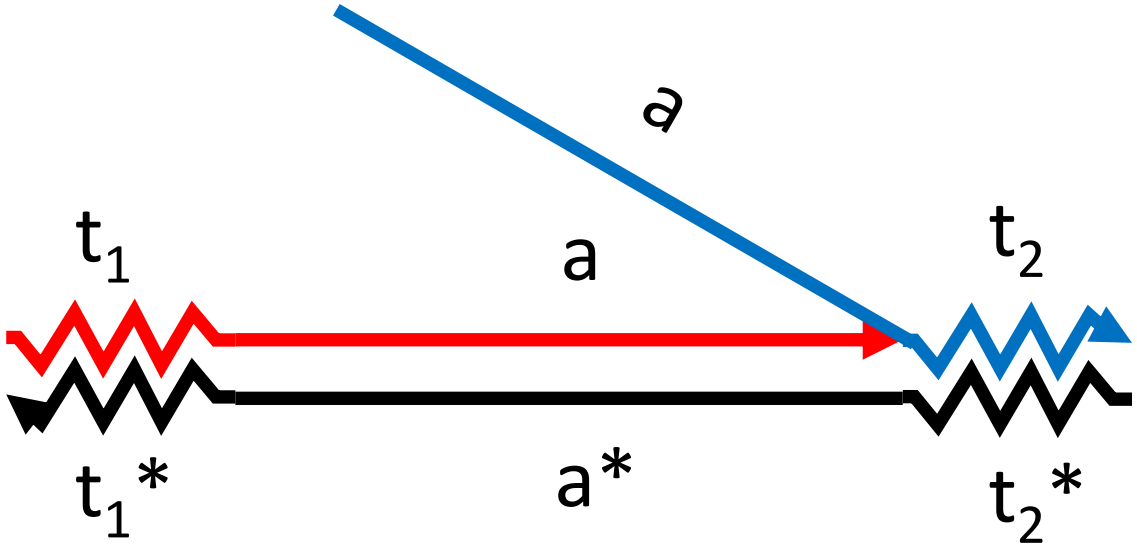
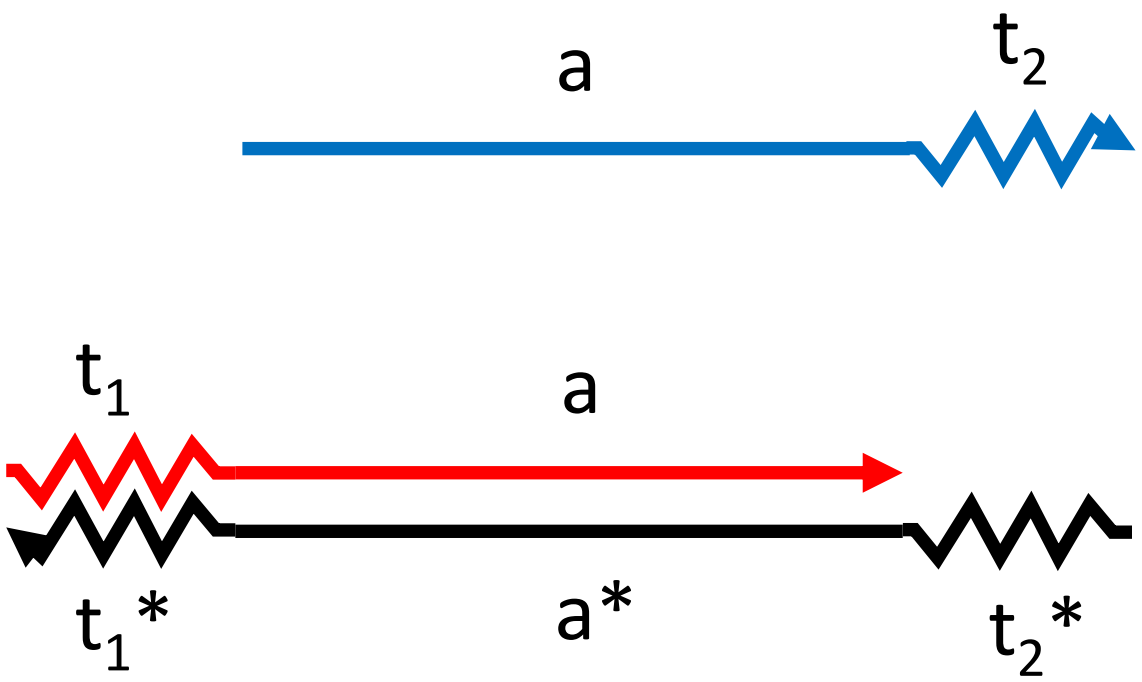


Displace

DNA strand displacement

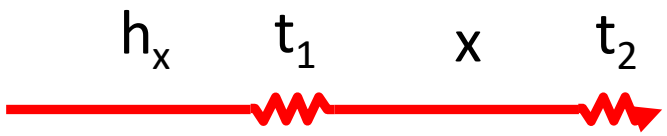


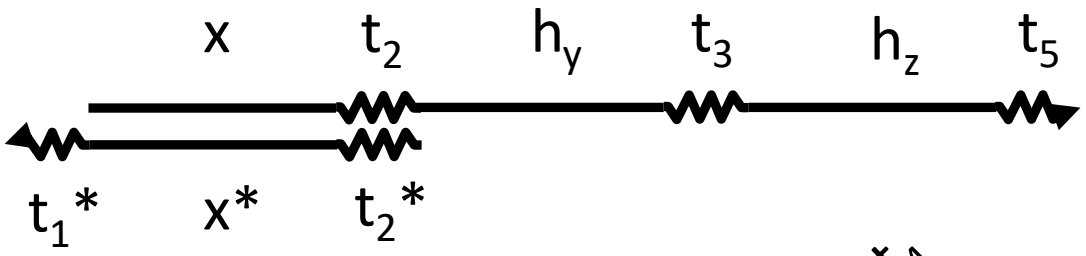
Bind

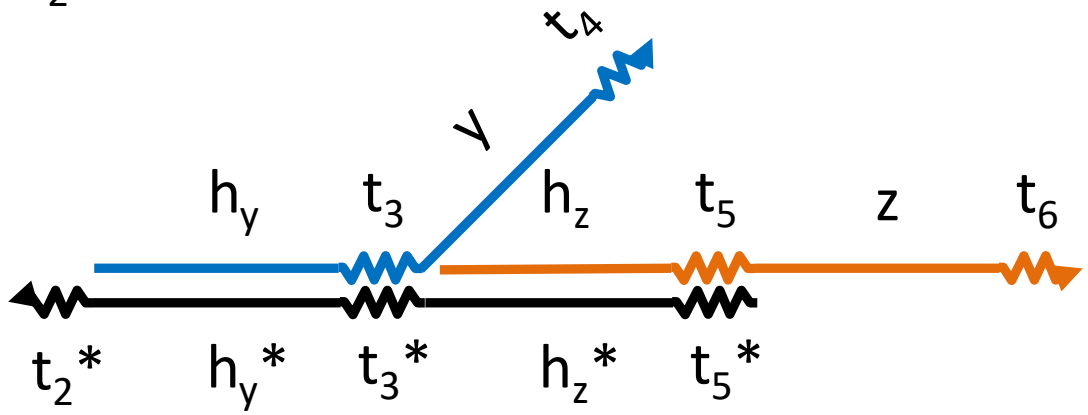
Displace

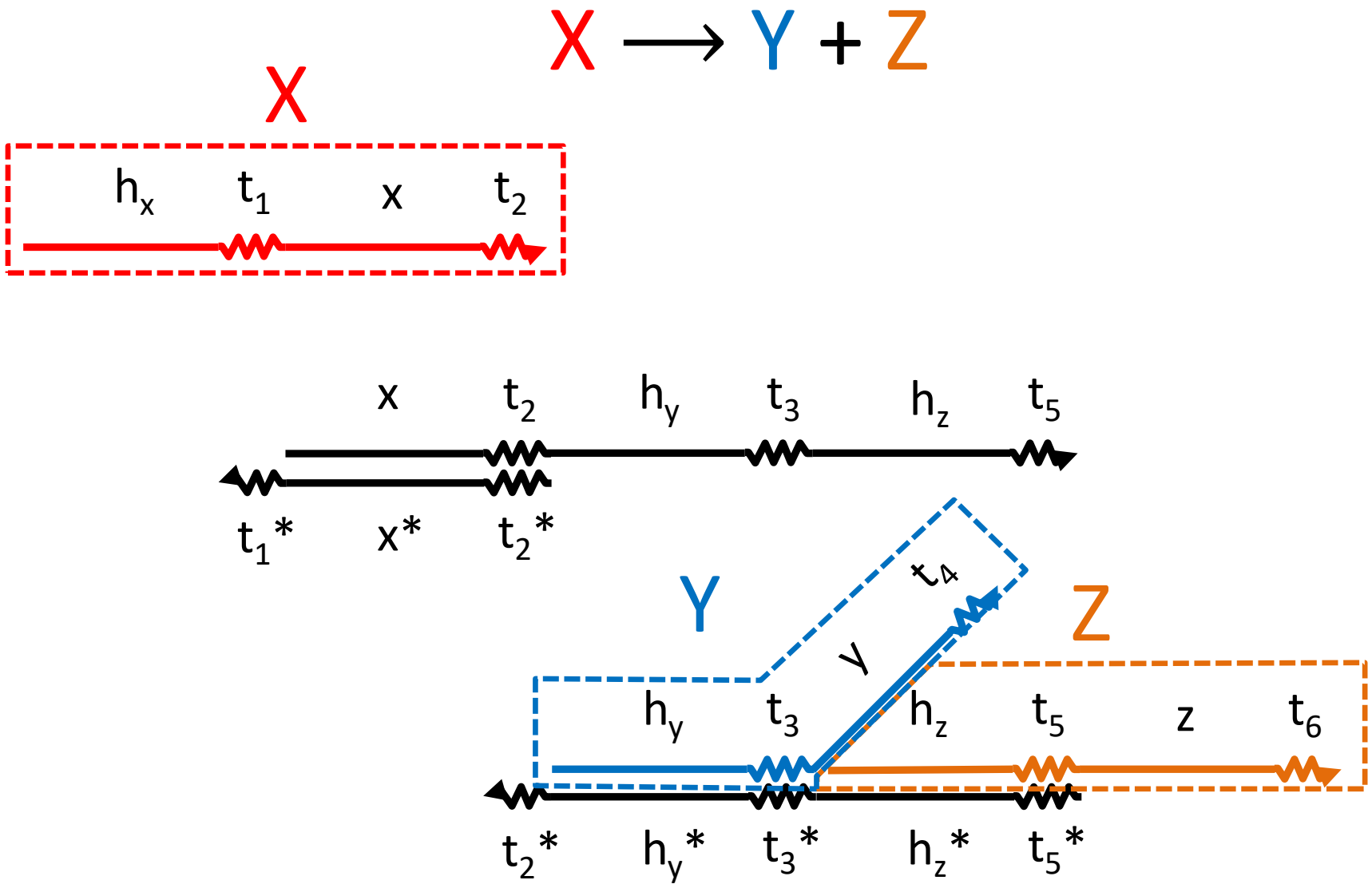
Release

$$X \longrightarrow Y + Z$$

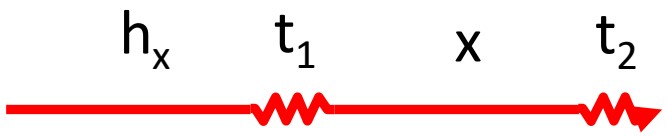


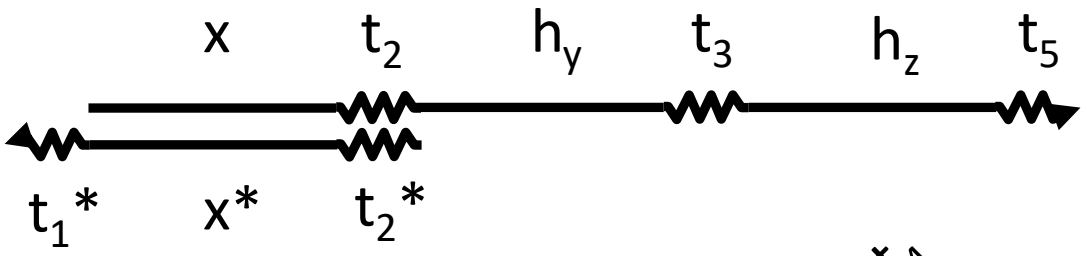


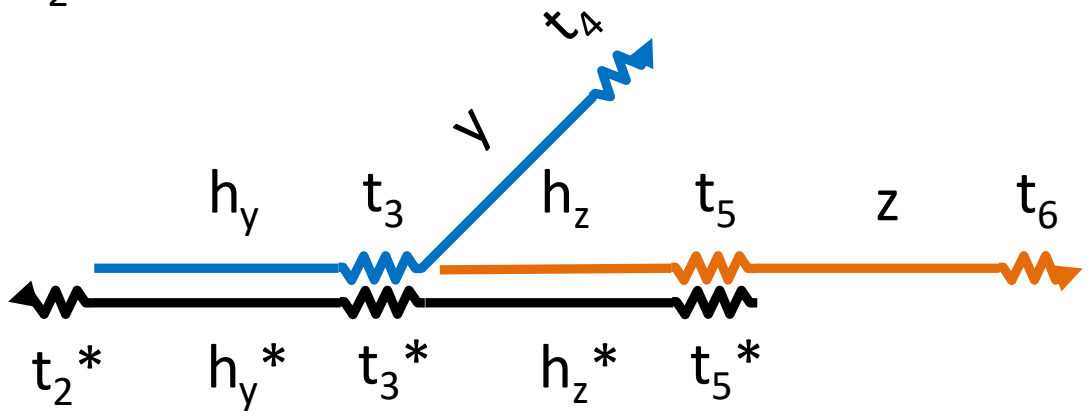



X ⟶ Y + Z
X
h_x t_1 x t_2
x t_2 h_y t_3 h_z t_5
t_1* x* t_2*
Y
Z
t_4
y
h_y t_3 h_z t_5 z t_6
t_2* h_y* t_3* h_z* t_5*

$$X \longrightarrow Y + Z$$







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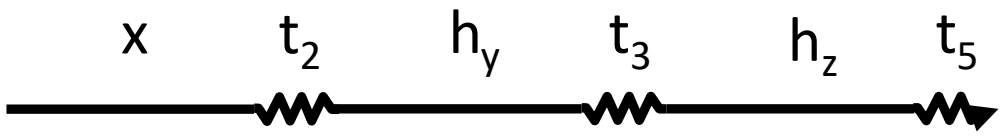

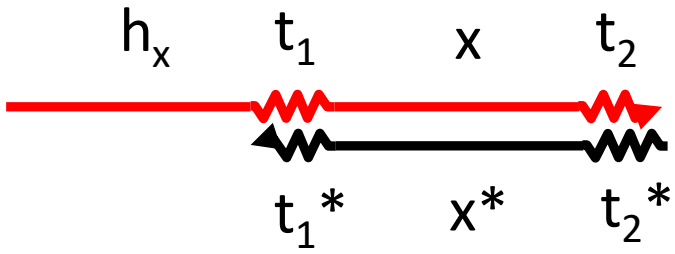

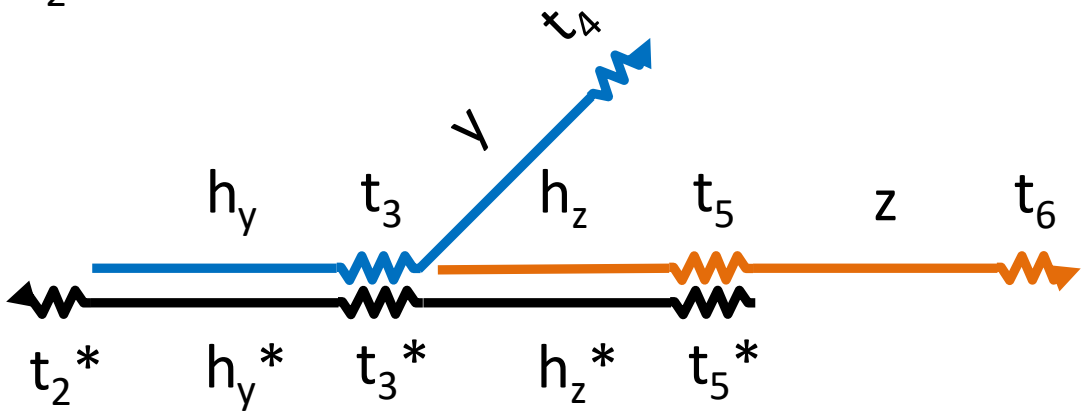

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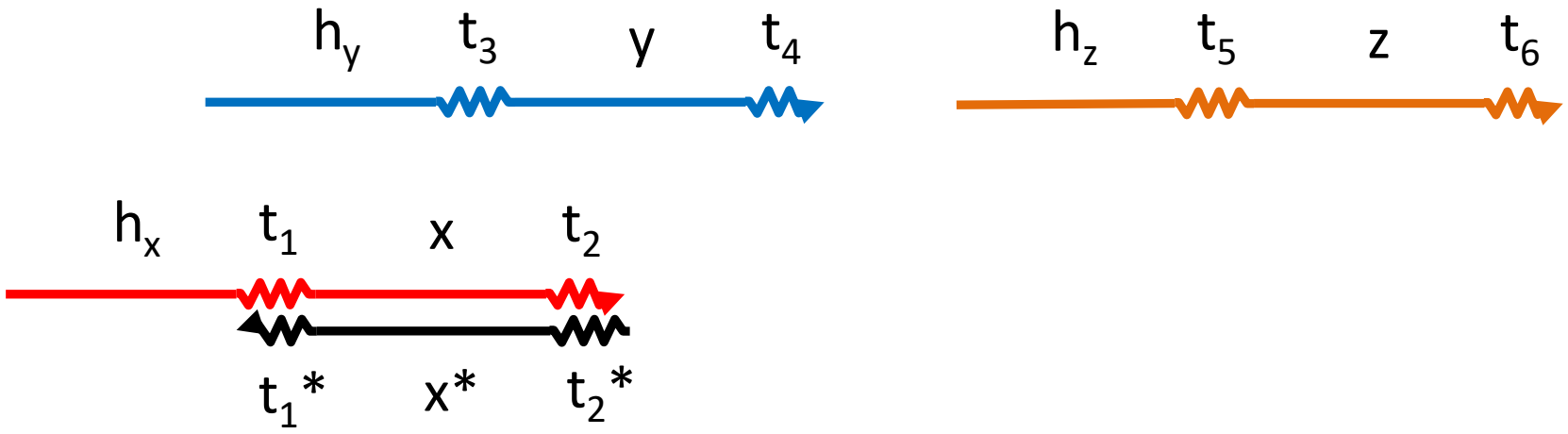
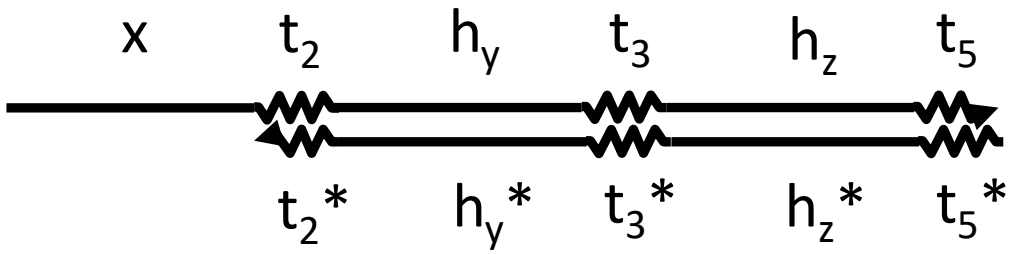
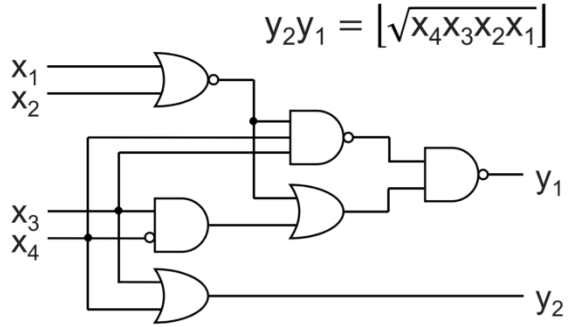




Leak in strand displacement experiments



Source:
Lulu Qian, Erik Winfree.
Scaling Up Digital Circuit Computation
Science 332, 2011

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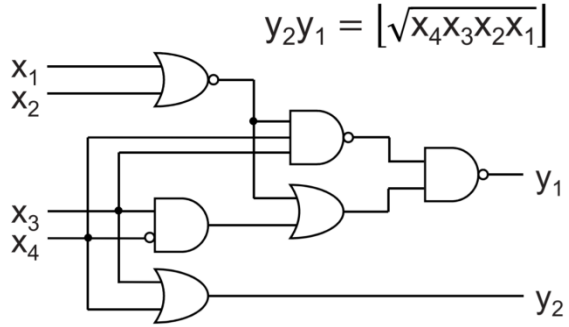

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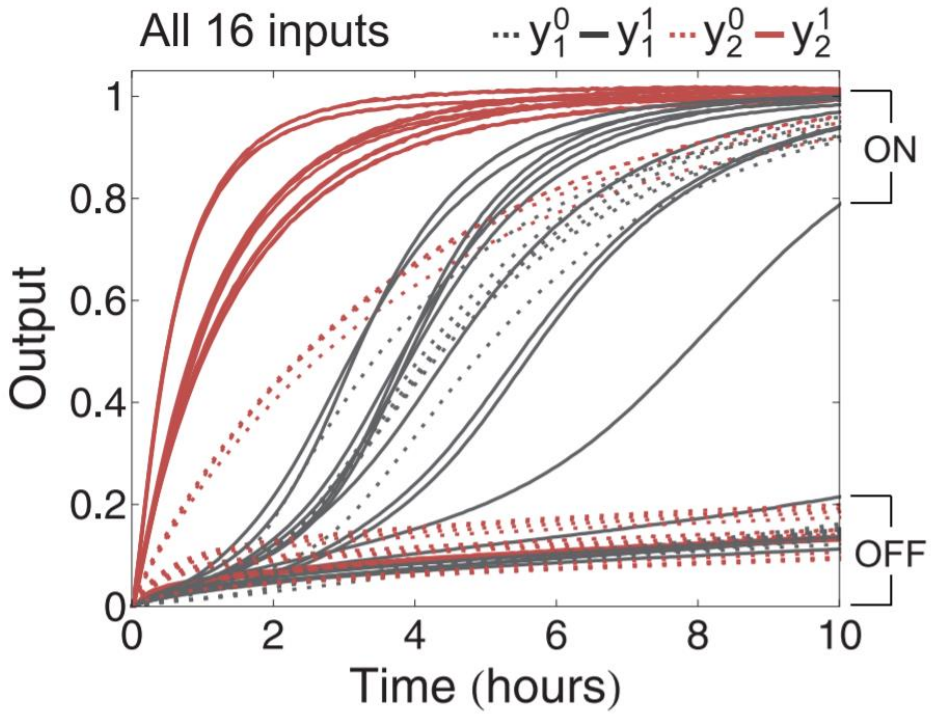
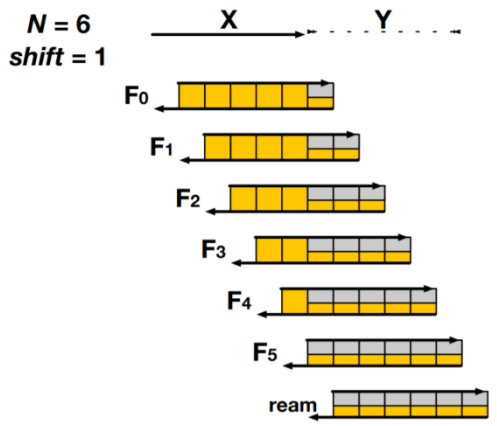


Reducing Leak



[Boya Wang, Chris Thachuk, Andrew Ellington, David Soloveichik. *The Design Space of Strand Displacement Cascades with Toehold-Size Clamps* DNA Computing Conference, 2017]

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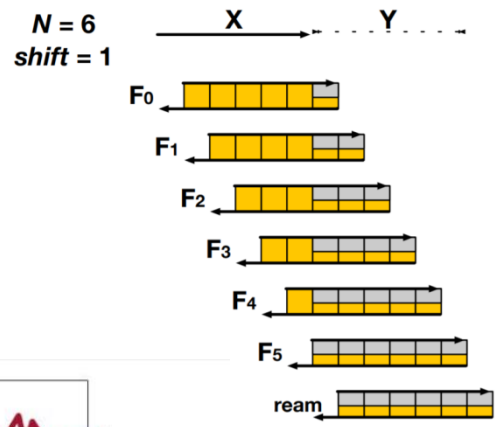

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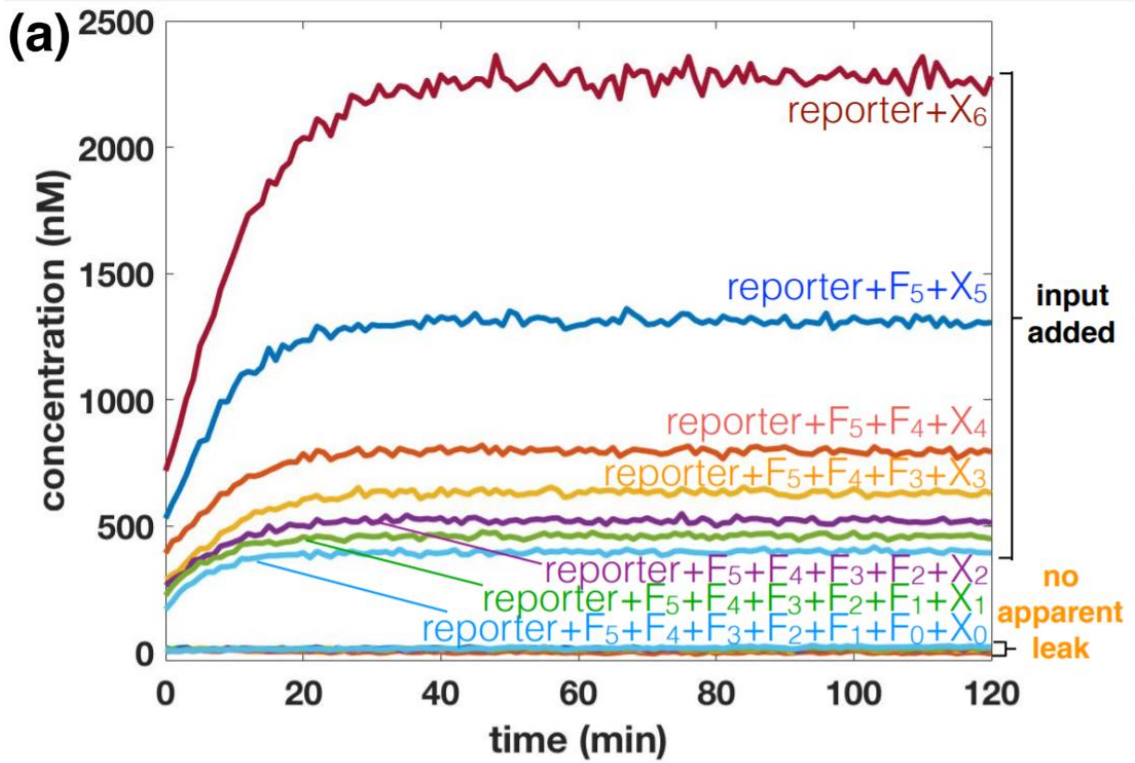

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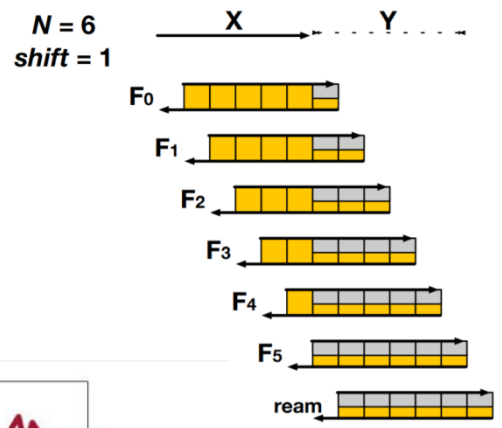

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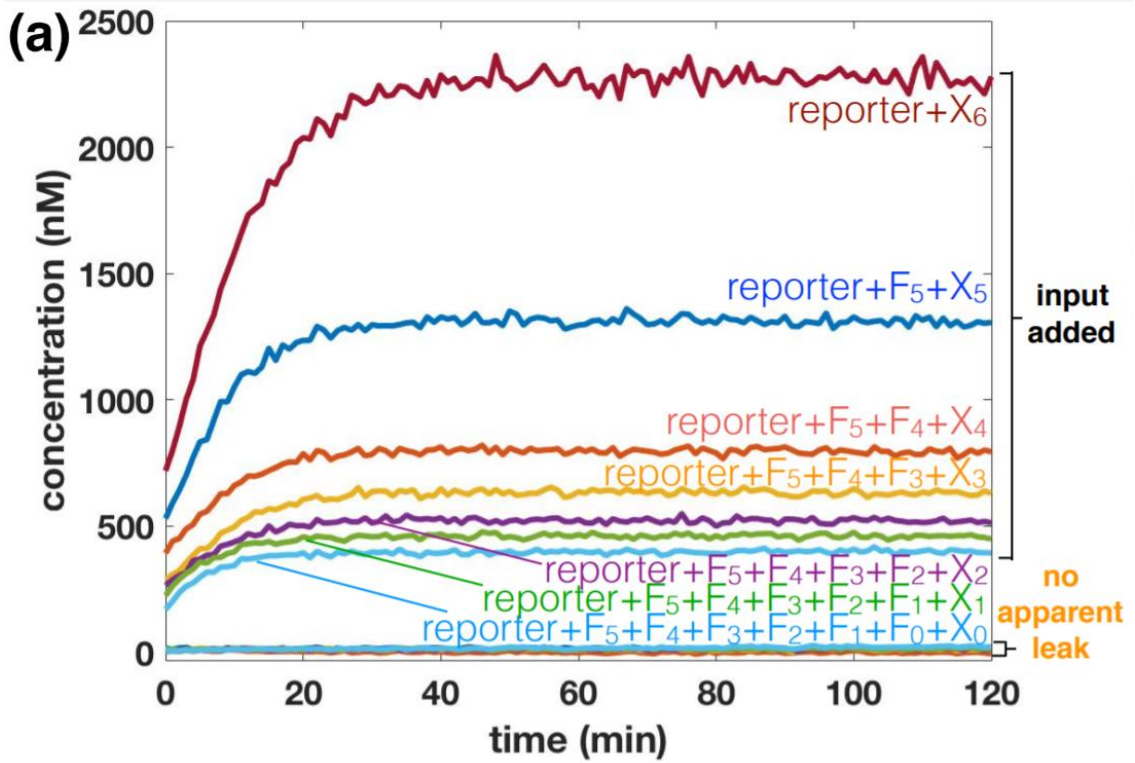
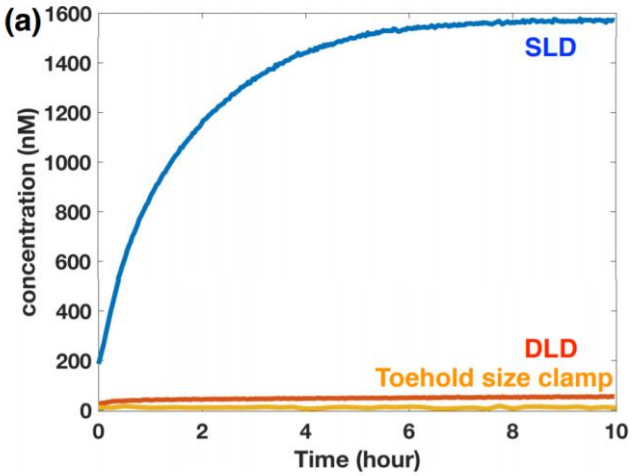
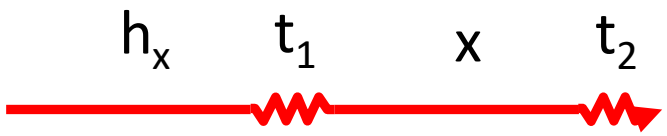
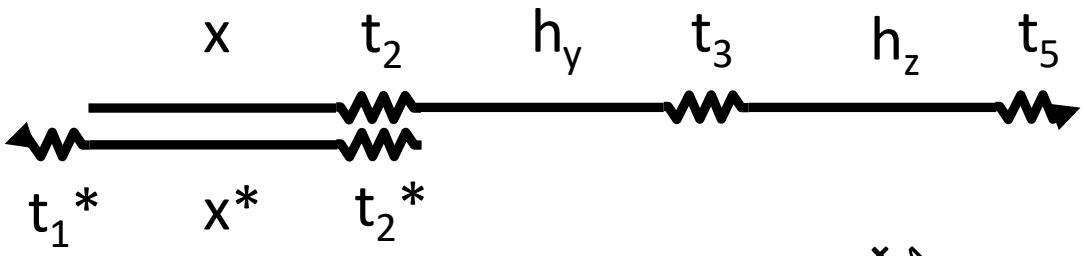


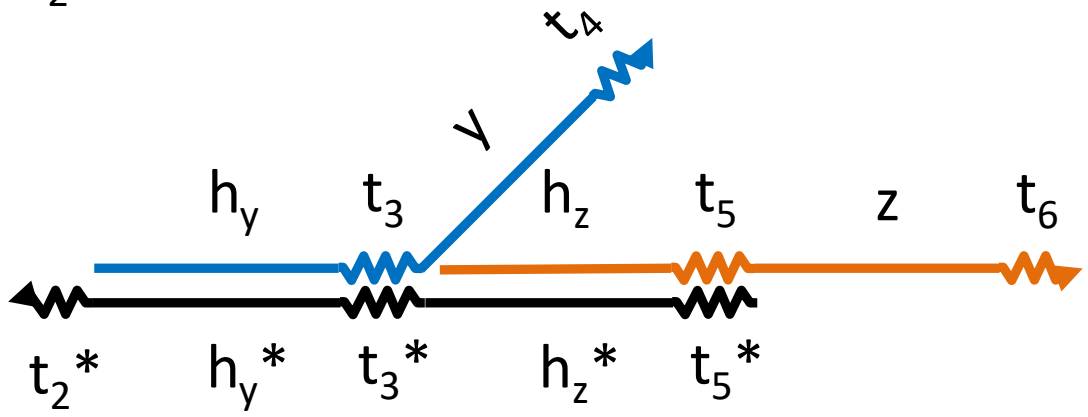
Leak:



$$X \longrightarrow Y + Z$$

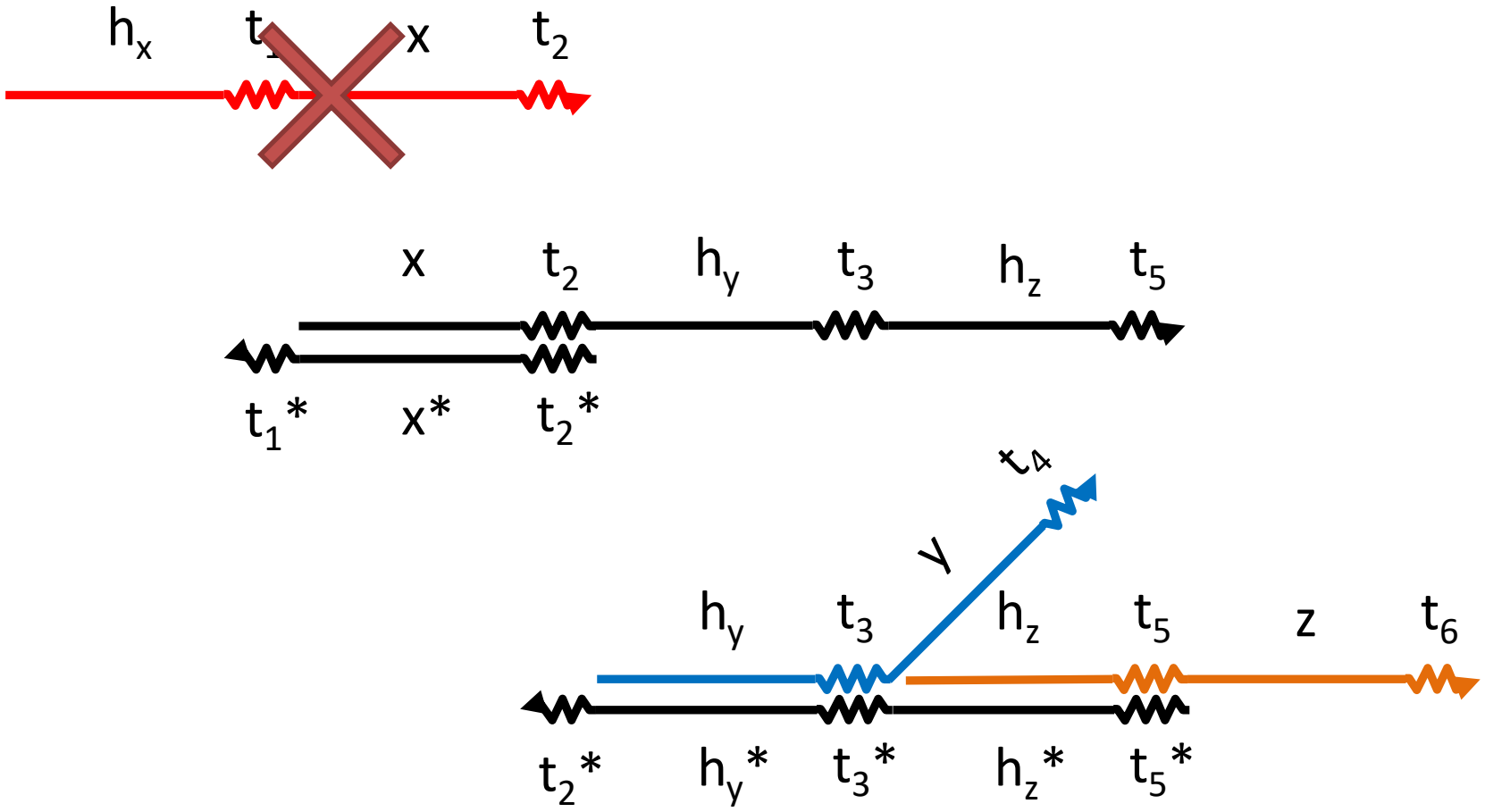






What causes leak “kinetically”?

$$\emptyset \longrightarrow Y + Z$$



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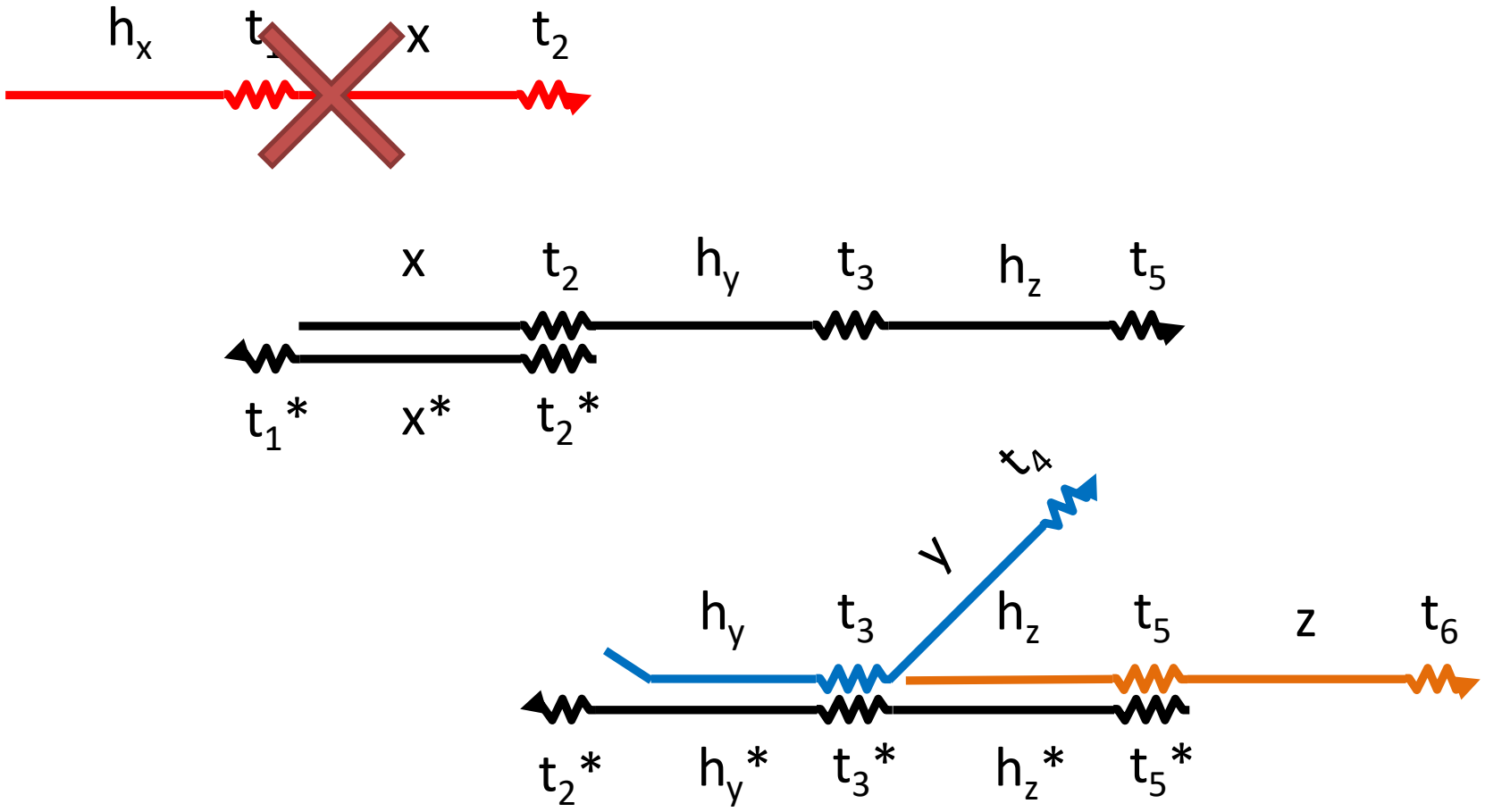

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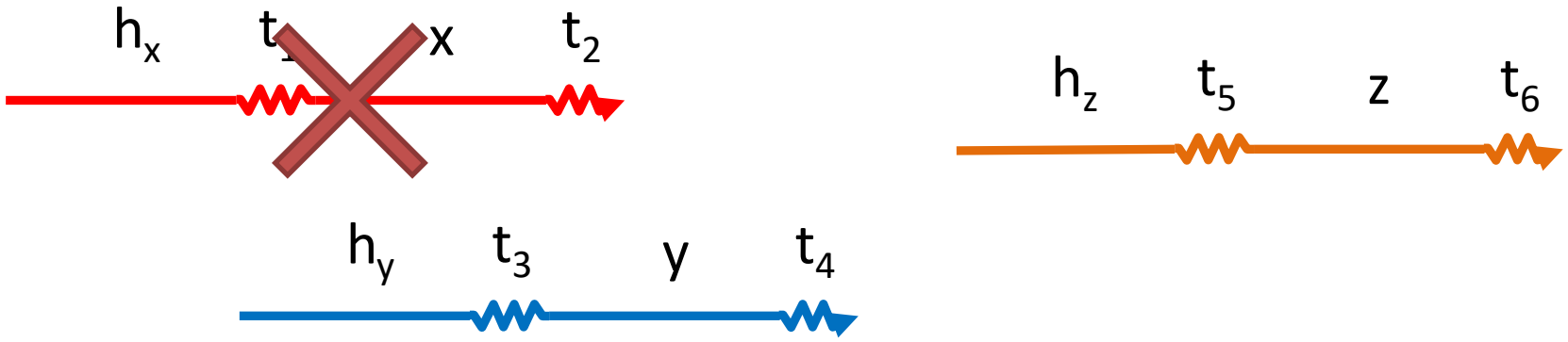

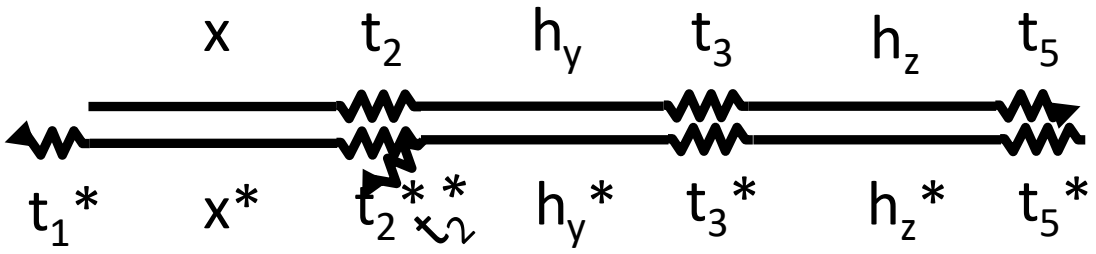

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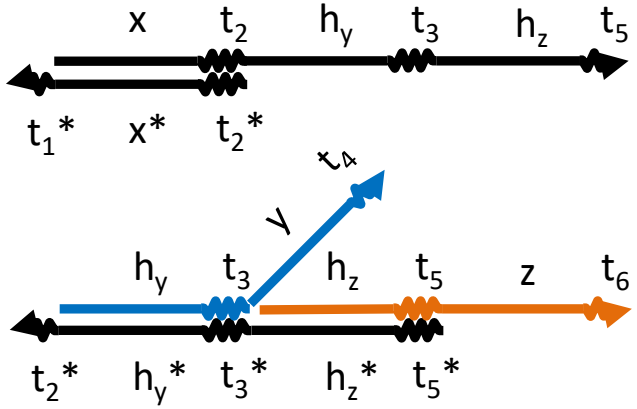
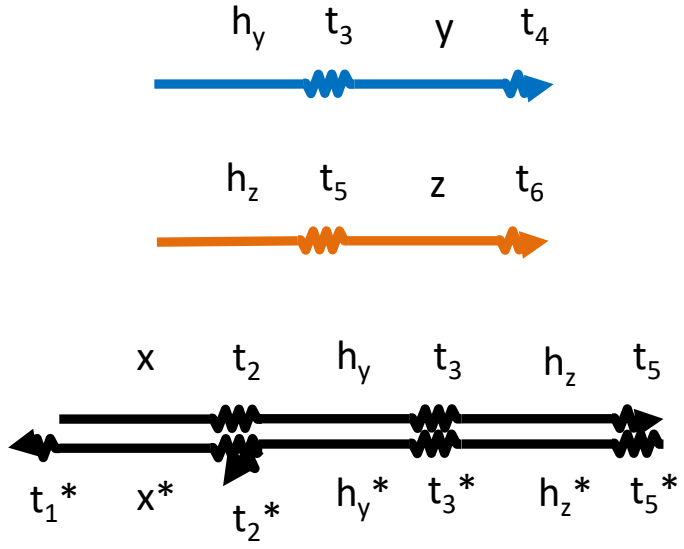


After:



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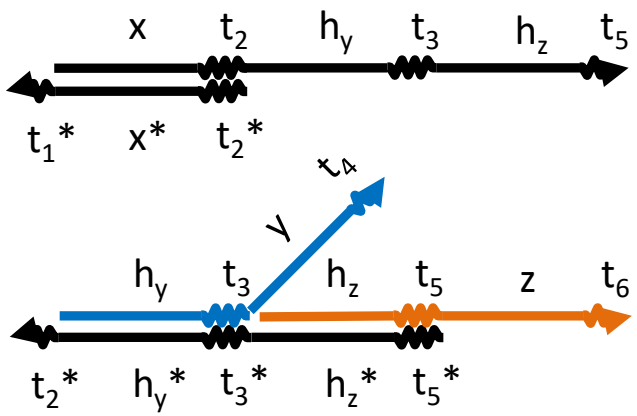
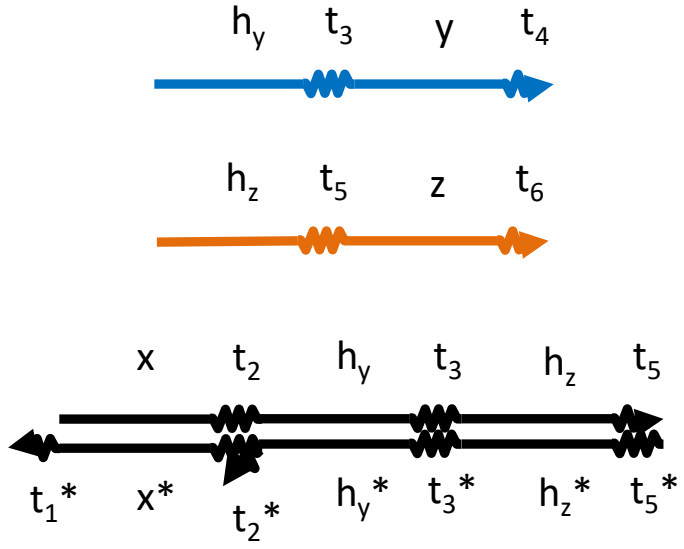


slow

After:



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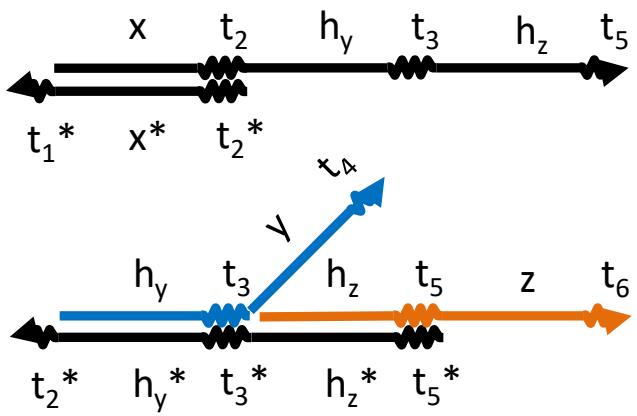

slow

very slow

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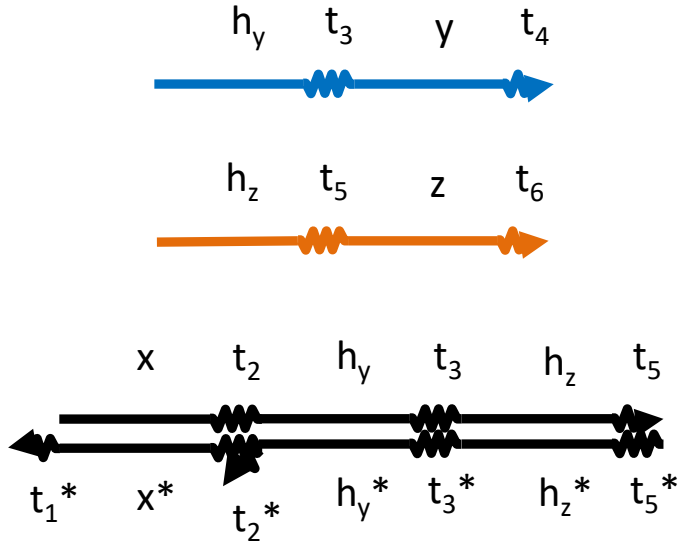

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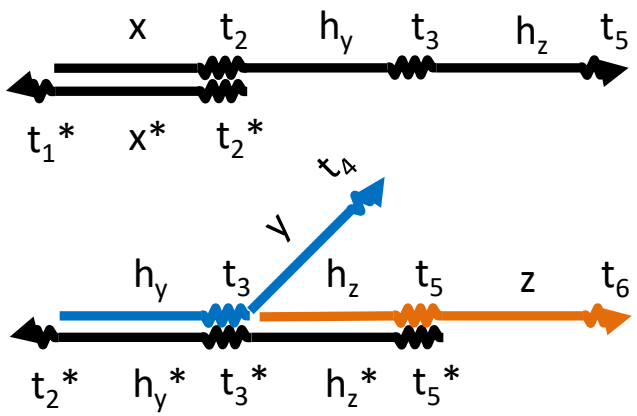

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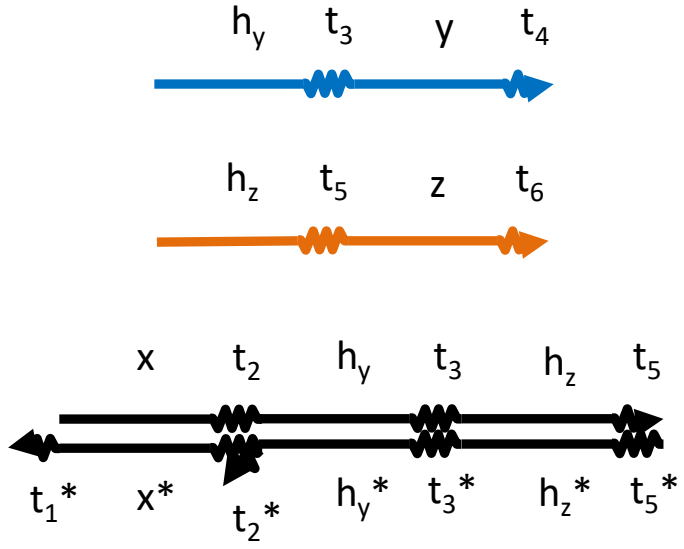

less favorable

more favorable

Need a *kinetic* binding network model

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- Can we design pathways that maintain local stability?

