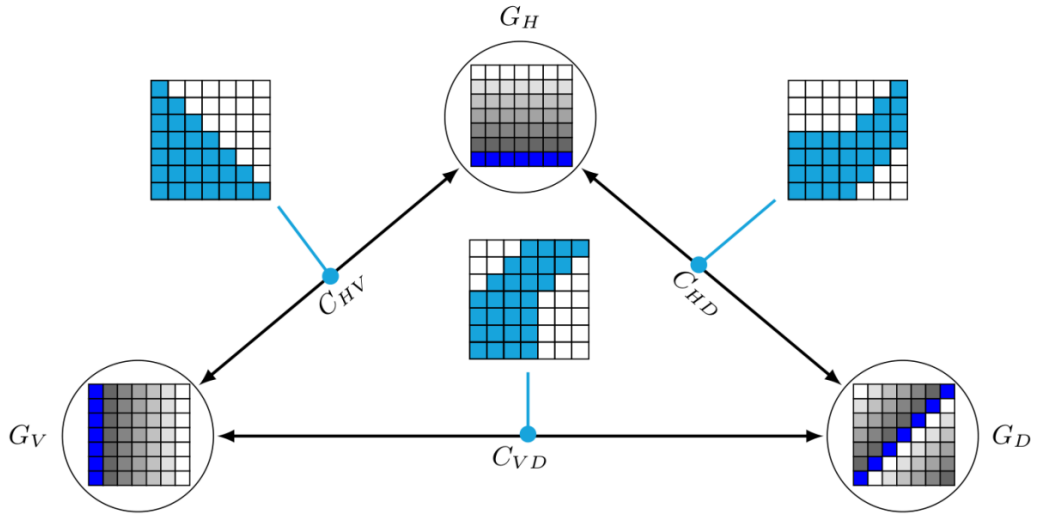

Digging (energy) wells for unknown substances:

Programming substrate-independent energy barriers in catalytic chemical reactions

David Doty

Maynooth University CS Colloquium, May 8th, 2019

Slides credit: David Haley

Joint work with: Keenan Breik, Cameron Chalk, David Haley, David Soloveichik

Acknowledgements

David Haley

Keenan Breik

Cameron Chalk

David Soloveichik

Goal

Build molecular computing systems that are reliable

Goal

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