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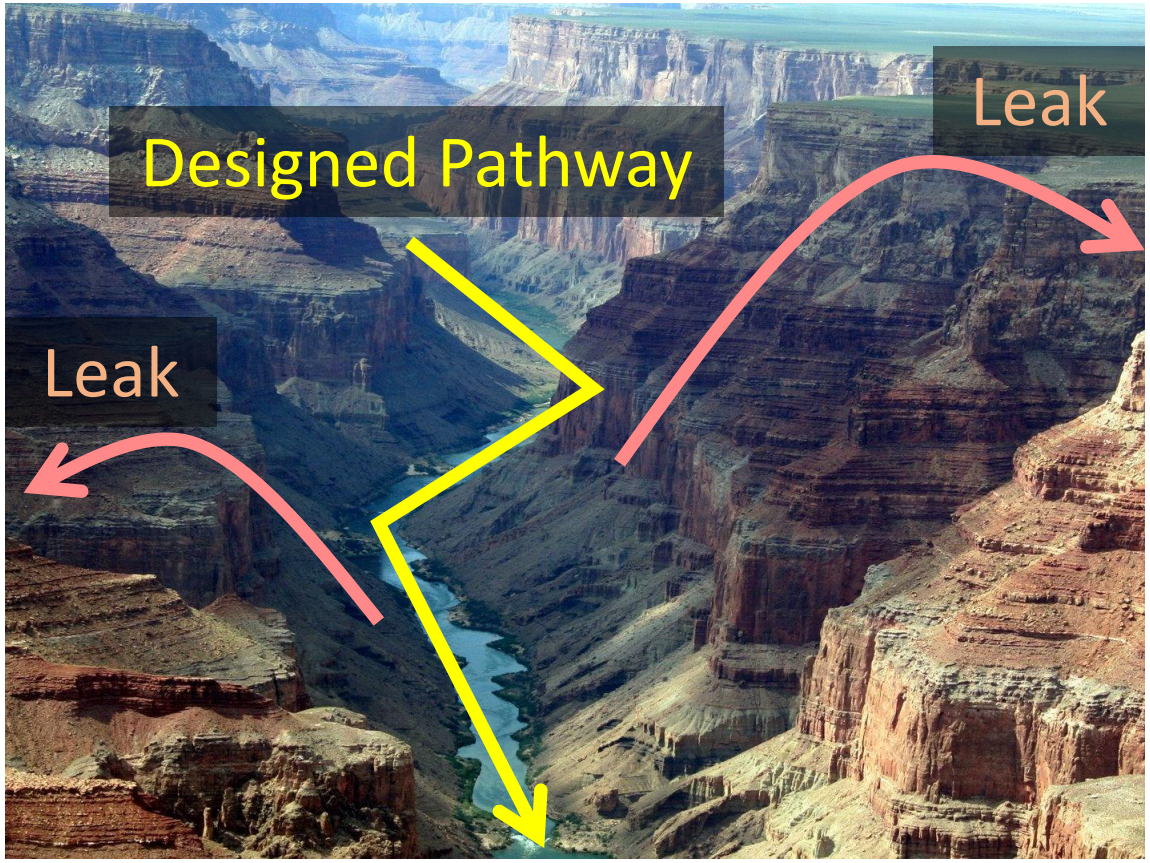
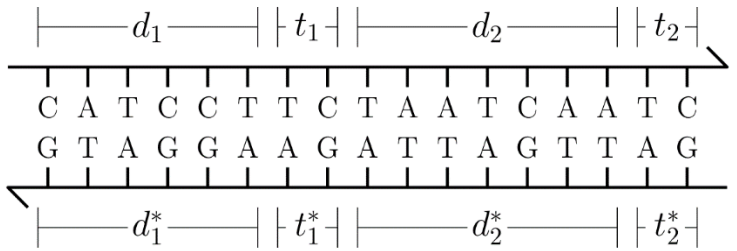


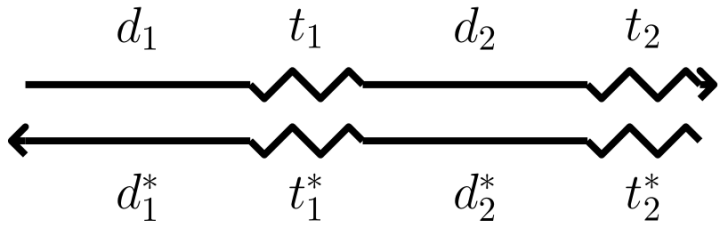
Levels of Abstraction

DNA

Base Pairs



Strands



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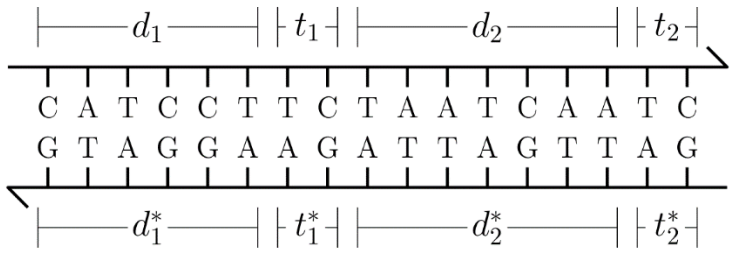

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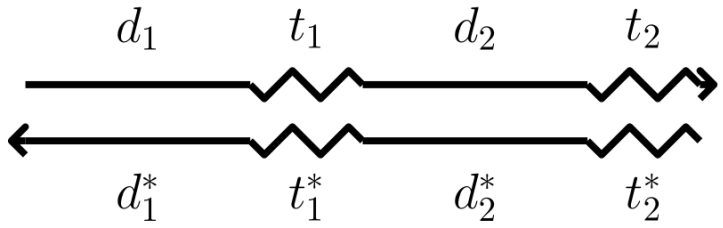
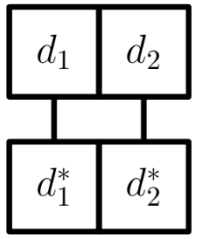


Thermodynamic Binding Network



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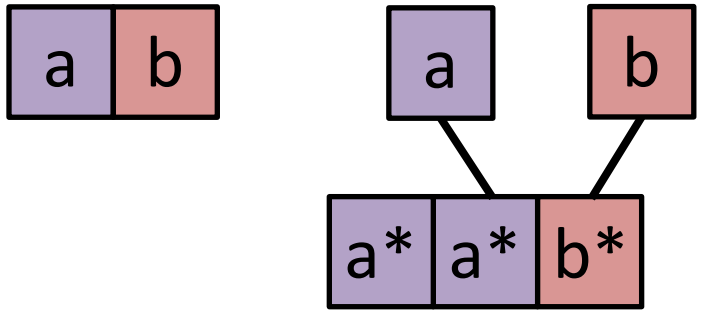


Geometry-Free Model:

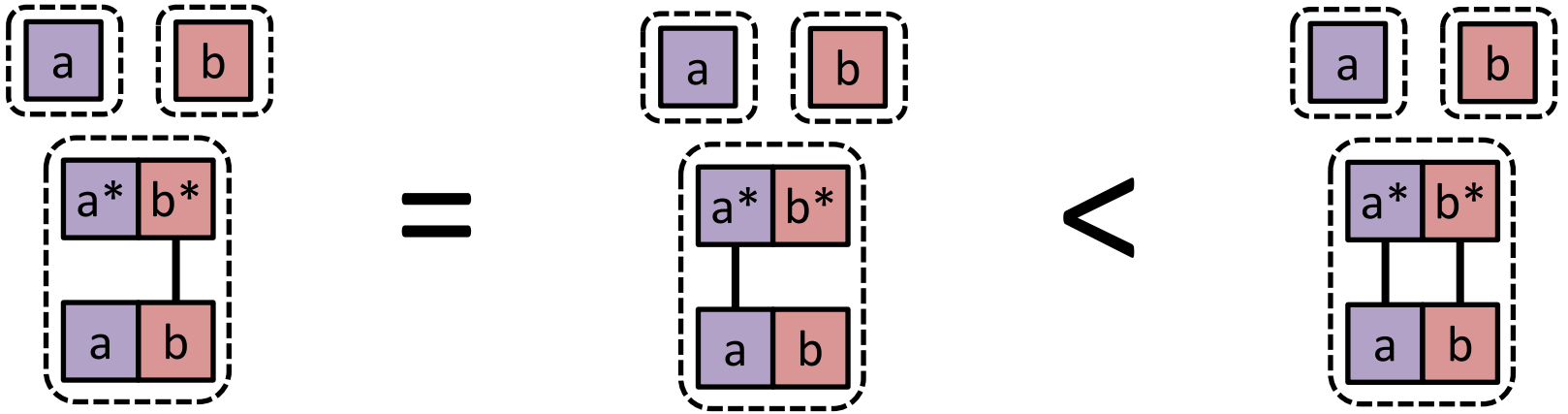
The domains within a monomer are unordered

Monomer = collection of domains

Configuration = how monomers are bound

Energetic favorability: Bonds and complexes

all else equal,
more bonds
= more favorable



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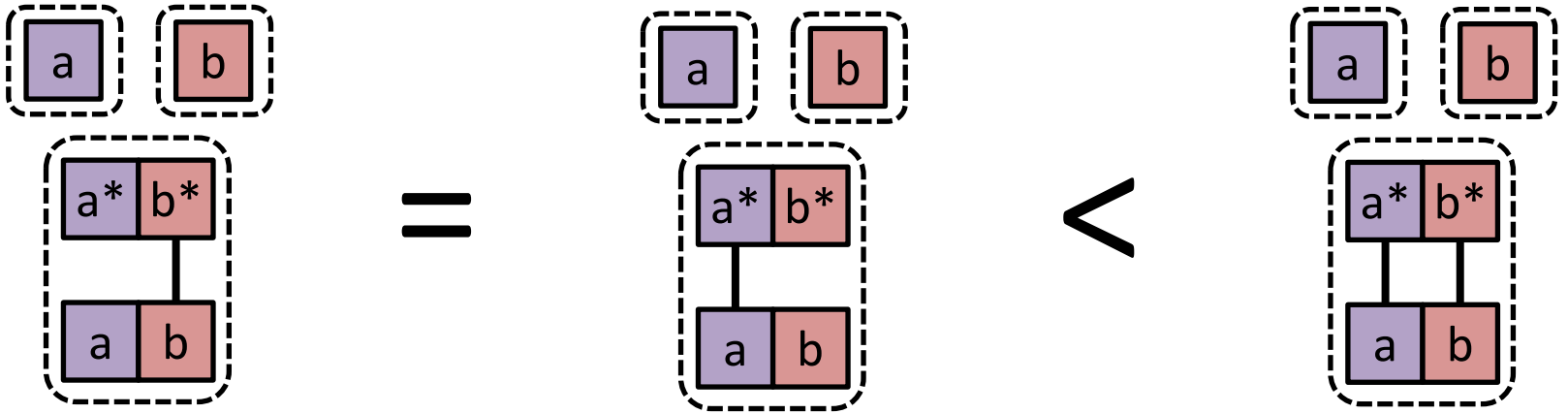

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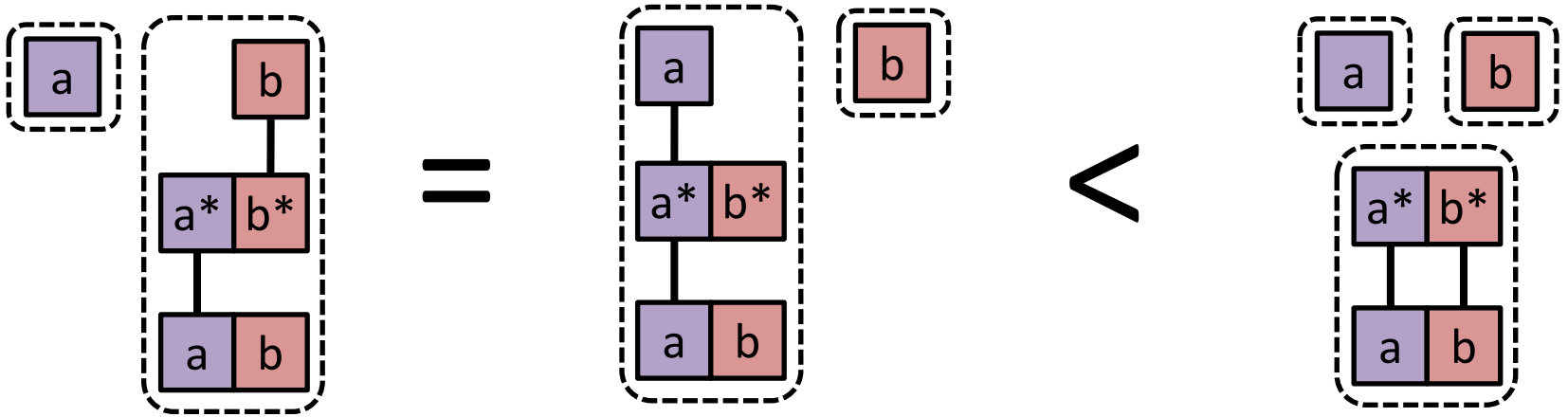

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  energy = w*#bonds + #complexes

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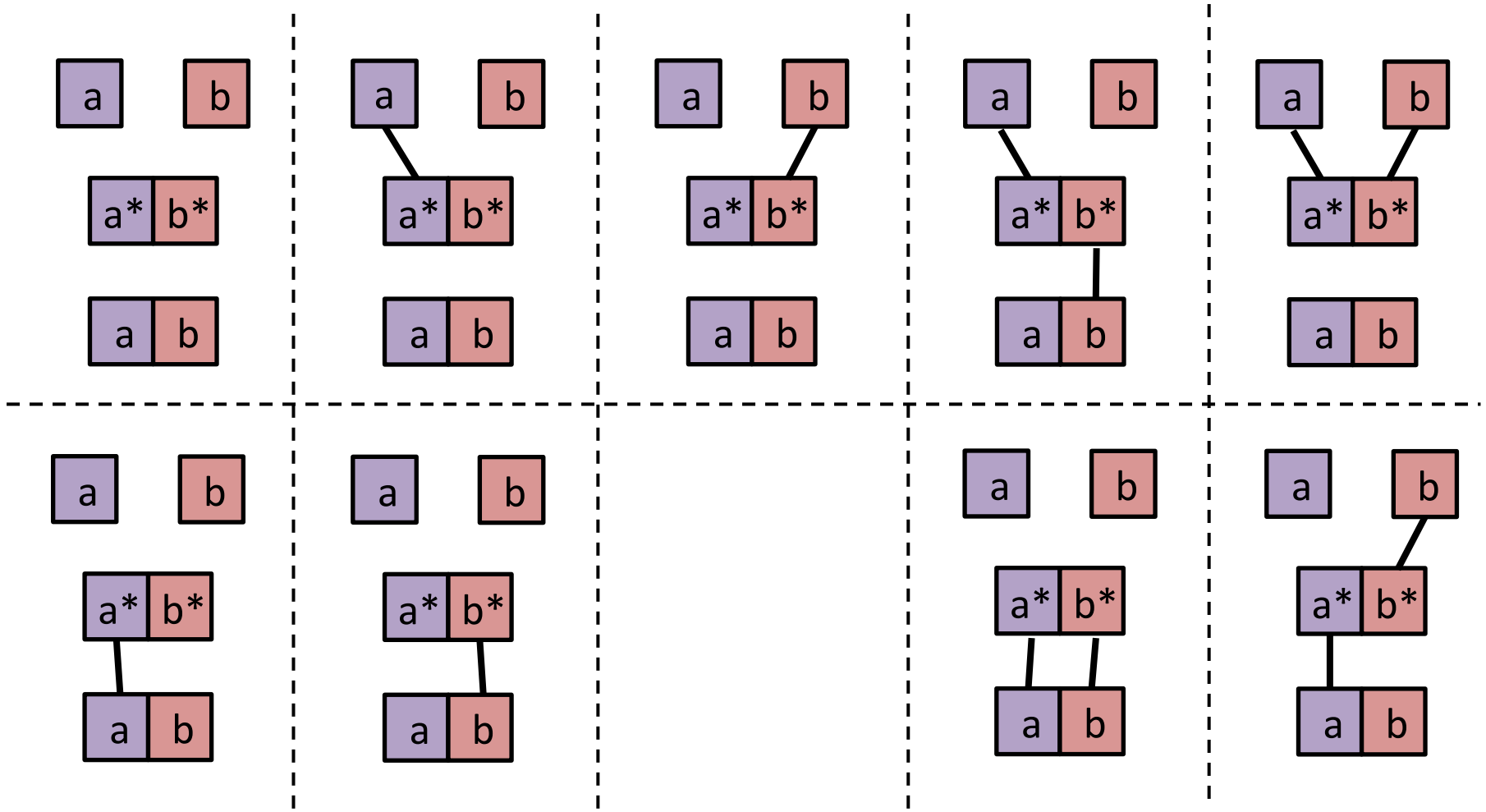
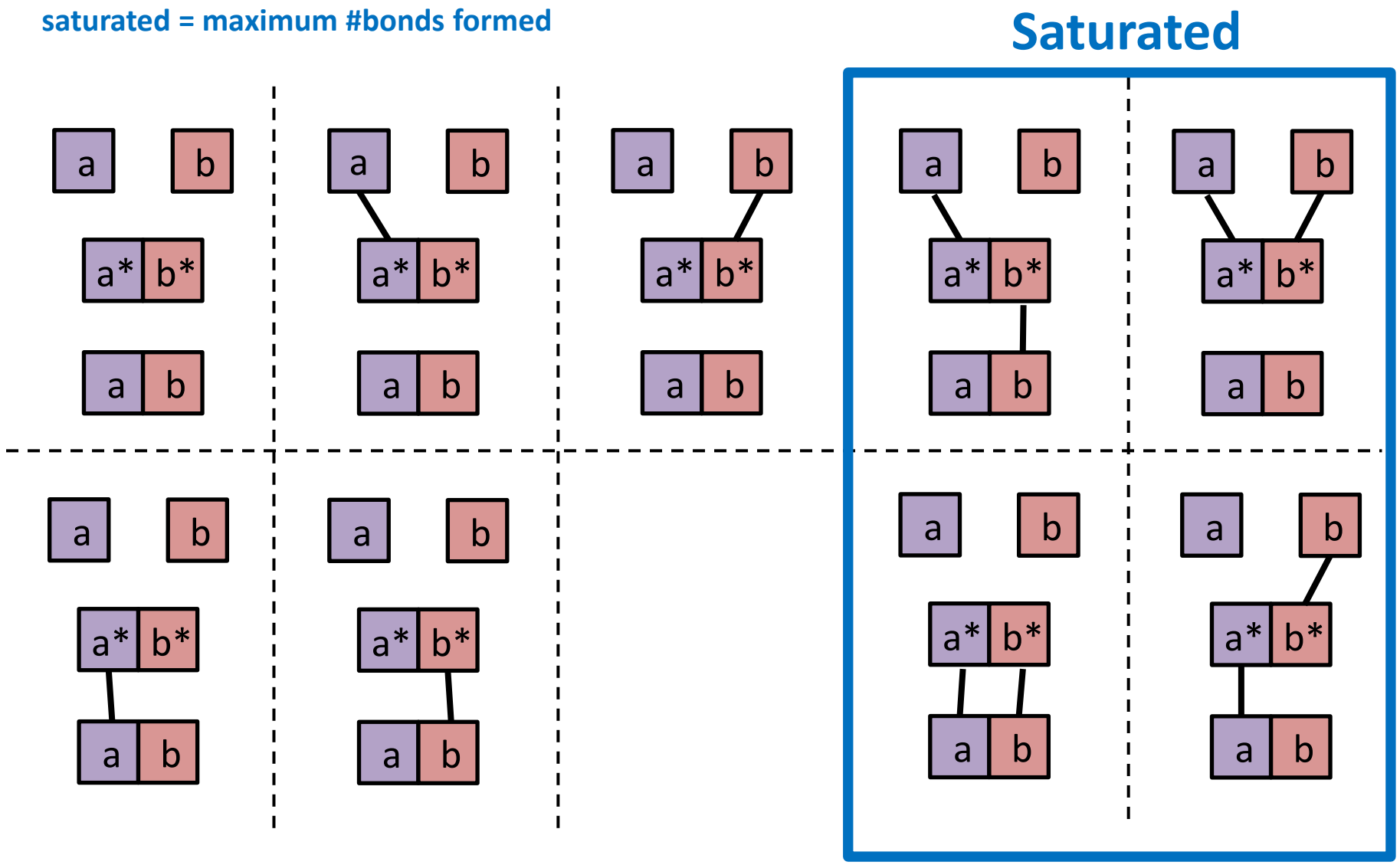
  - Corresponds to bonds that are so strong they cannot spontaneously dissociate, but can exchange with each other to find configurations with more complexes

Thermodynamic Binding Networks



Thermodynamic Binding Networks

saturated = maximum #bonds formed



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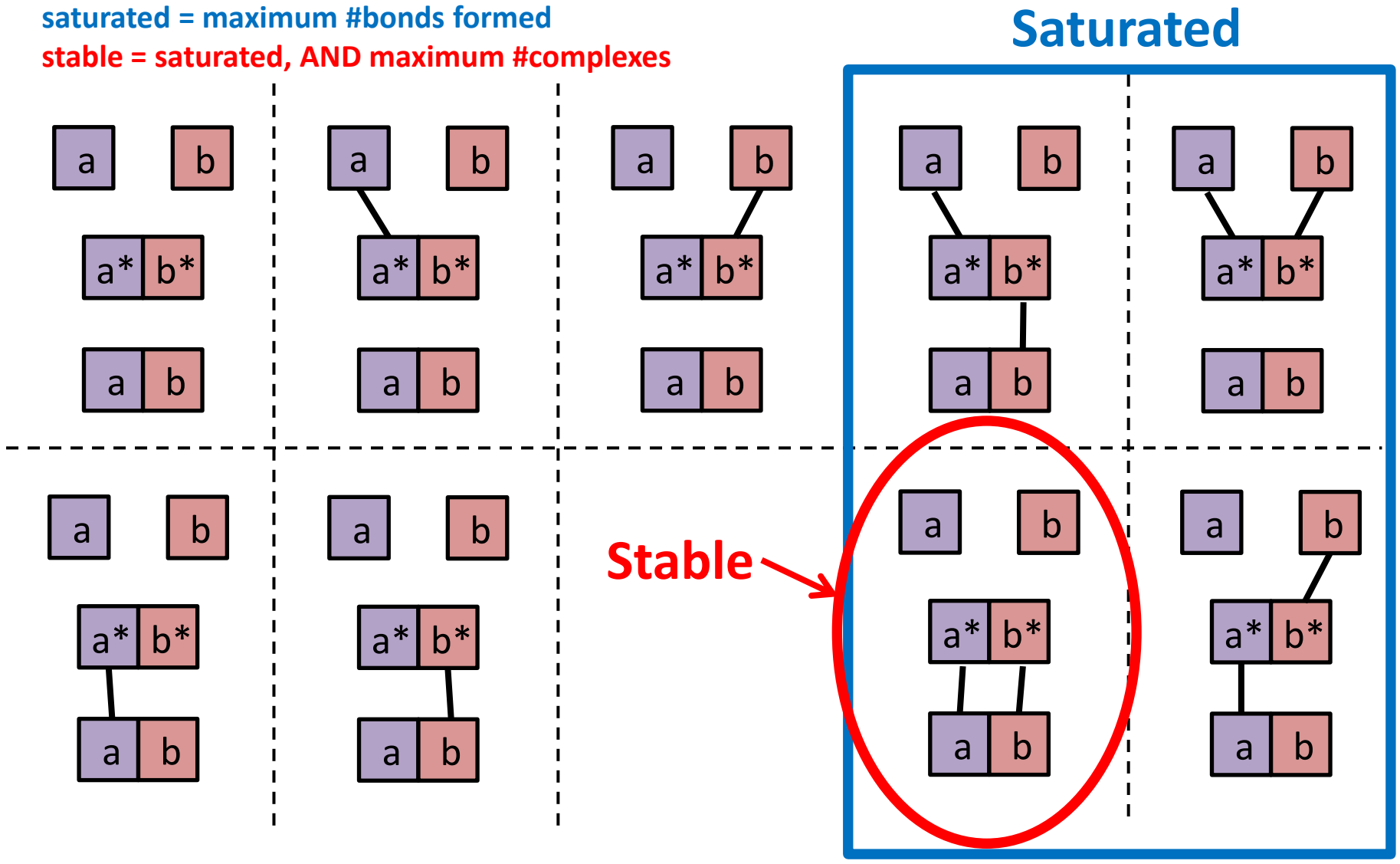
saturated = maximum #bonds formed

stable = saturated, AND maximum #complexes



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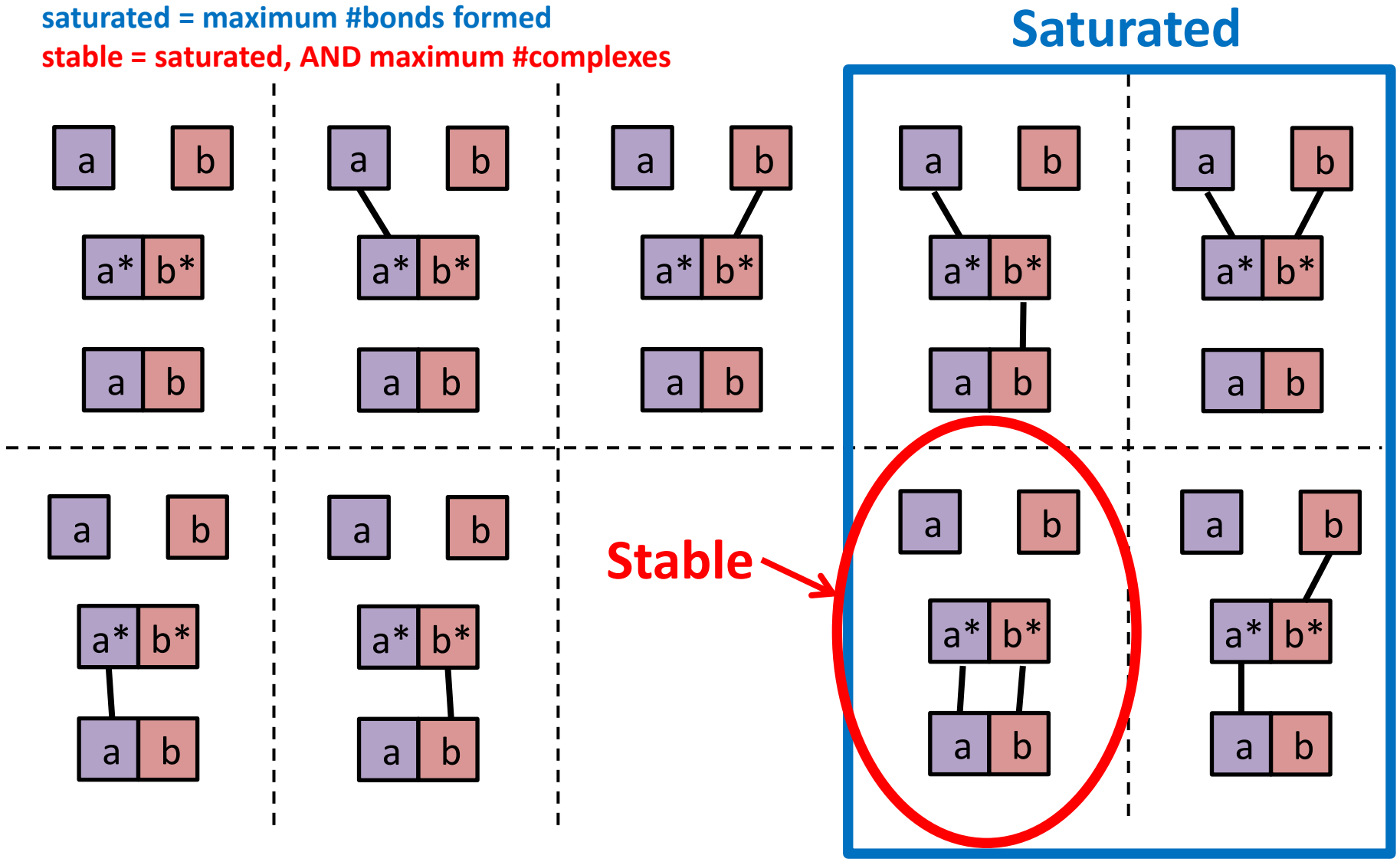
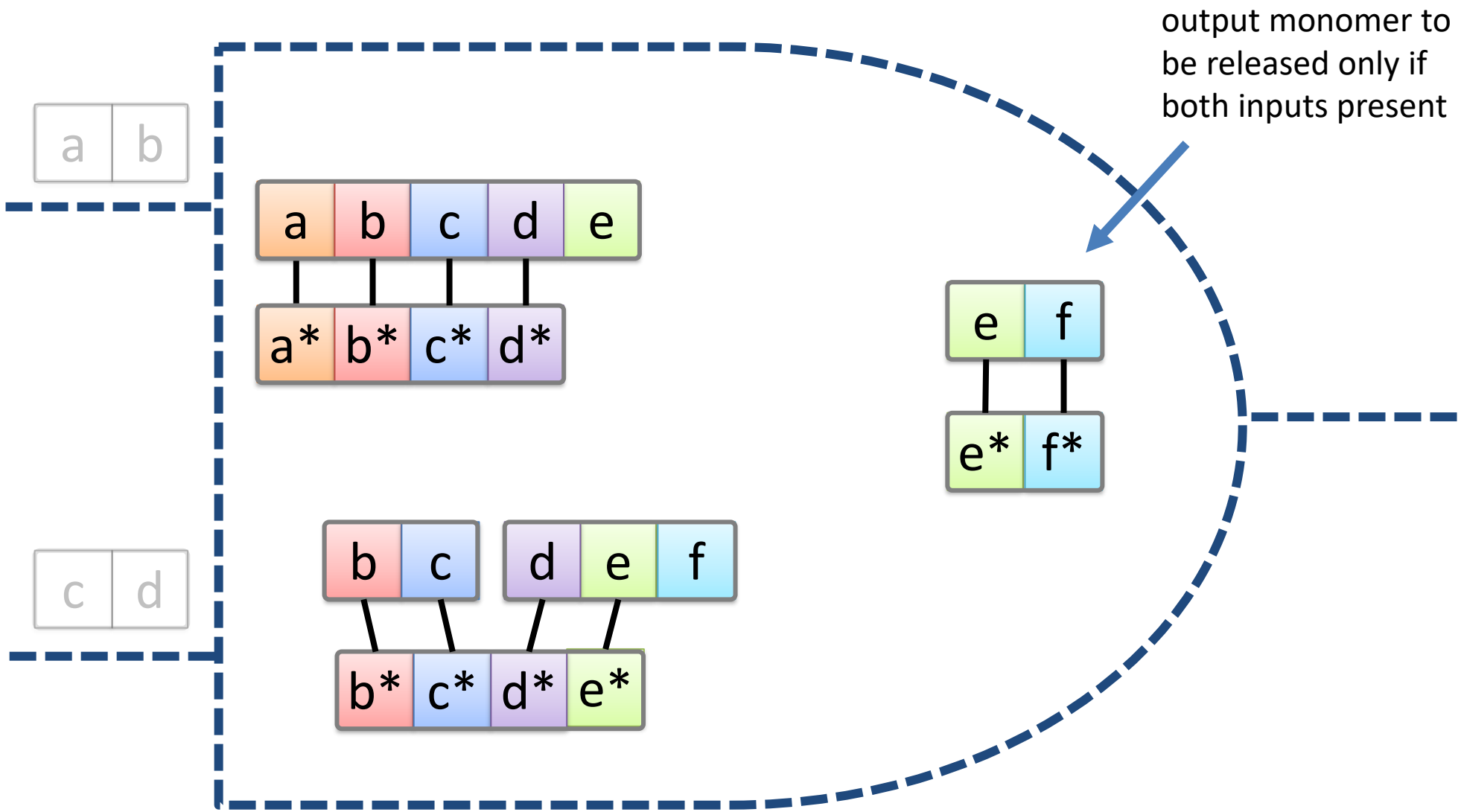


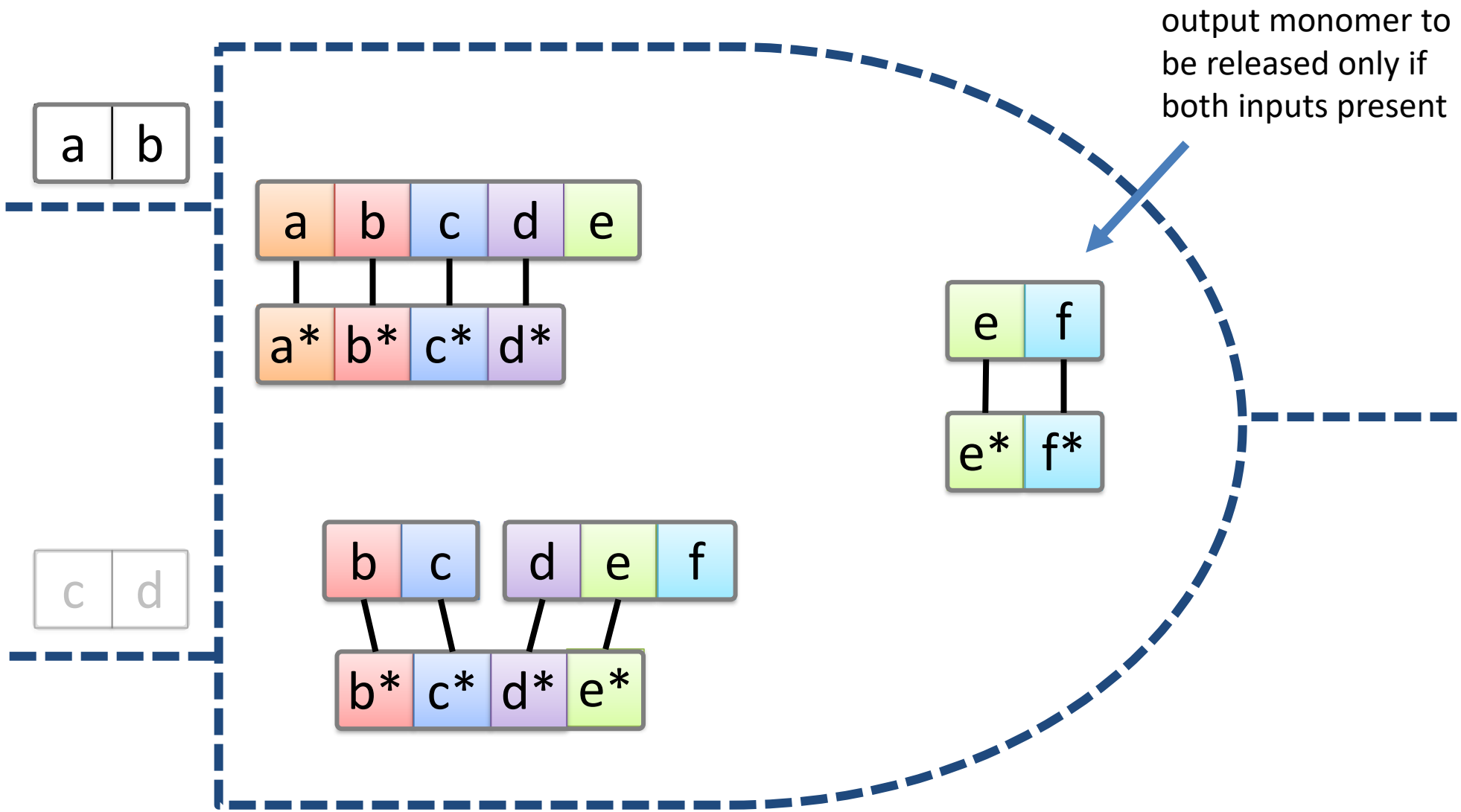
If we're careful to make starred binding sites limiting, then *saturated = all starred sites are bound*

Computing via Thermodynamic Equilibrium

AND gate


output monomer to be released only if both inputs present
a
b
c
d
a
b
c
d
e
a*
b*
c*
d*
e
f
e*
f*
b
c
d
e
f
b*
c*
d*
e*

AND gate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a
b
a
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e
a*
b*
c*
d*
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f
e*
f*
c
d
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c
d
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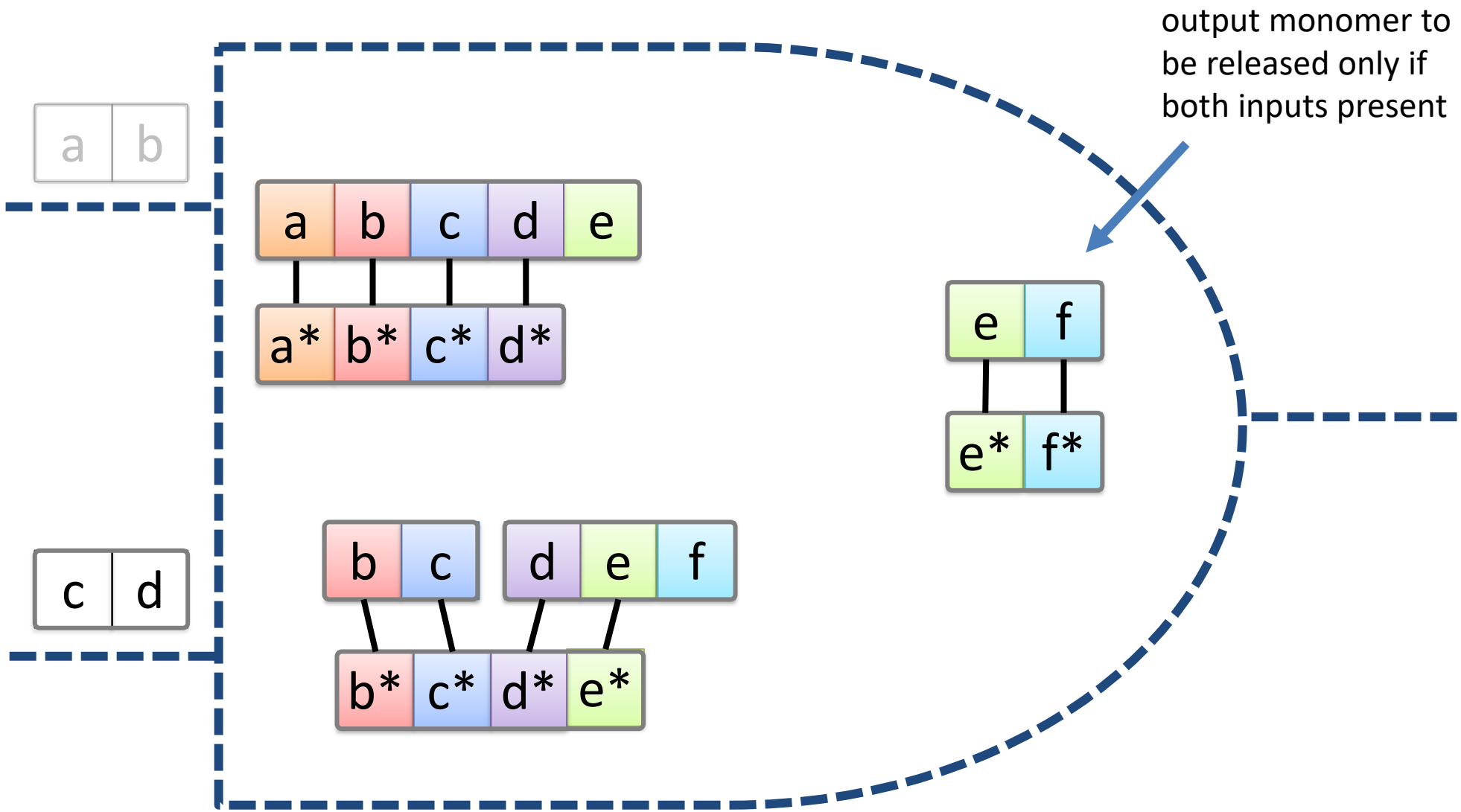
f
b*
c*
d*
e*

AND gate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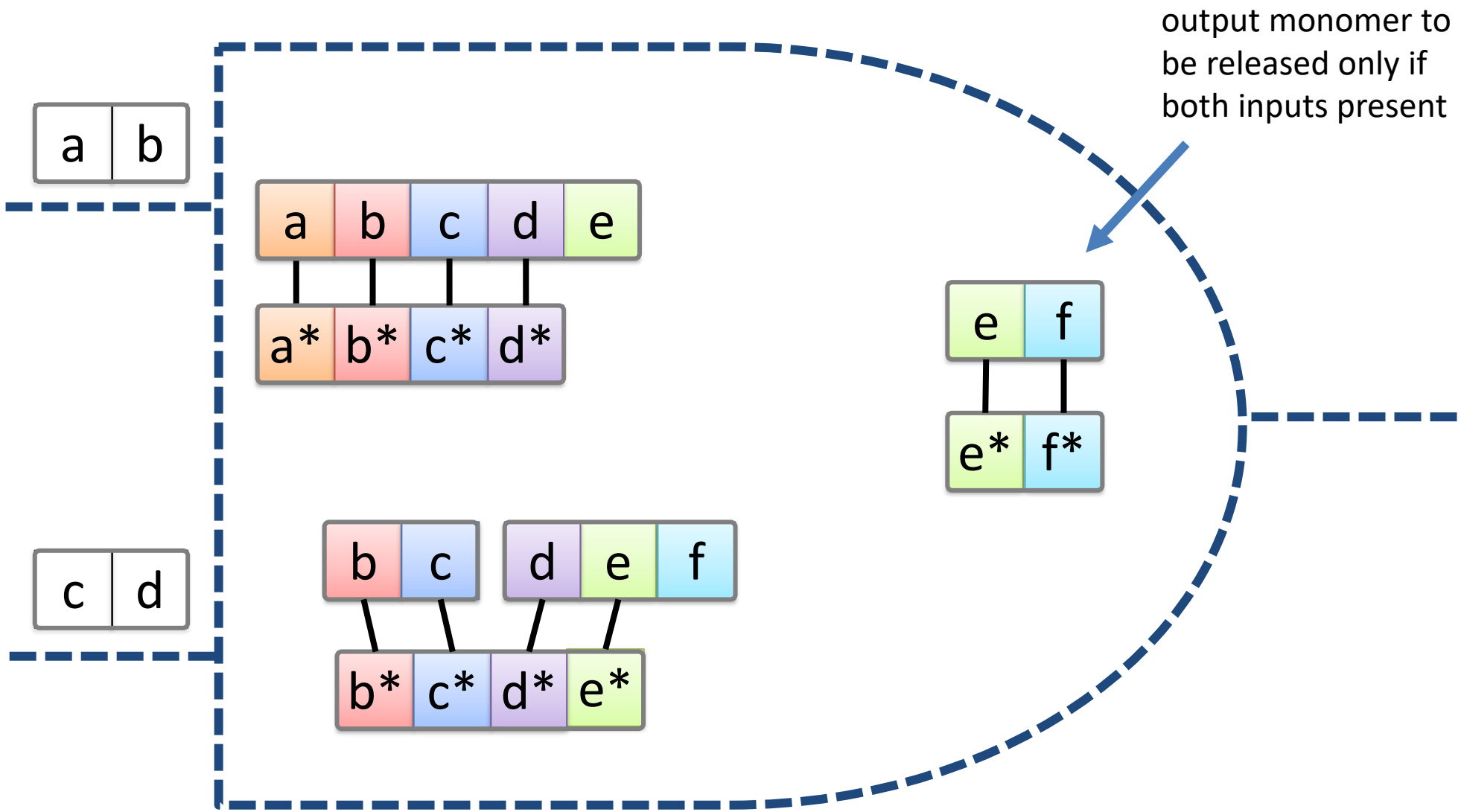
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c
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b*
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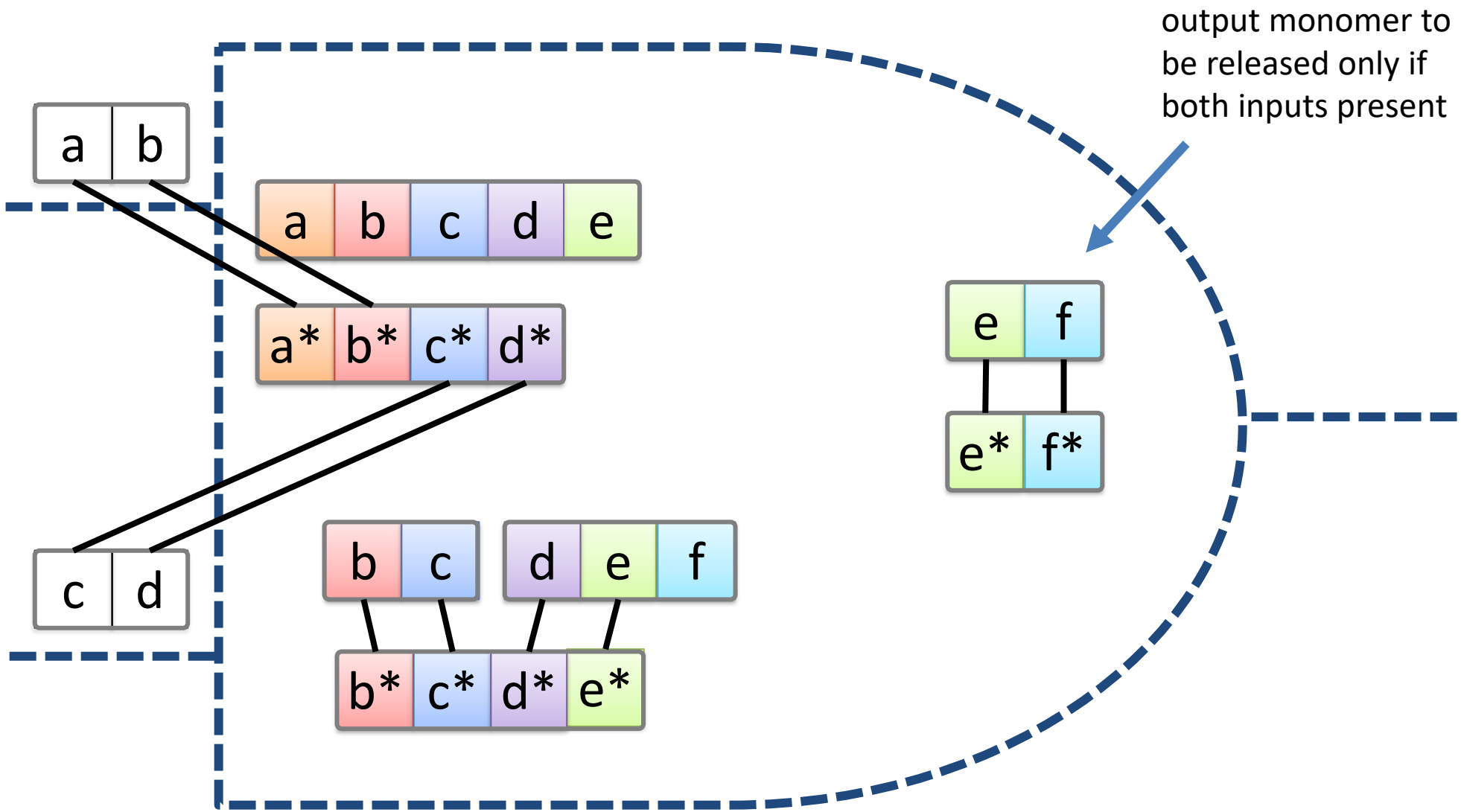
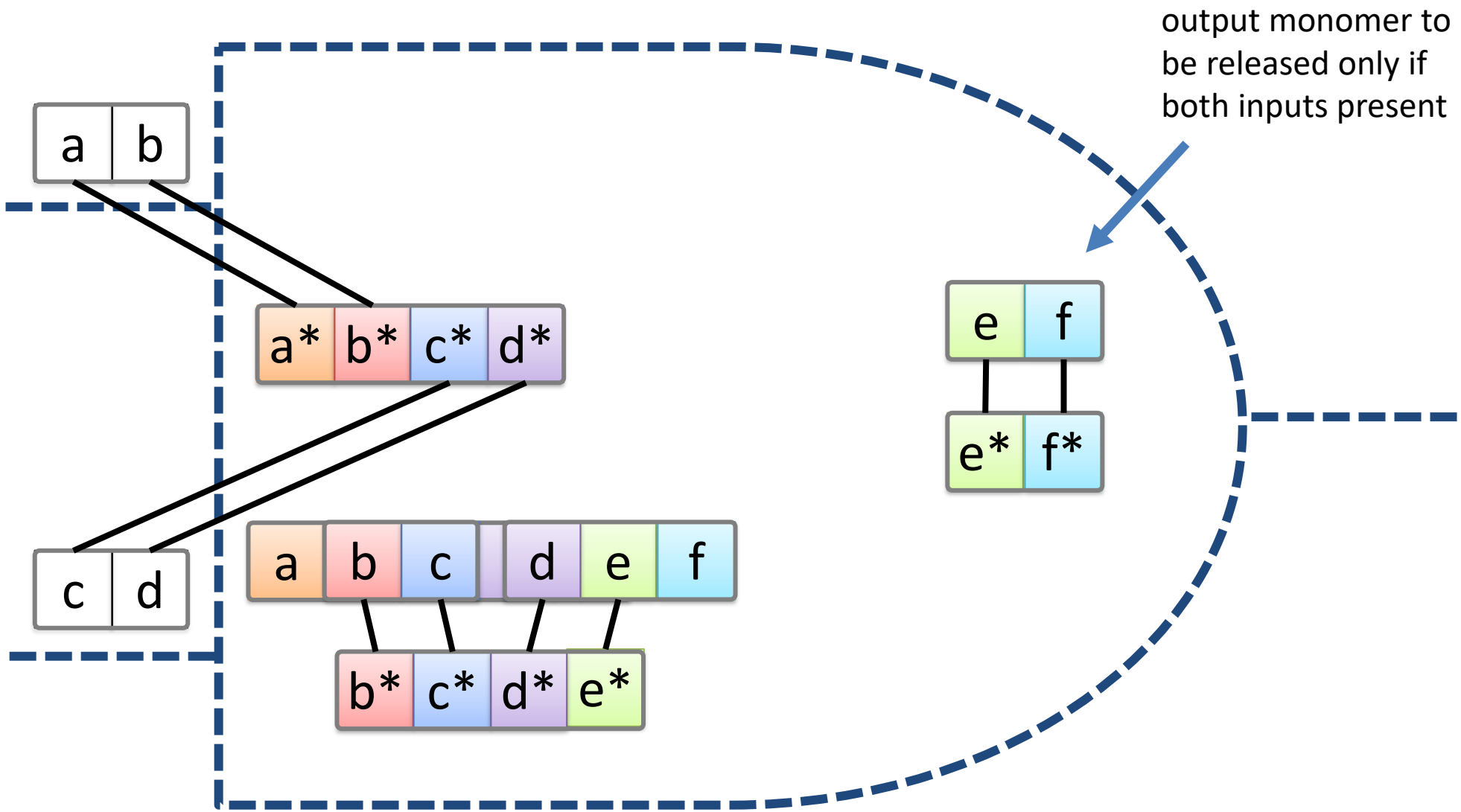
AND gate


output monomer to be released only if both inputs present
a
b
a b c d e
a* b* c* d*
c
d
b c
d e f
b* c* d* e*
e
f
e*
f*

AND gate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b*
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f*

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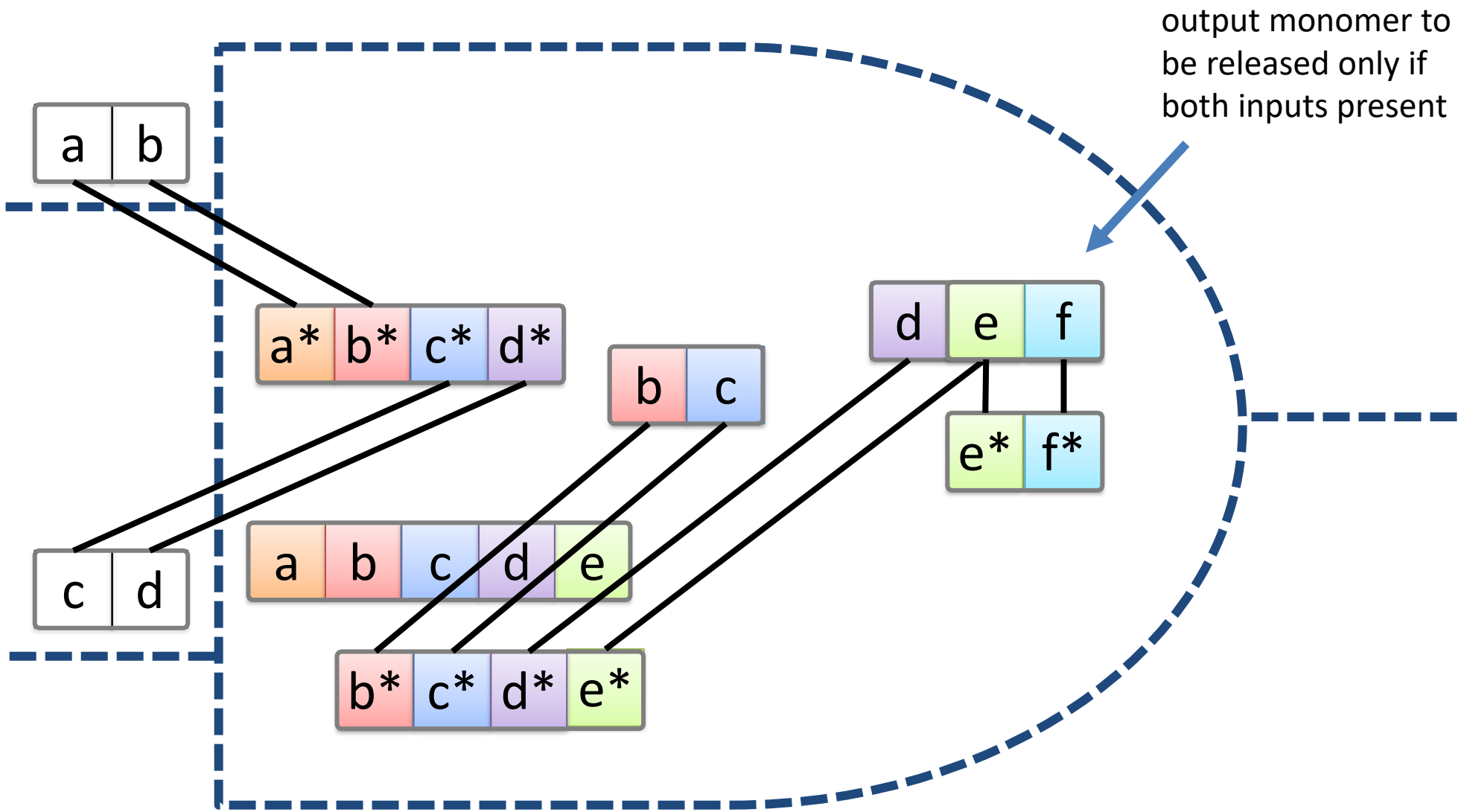
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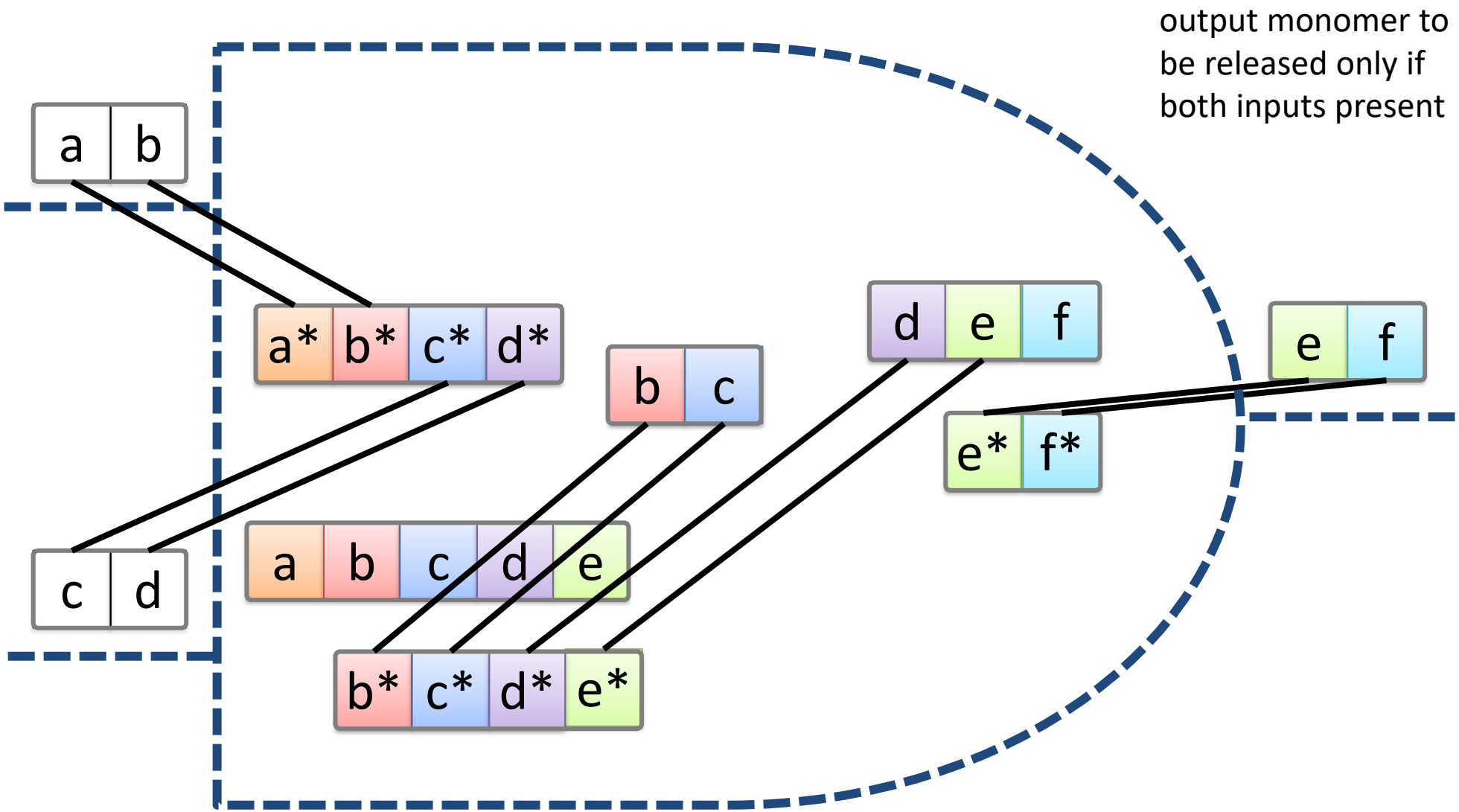
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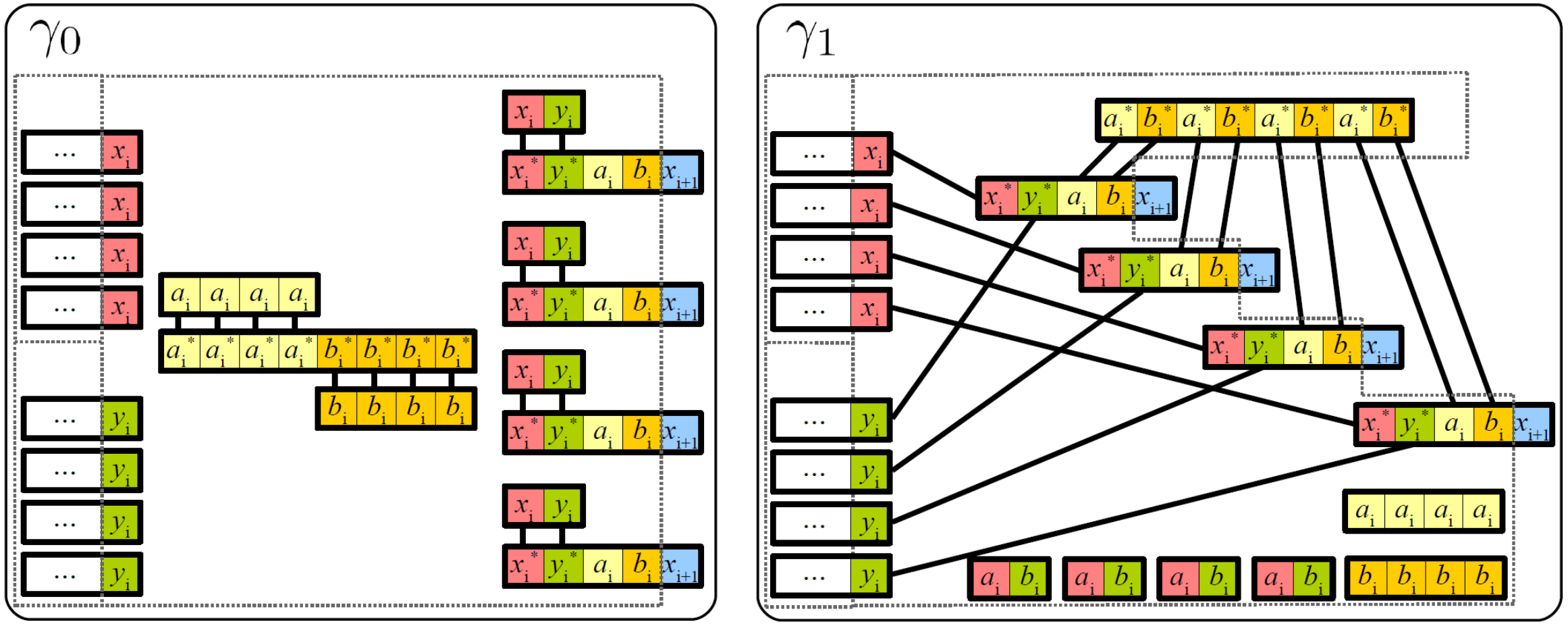
  - We can use $O(n)$ domain/monomer types to achieve an entropy gap of n.
- Output convention?
  - Obvious one: "there's a unique stable configuration with the correct output"
  - It's problematic, so we have a one-sided convention:
    - if correct output is 0, unique stable configuration with correct answer
    - if correct output is 1, then both the "output=1" and "output=0" configurations are stable

Composable AND gate with entropy gap 3



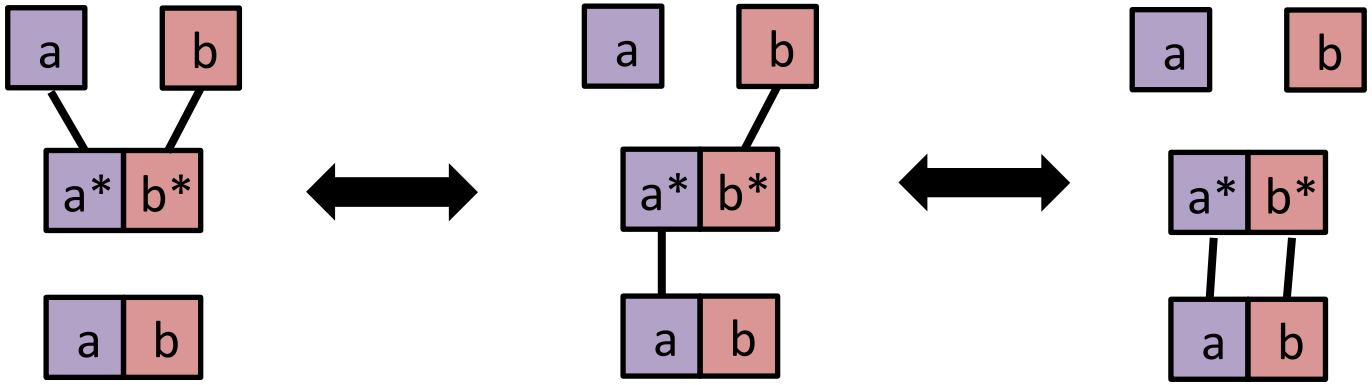
Rather than release a single output monomer, it suffices to gather all output domains on one complex.

Kinetic pathways and energy barriers

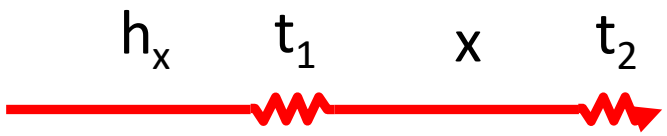
Pathways

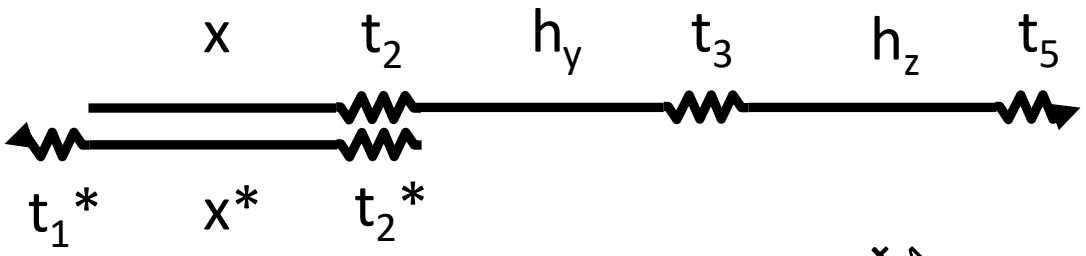
Thermodynamics: Which configurations are energetically favorable

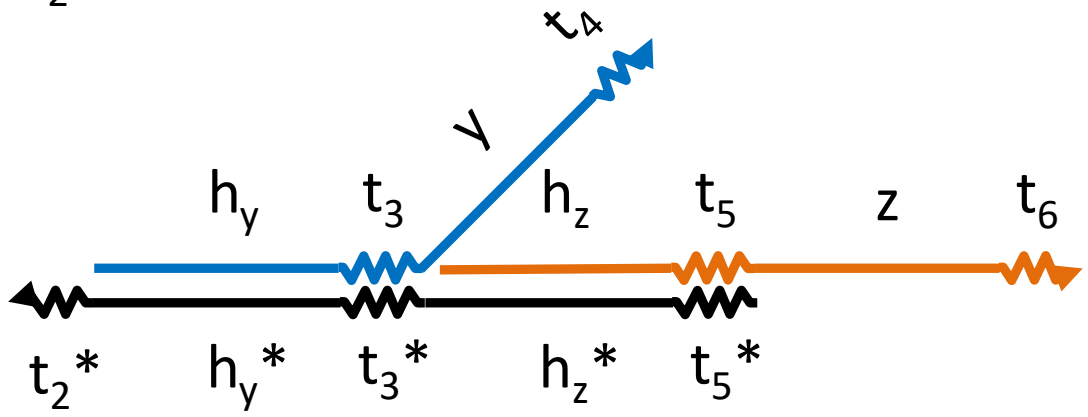
Kinetics: How a system moves between configurations over time



$$X \longrightarrow Y + Z$$







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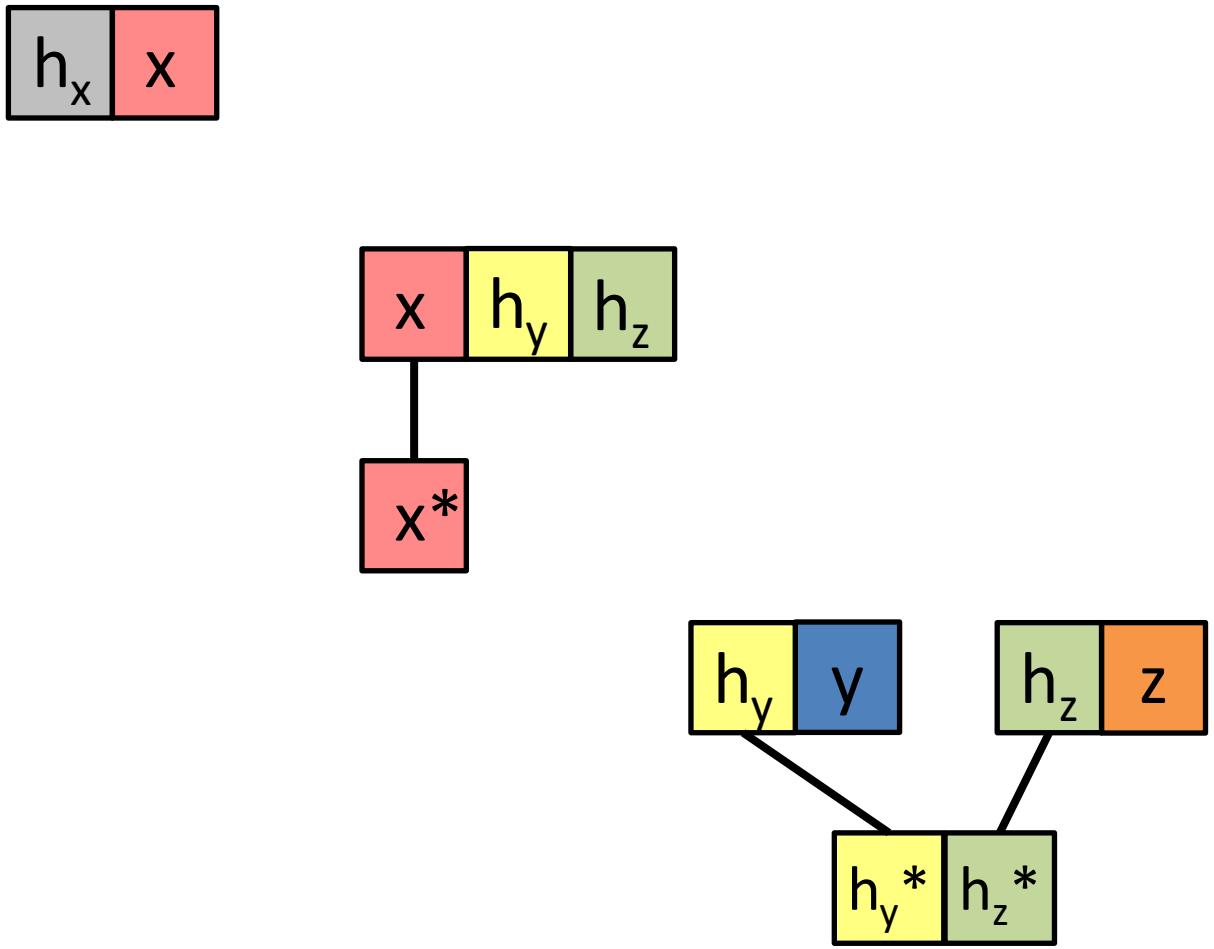

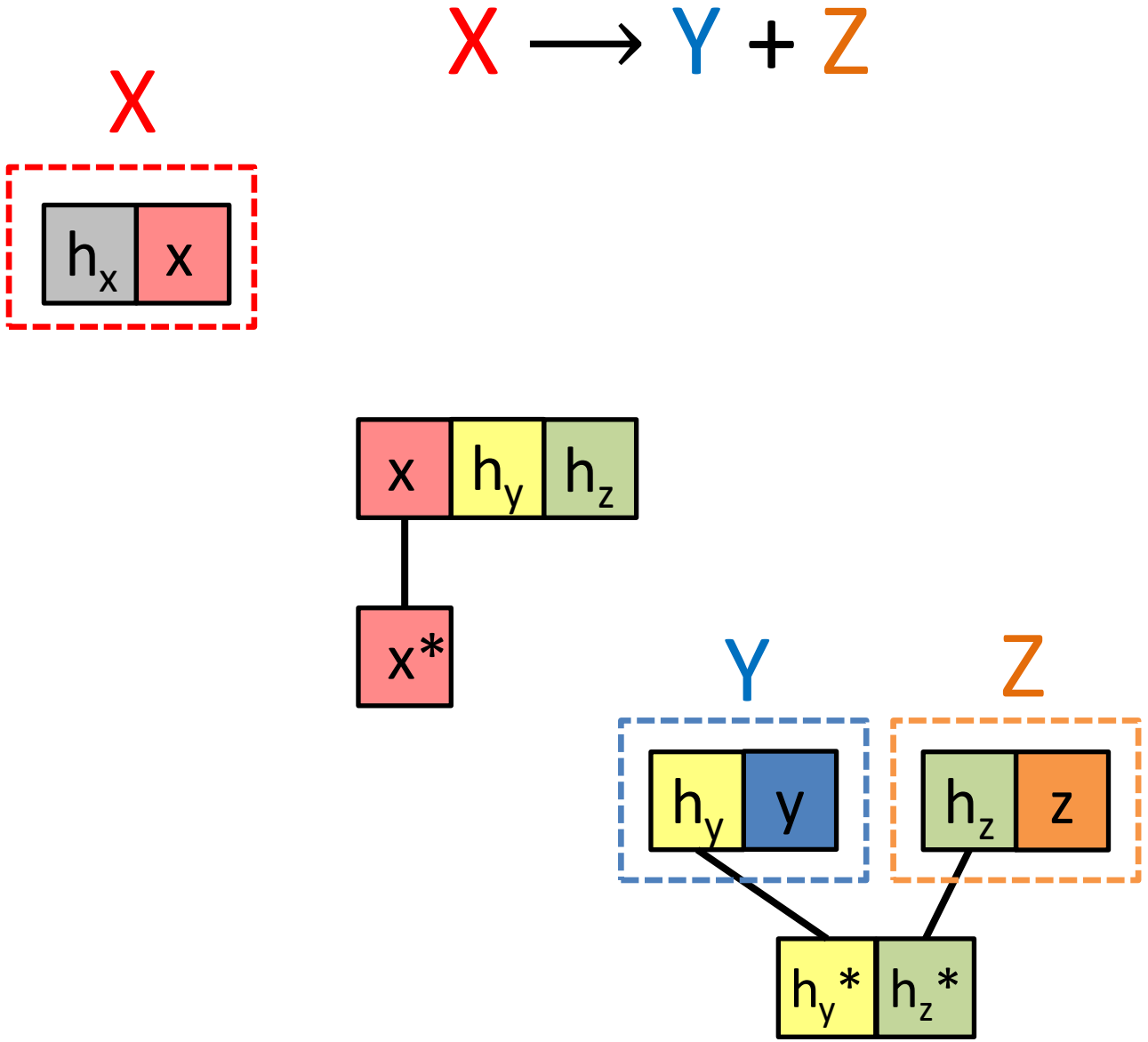
X ⟶ Y + Z
X
h_x
x
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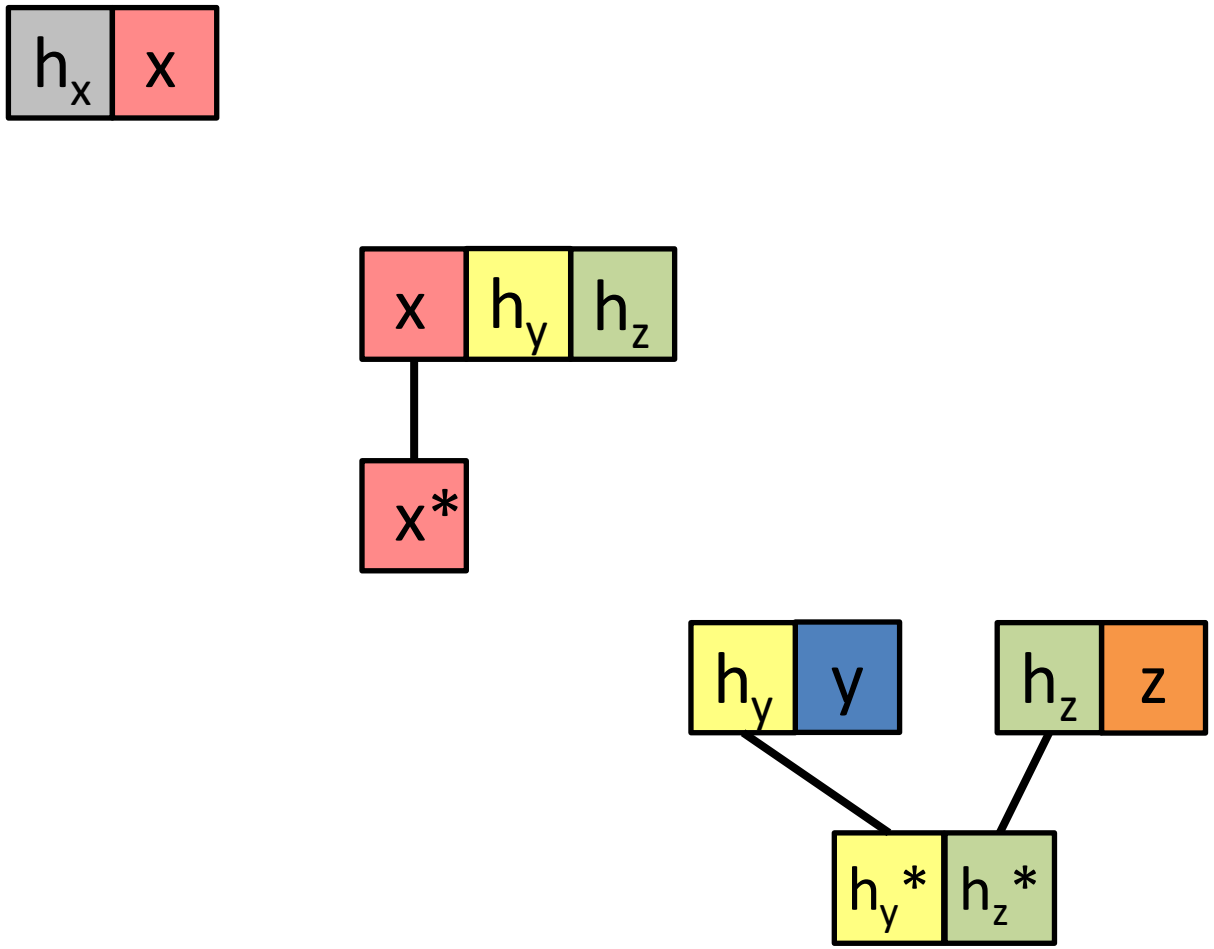
y
h_z
z
h_y*
h_z*

$$X \longrightarrow Y + Z$$



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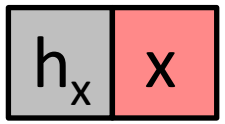
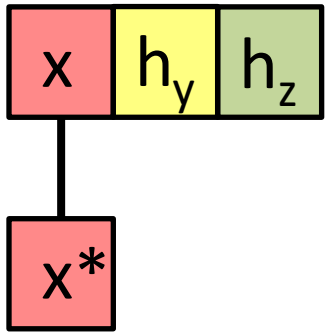
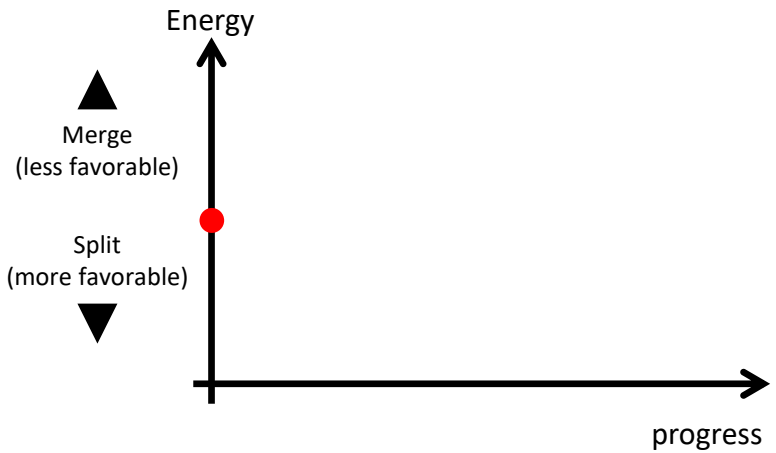
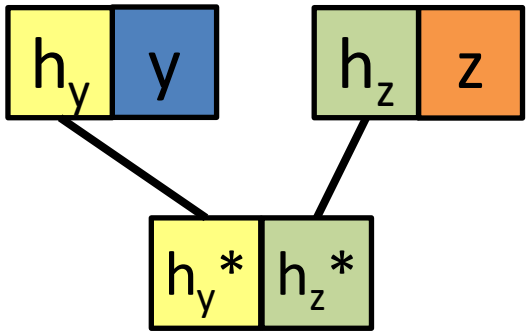
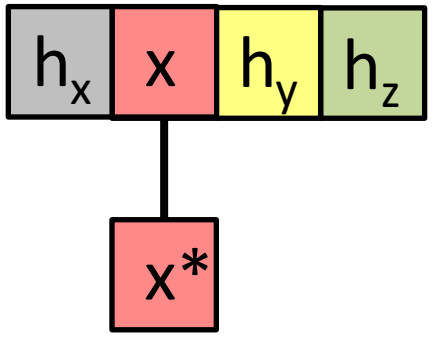


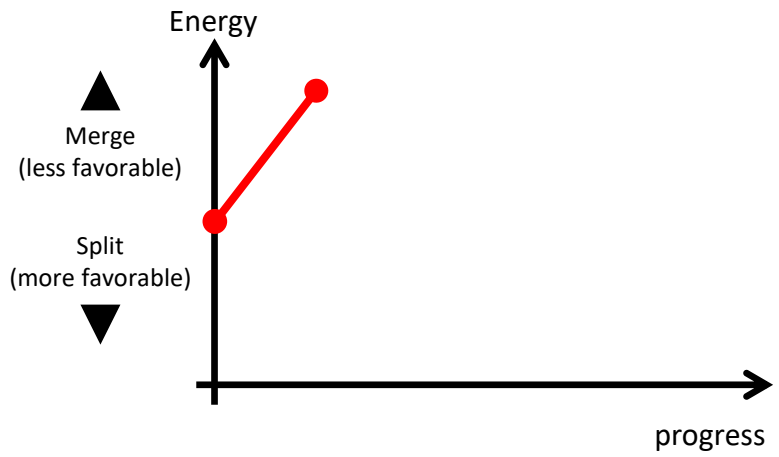


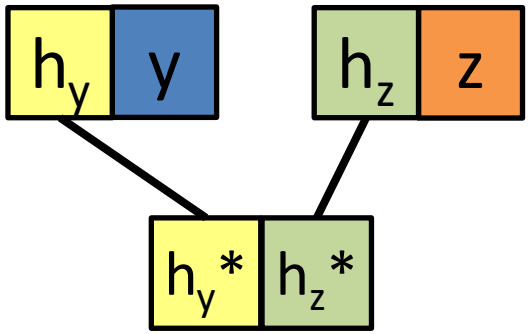




$$X \longrightarrow Y + Z$$







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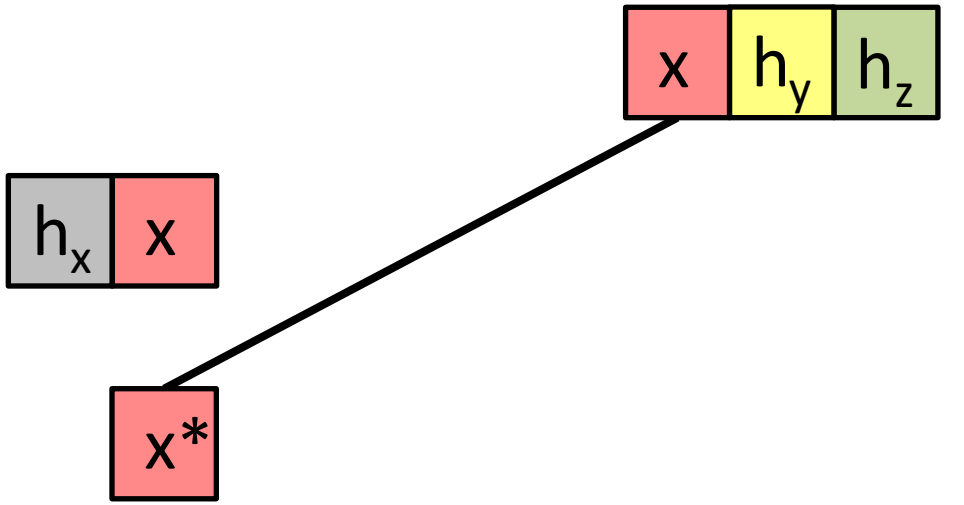

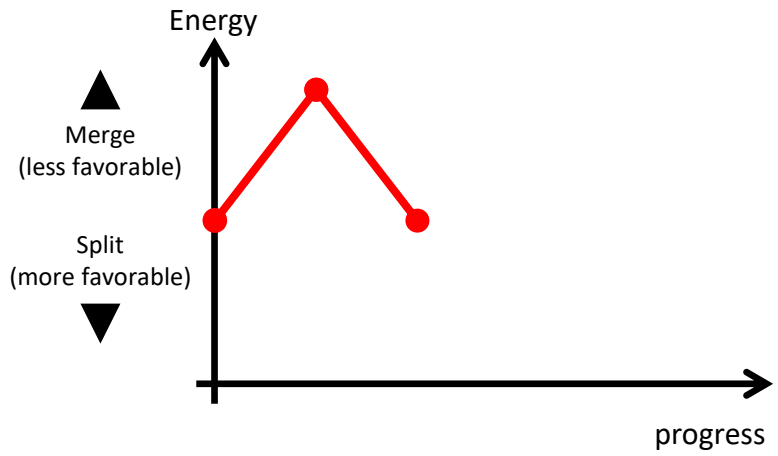

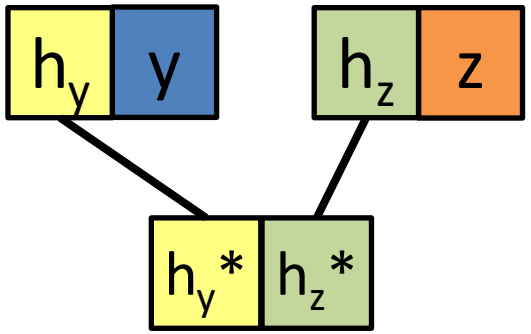

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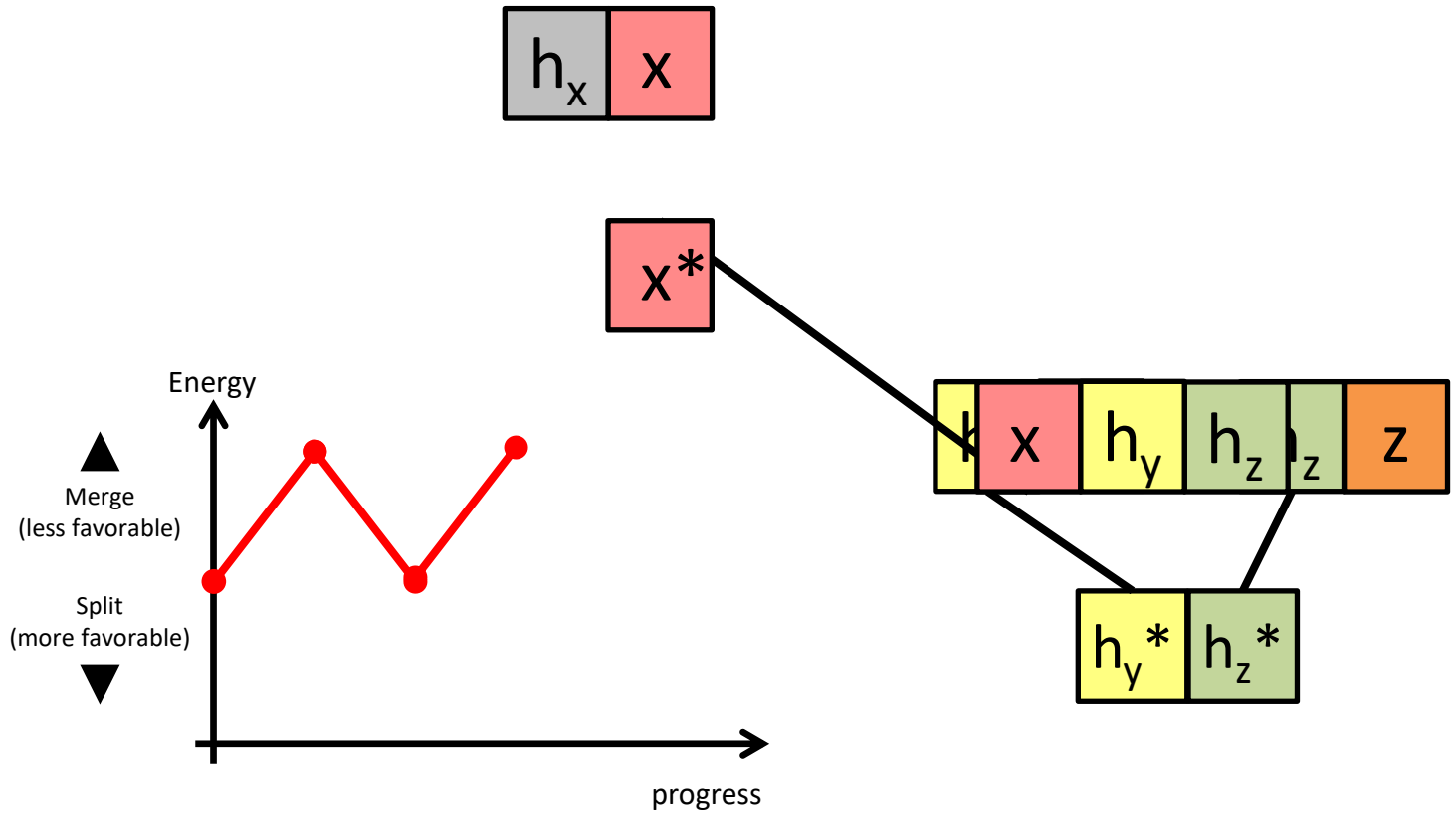

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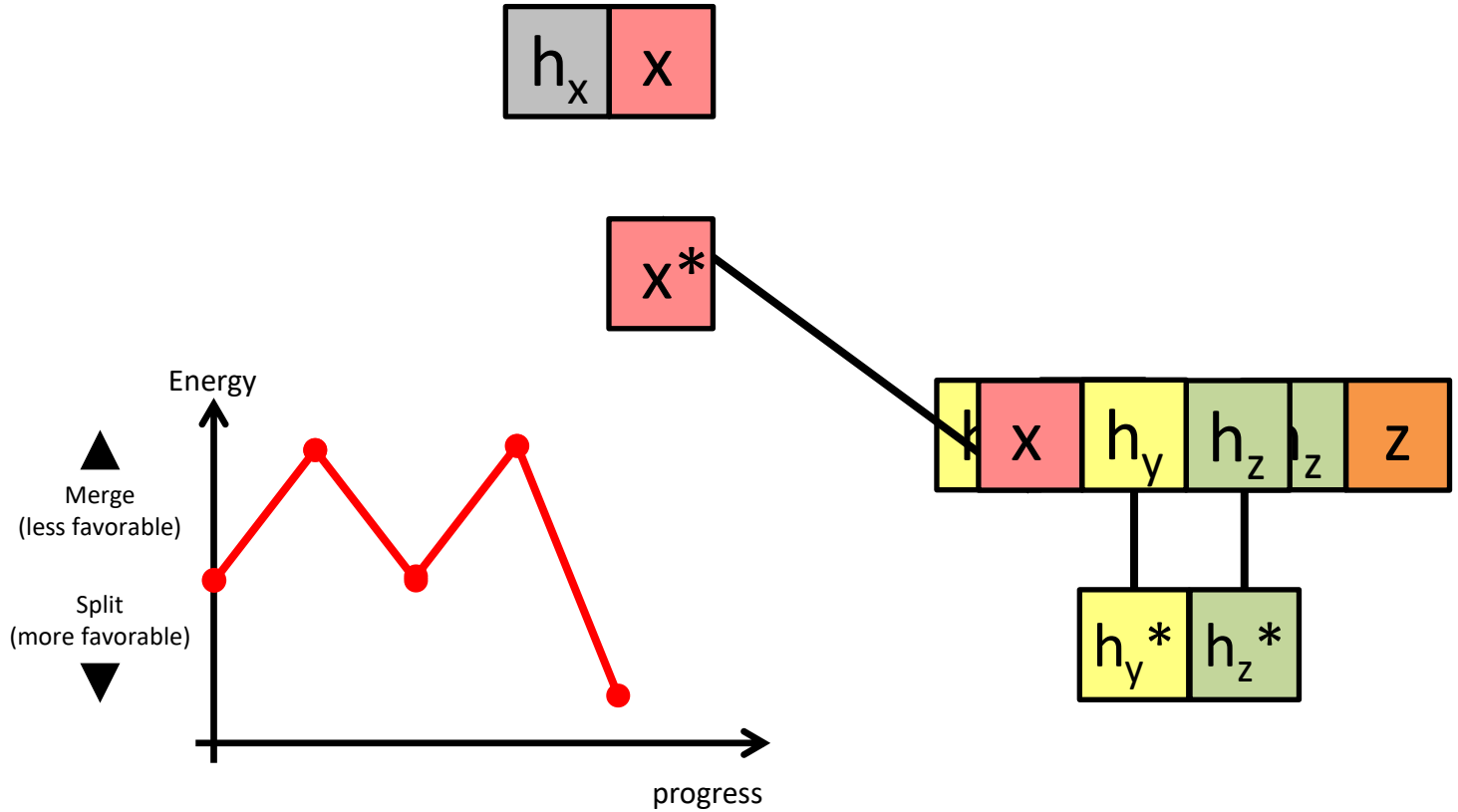

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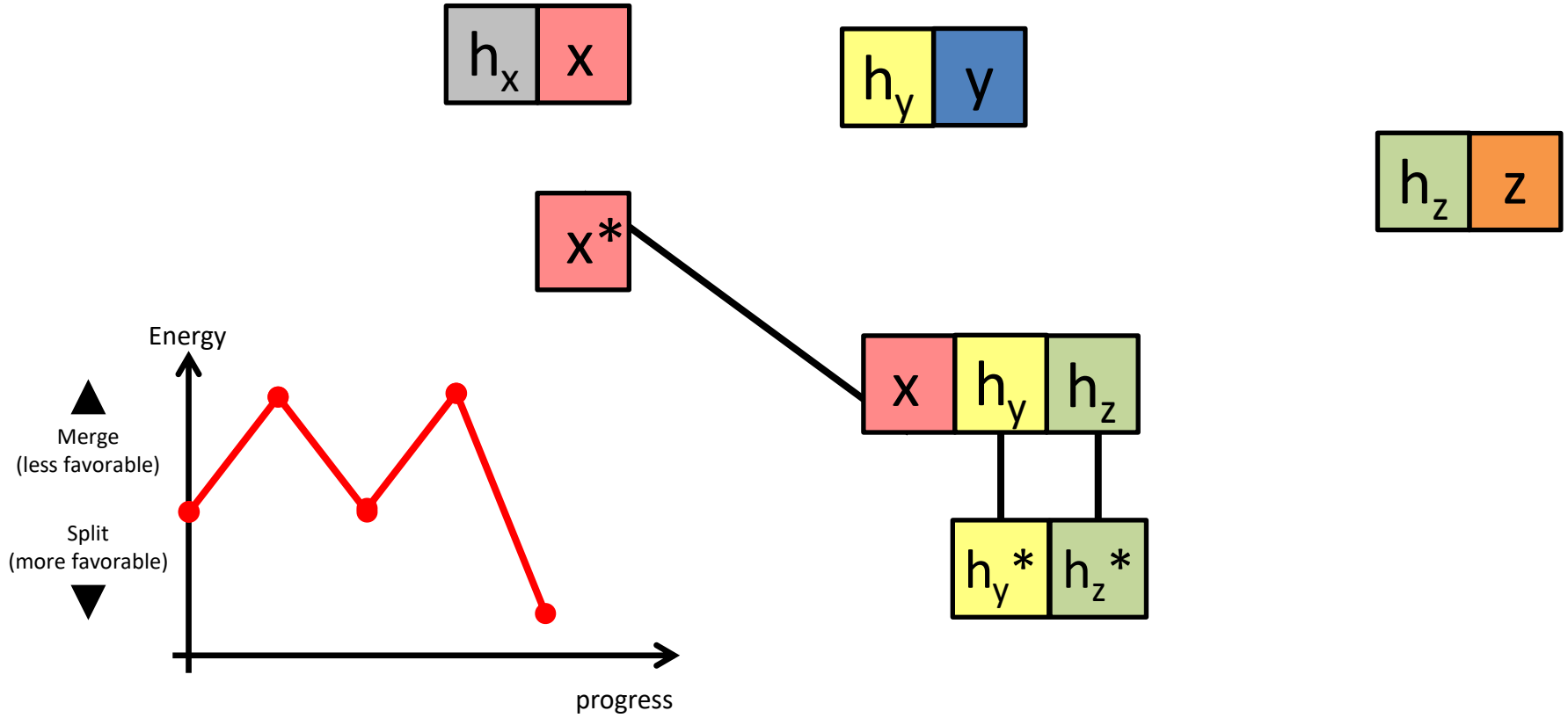
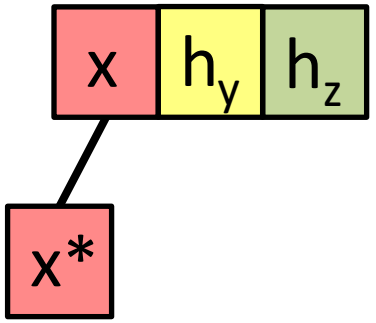
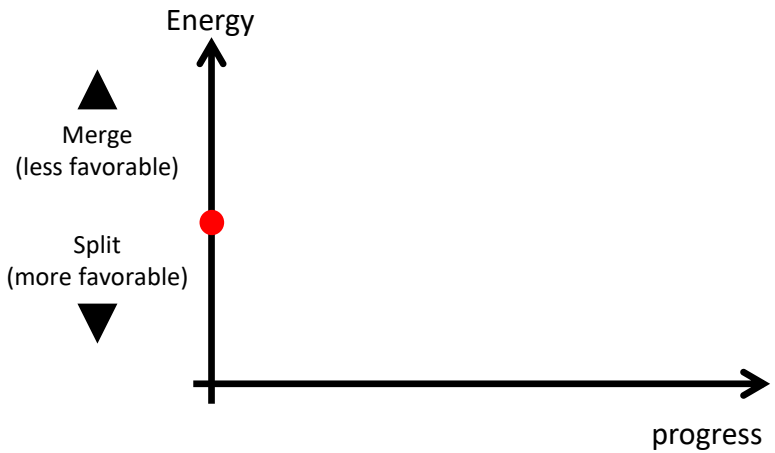
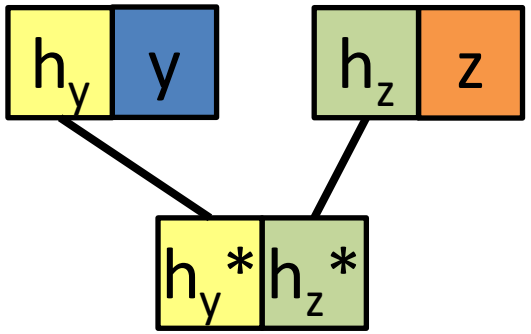


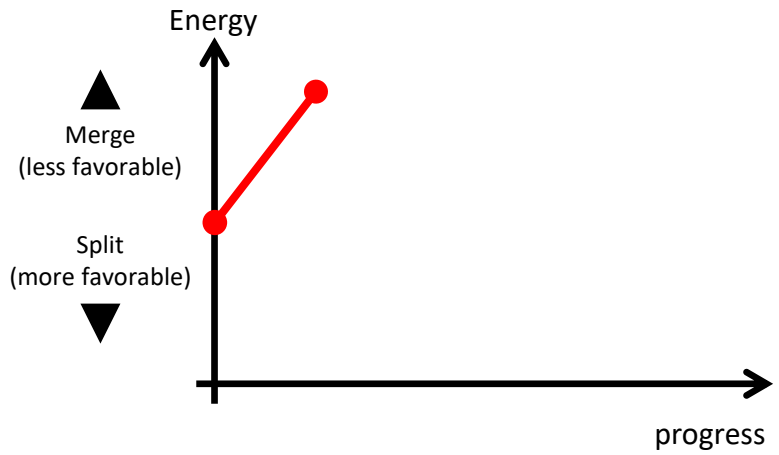
$$\emptyset \longrightarrow Y + Z$$

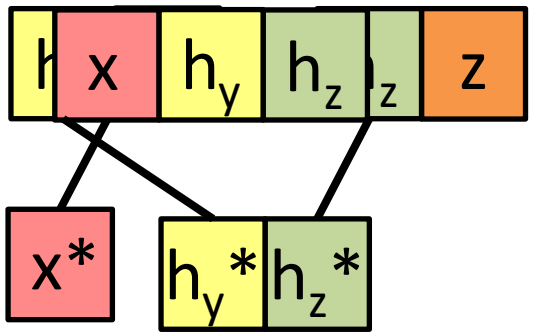






$$\emptyset \longrightarrow Y + Z$$





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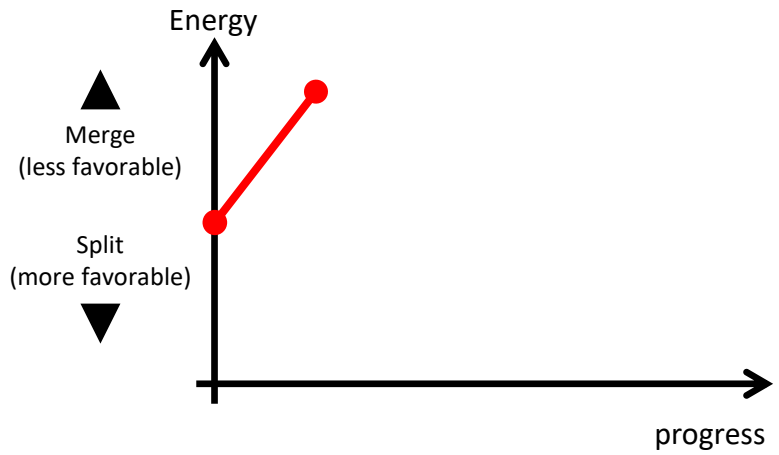
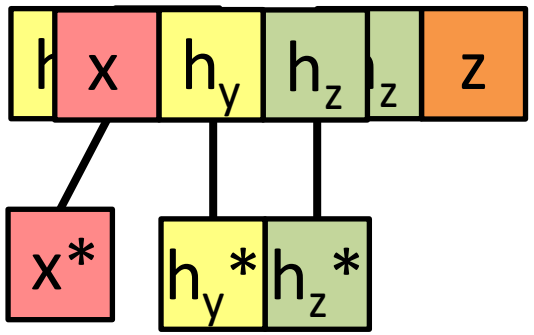
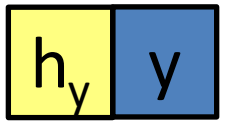
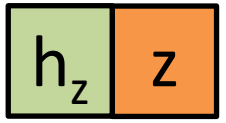


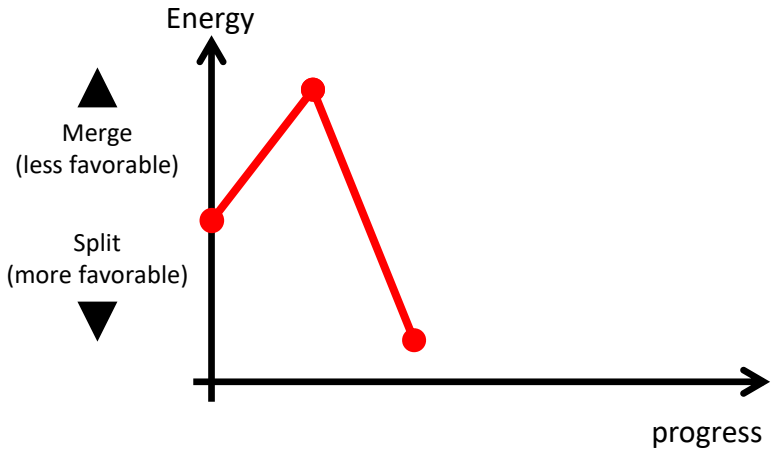


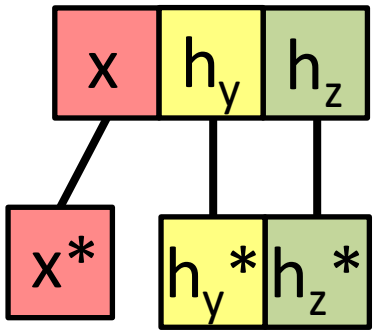
What causes leak "kinetically"?

$$\emptyset \longrightarrow Y + Z$$









Kinetic Binding Networks

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- Favorability is a combination of bond count and complex count

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[Keenan Breik, Cameron Chalk, David Doty, David Haley, David Soloveichik. *Programming Substrate-Independent Kinetic Barriers with Thermodynamic Binding Networks*. Computational Methods in Systems Biology 2018]

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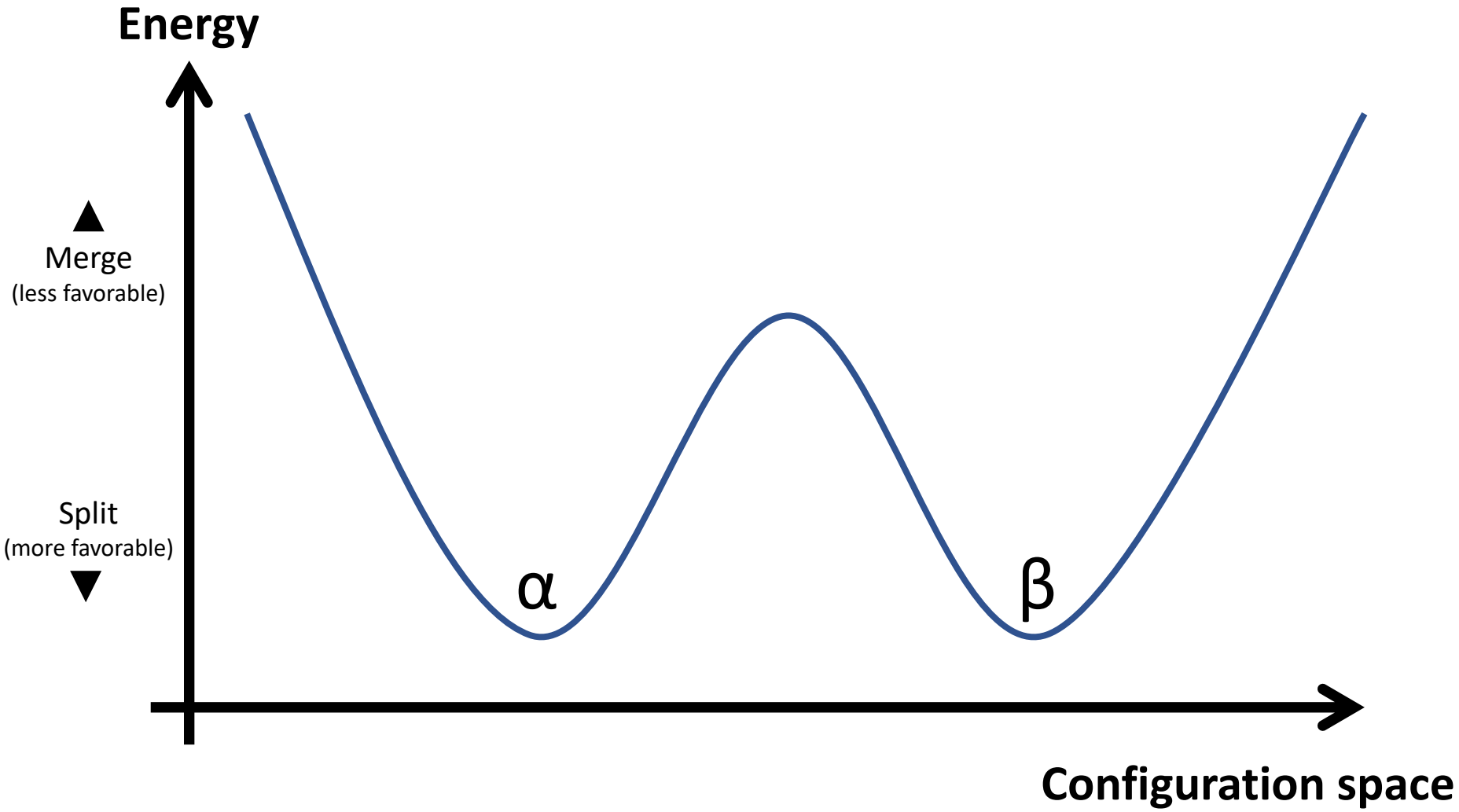
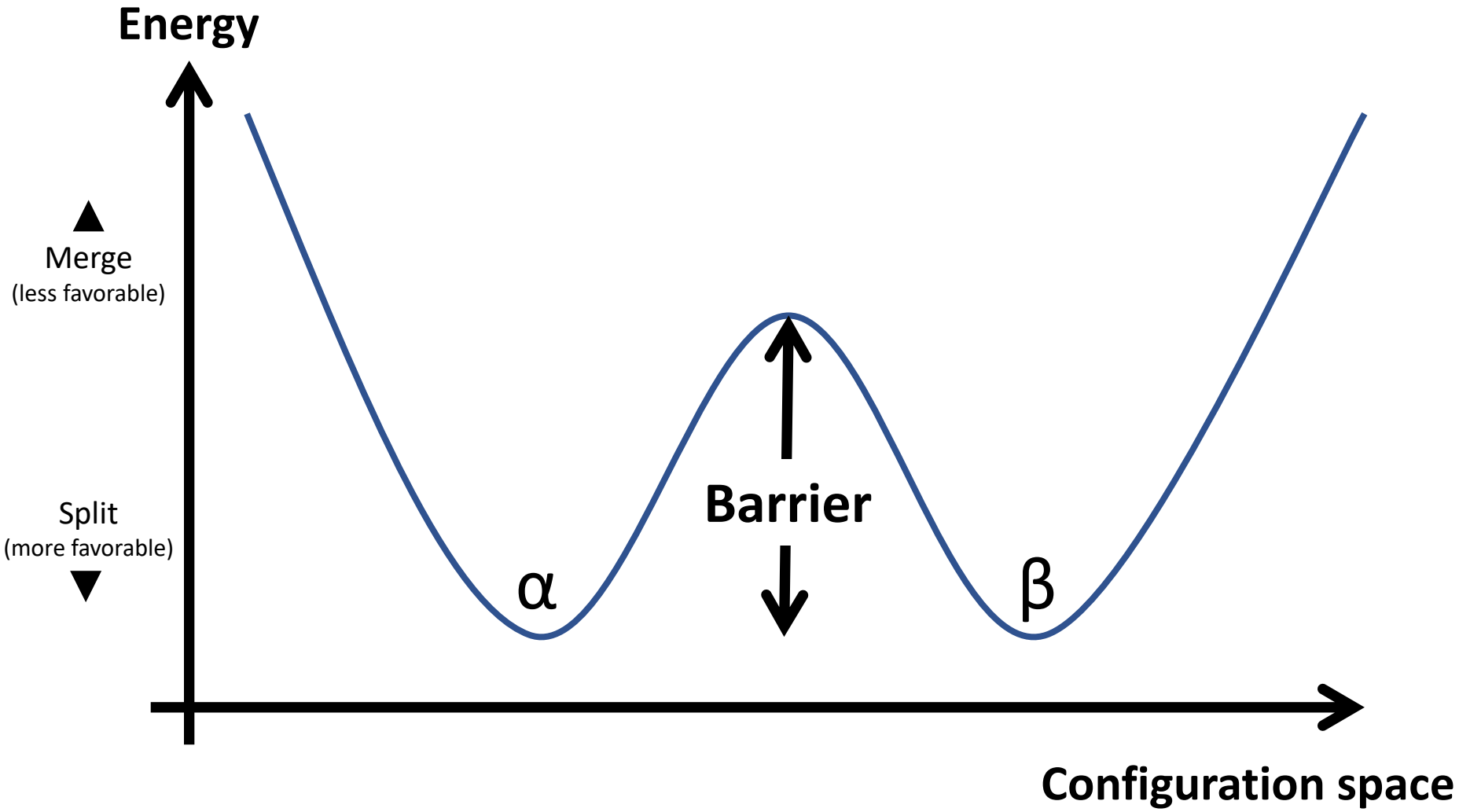
Since all saturated configurations have an equal number of bonds, we can focus solely on the number of complexes

[Keenan Breik, Cameron Chalk, David Doty, David Haley, David Soloveichik. *Programming Substrate-Independent Kinetic Barriers with Thermodynamic Binding Networks*. Computational Methods in Systems Biology 2018]

Large Energy Barriers



Large Energy Barriers



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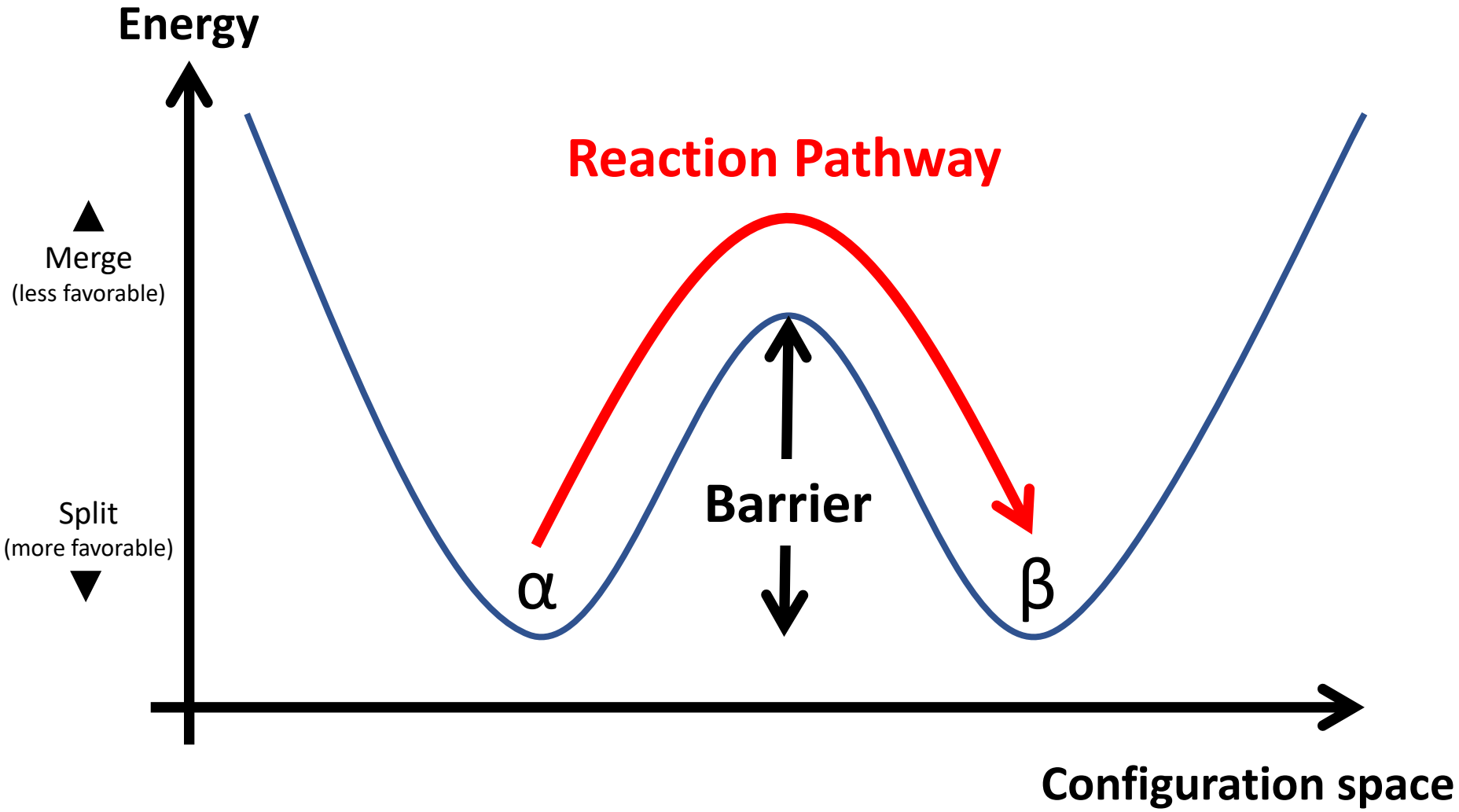
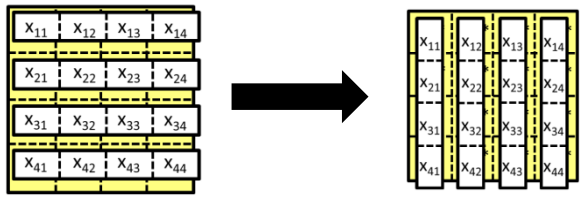
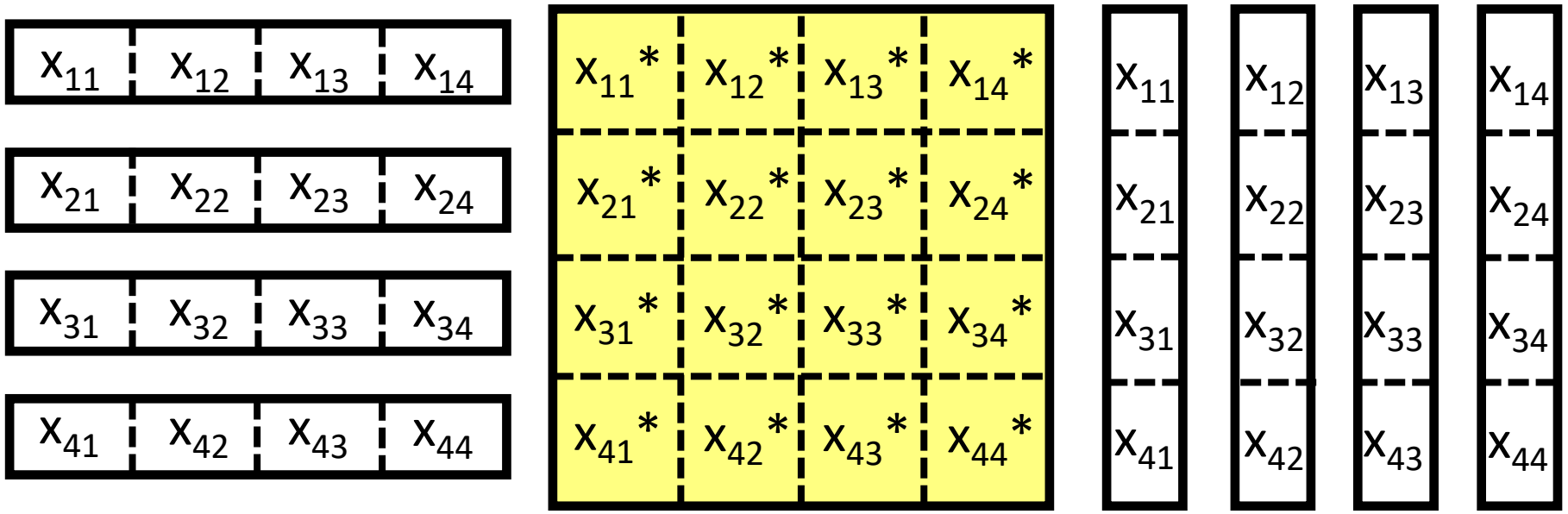


A Network with a Programmable Energy Barrier





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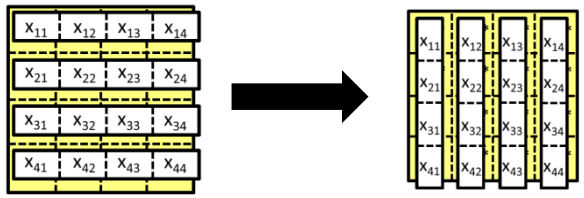

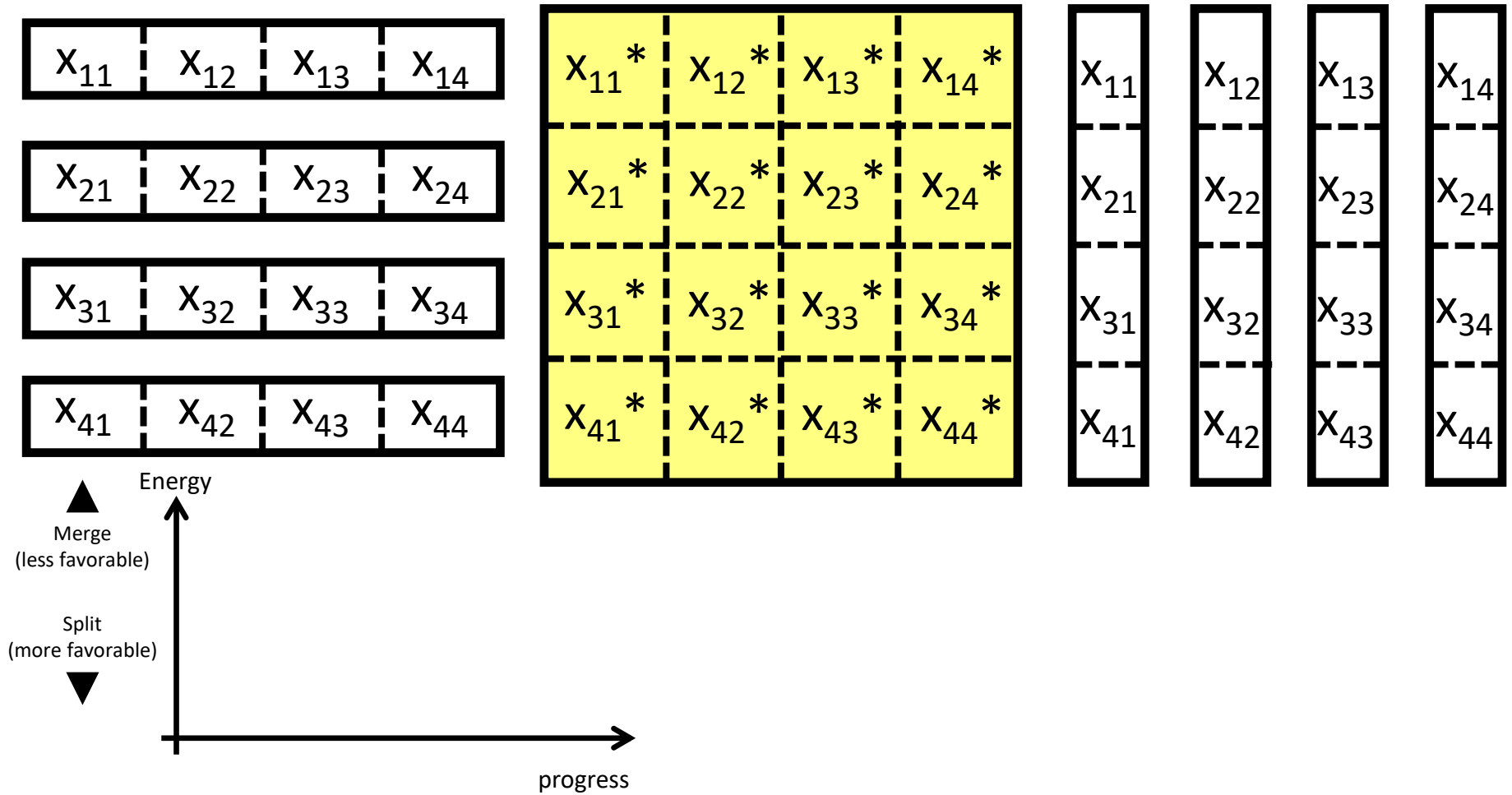

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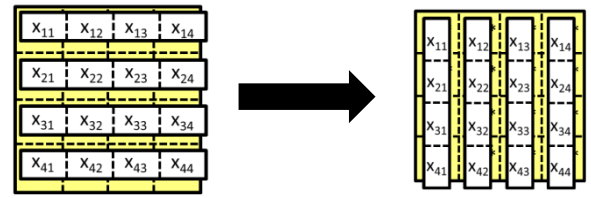

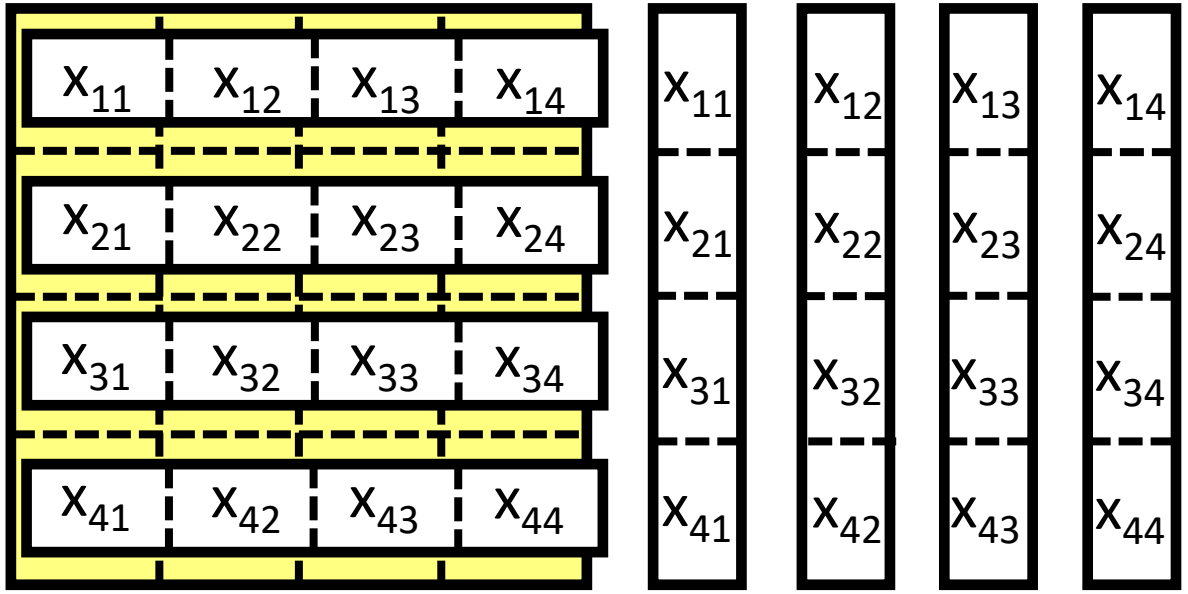

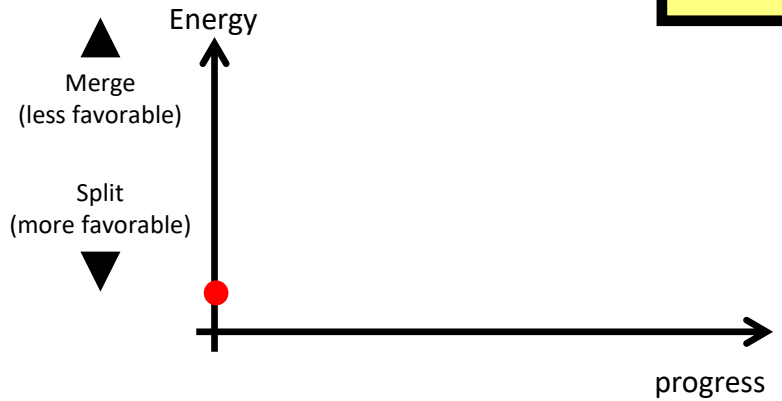

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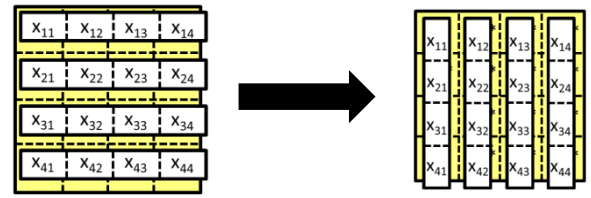

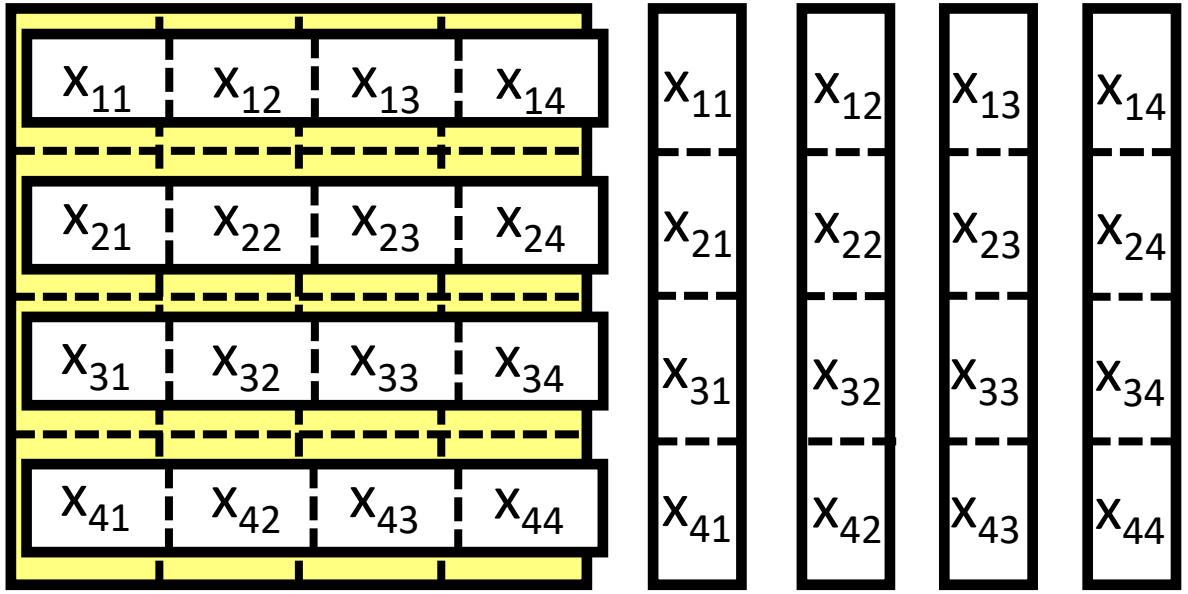

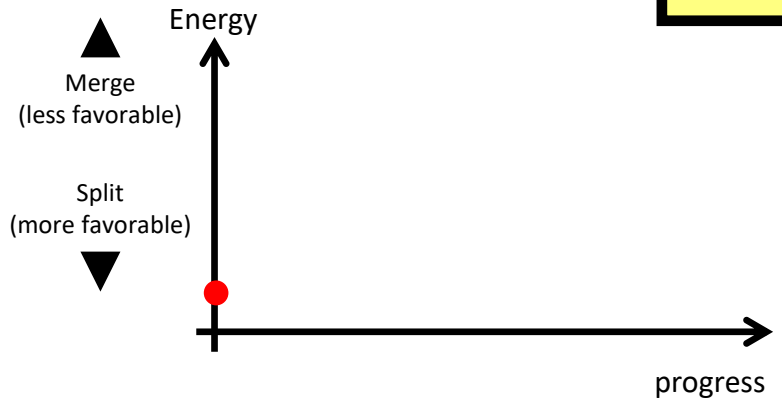

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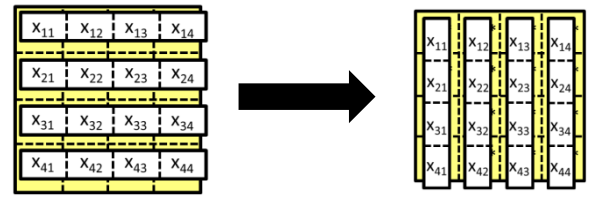

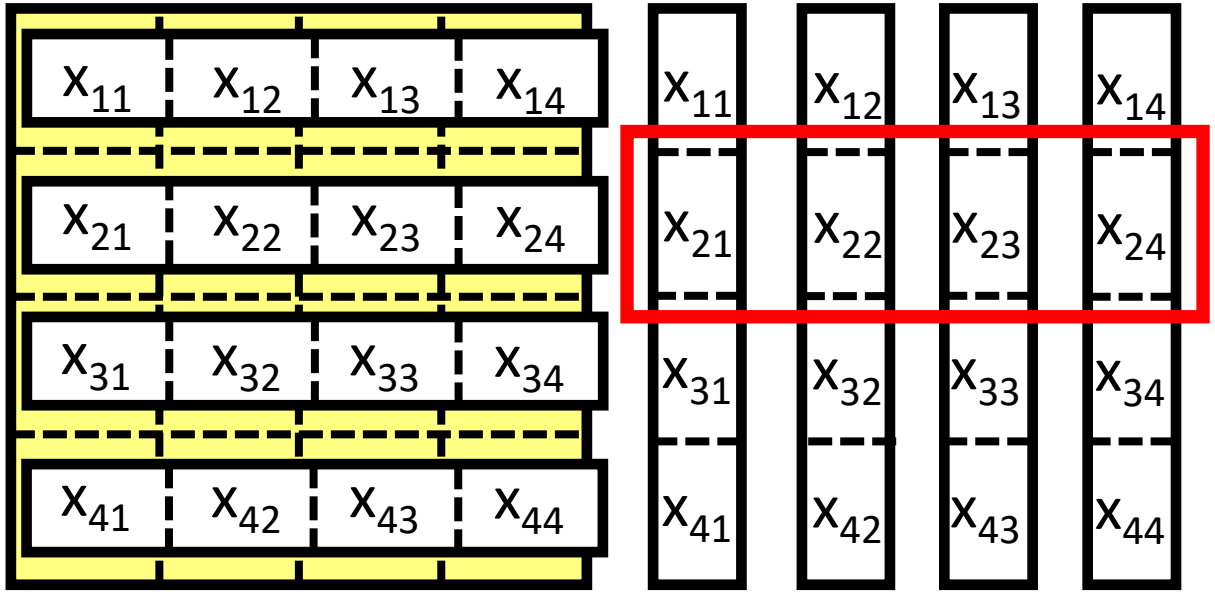

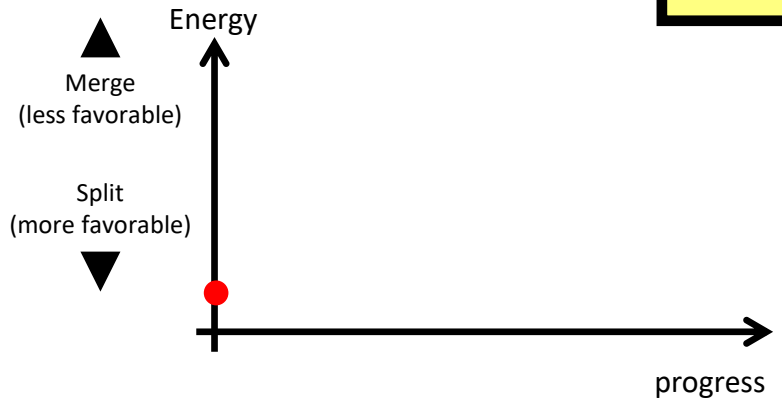

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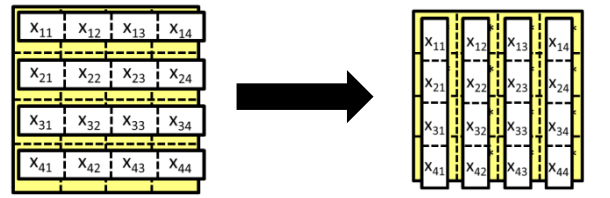

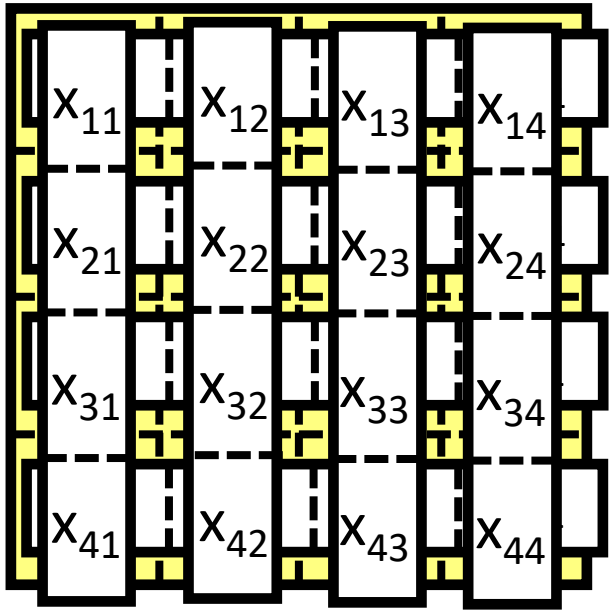

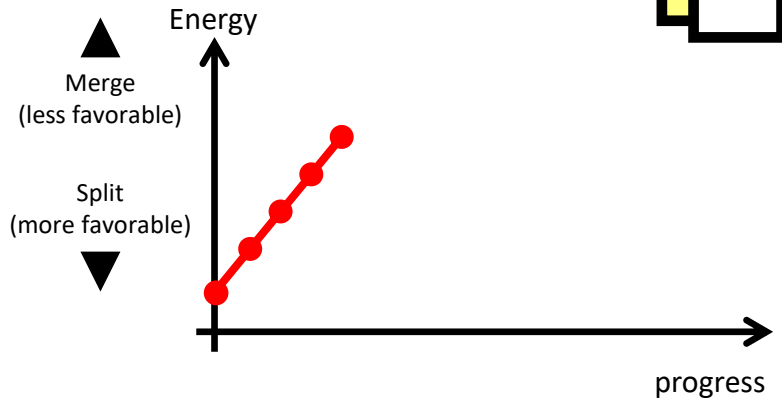

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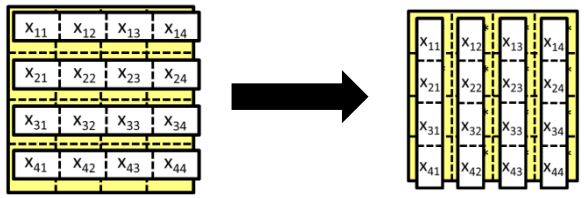
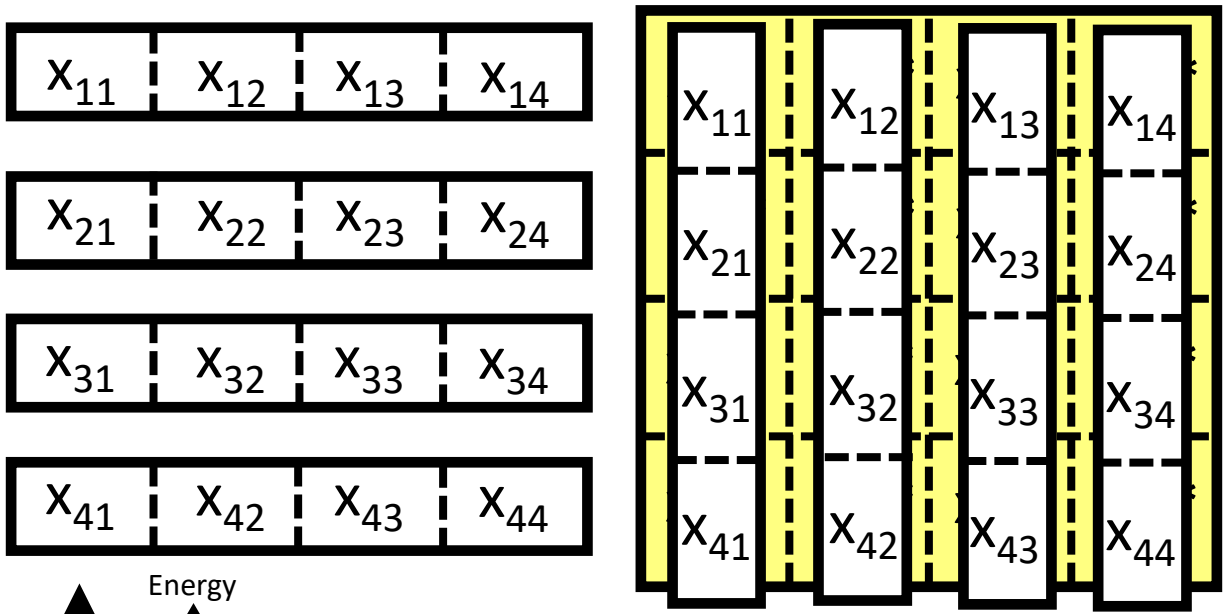
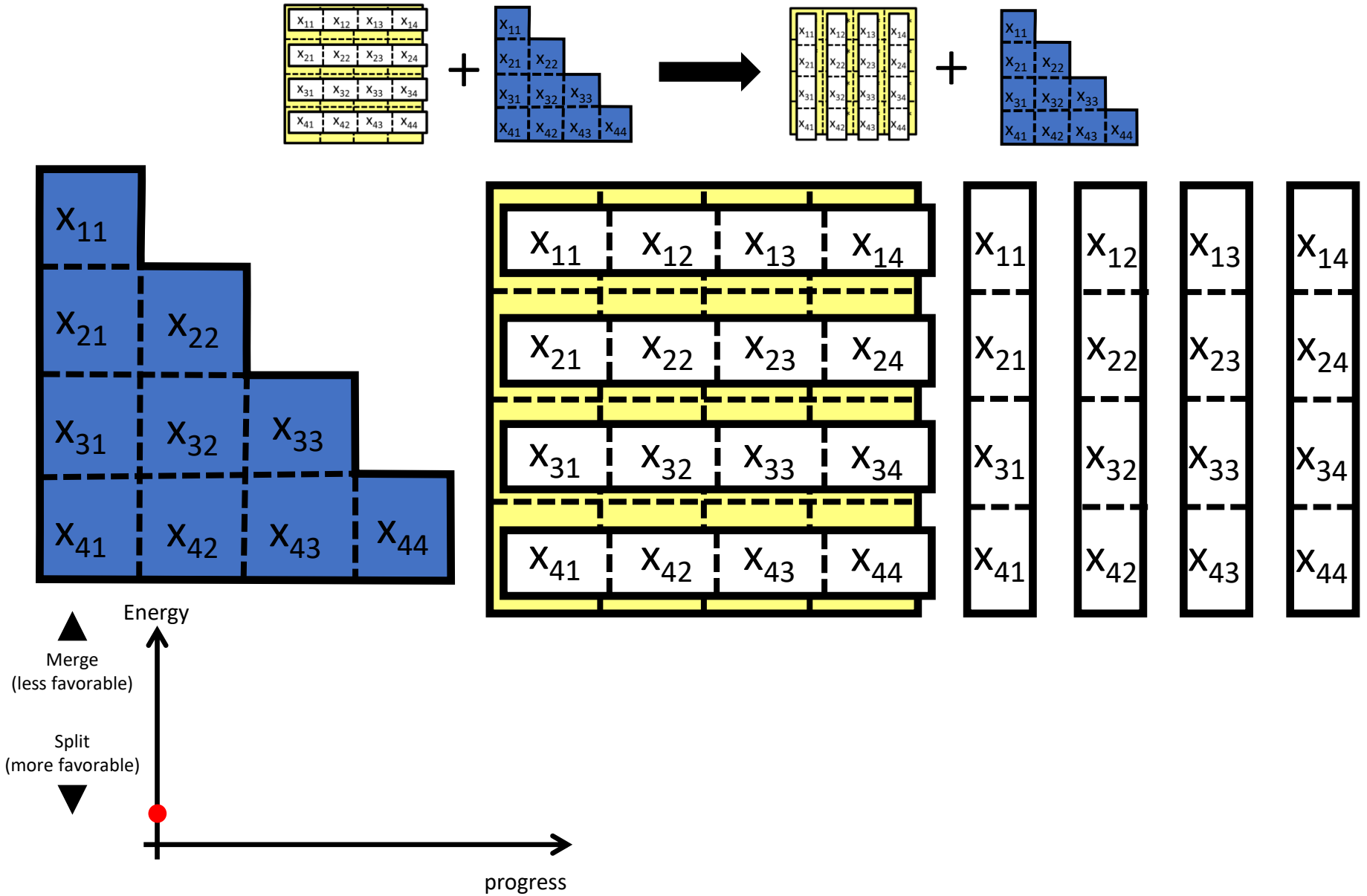
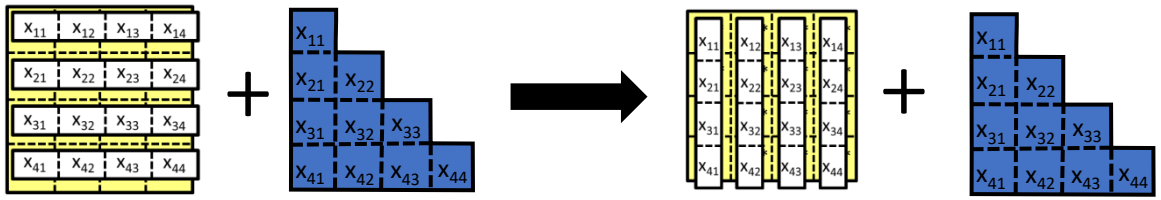


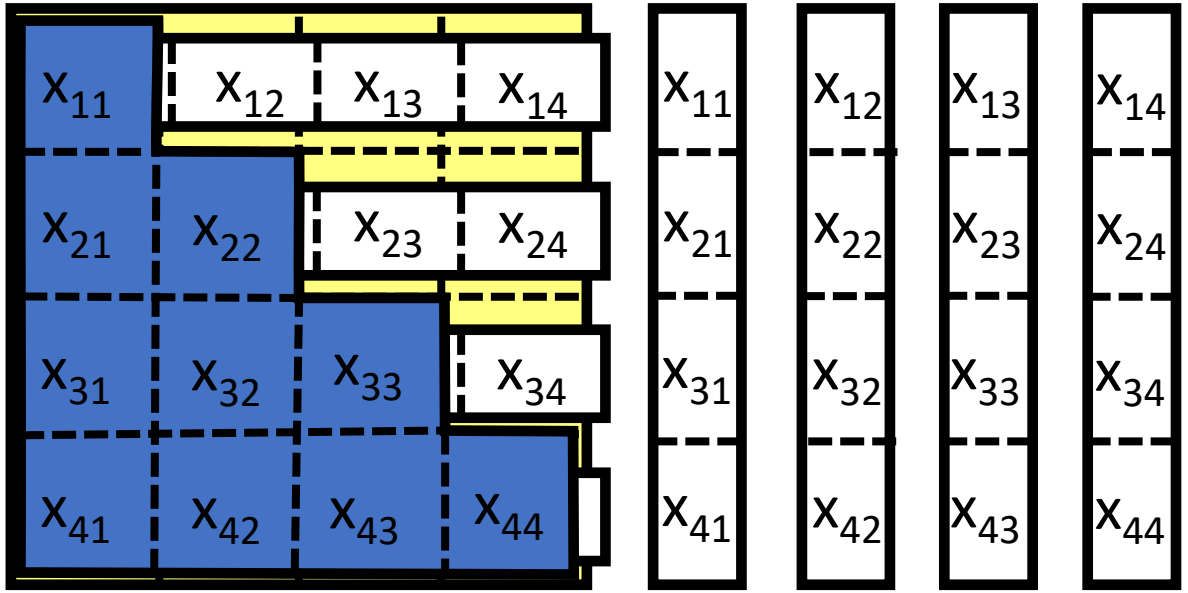


Catalysis


Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis


x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44


x11 x12 x13 x14
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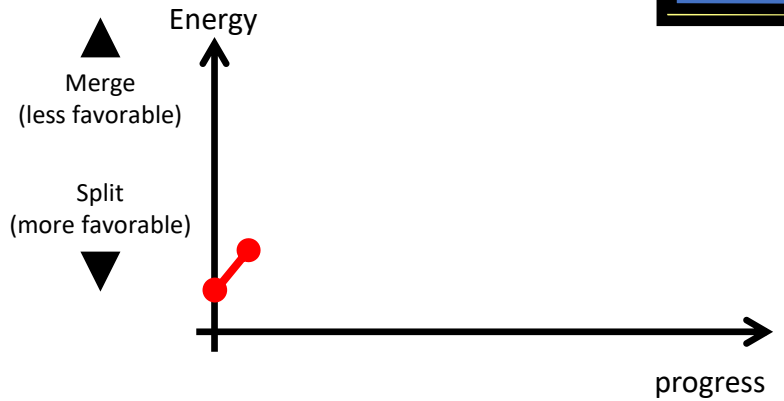
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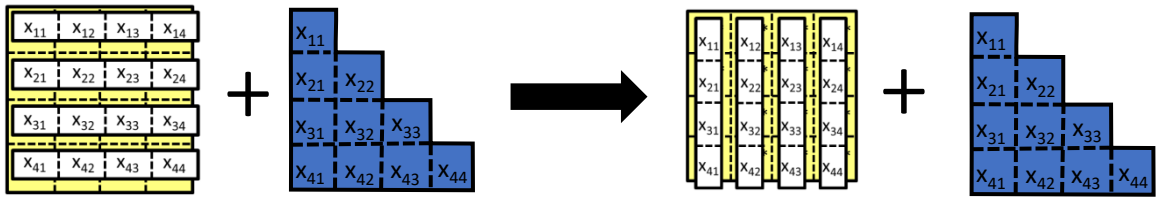
x11 x12 x13 x14
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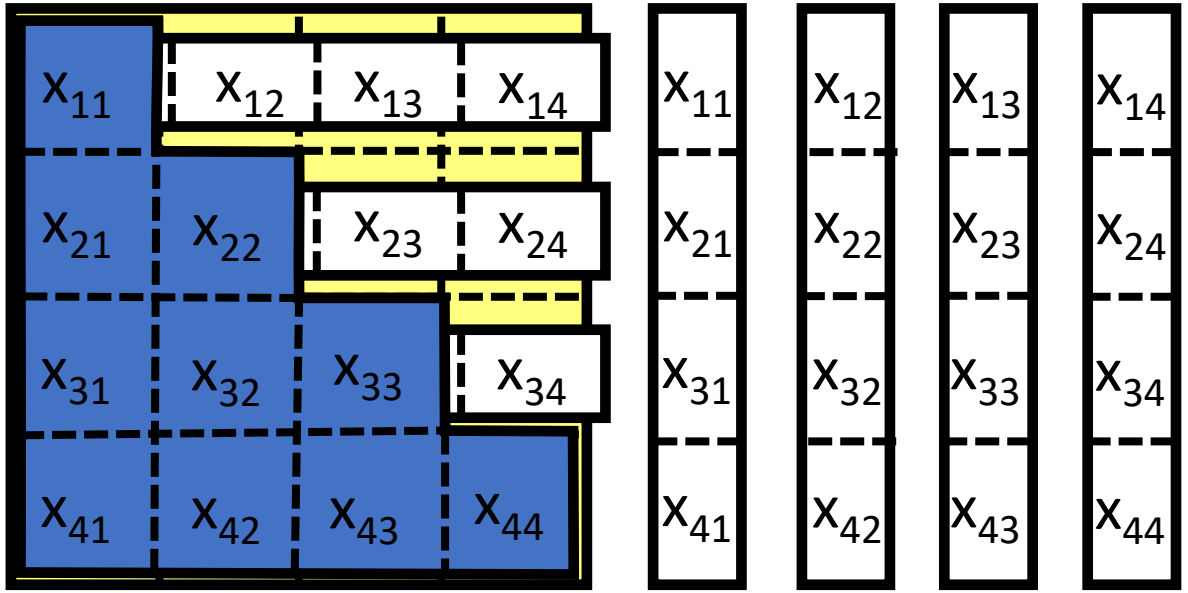
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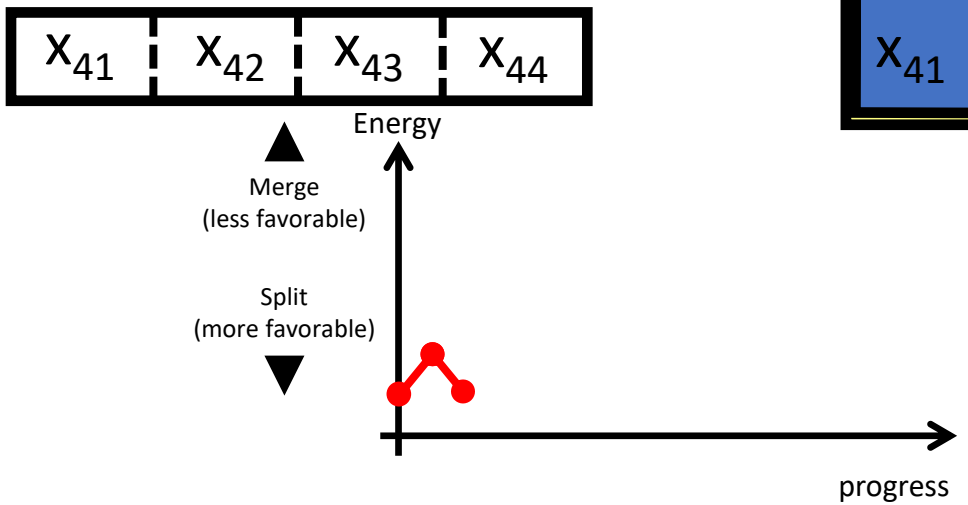
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44


x41 x42 x43 x44
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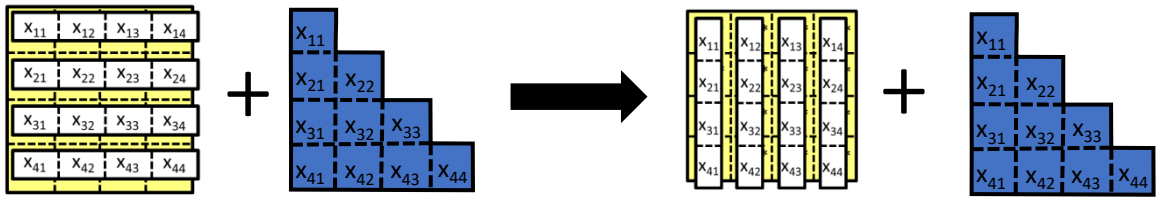
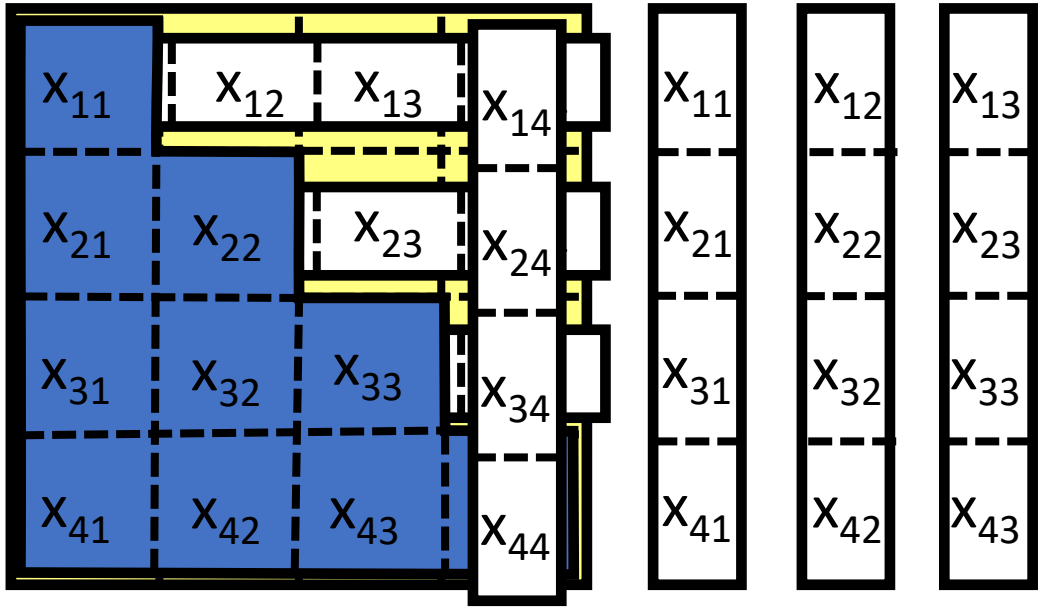
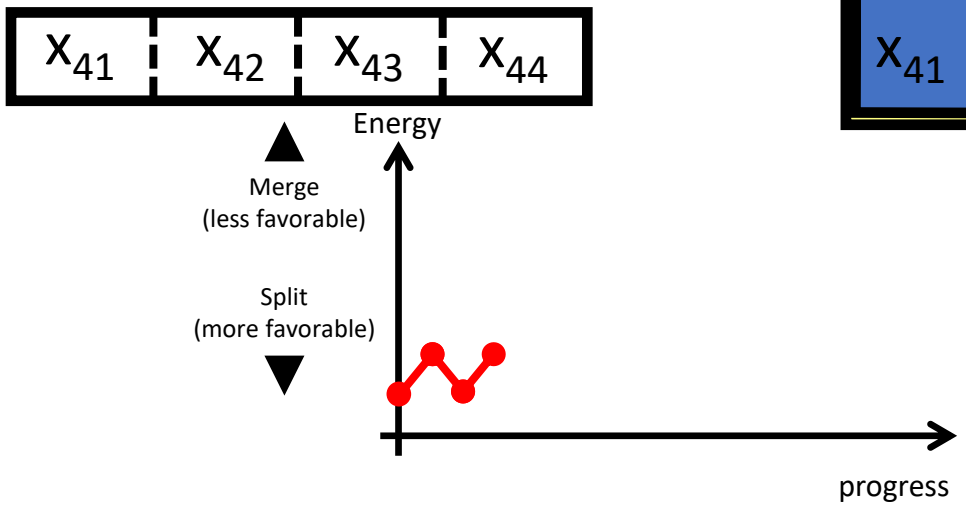
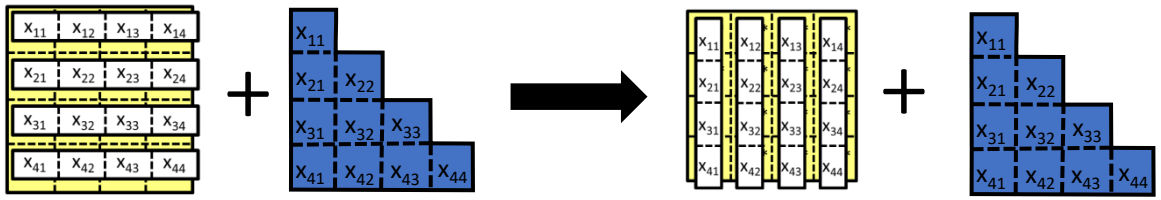
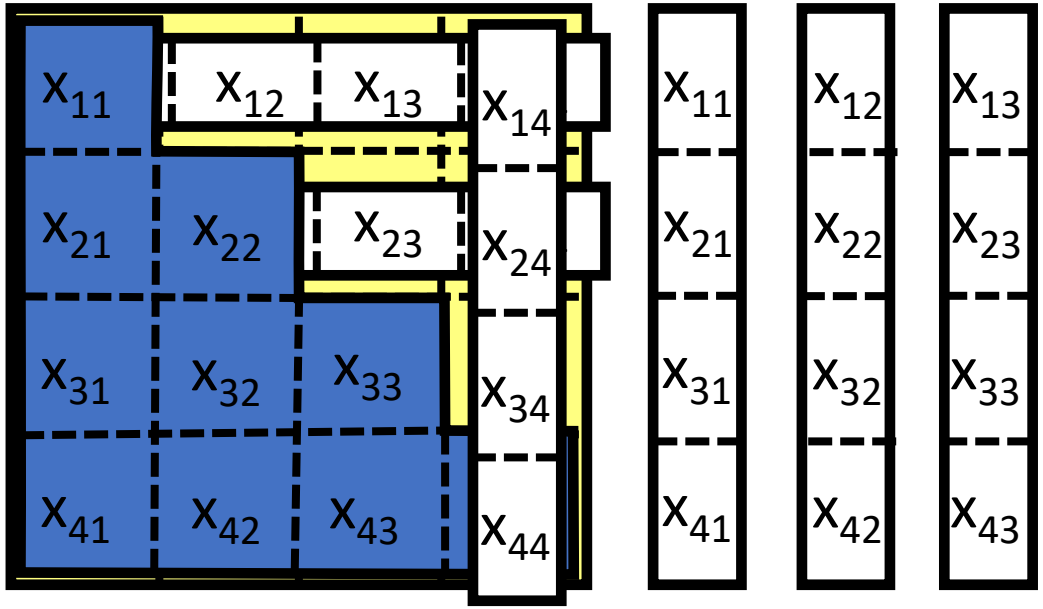

x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
x11
x21 x22
x31 x32 x33
x41 x42 x43 x44
x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
x11
x21 x22
x31 x32 x33
x41 x42 x43 x44


x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
x11 x12 x13
x21 x22 x23
x31 x32 x33
x41 x42 x43
x14 x24 x34 x44
x11 x21 x31 x41
x12 x22 x32 x42
x13 x23 x33 x43


x41 x42 x43 x44
Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis


x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
+
x11
x21 x22
x31 x32 x33
x41 x42 x43 x44
x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
+
x11
x21 x22
x31 x32 x33
x41 x42 x43 x44


x11 x12 x13 x14
x21 x22 x23 x24
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x41 x42 x43 x44
x11 x12 x13
x21 x22 x23
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x21 x22 x23
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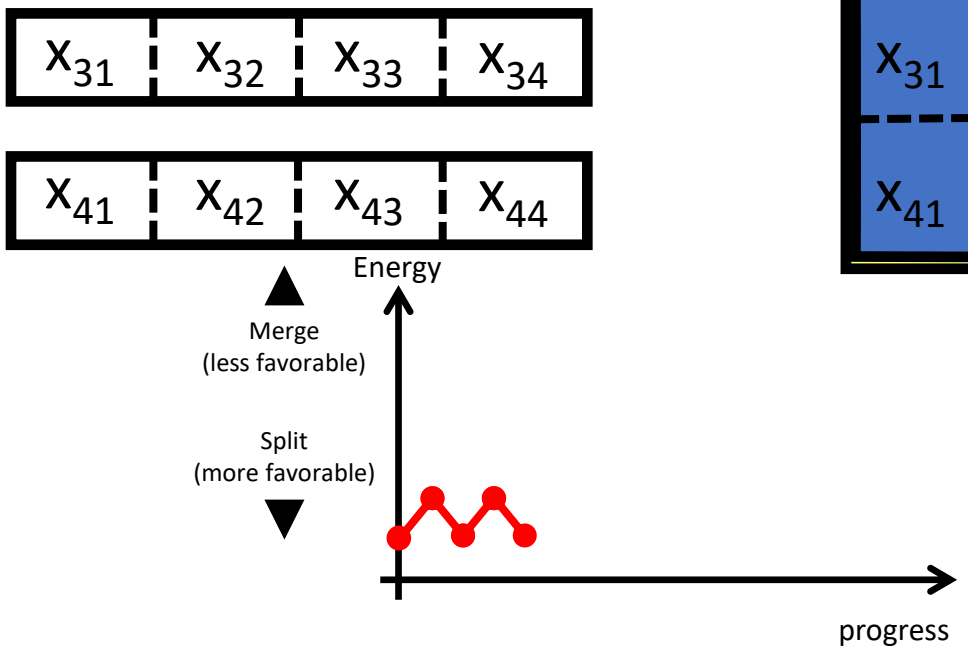
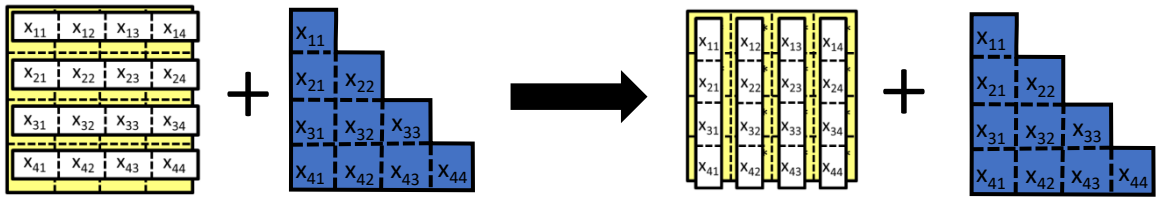
x41 x42 x43


x31 x32 x33 x34
x41 x42 x43 x44
Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis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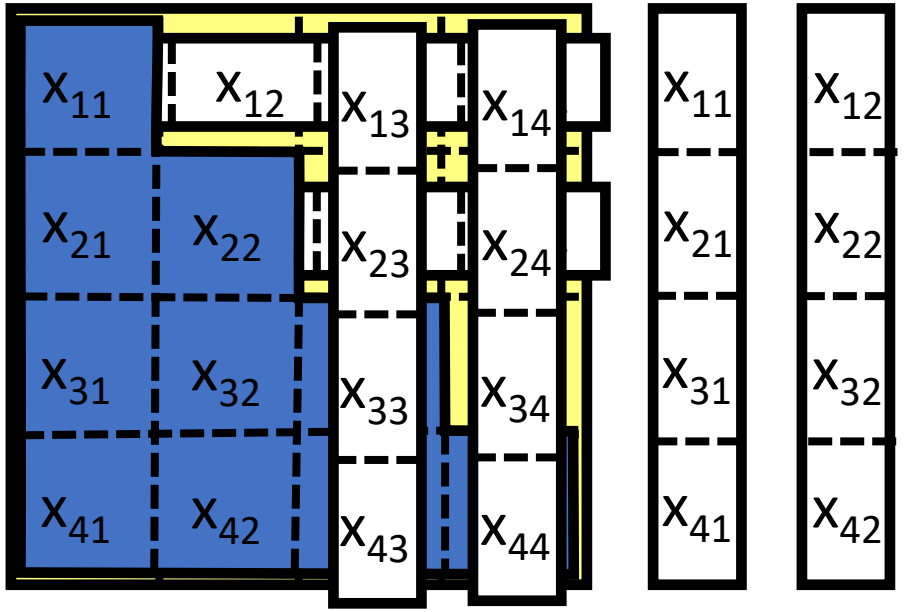
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44


x11 x12 x13 x14
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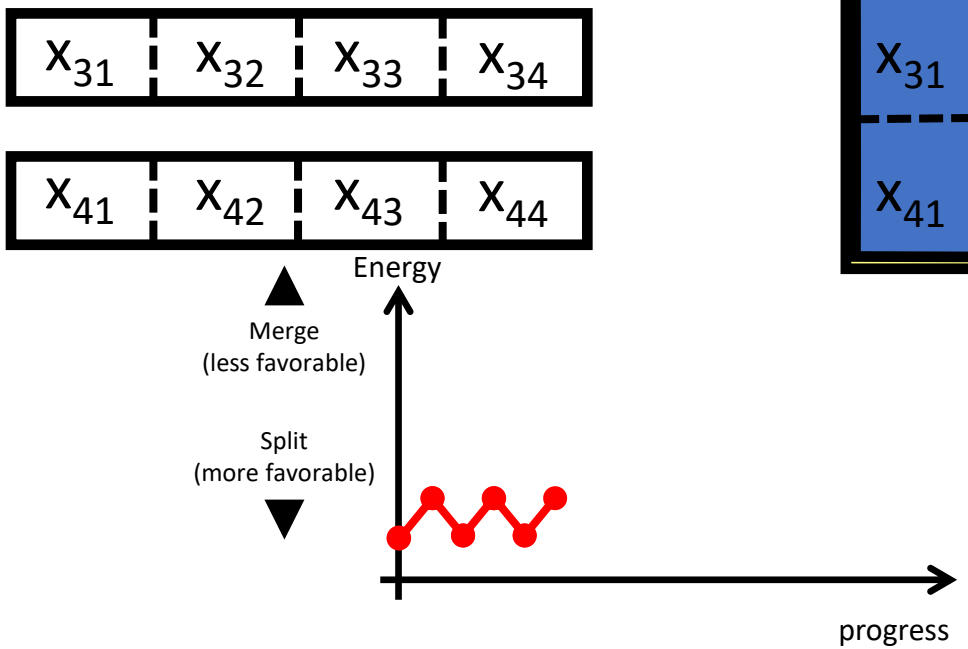
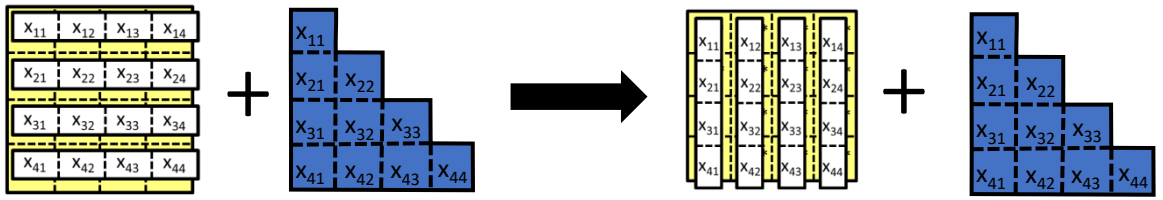
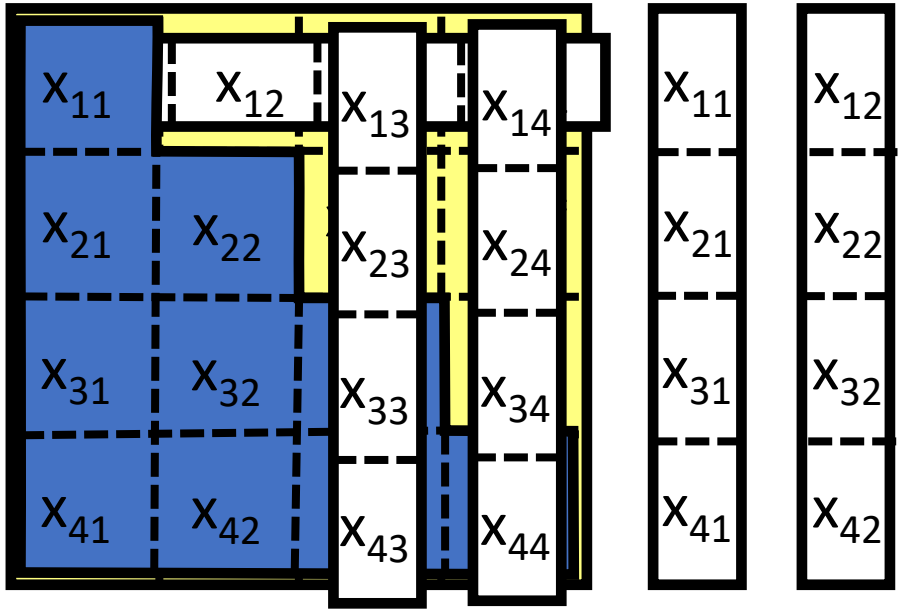
x11 x12
x21 x22
x31 x32
x41 x42


x31 x32 x33 x34
x41 x42 x43 x44
Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis


x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44


x11 x12 x13 x14
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x11 x12
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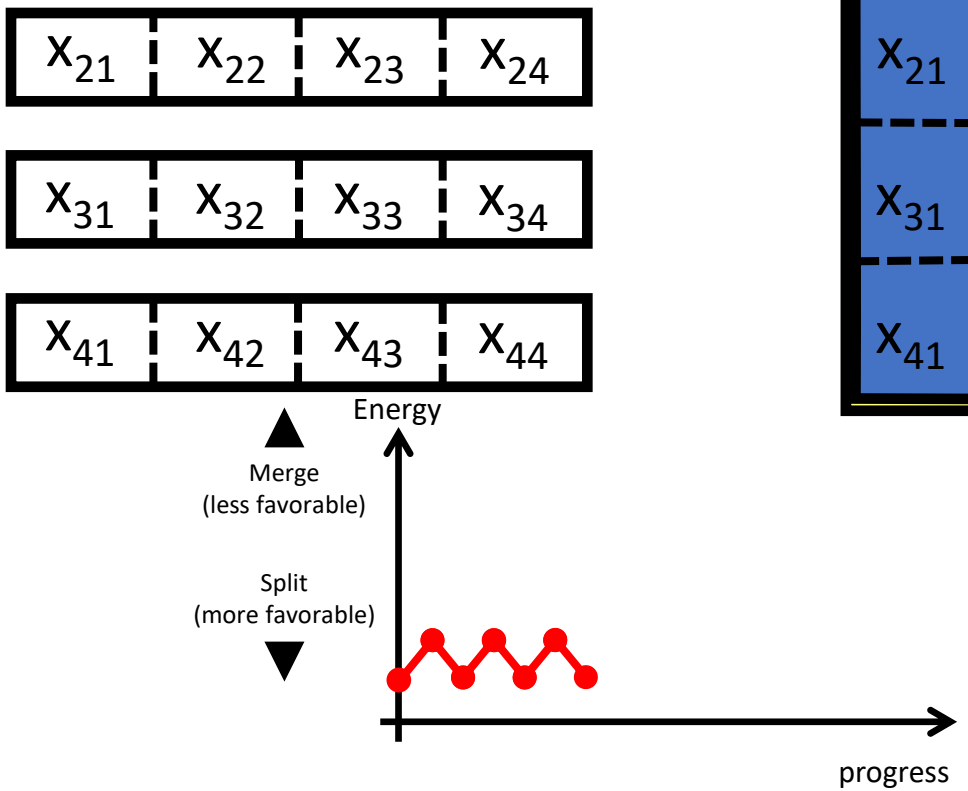
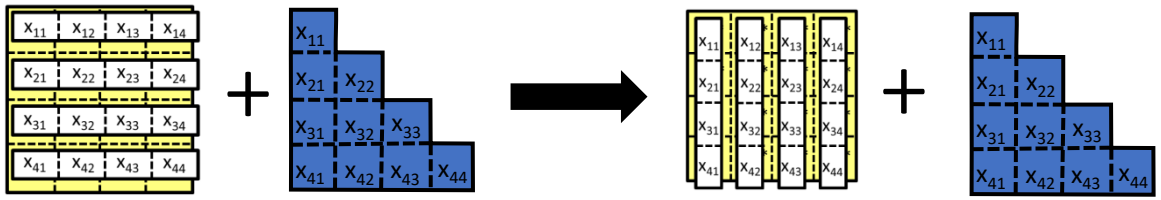
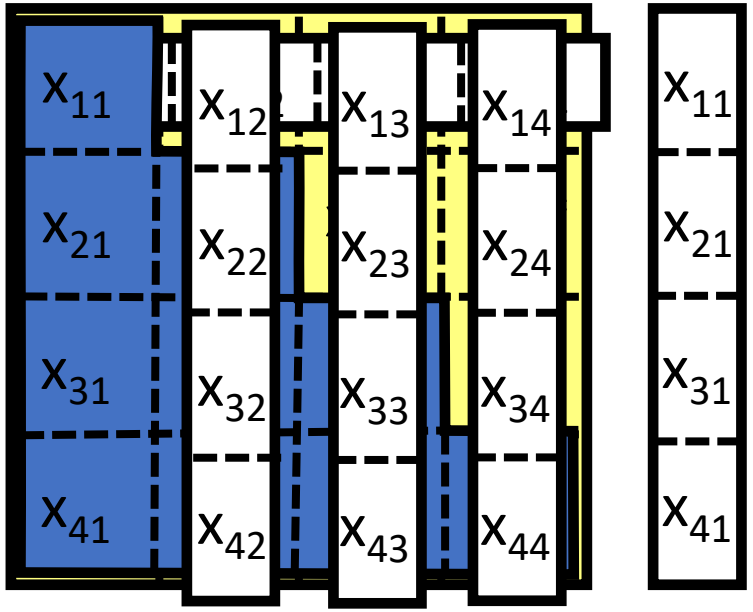
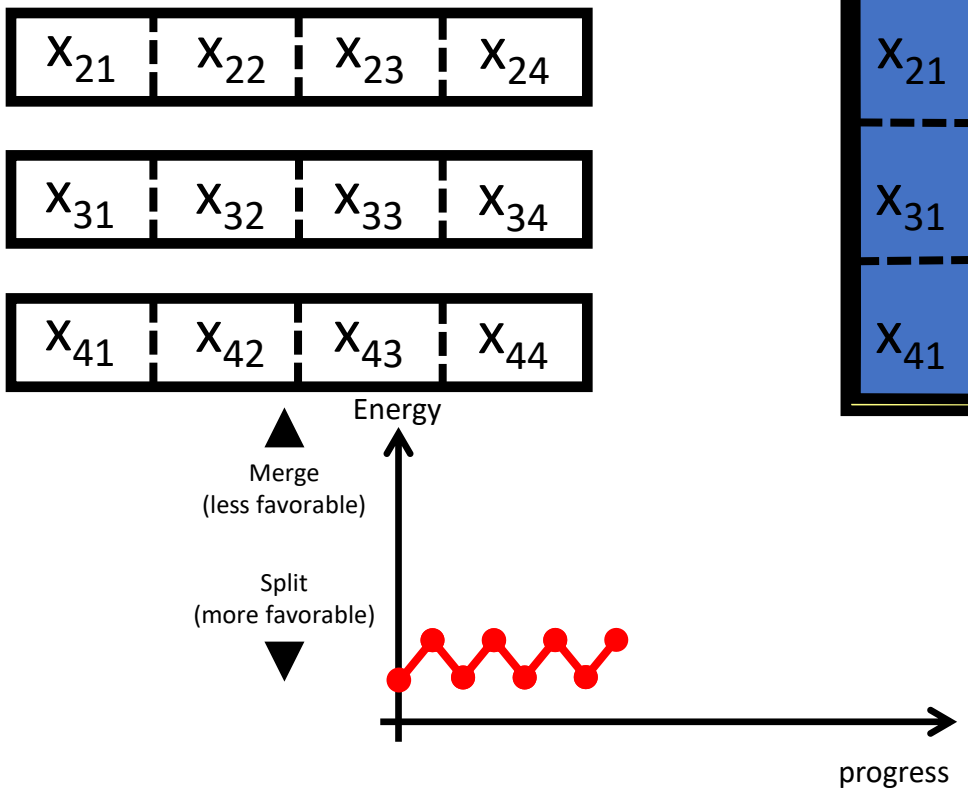
x41 x42


x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
Energy
Merge
(less favorable)
Split
(more favorable)
progress

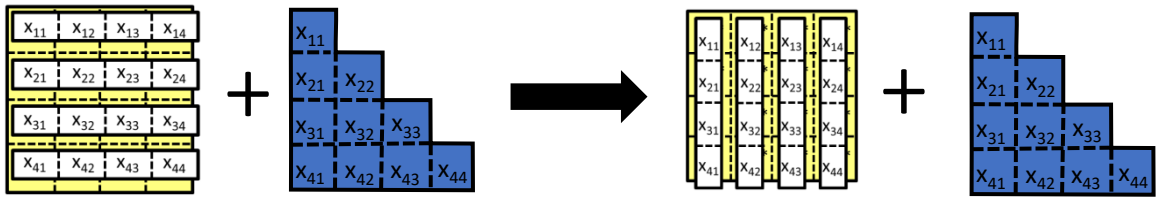
Catalysis

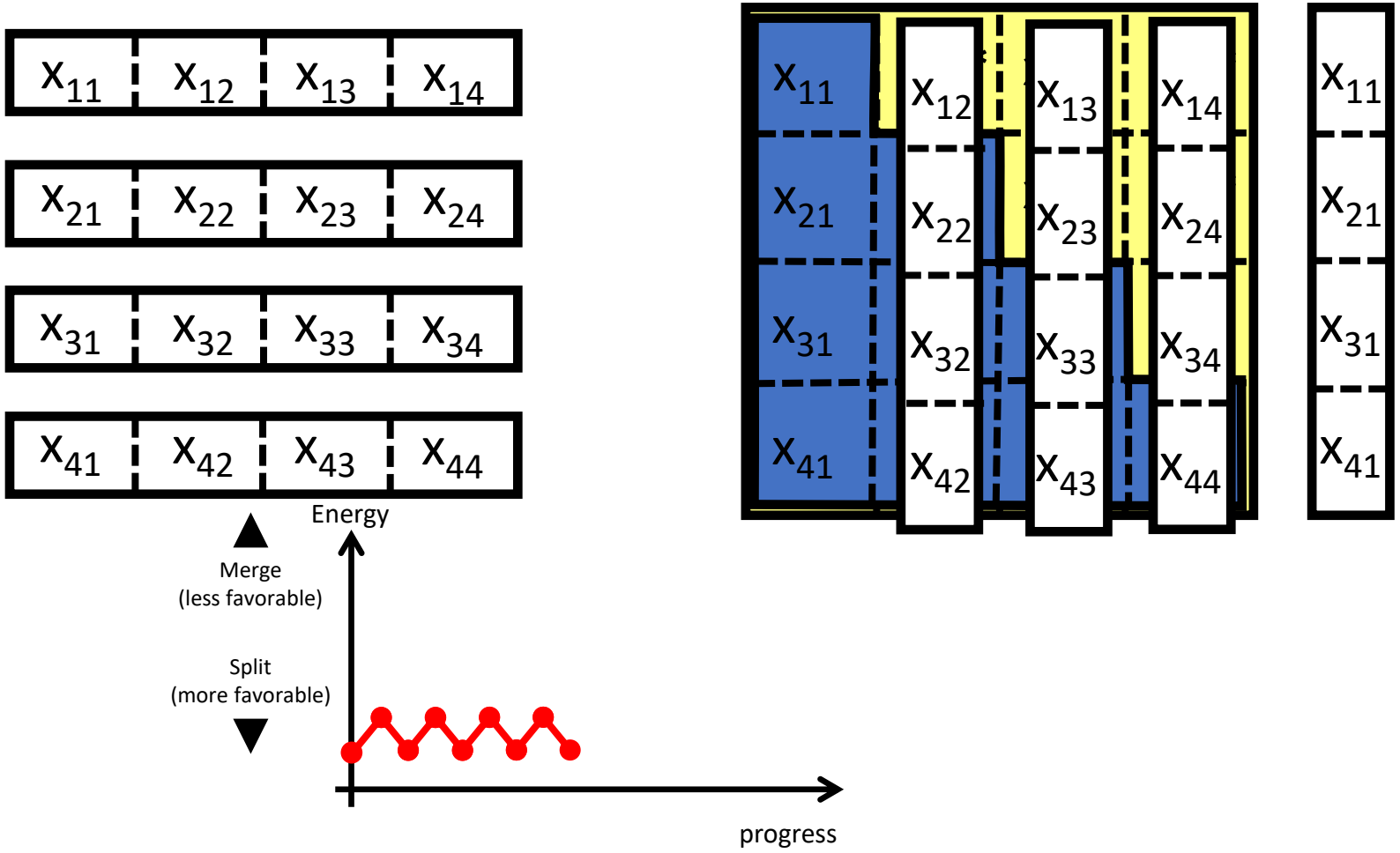

x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
+
x11
x21 x22
x31 x32 x33
x41 x42 x43 x44
x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
+
x11
x21 x22
x31 x32 x33
x41 x42 x43 x44


x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
x11
x21
x31
x41


x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
Energy
Merge
(less favorable)
Split
(more favorable)
progress

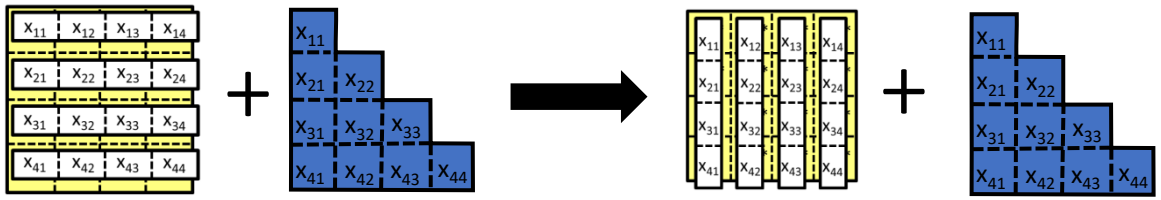
Catalysis

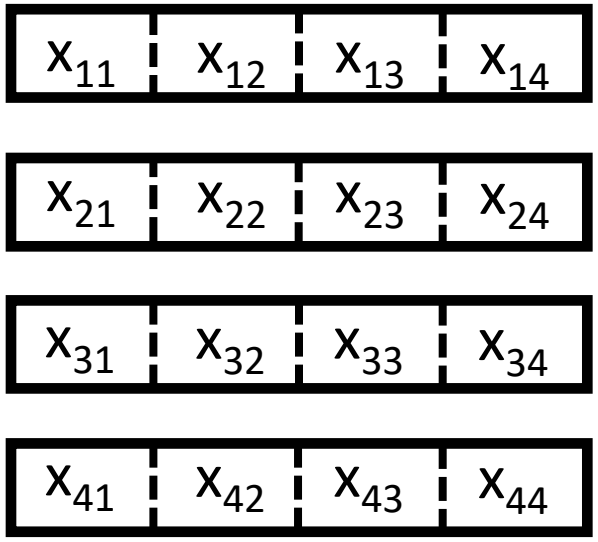

x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44


x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
Energy
Merge
(less favorable)
Split
(more favorable)
progress

x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44

Catalysis


x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44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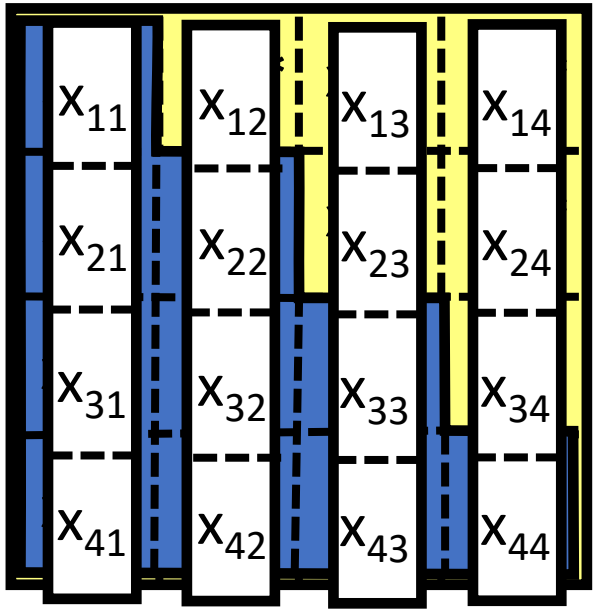
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44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x21 x22 x23 x24
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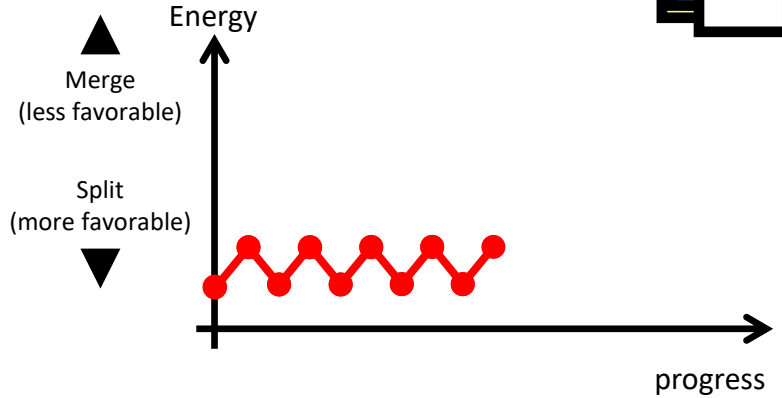
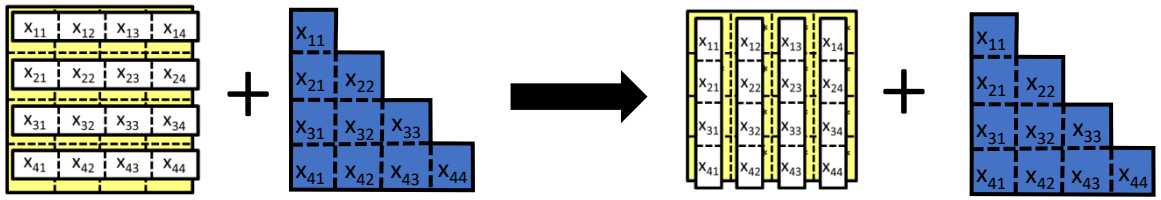

Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis


x11 x12 x13 x14
x21 x22 x23 x24
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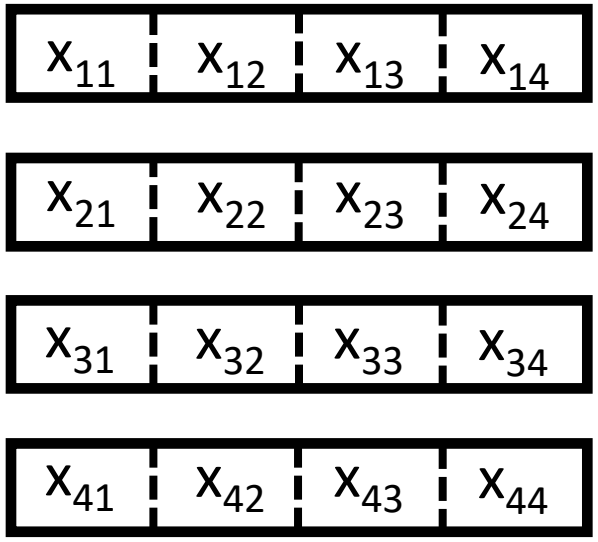
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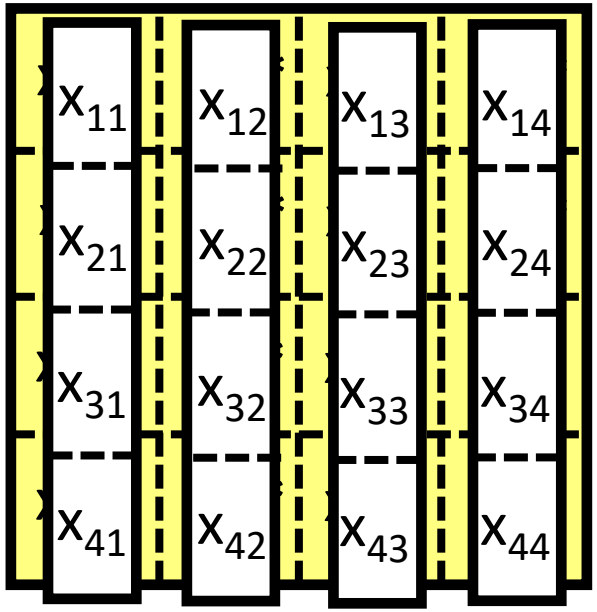
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44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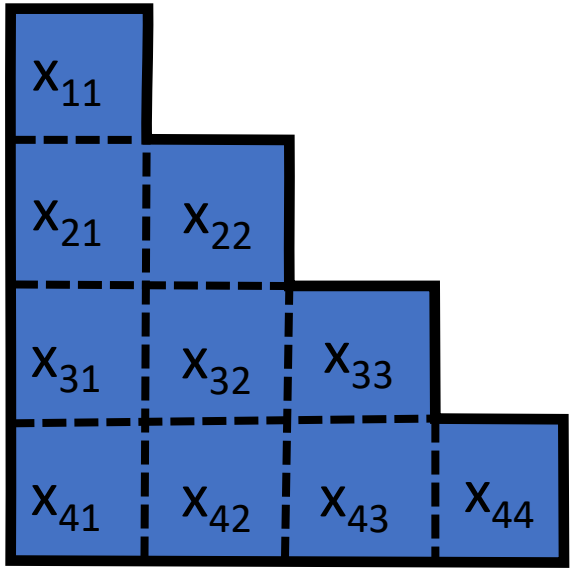
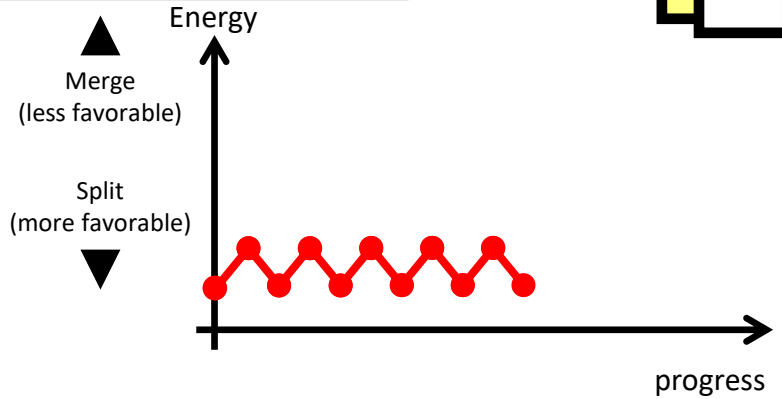
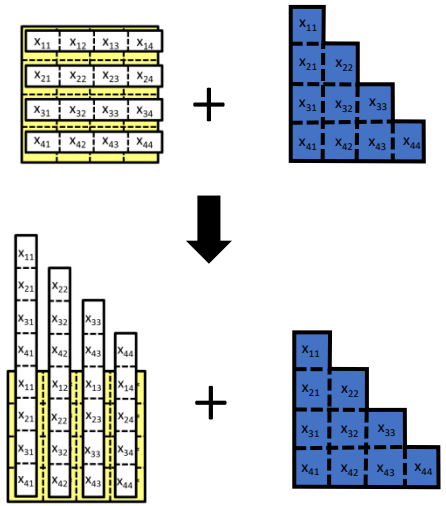
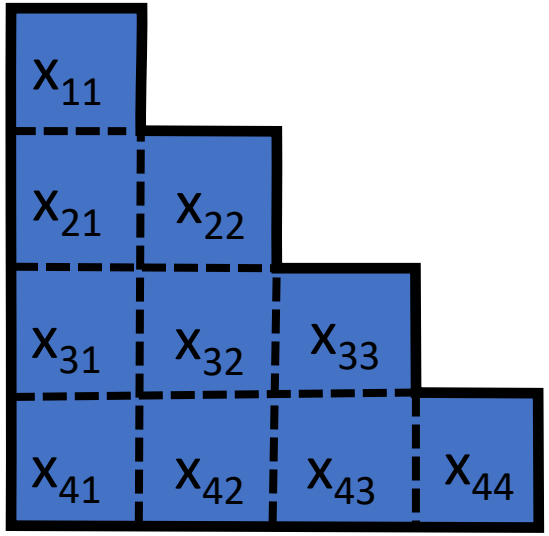
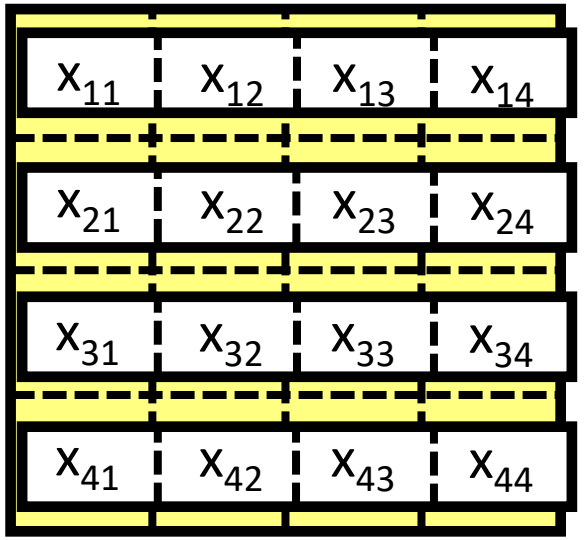

x11
x21 x22
x31 x32 x33
x41 x42 x43 x44

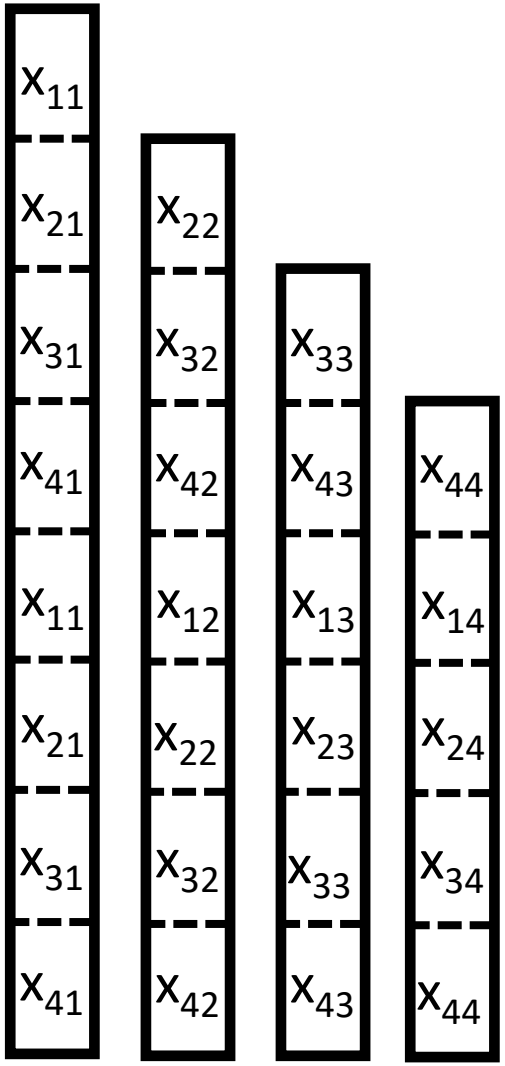

Energy
Merge
(less favorable)
Split
(more favorable)
progress

Autocatalysis

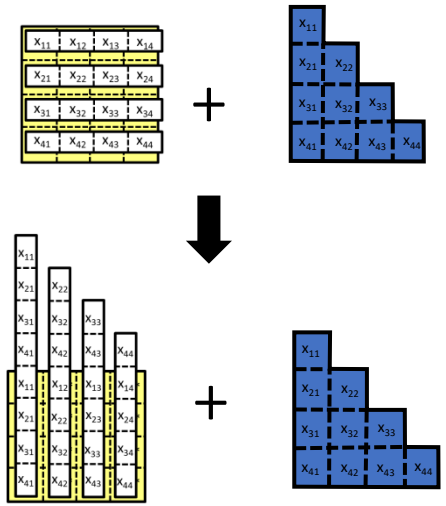


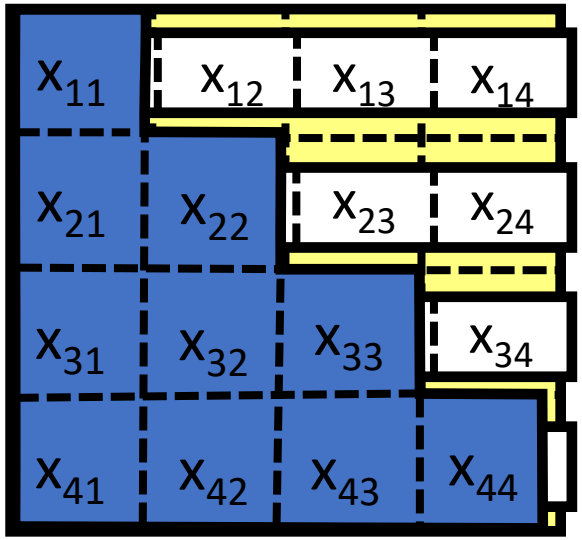


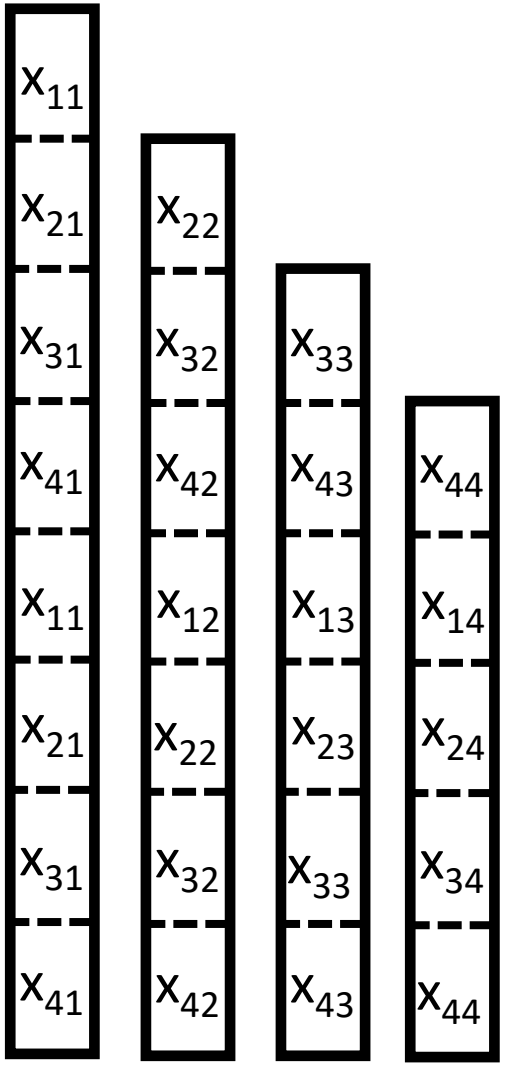




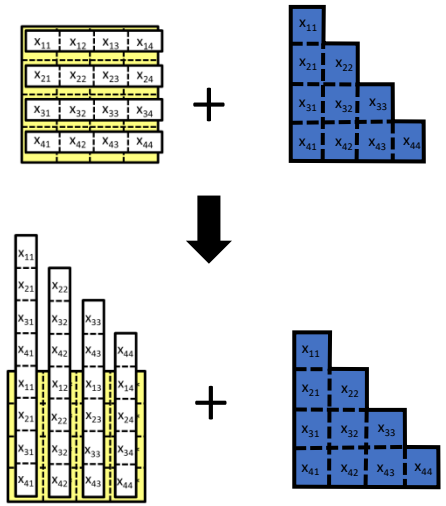
Autocatalysis

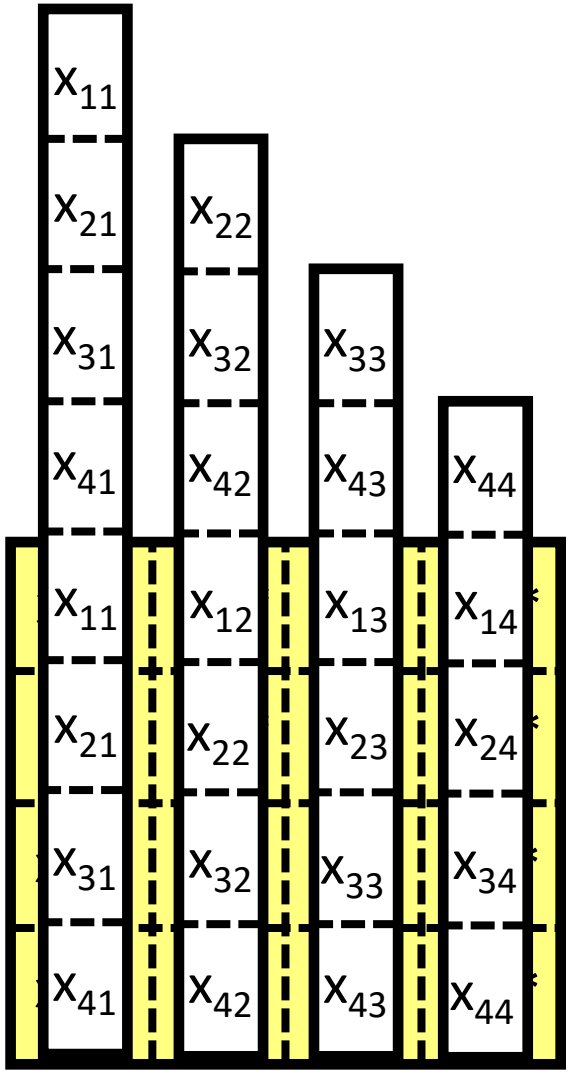


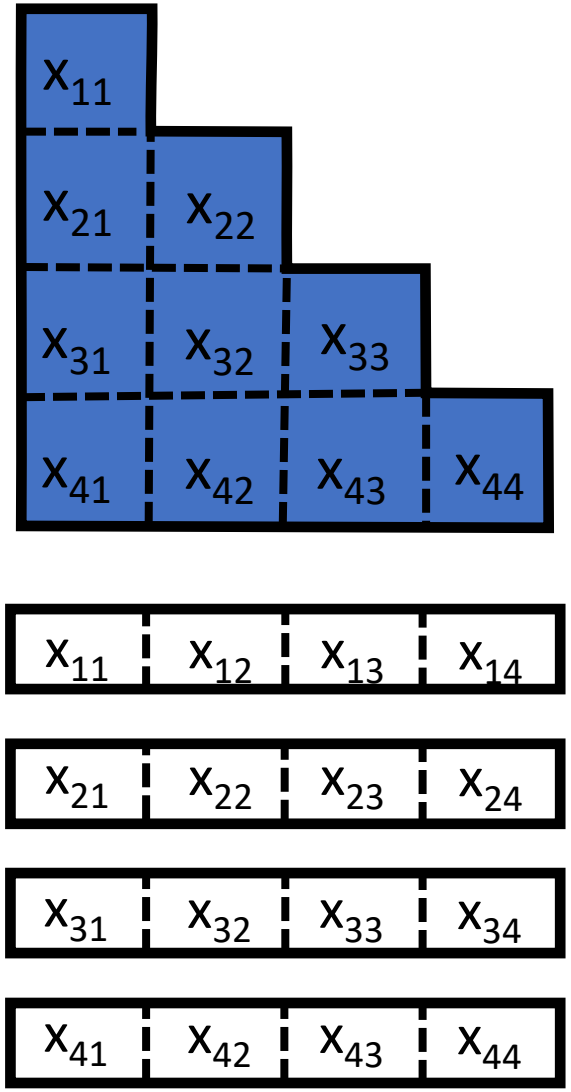




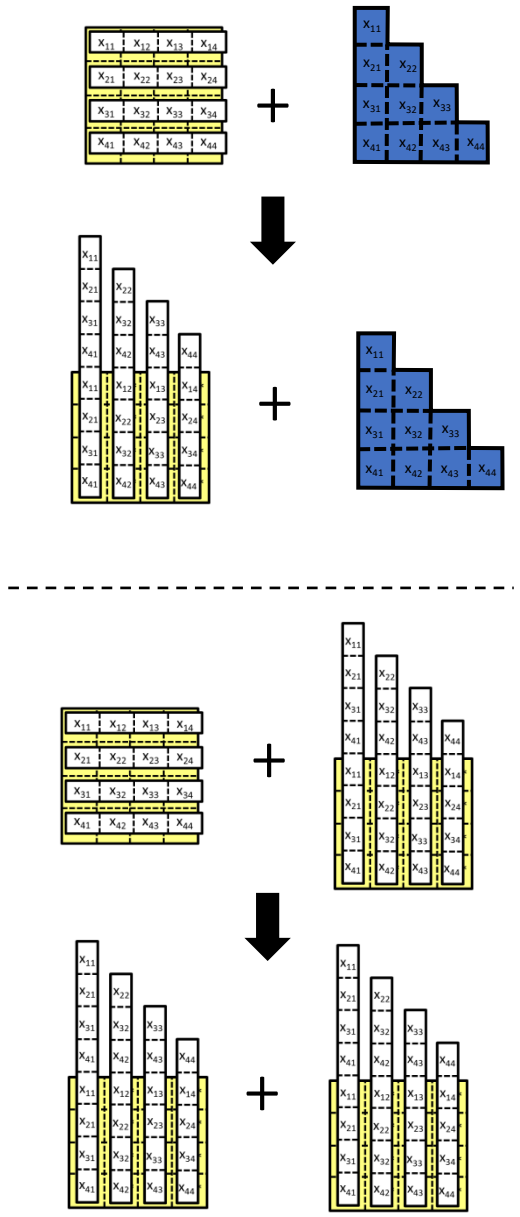
Autocatalysis

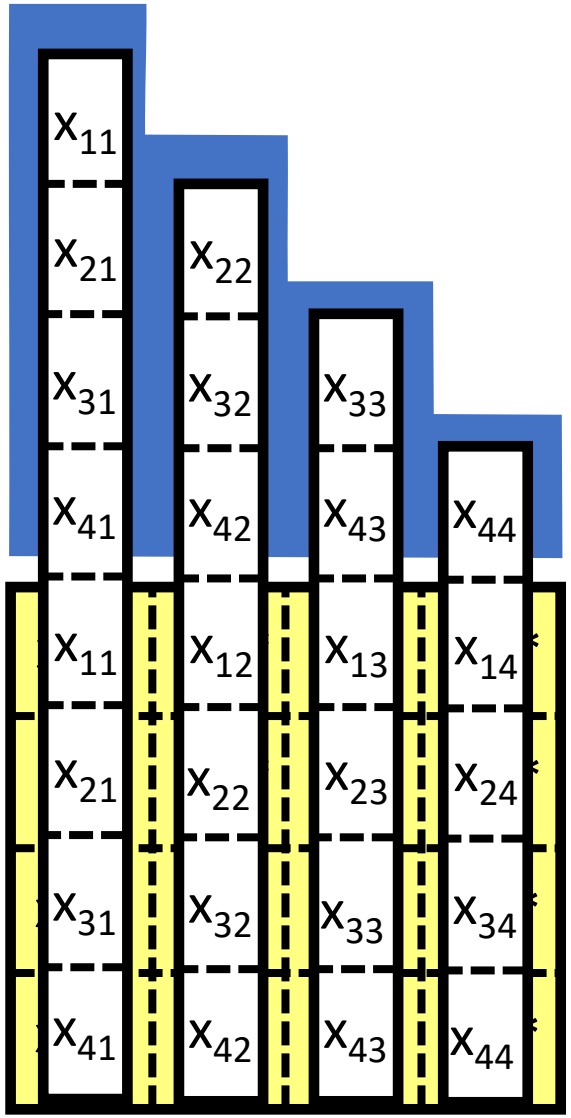


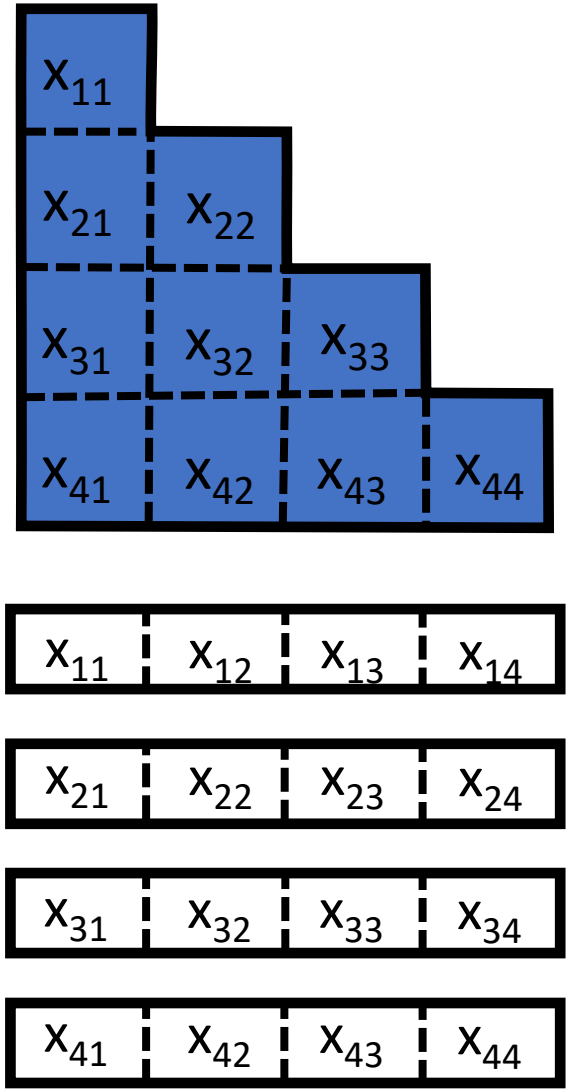




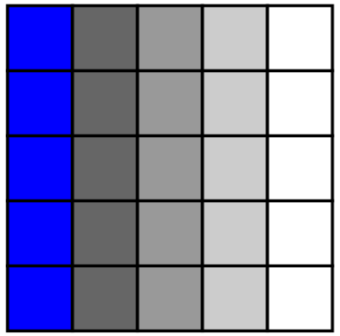
Autocatalysis

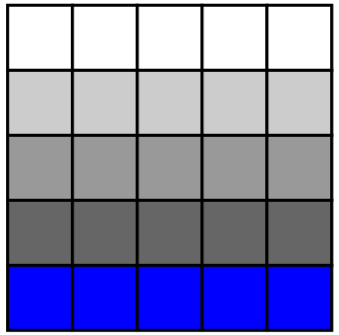




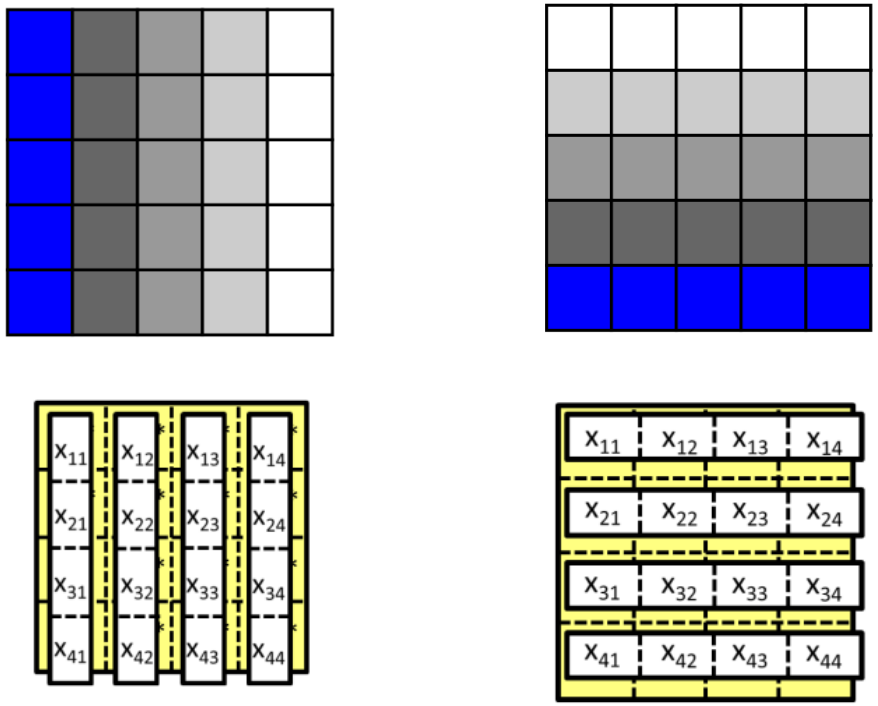


Multiple Stable Configurations

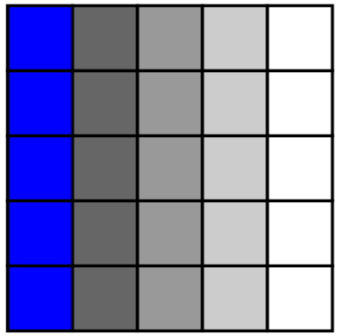


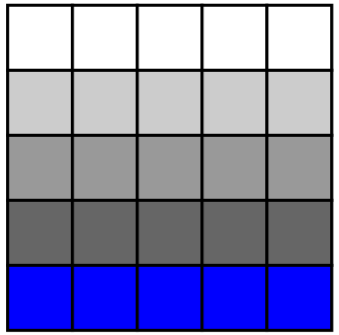


Multiple Stable Configurations

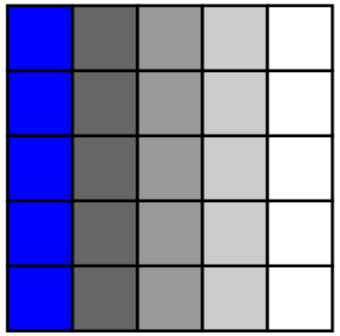


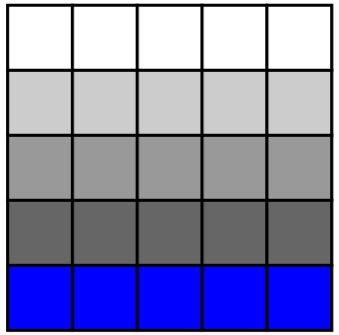
Multiple Stable Configurations

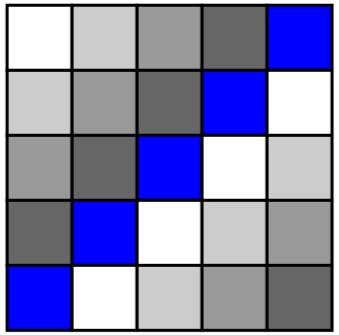




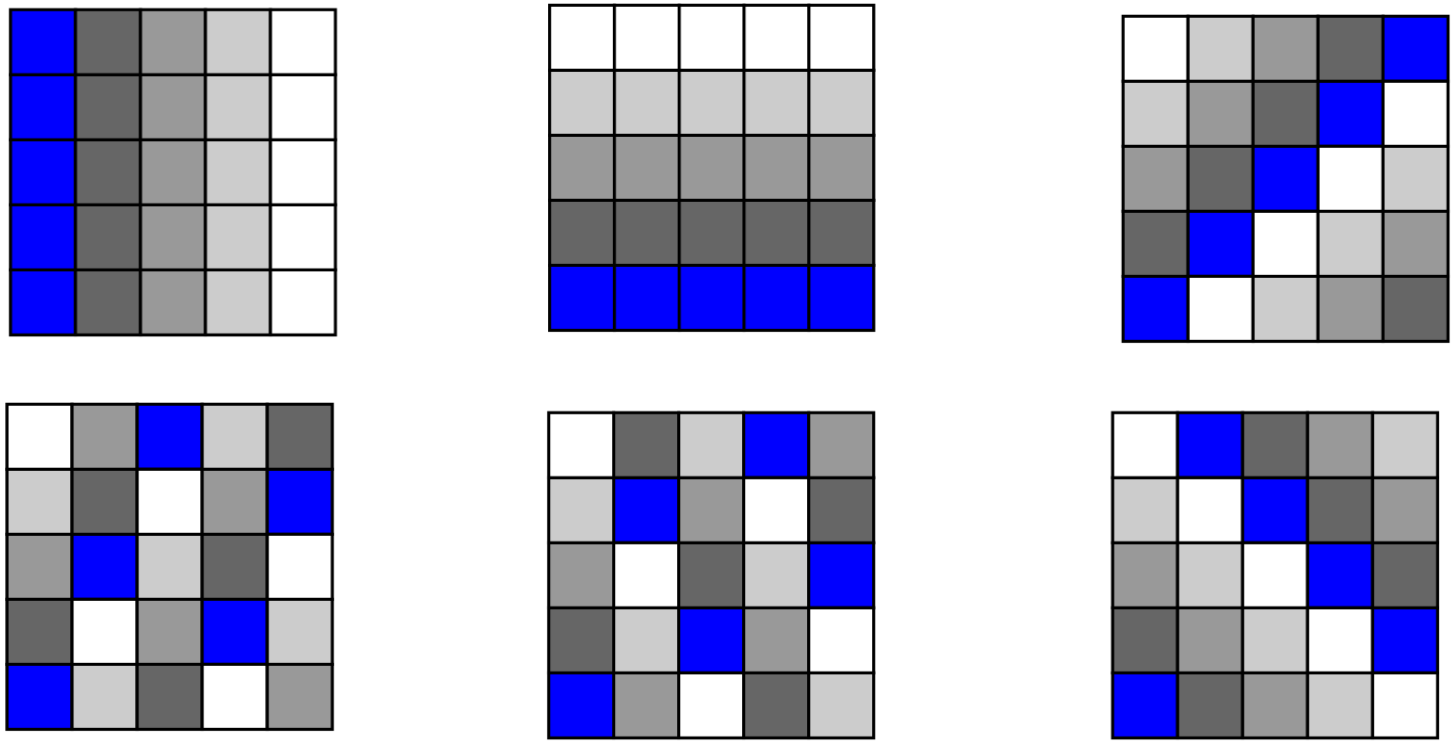
Multiple Stable Configurations





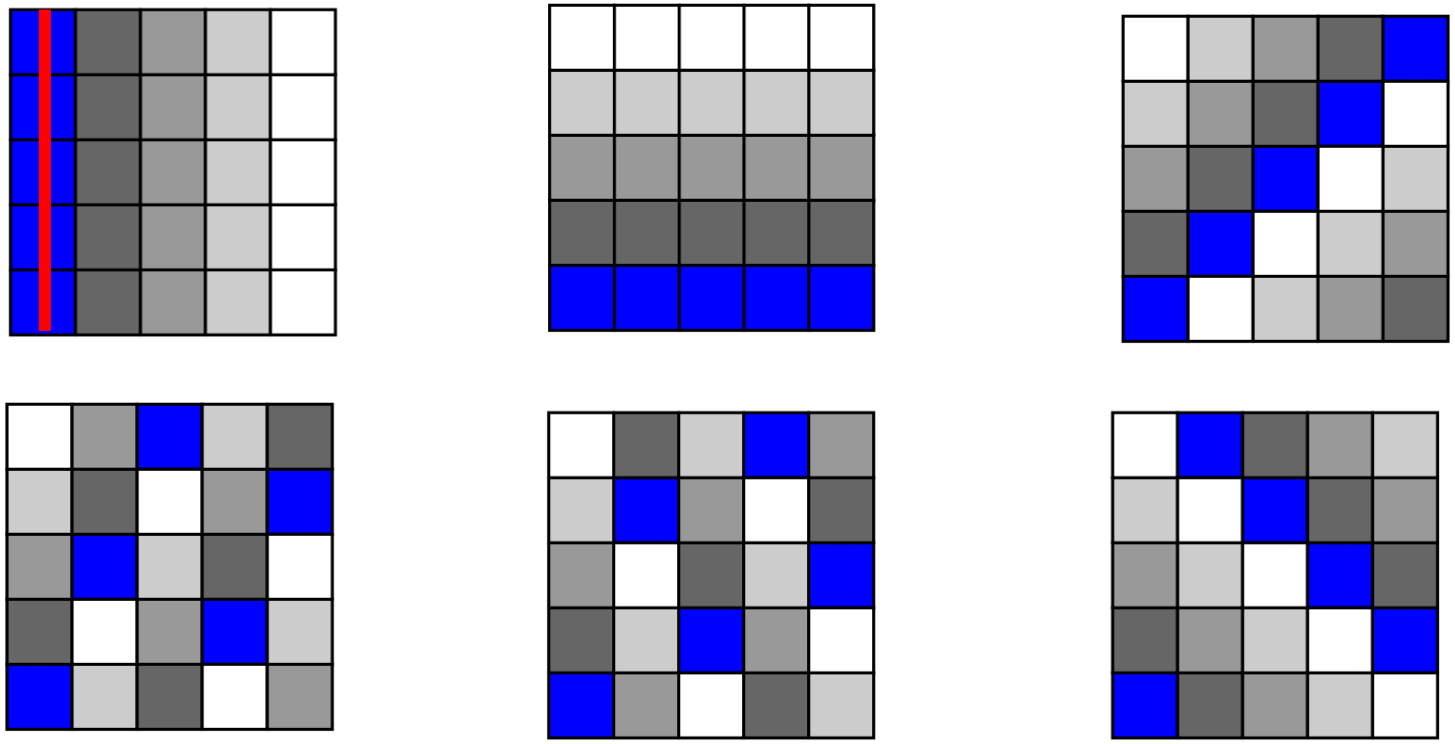


Multiple Stable Configurations



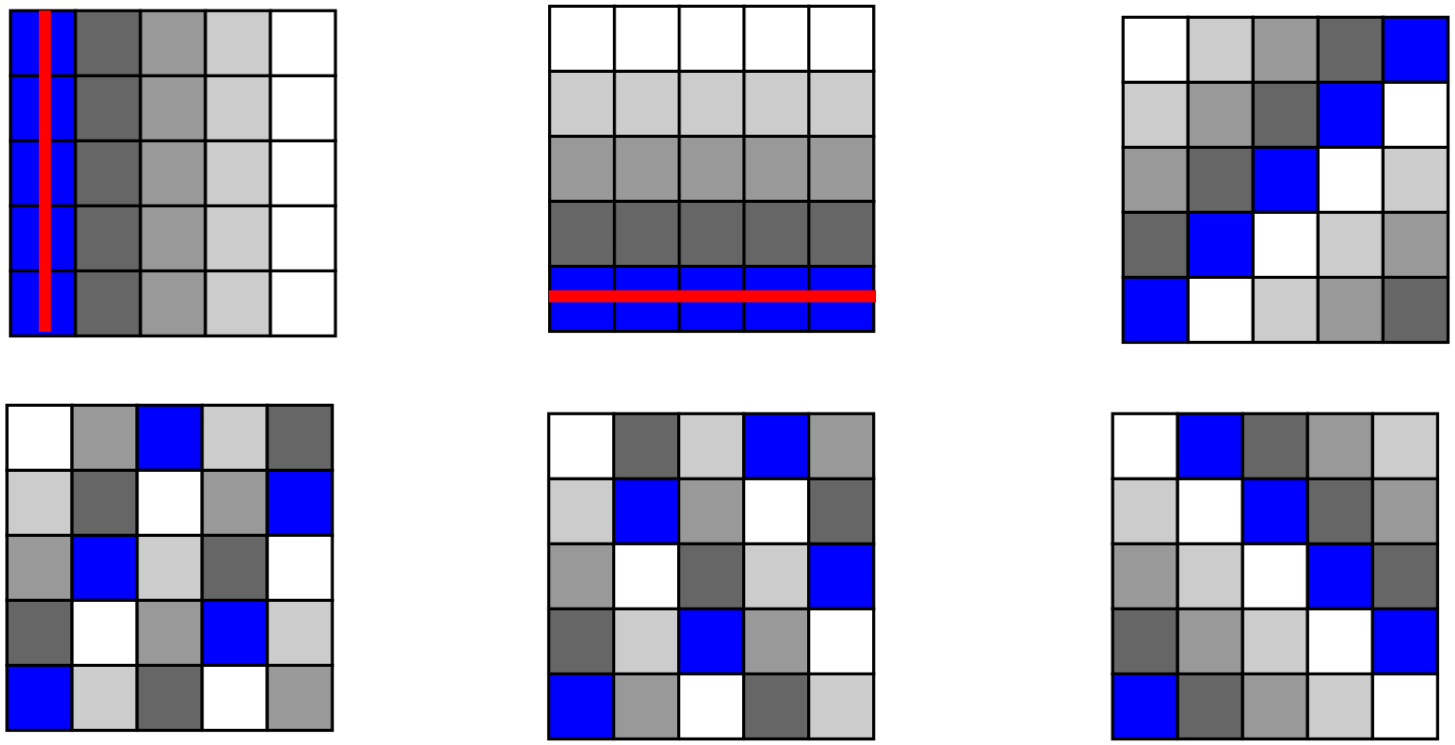
For a grid of prime size *n* x *n*, there can be at most *n*+1 different stable configurations with barrier *n* to pass between any of them

Multiple Stable Configurations



For a grid of prime size *n* x *n*, there can be at most *n*+1 different stable configurations with barrier *n* to pass between any of them

Multiple Stable Configurations



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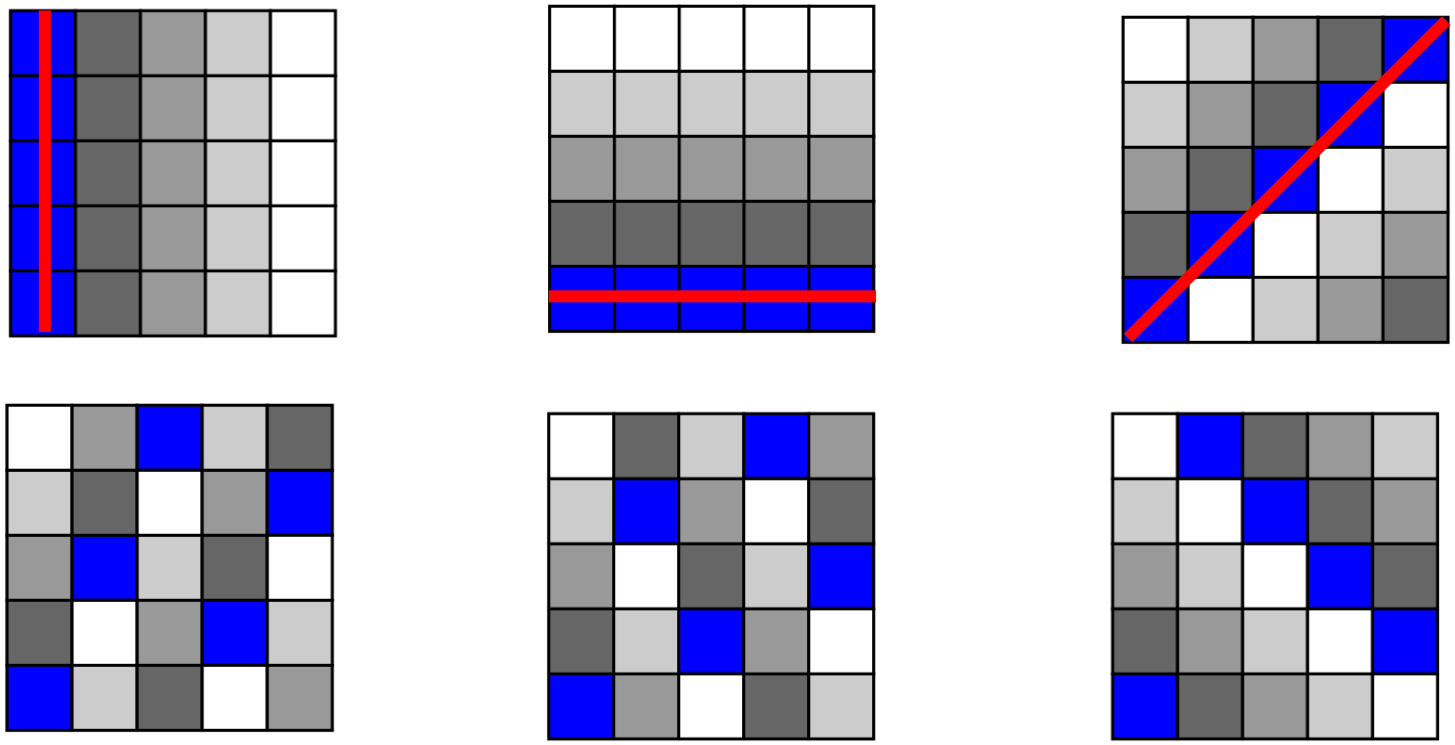
Multiple Stable Configurations



For a grid of prime size *n* x *n*, there can be at most *n*+1 different stable configurations with barrier *n* to pass between any of them

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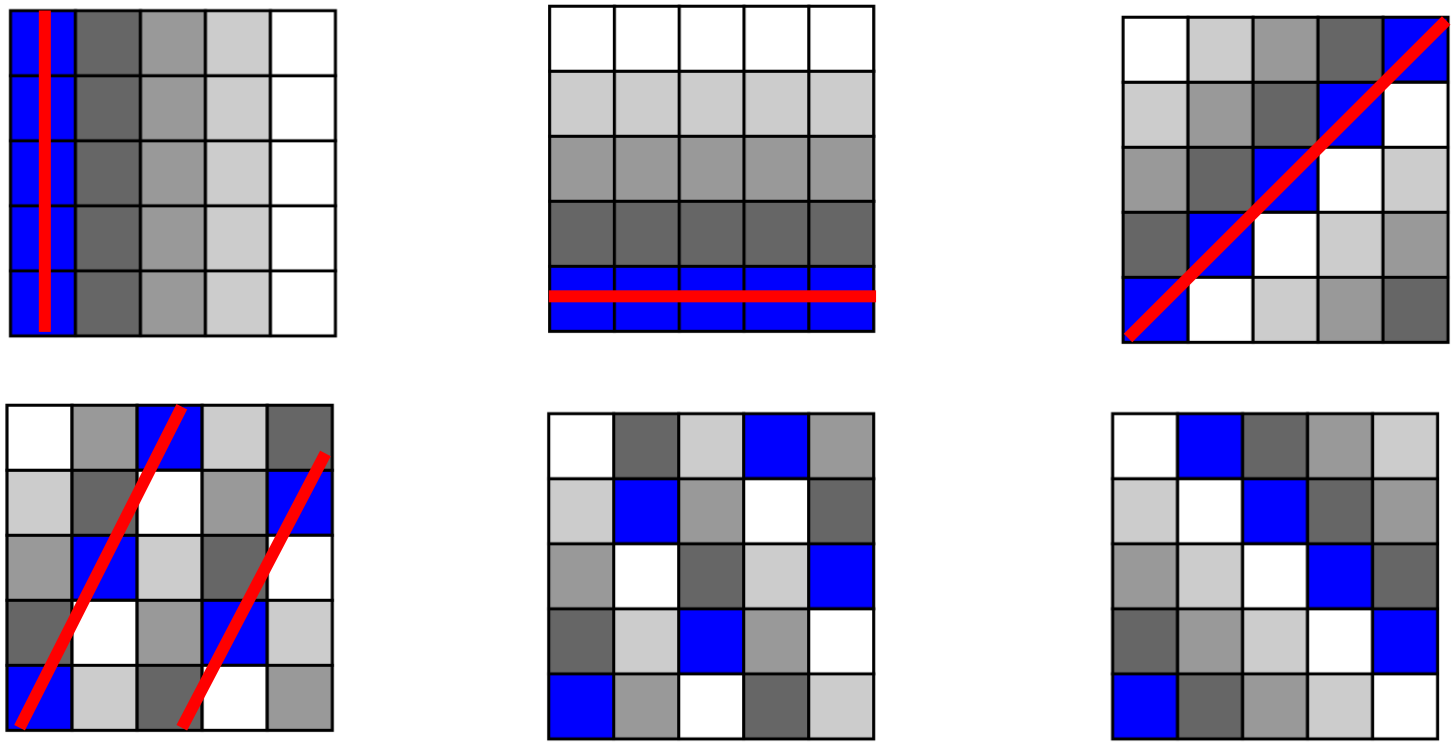

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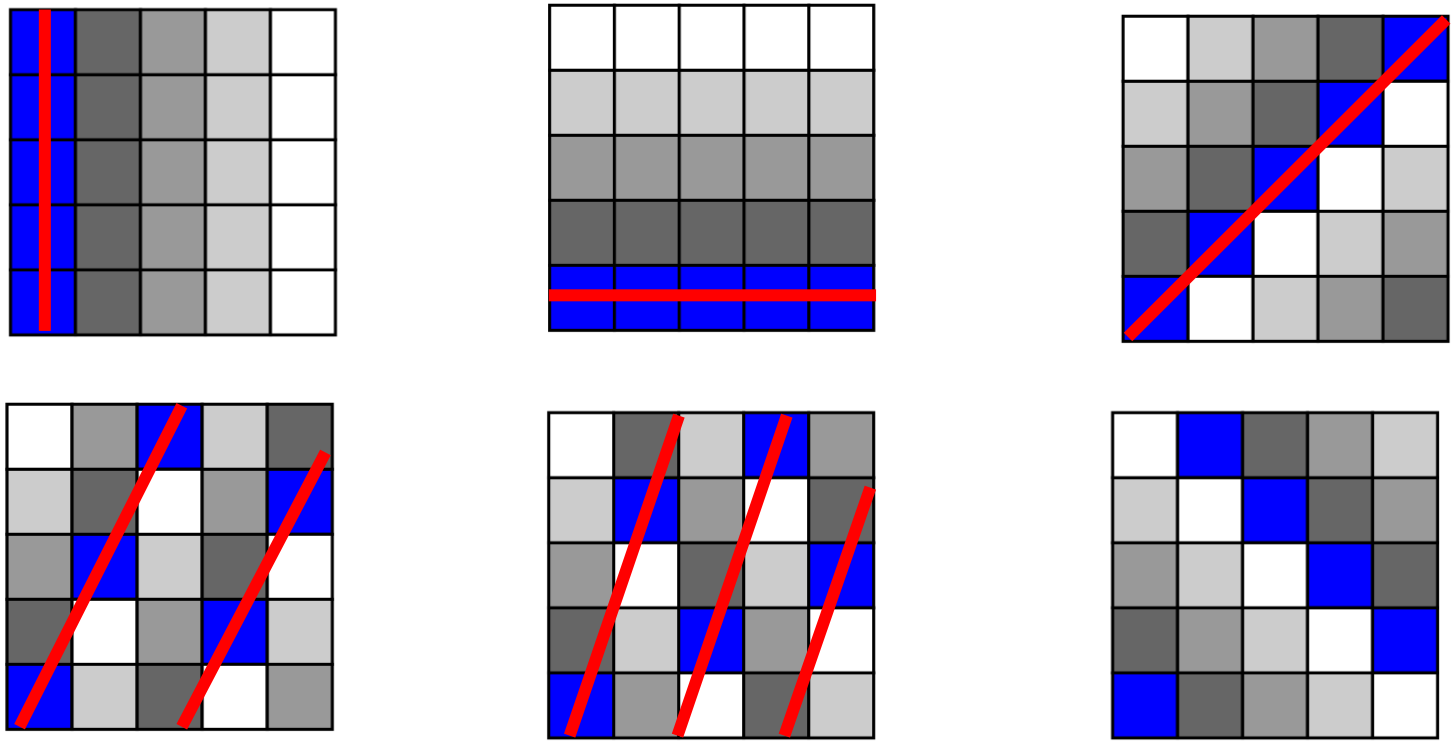

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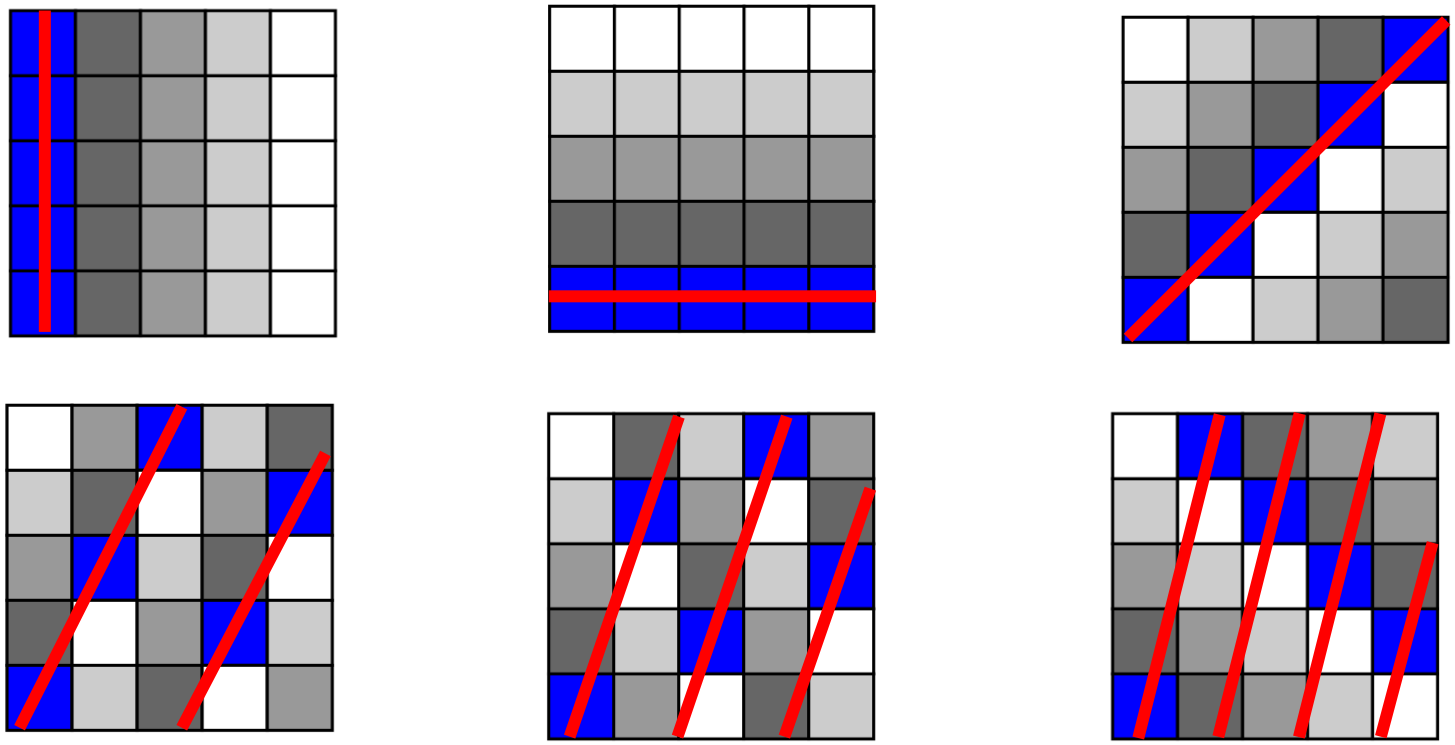

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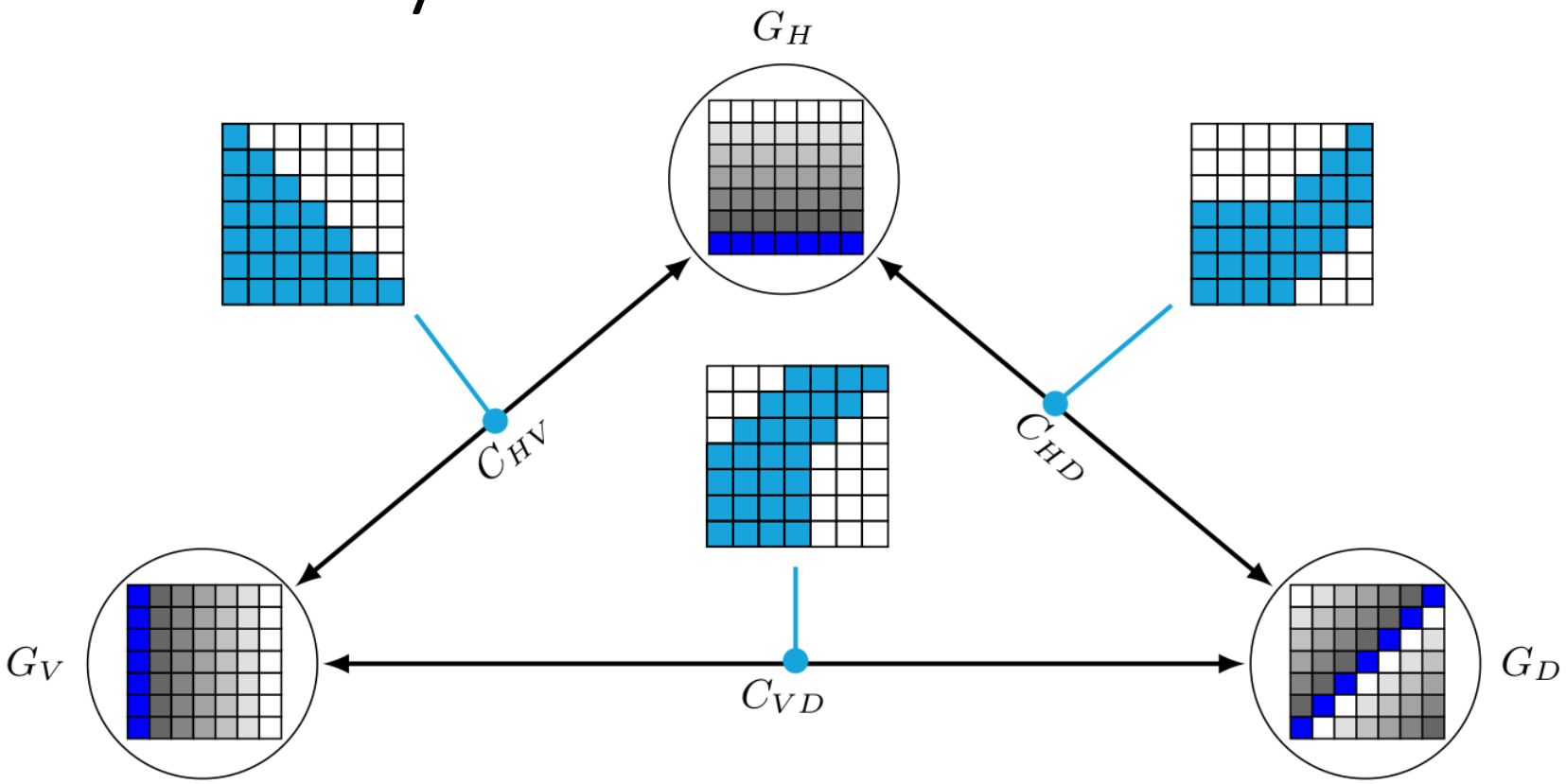

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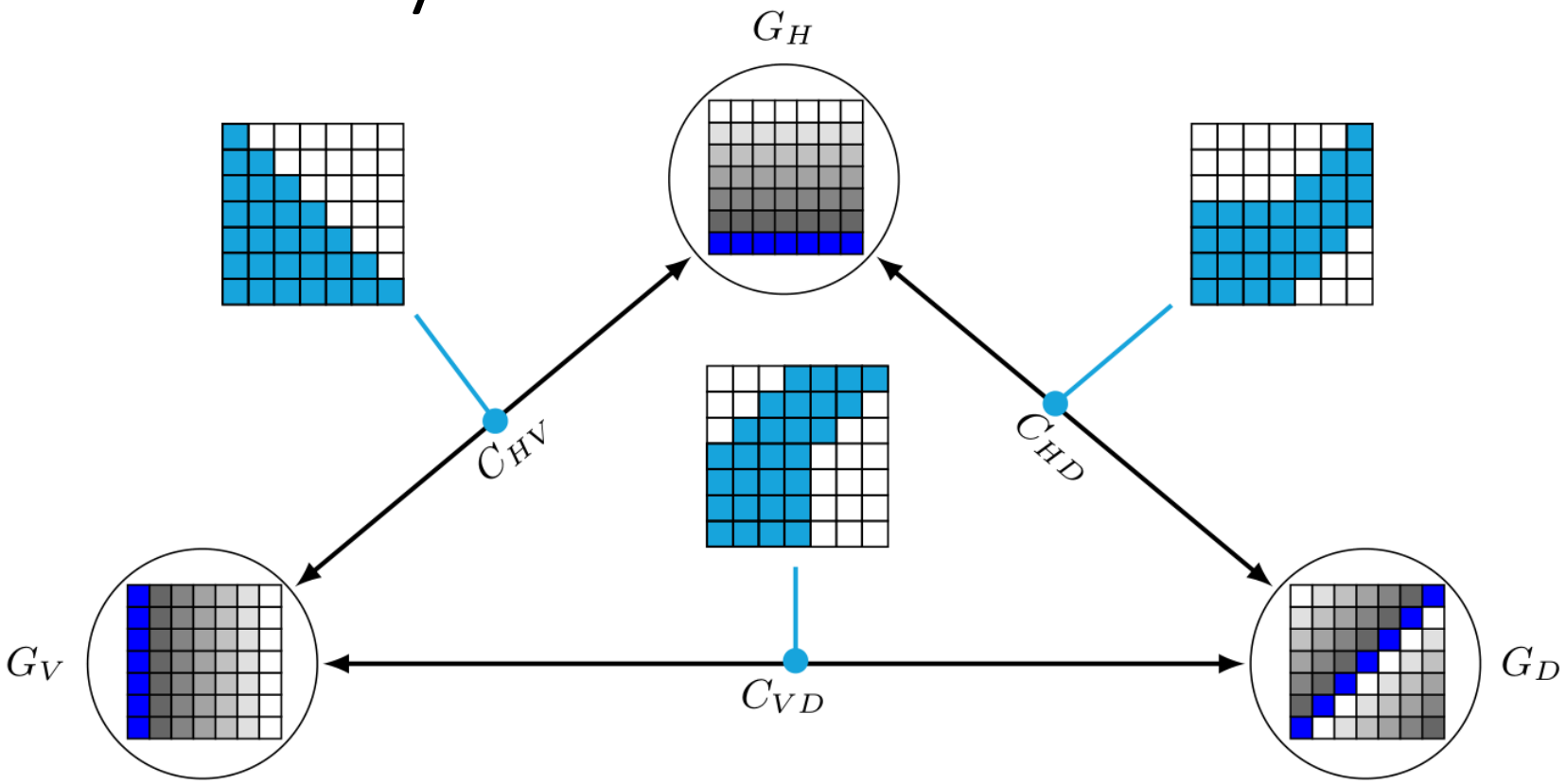

Along a catalyzed pathway, the barrier is 1

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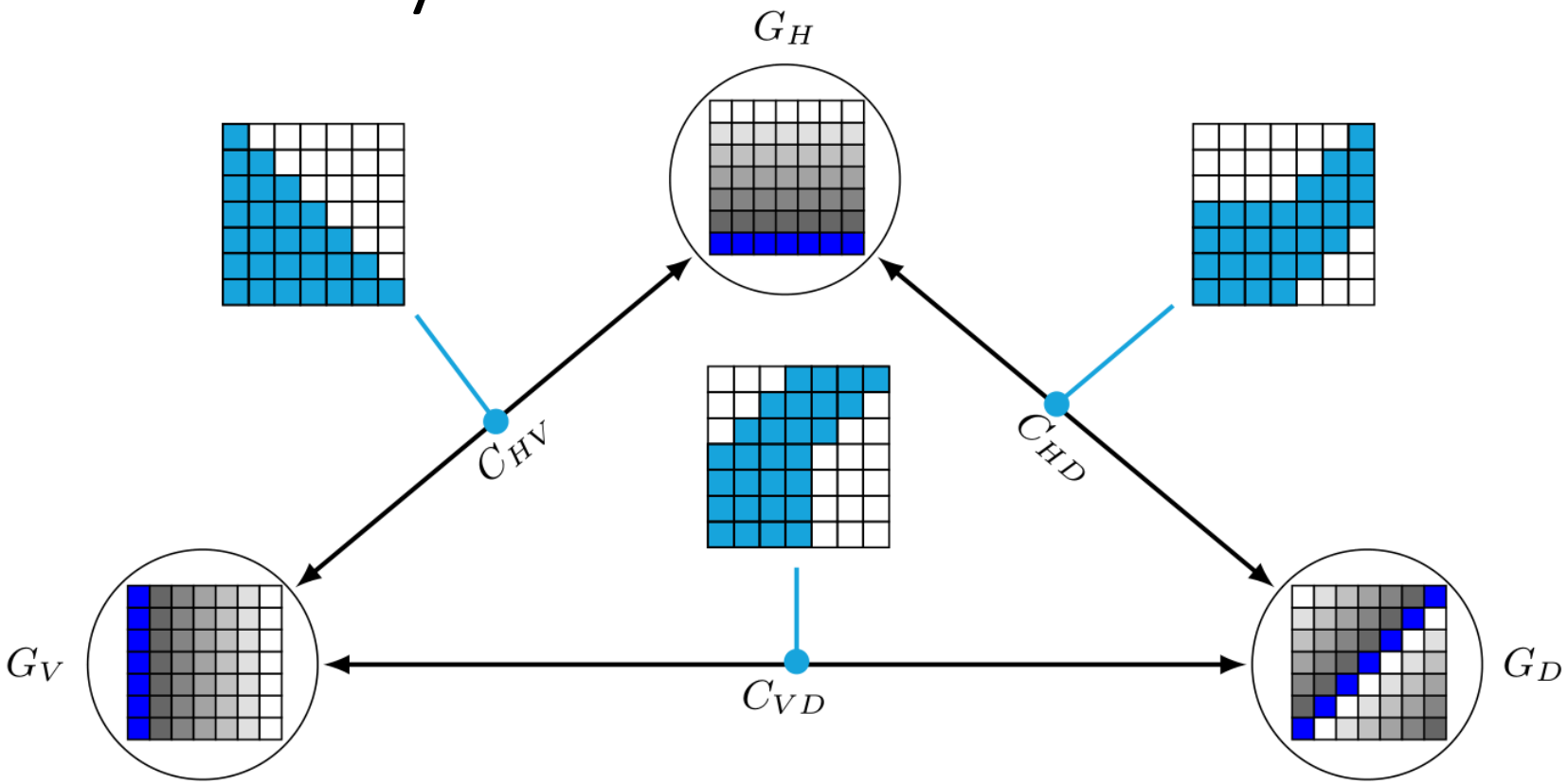

Along a catalyzed pathway, the barrier is 1

Otherwise the barrier is n/2

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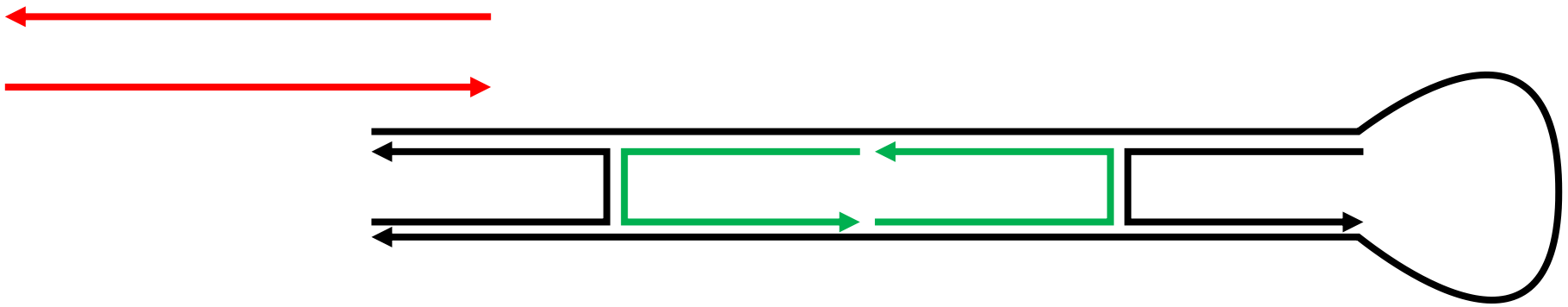
- Unknown for next prime power n=10:
  - trivial upper bound is 11 days
  - best known lower bound is 3

(Feasible?) DNA implementation



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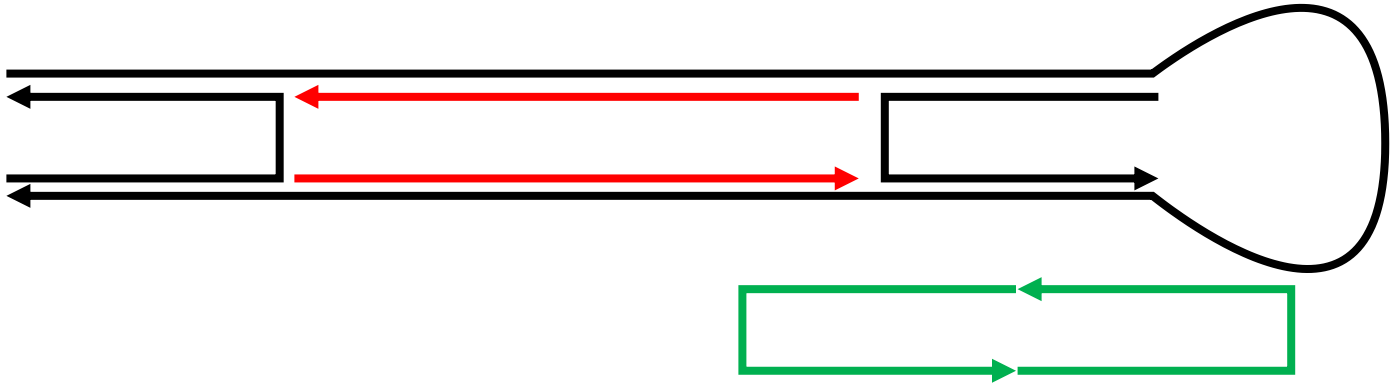

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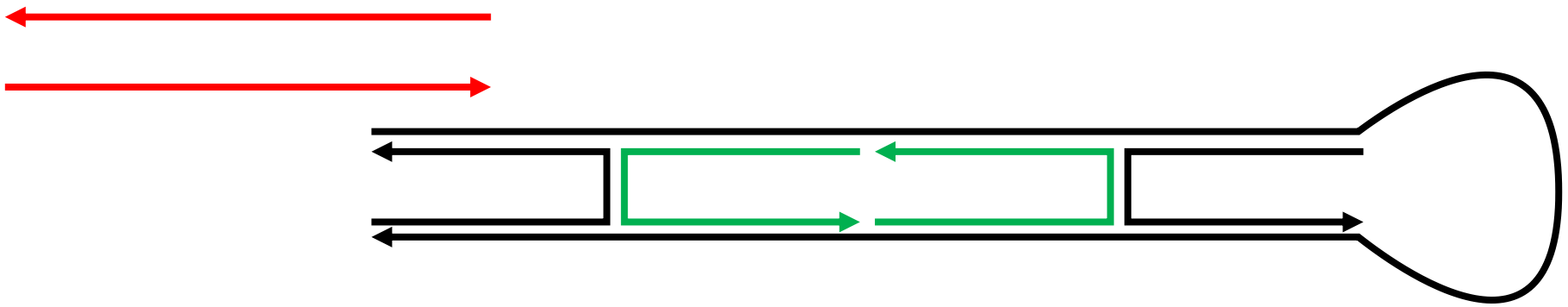

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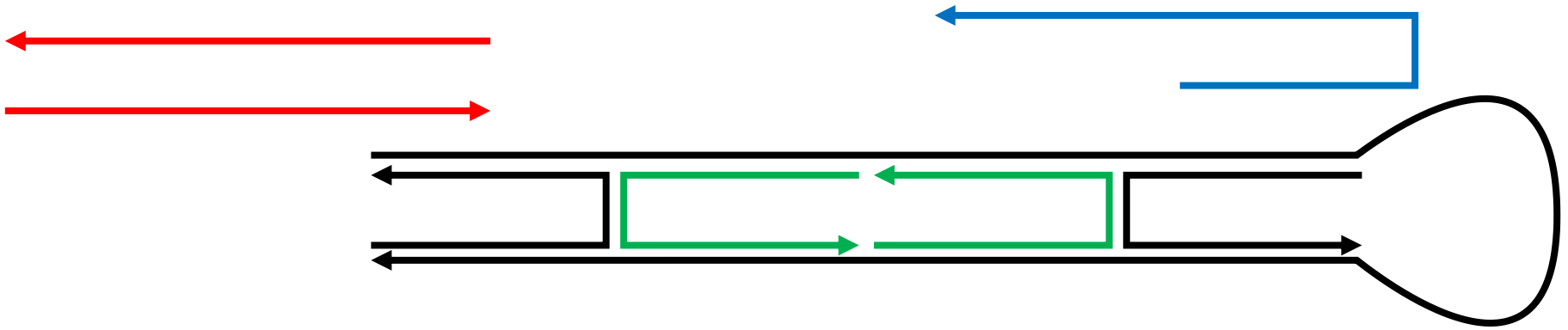

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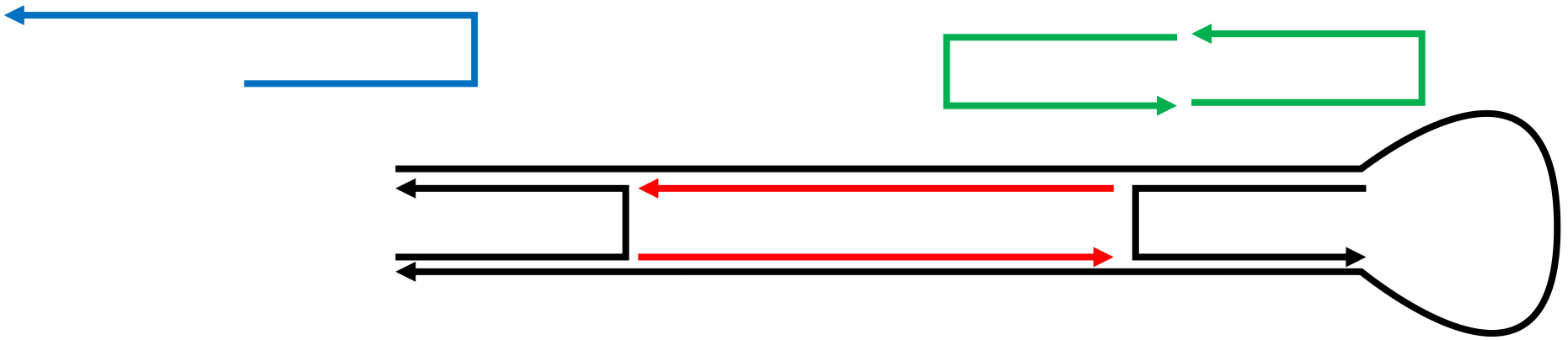

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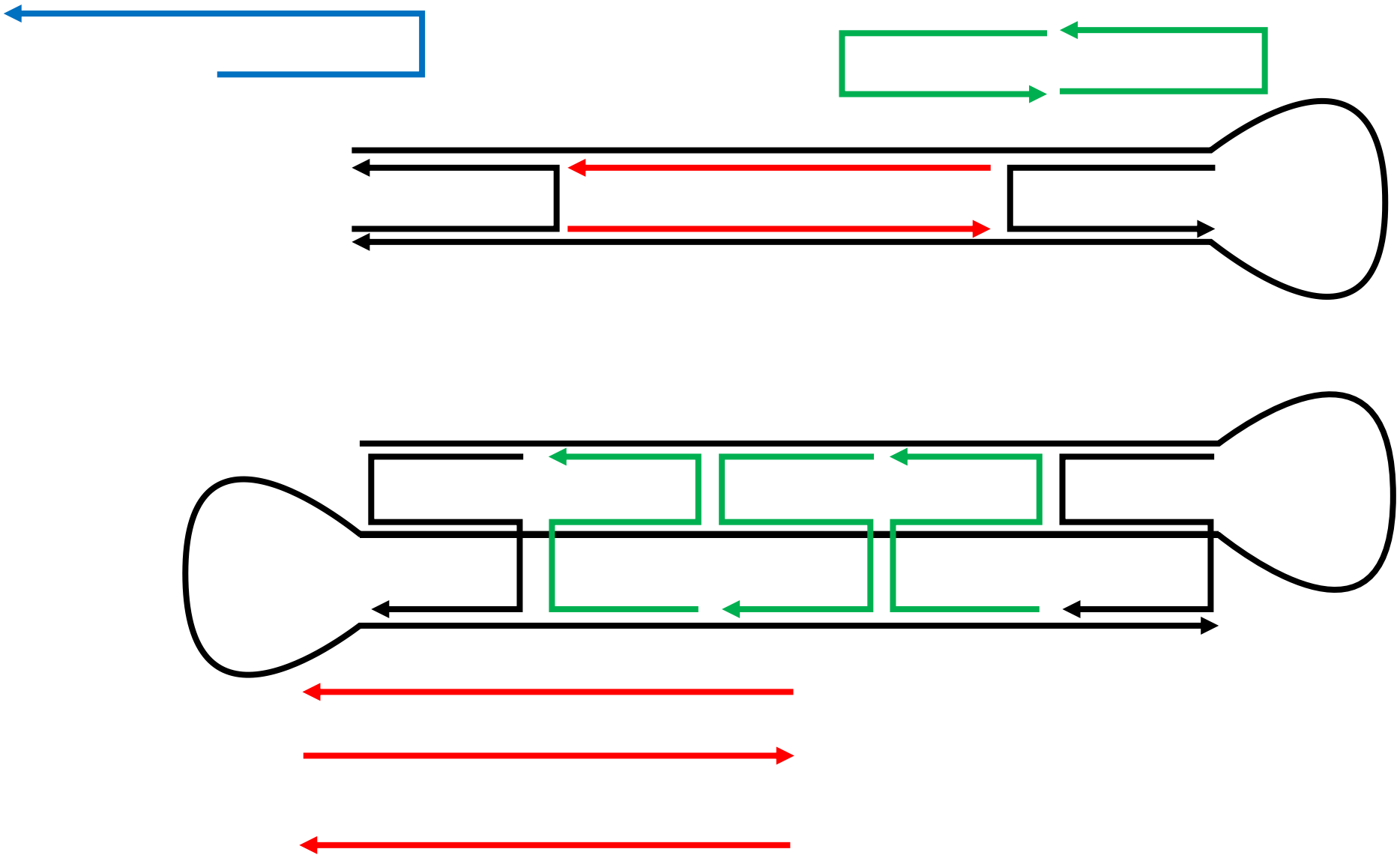

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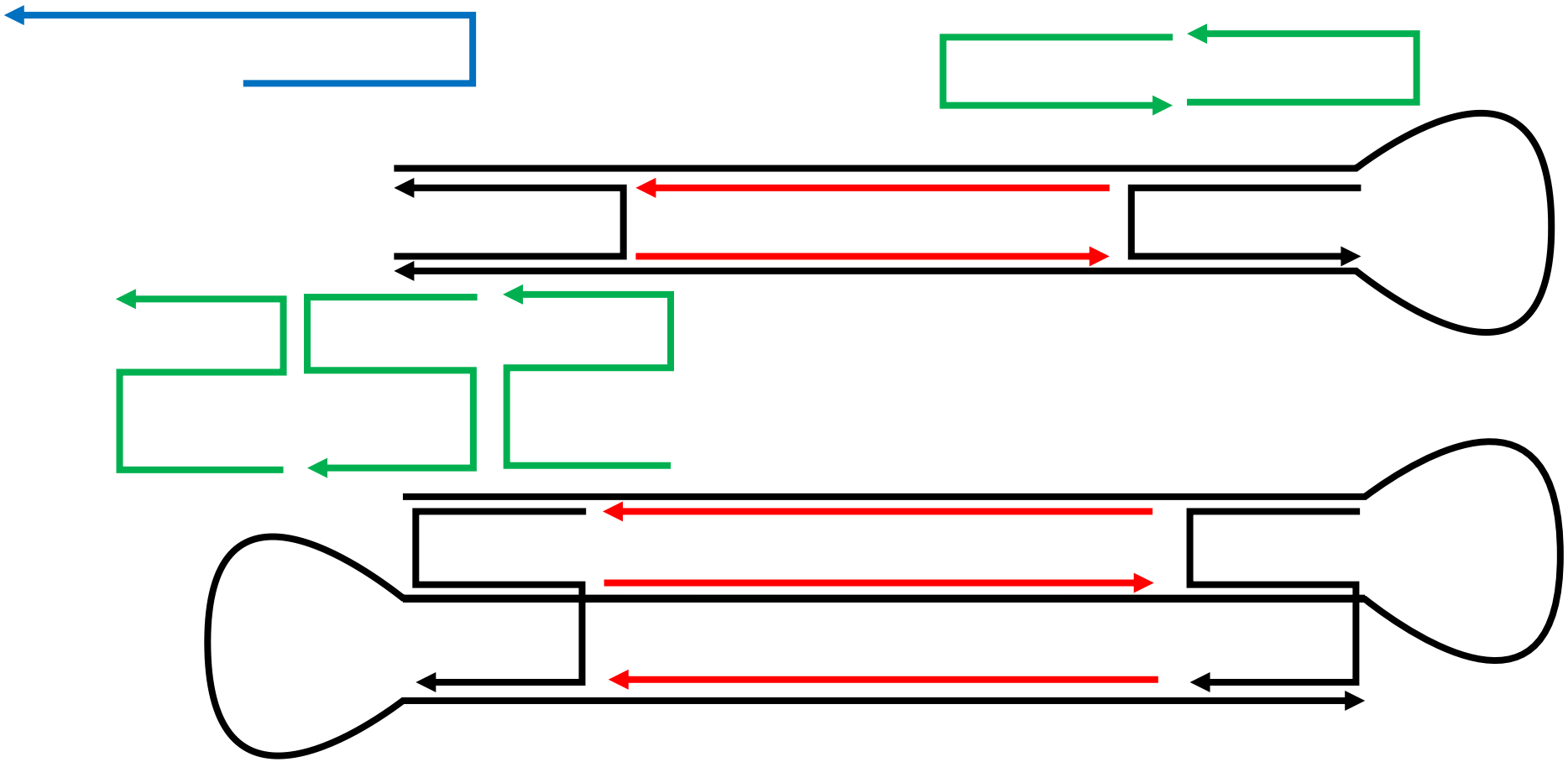

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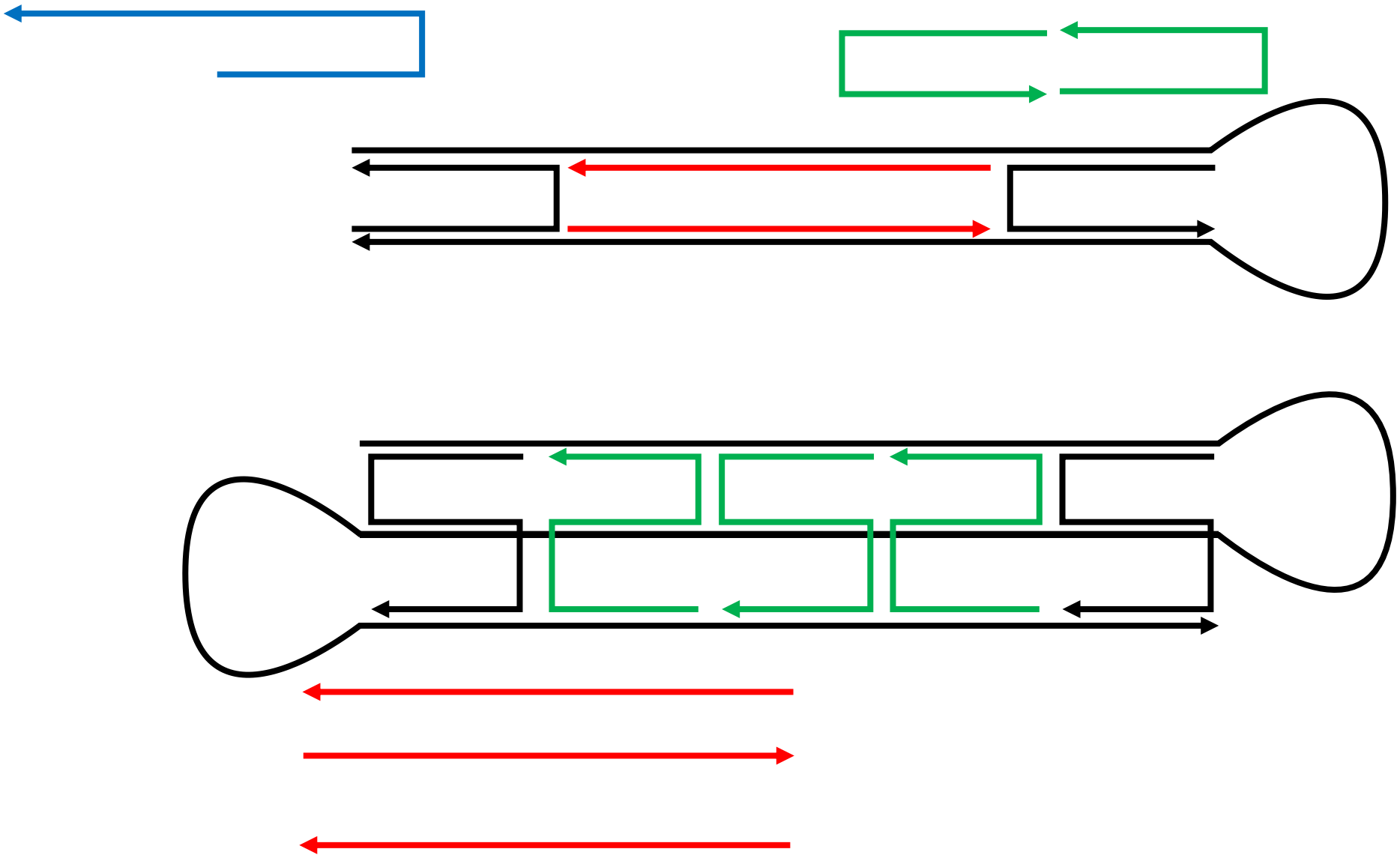

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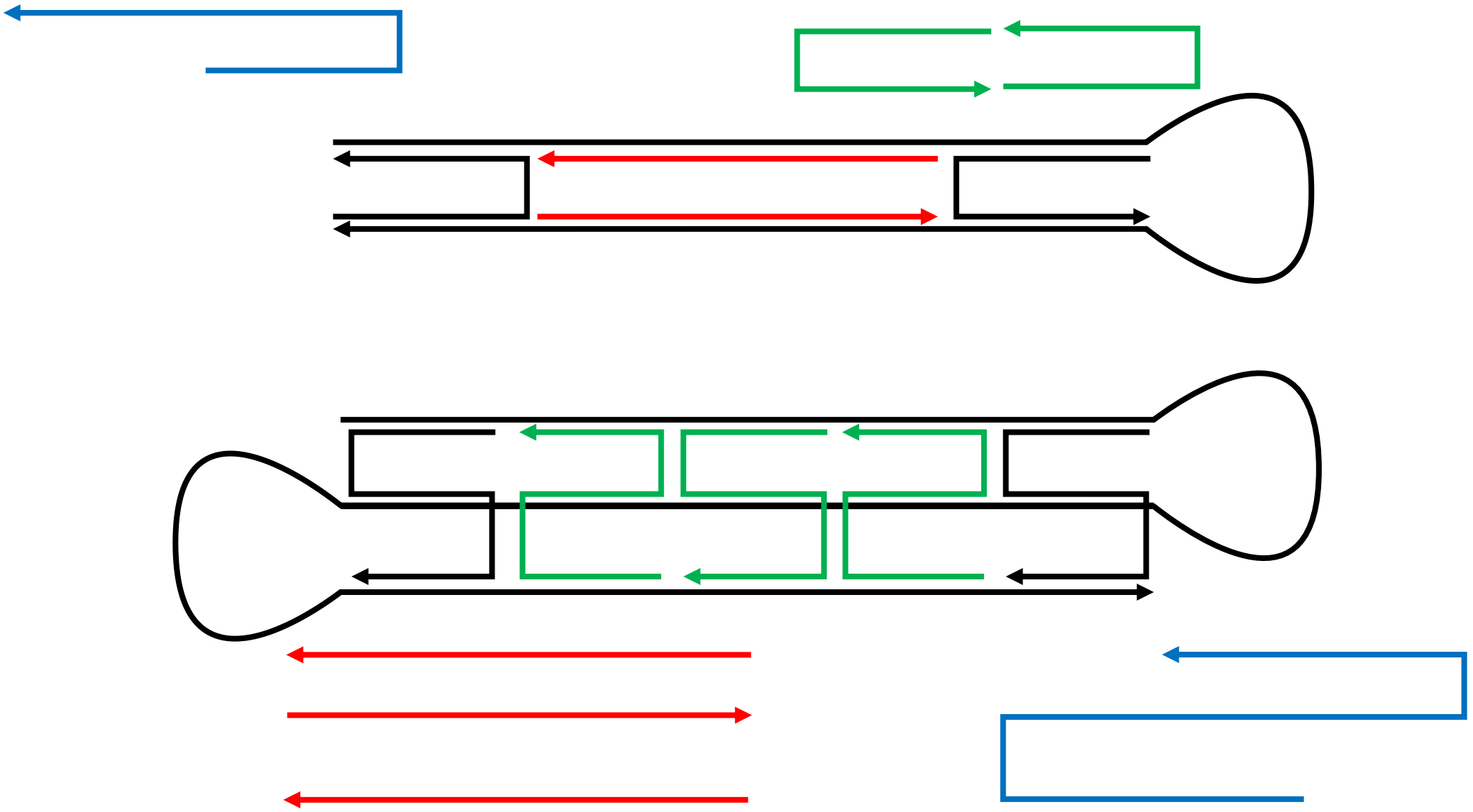

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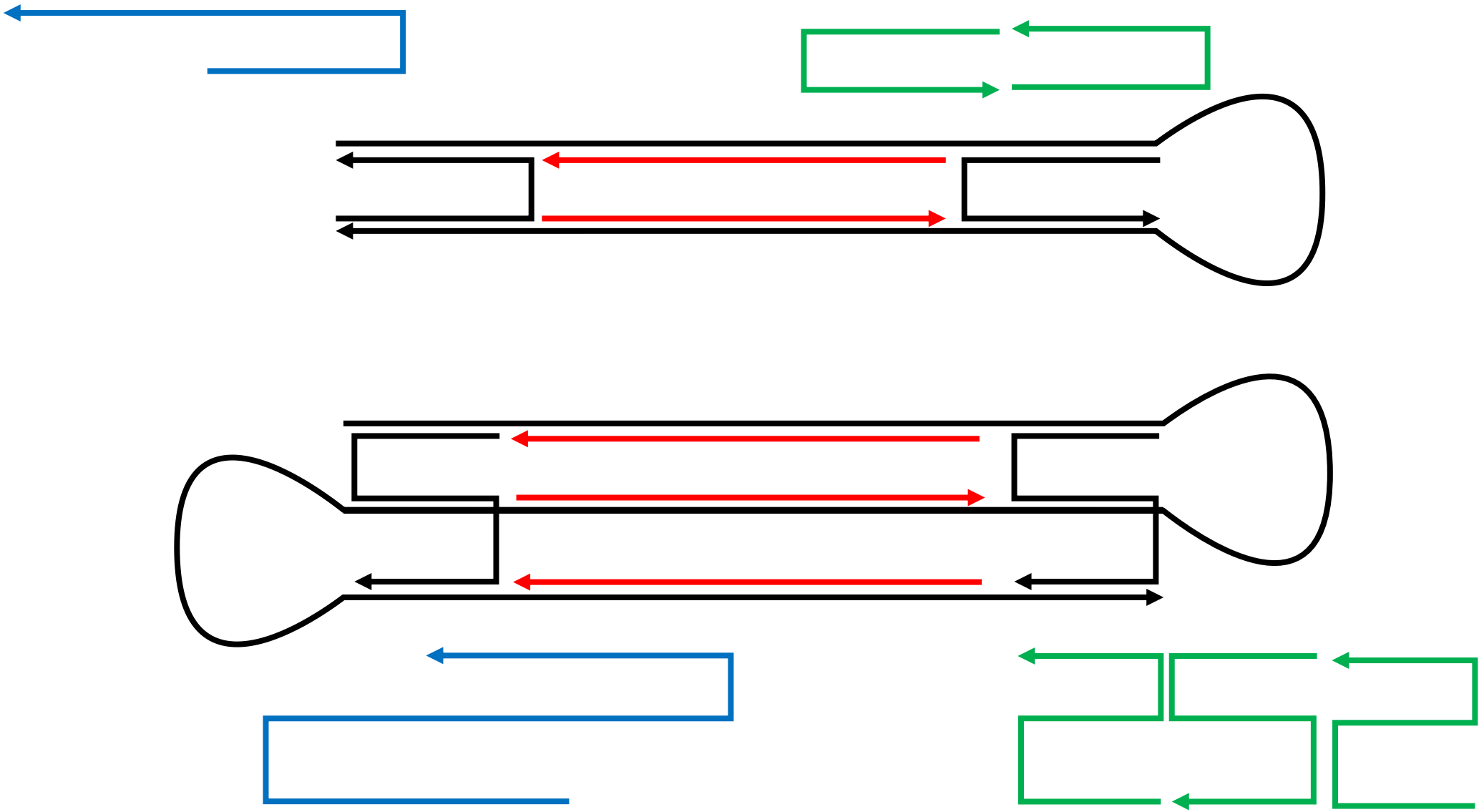

Thermodynamic self-assembly

Grafting the TBN model onto self-assembly

A modest goal

- **Informal**: Design monomers that self-assemble arbitrarily large complexes.
  - size of a complex = # monomers in the complex

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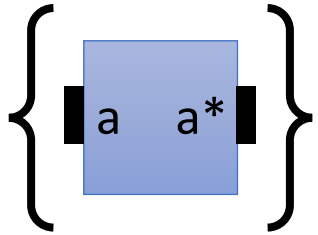
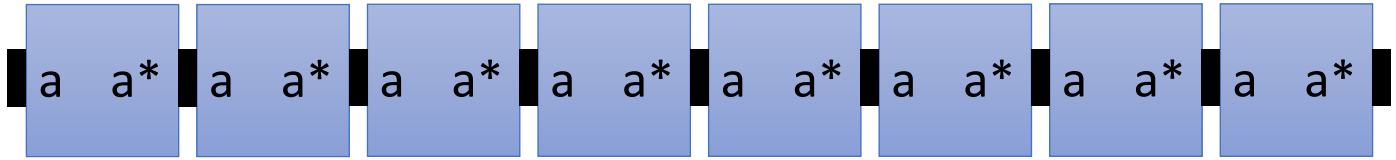
- Easy to do in Abstract Tile Assembly Model:

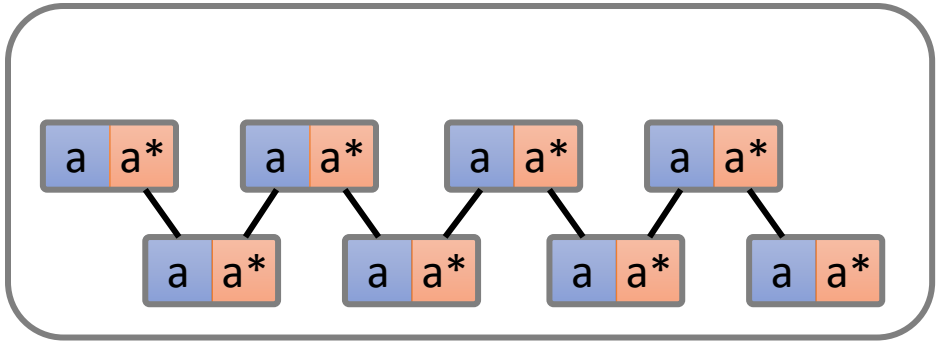
set of monomer types:



size-8 complex (assembly) formed with 8 copies of monomer



Difficulty of self-assembling large complexes



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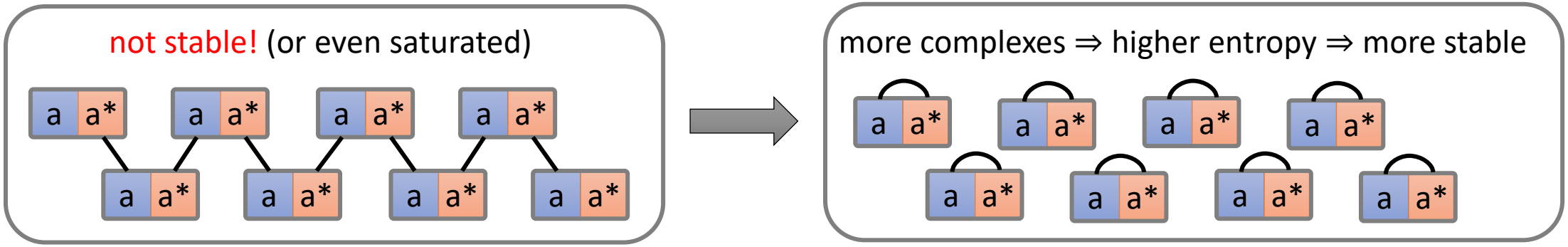

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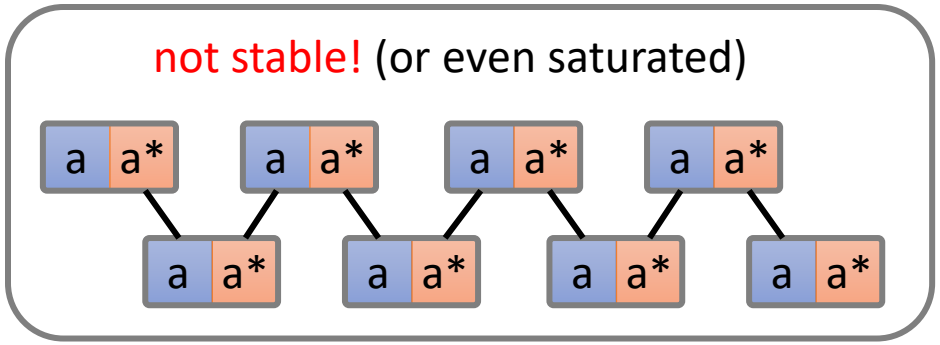
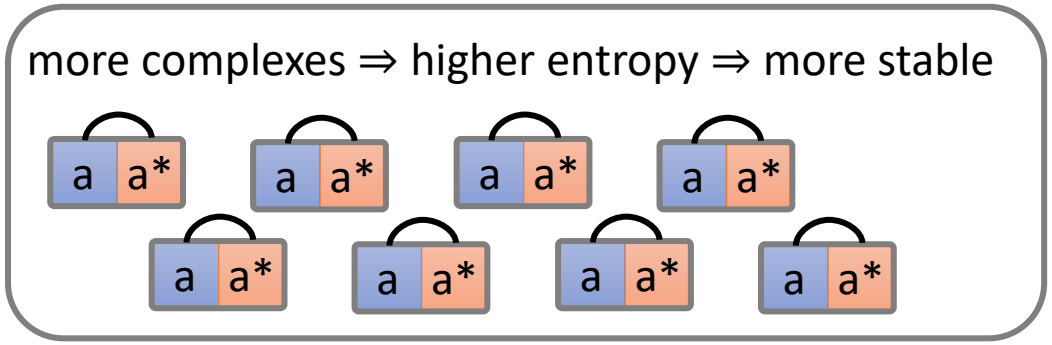
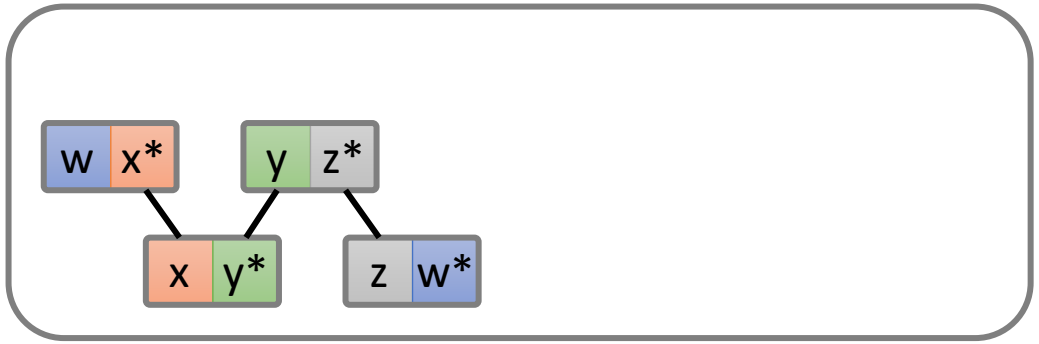




attempt 2:



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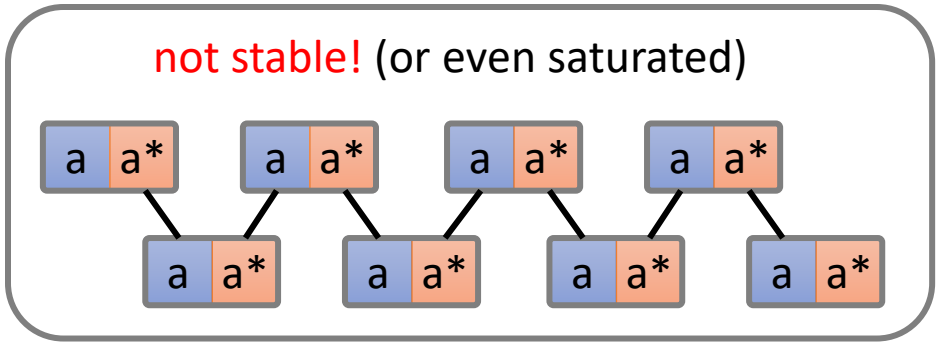

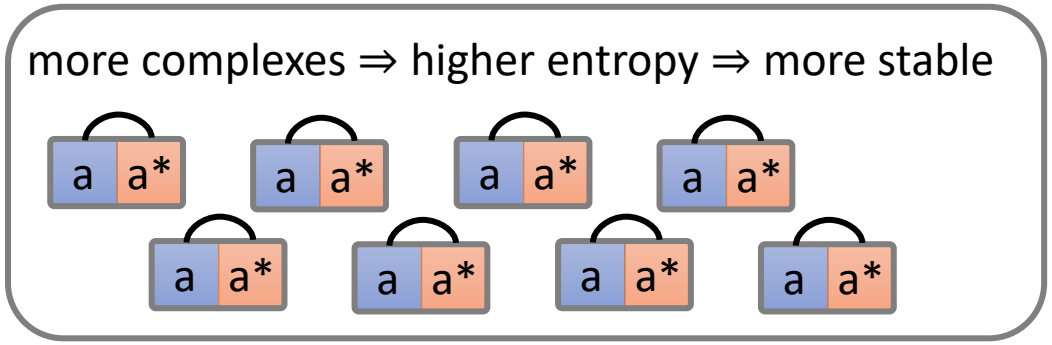

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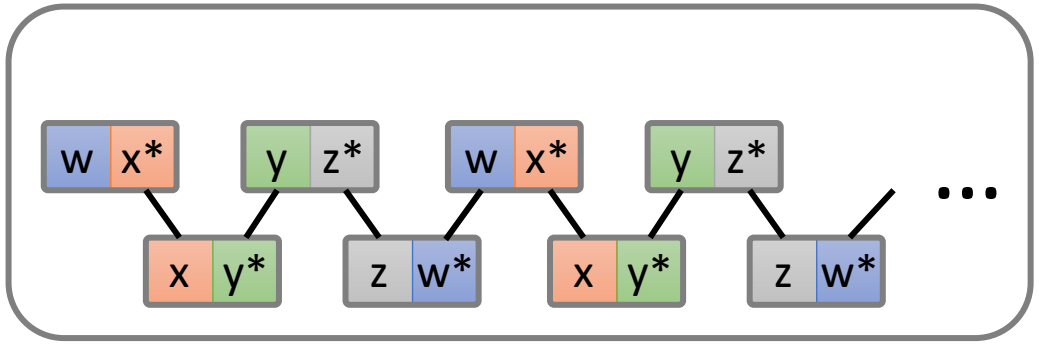

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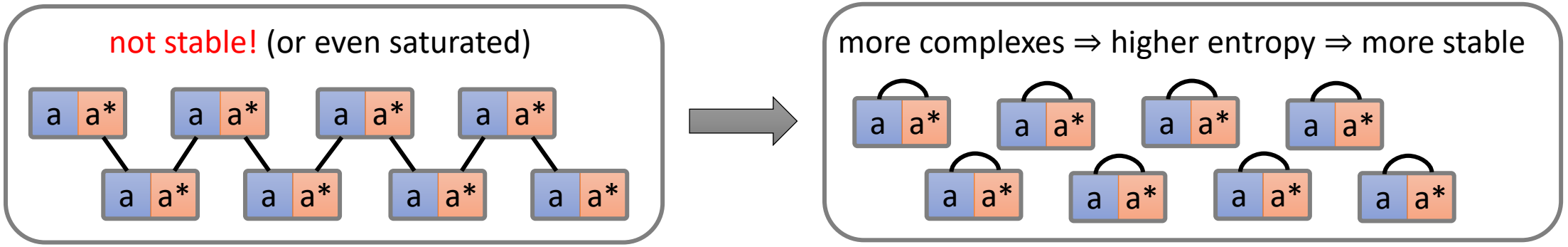

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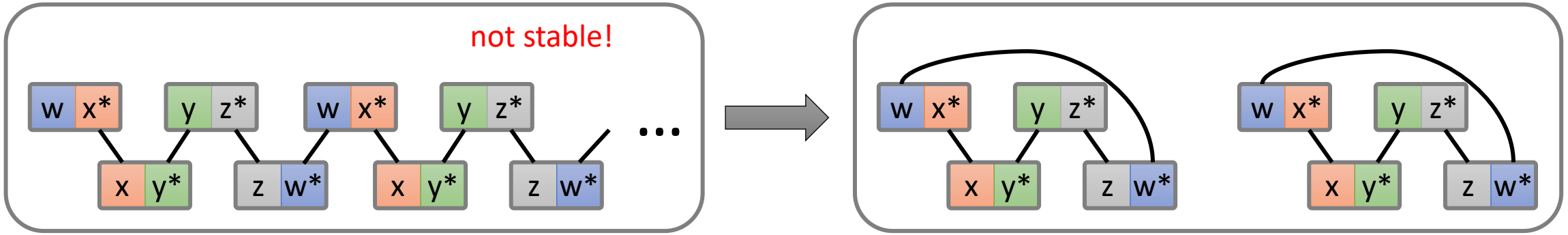

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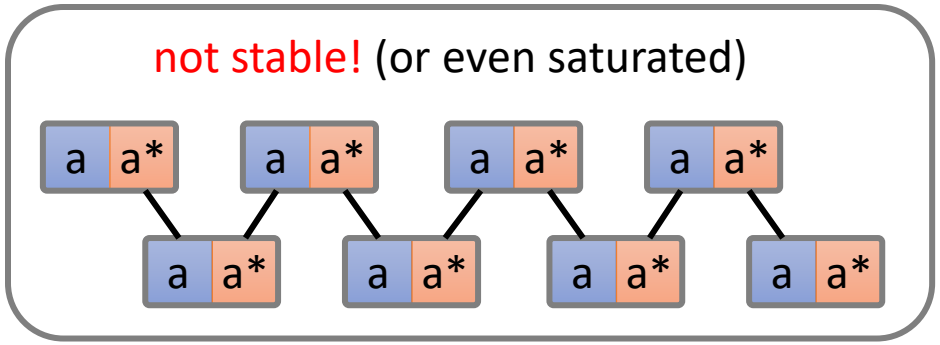

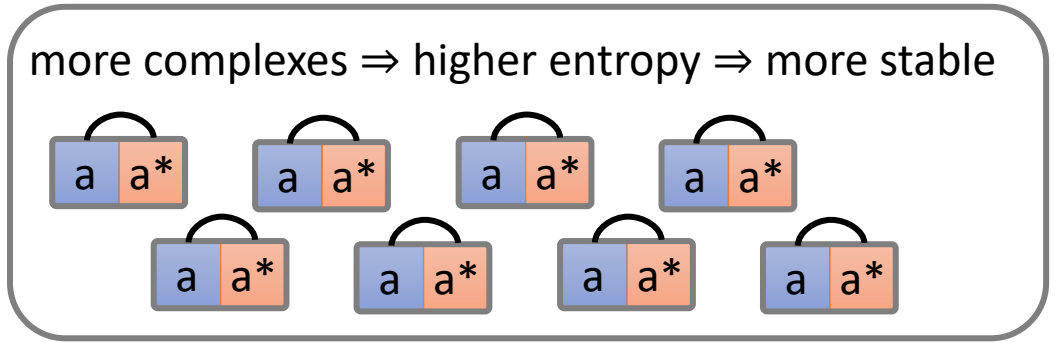

These have more complexes, and each is self-saturating
(every domain can be bound *within* the complex)

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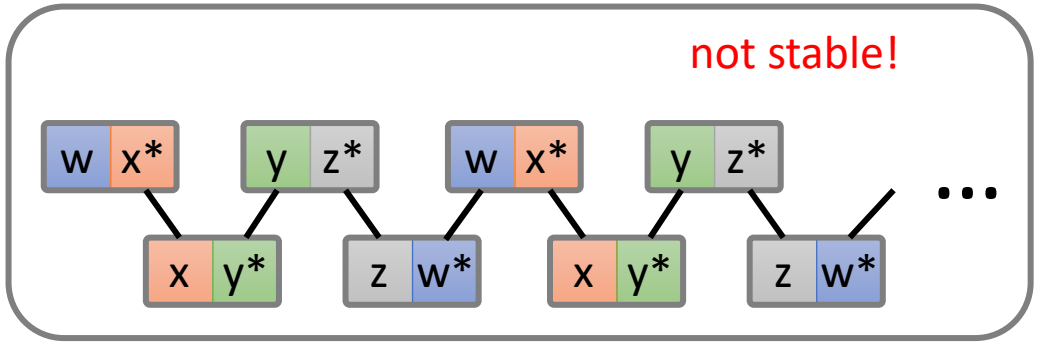

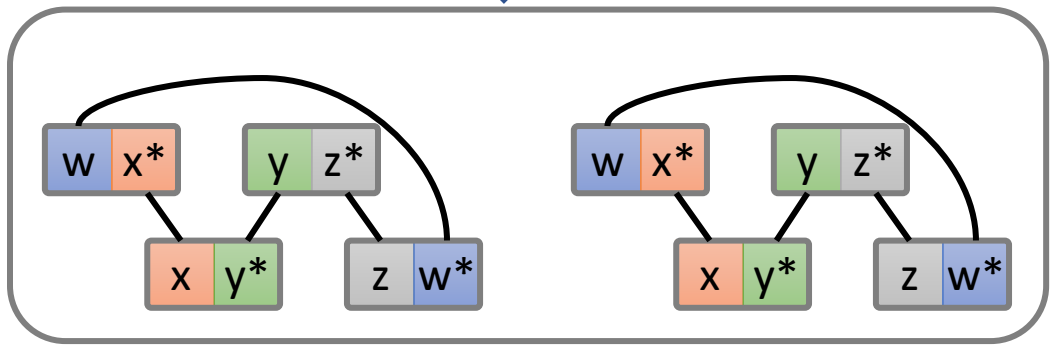

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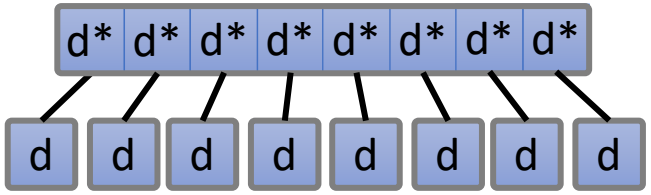

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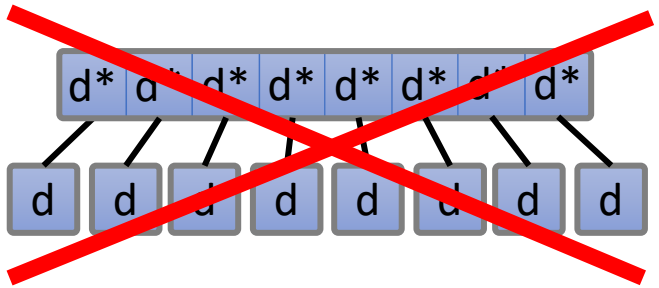

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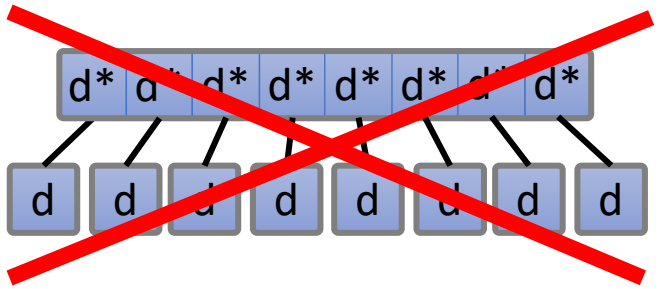

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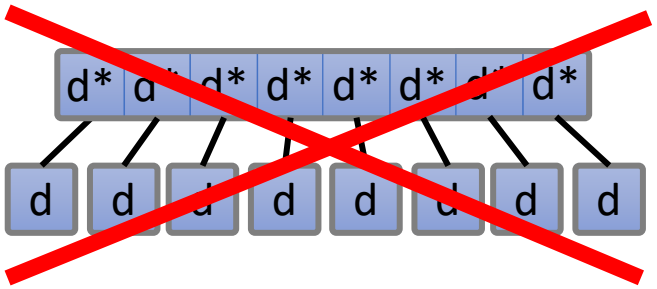

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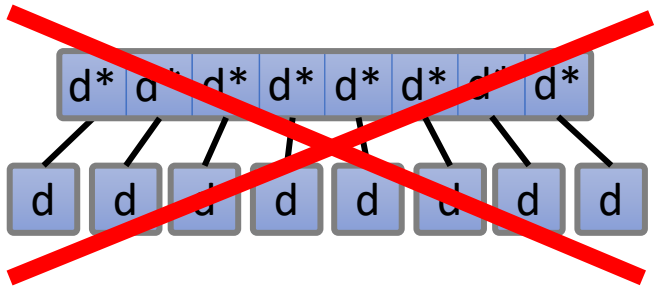

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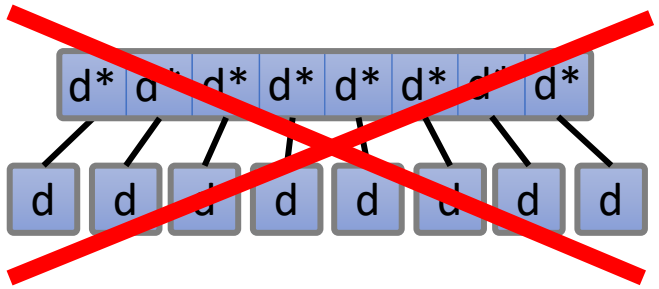

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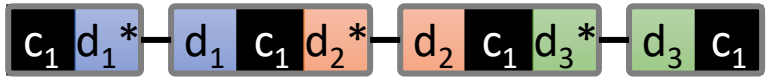

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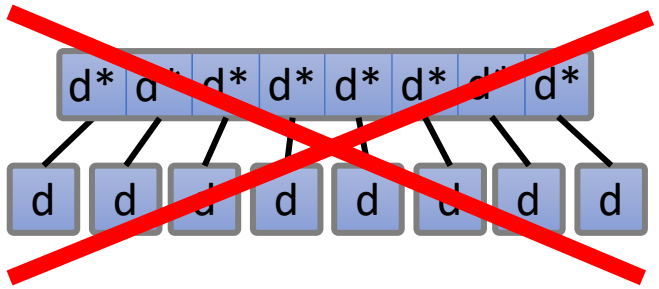

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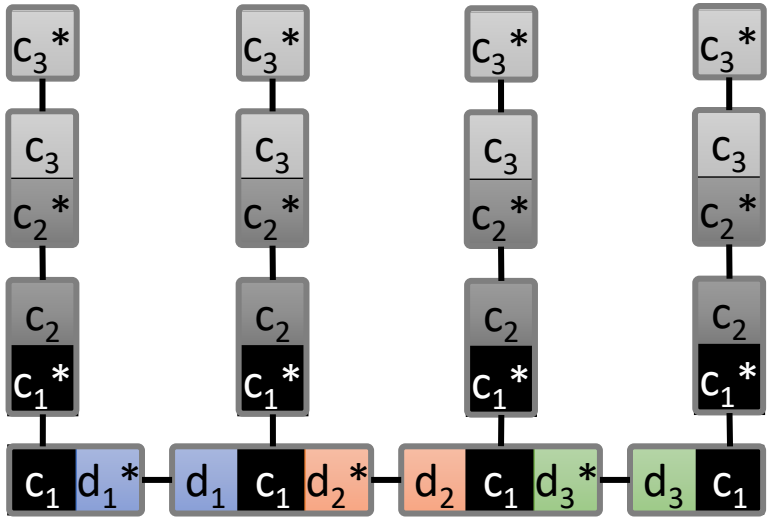

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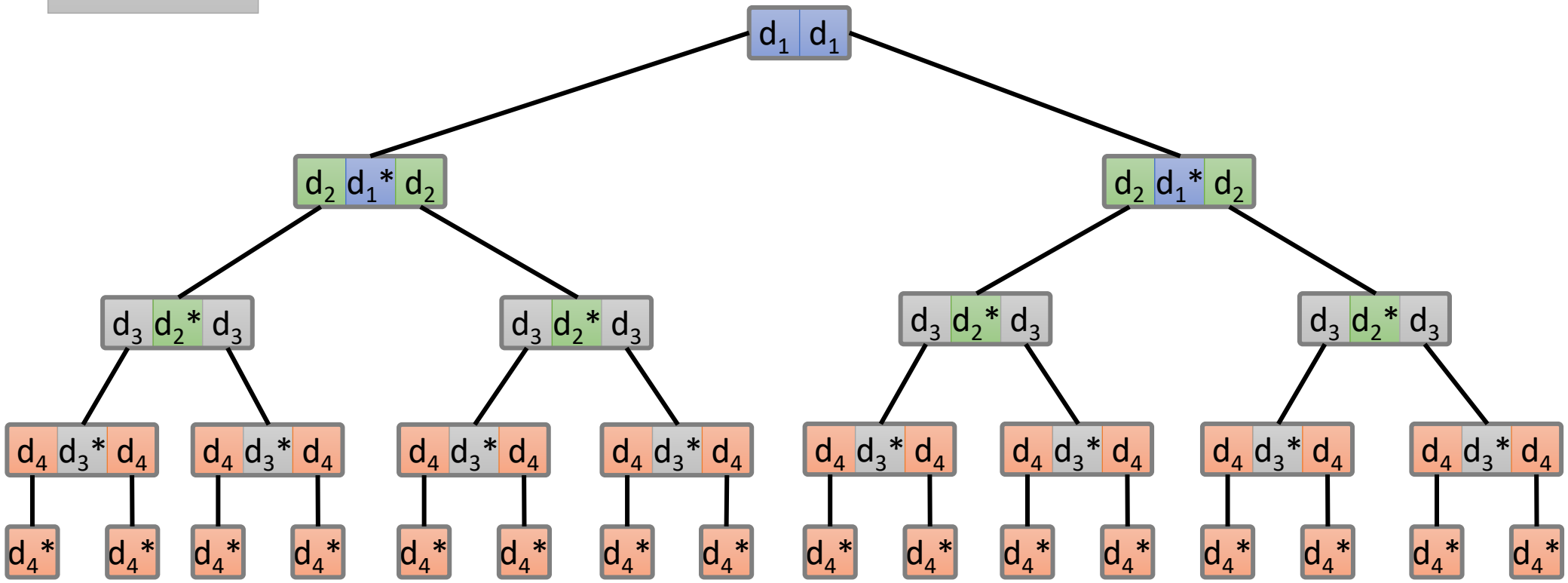

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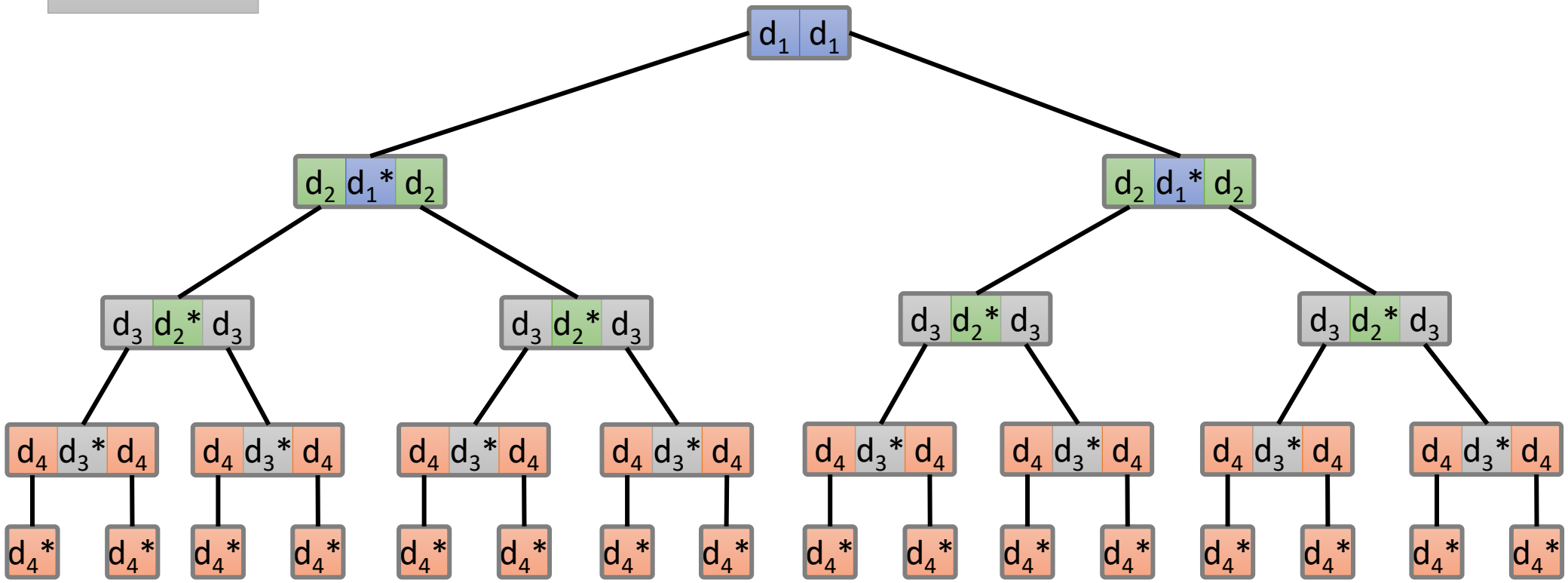

How large can we make *S* relative to *D* and *M*?

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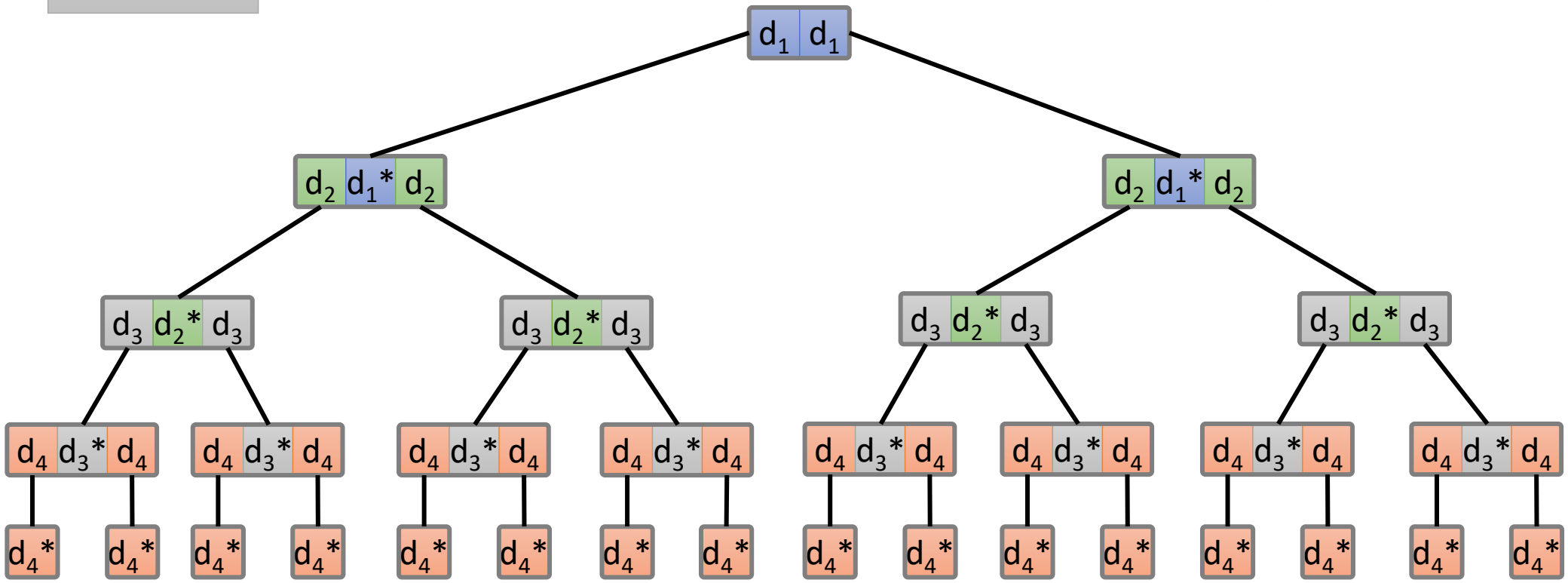


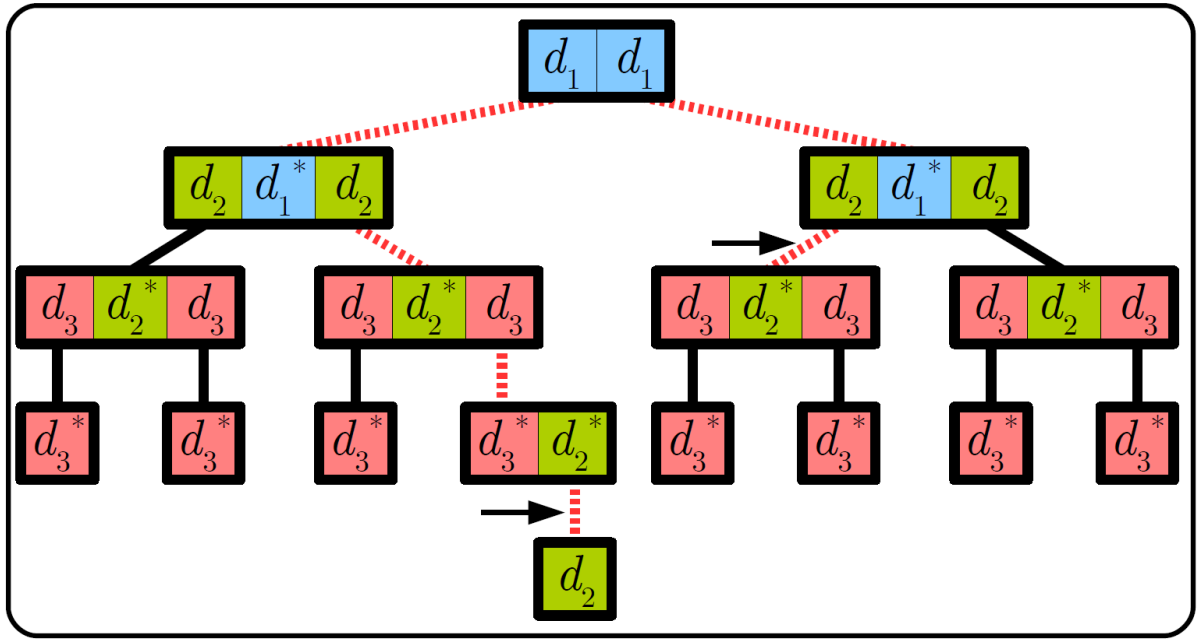
Stable complexes have at most exponential size

Theorem: Any thermodynamic binding network with

- D domain types,
- M monomer types,
- $\leq A$ domains per monomer type (note $D/A \leq M \leq A^{D+1}$)

Has stable complexes of size $\leq 2(M+D)(AD)^{2D+3} = \text{poly}(D^D)$ if $A = O(1)$

Easy proof if binding graph is acyclic (tree)



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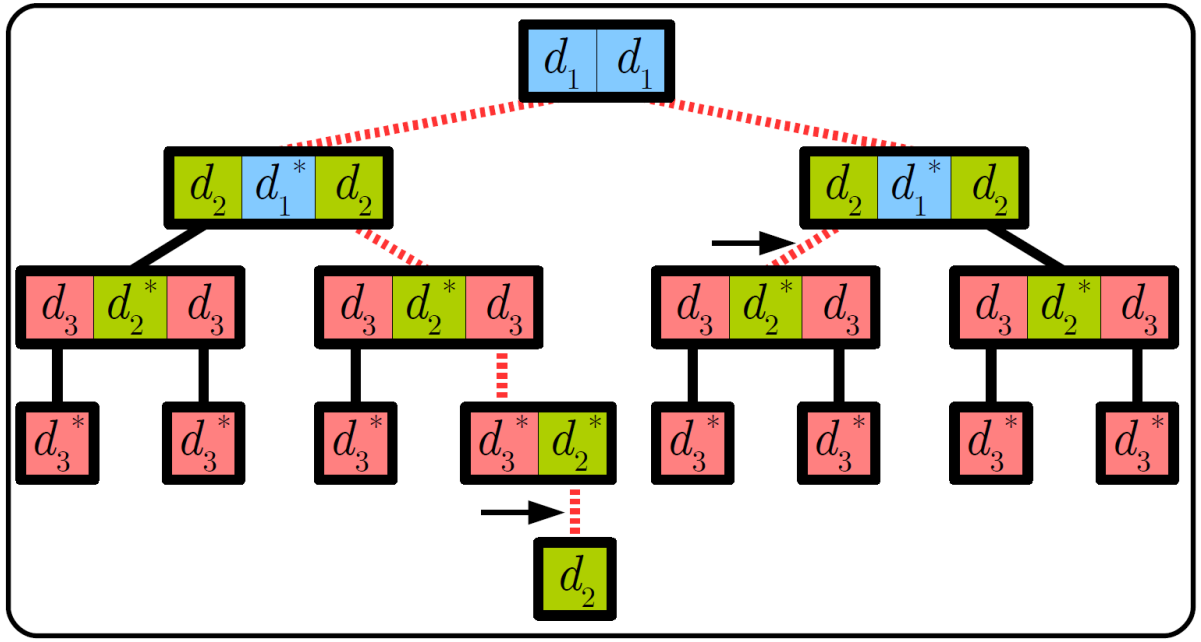

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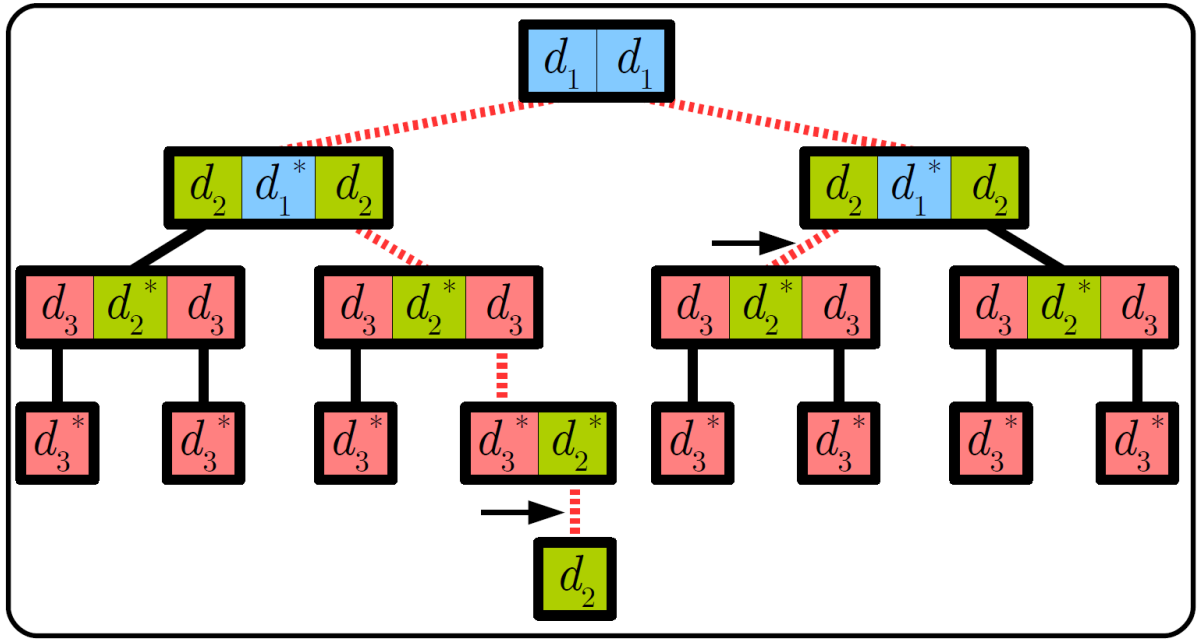

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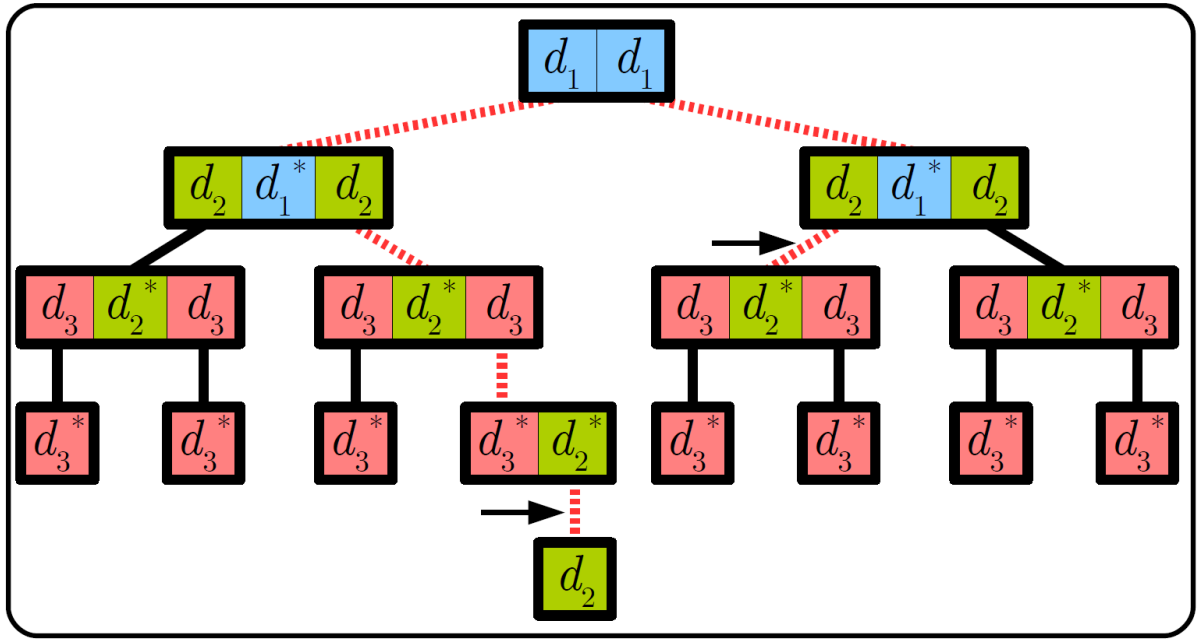

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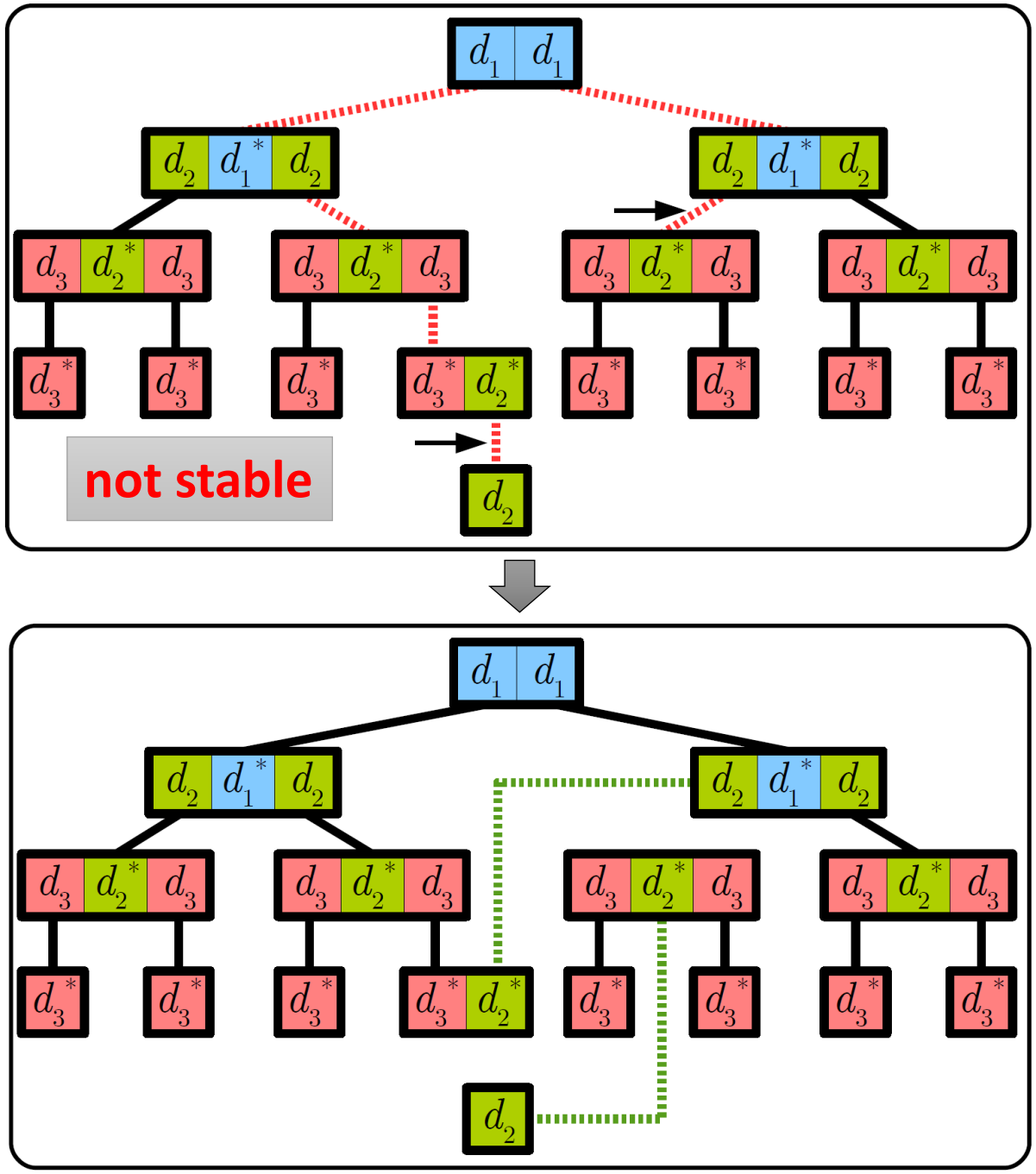
- Break into two saturated complexes as shown.



Monomers as vectors

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- sum of many monomers gives the number of excess domains in a fully bound (saturated) complex with those monomers
  - i.e., 2 copies of above monomer 2·(1,-2,0,3,0) = (**2**,**-4**,**0**,**6**,**0**) have an excess of **2** a's, **4** b*'s, **0** c's, **6** d's, **0** e's

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Original goal: Design a set of monomer types so that, for all $S \in \mathbb{N}$, there is a stable complex P of size $\geq S$.

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6. i.e., we can split S_2 into 2 disjoint nonempty nonnegative subsets, S_1 and $M \cdot d$. **QED**

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  - So **z** is a strictly smaller solution than **x**: **x** cannot be the *smallest* solution.

Farkas' Lemma

Given vectors $\mathbf{m}_1$, $\mathbf{m}_2$, … , they obey one of two constraints:

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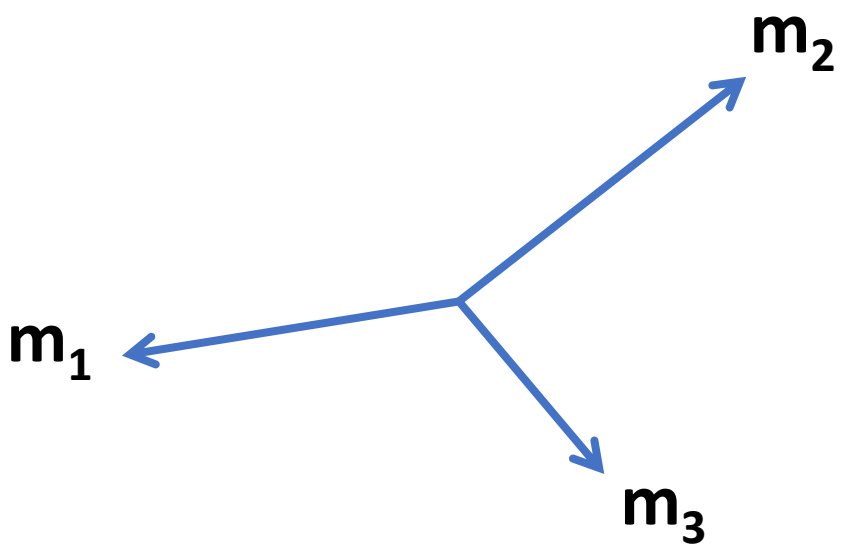
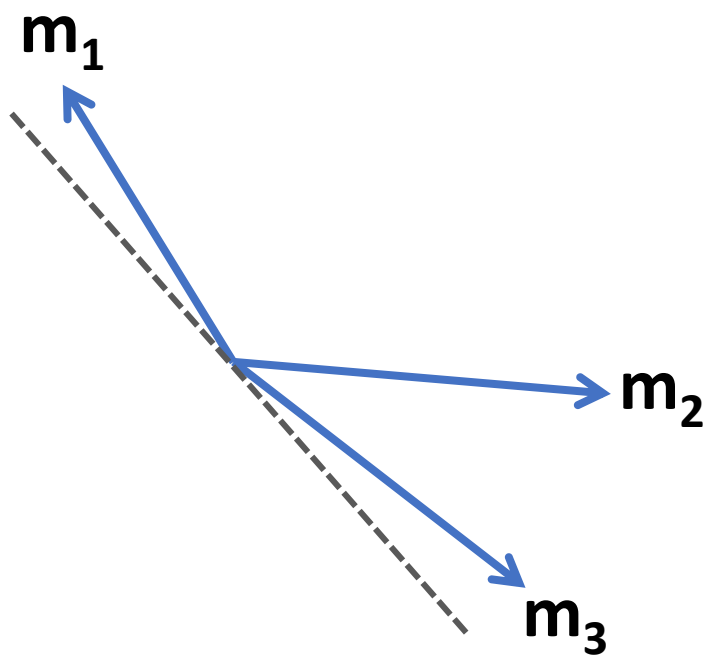


b) lie on one side of some hyperplane



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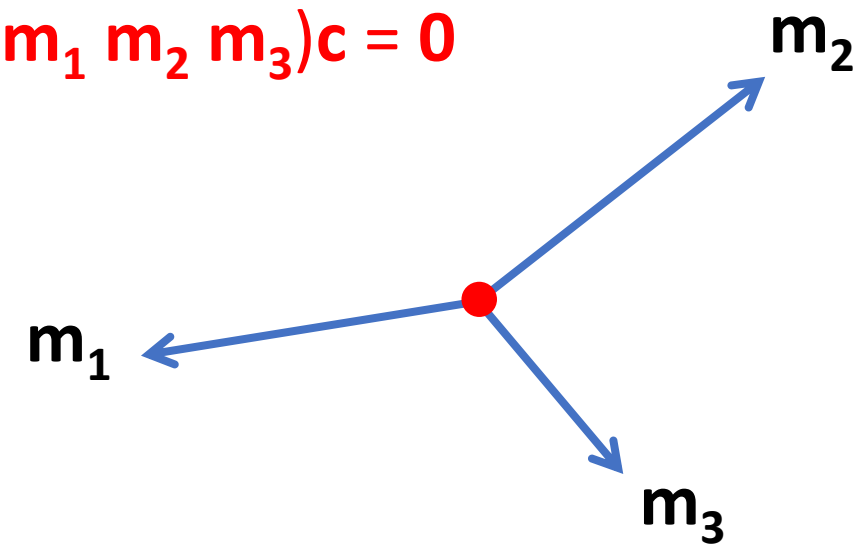
$\exists \mathbf{c}$ (counts of monomers)

$(\mathbf{m}_1\ \mathbf{m}_2\ \mathbf{m}_3)\mathbf{c} = \mathbf{0}$



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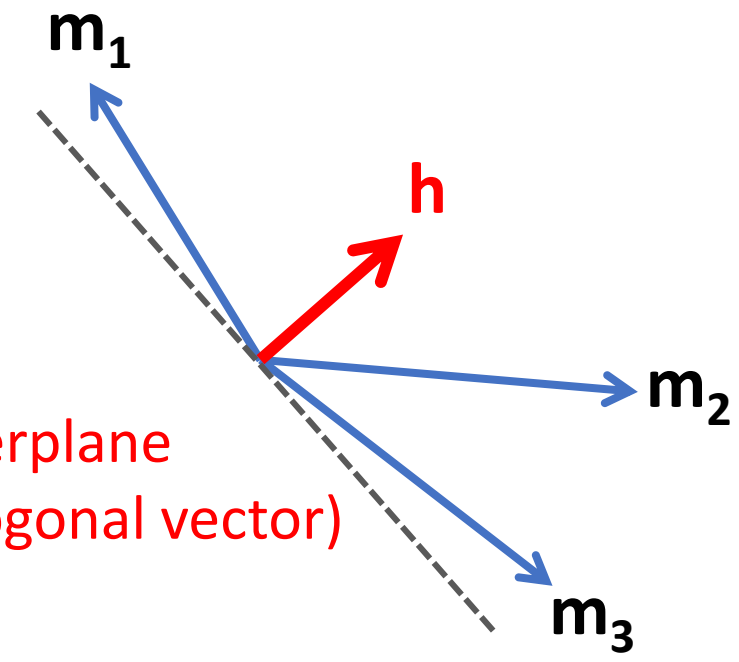
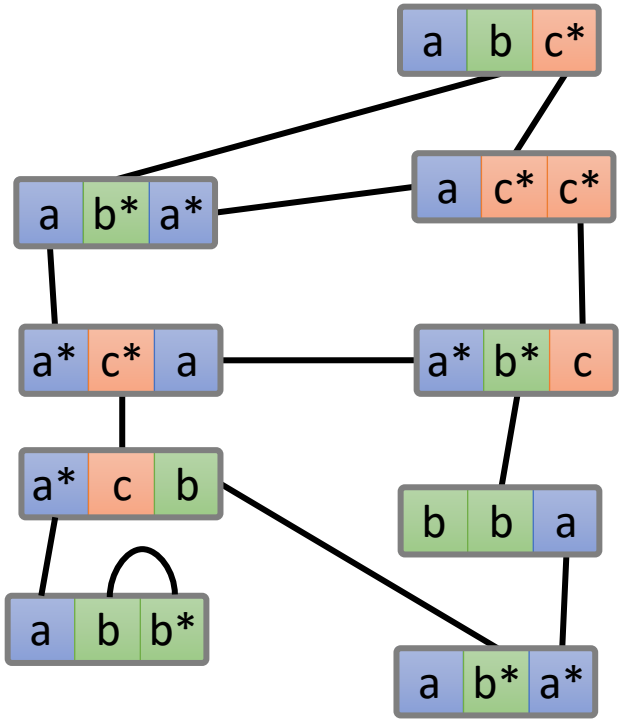


$\exists \mathbf{h}$ (hyperplane orthogonal vector)

$\mathbf{h} \cdot \mathbf{m}_i \geq 1$

How to prove exponential complex size bound for complexes with cycles in binding graph?

monomer collection $\mathbf{c} \in \mathbb{N}^M$



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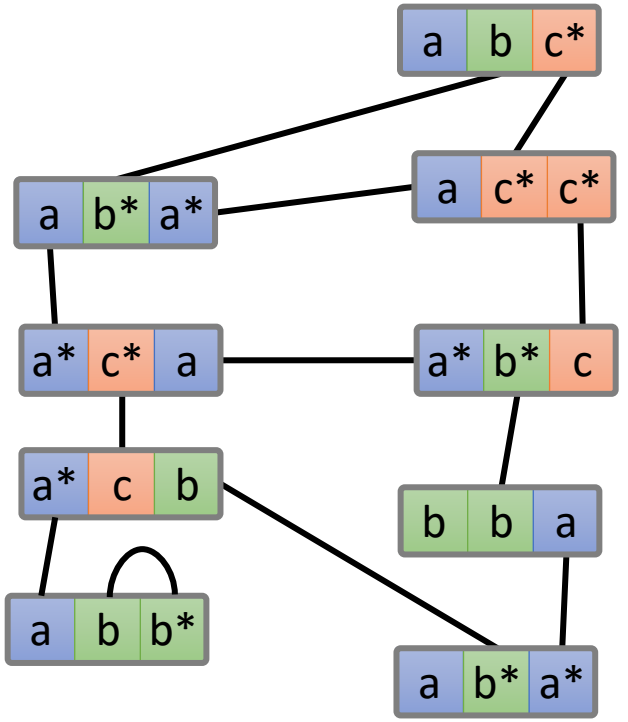

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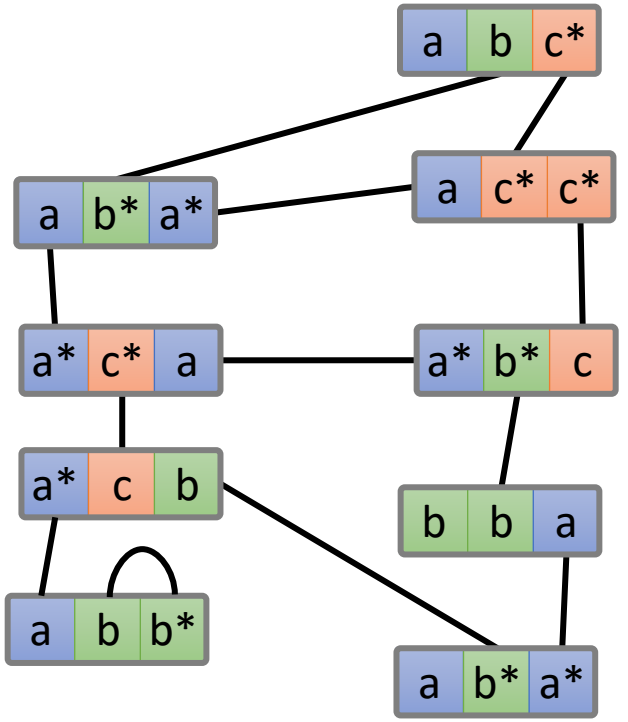

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a b c

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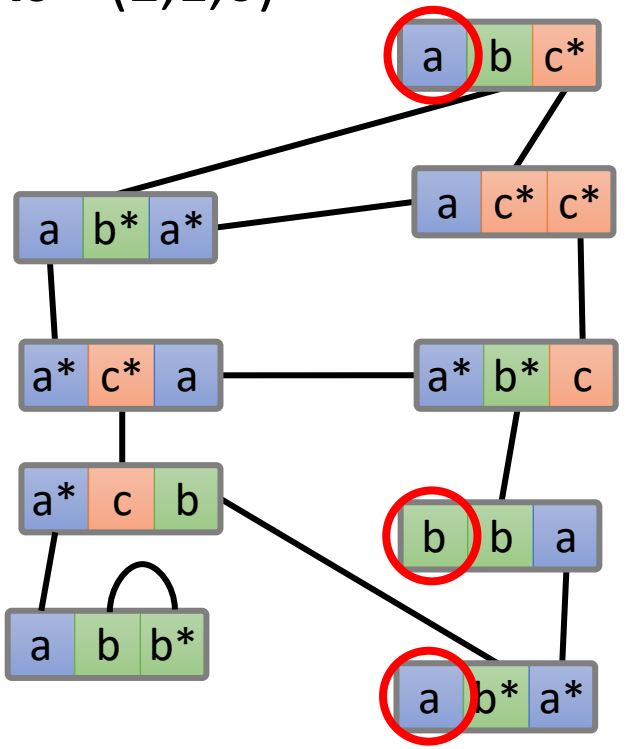

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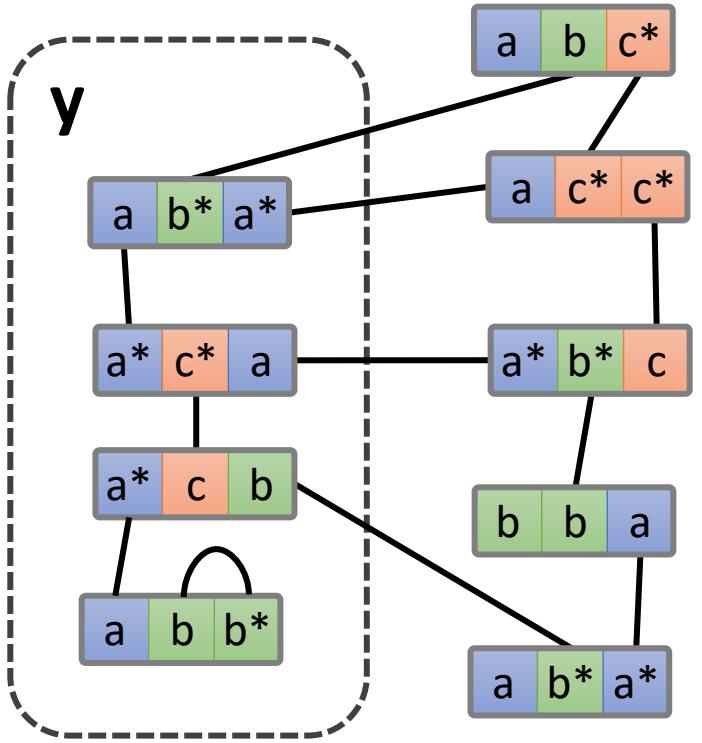

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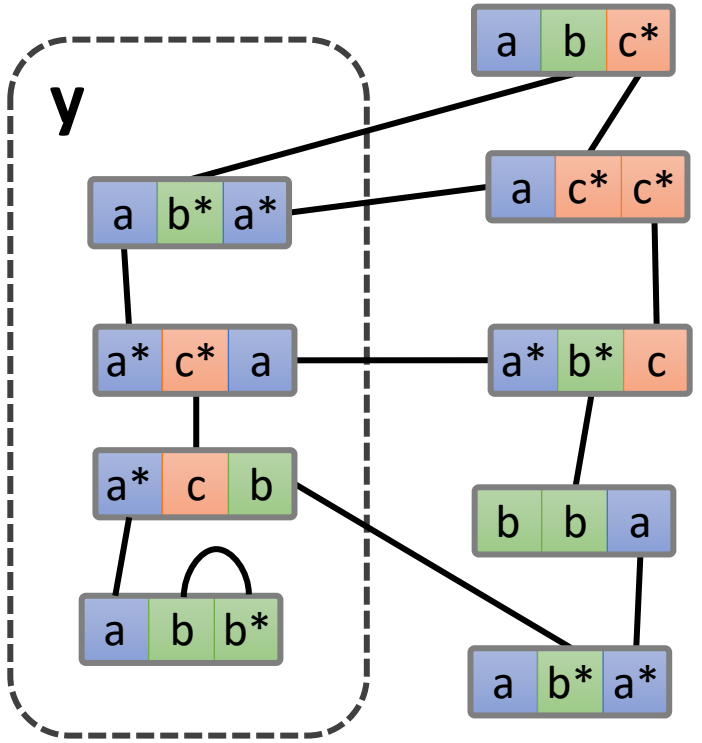

How to prove exponential complex size bound for complexes with cycles in binding graph?

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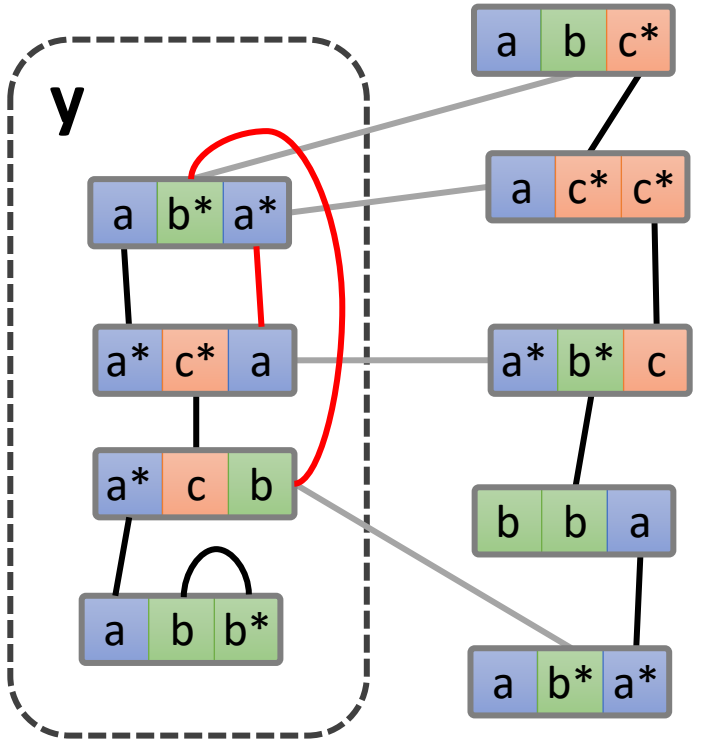

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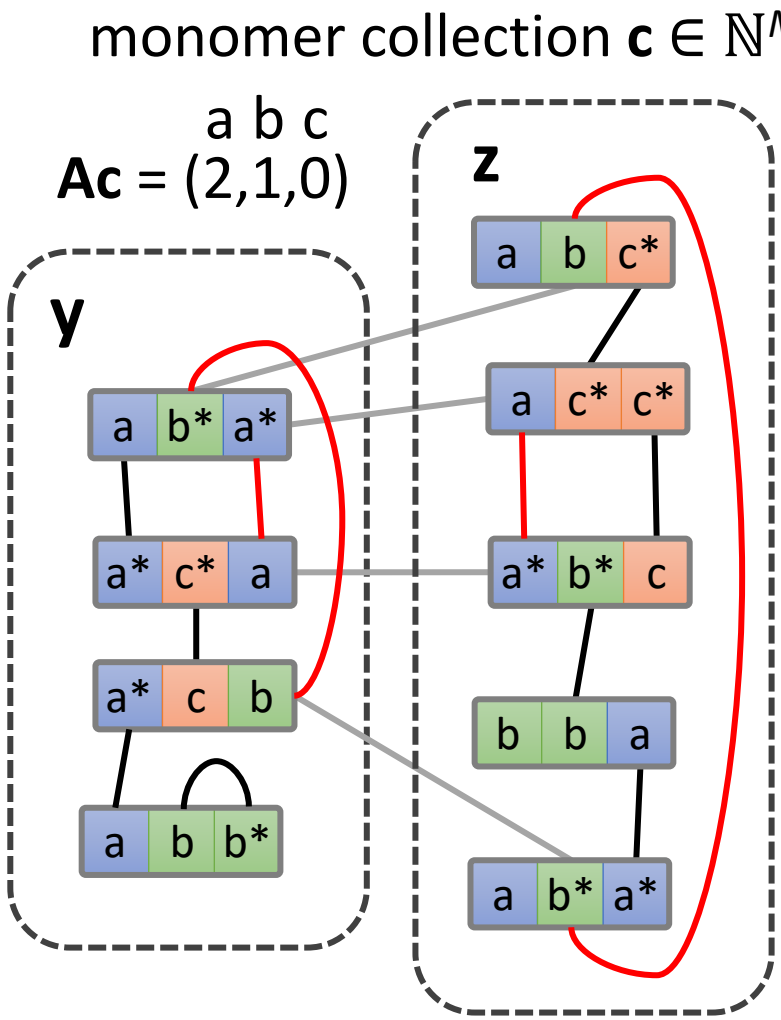
- By symmetry, the same bonds in **z** = **c** – **y** can be re-bound within **z**.



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- Then "small"$_2 \geq -\sum_{i\in S}(\mathbf{h}\cdot\mathbf{m_i})\mathbf{c}(i) = \sum_{i\notin S}(\mathbf{h}\cdot\mathbf{m_i})\mathbf{c}(i) \geq \sum_{i\notin S}\mathbf{c}(i)$

c(i) (count of i'th monomer) is small by definition, and $\mathbf{h}\cdot\mathbf{m_i} = O(1)$

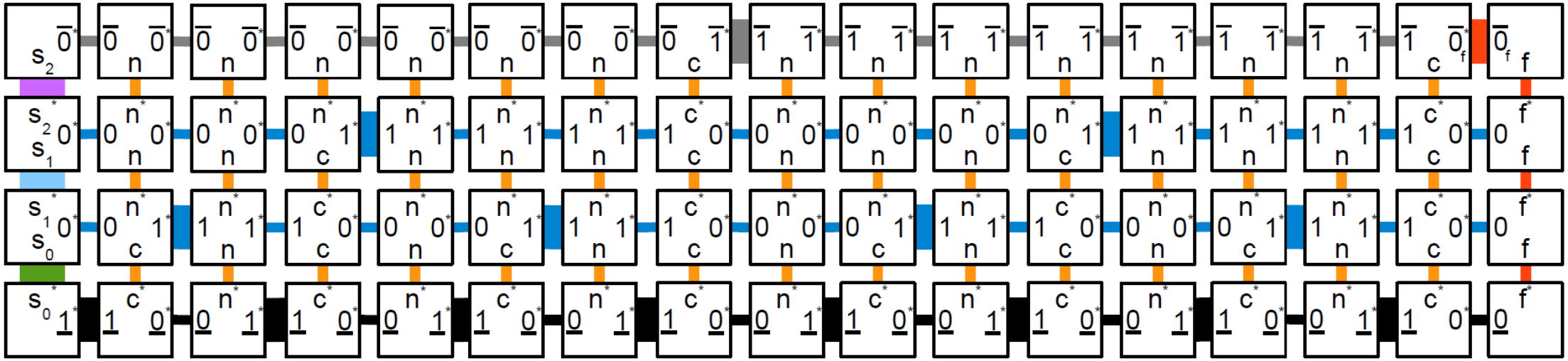
above

since $\mathbf{h}\cdot\mathbf{m_i} \geq 1$

Applying thermodynamic model to tile assembly

- Let’s incorporate the thermodynamic binding network model into the abstract tile assembly model.
- How can we create a large assembly from a small number of tile types?

A thermodynamically unstable tile assembly counter



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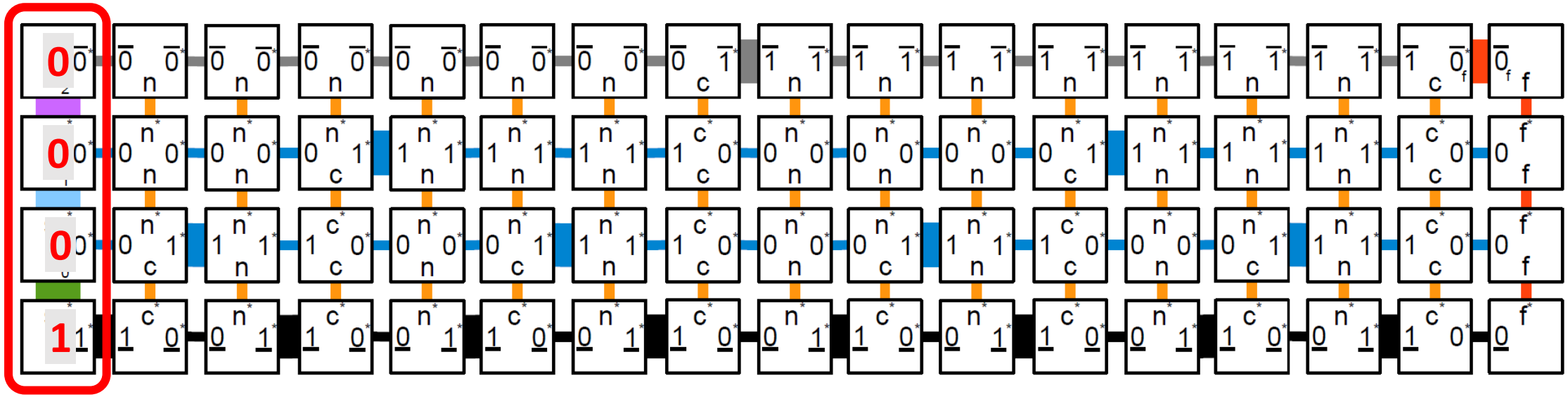

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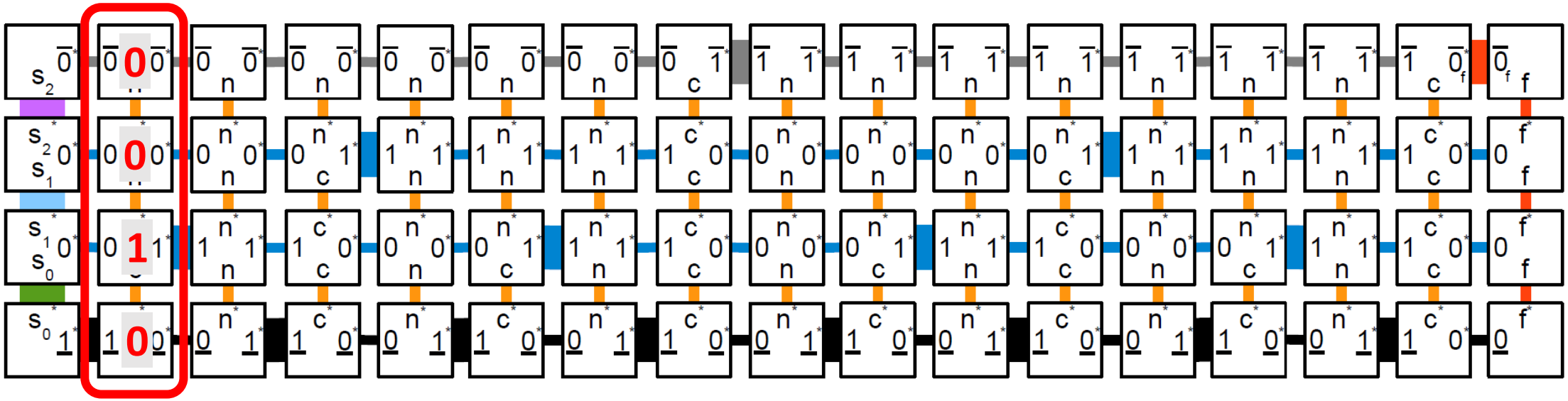

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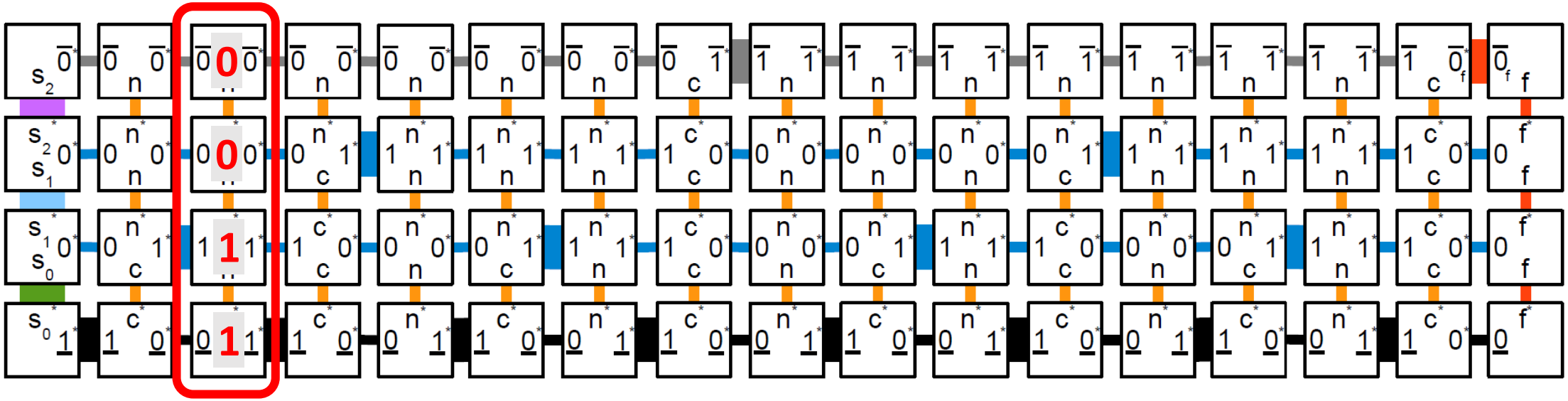

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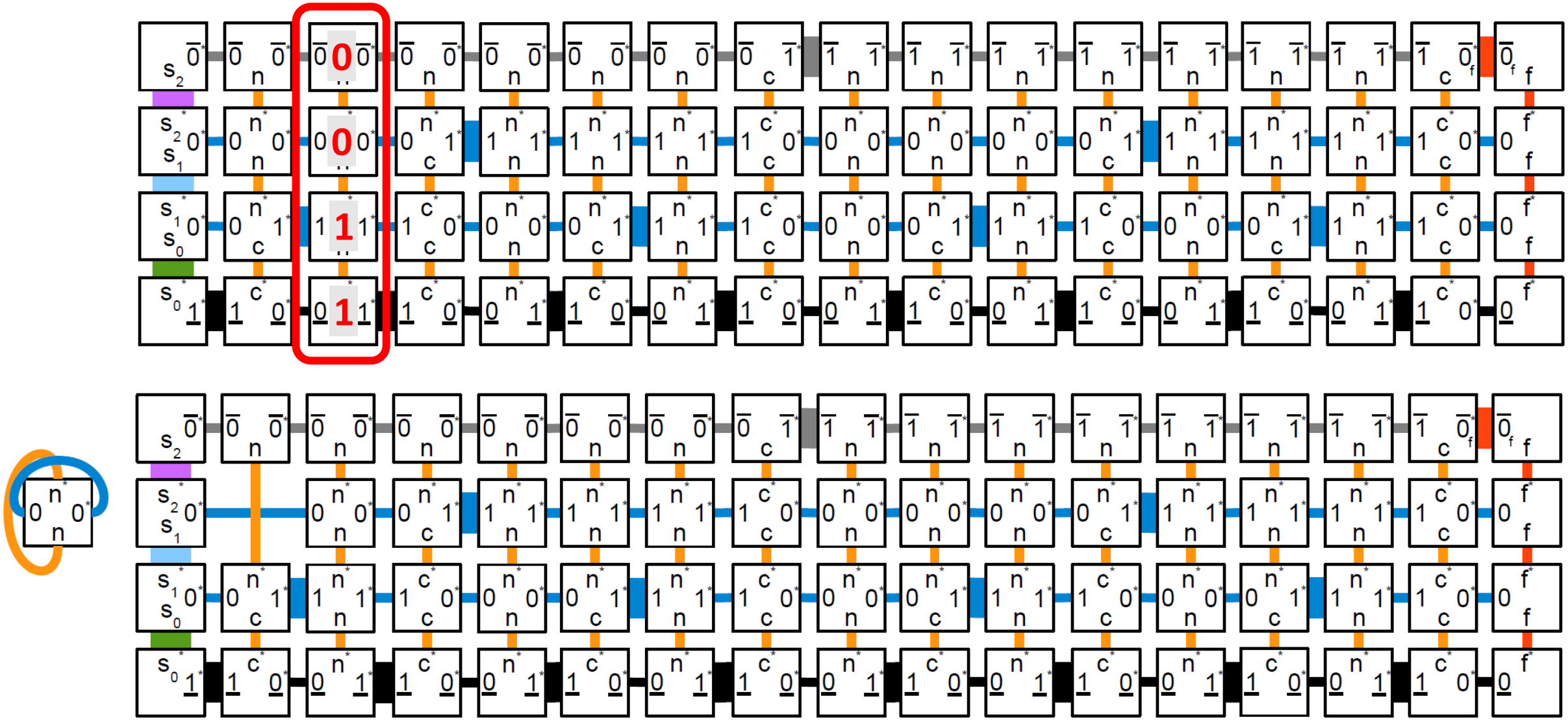
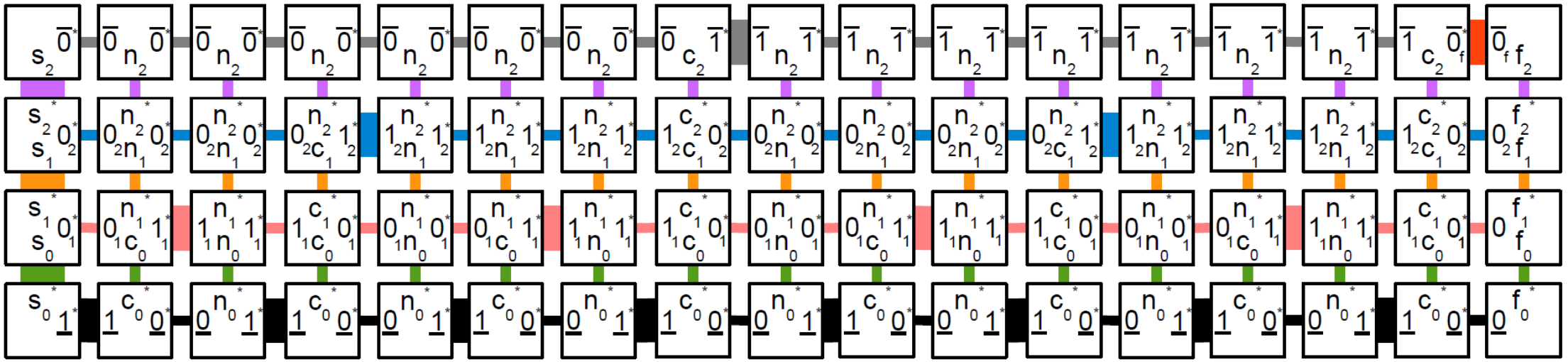


A thermodynamically stable tile assembly counter

Difference is that each row (corresponding to bits of the same significance) has glues labeled with the row number



Conclusions

- Strong bonds (surprisingly) aren't sufficient to self-assemble large thermodynamically stable structures. *Geometry helps*!
- Kinetically self-assembling a thermodynamically stable structure has very strong guarantees on errors:
  - target structure eventually results despite arbitrary kinetic errors.
  - If it's the only stable structure, and free energy of other structures is much less, then it's the only result you'll see.
- Bad news: **NP**-complete to tell if a given configuration is unstable… even **NP**-hard to approximate entropy of stable configuration:

  [Breik, Thachuk, Heule, Soloveichik, *Computing properties of stable configurations of thermodynamic binding networks*, Theoretical Computer Science 2019]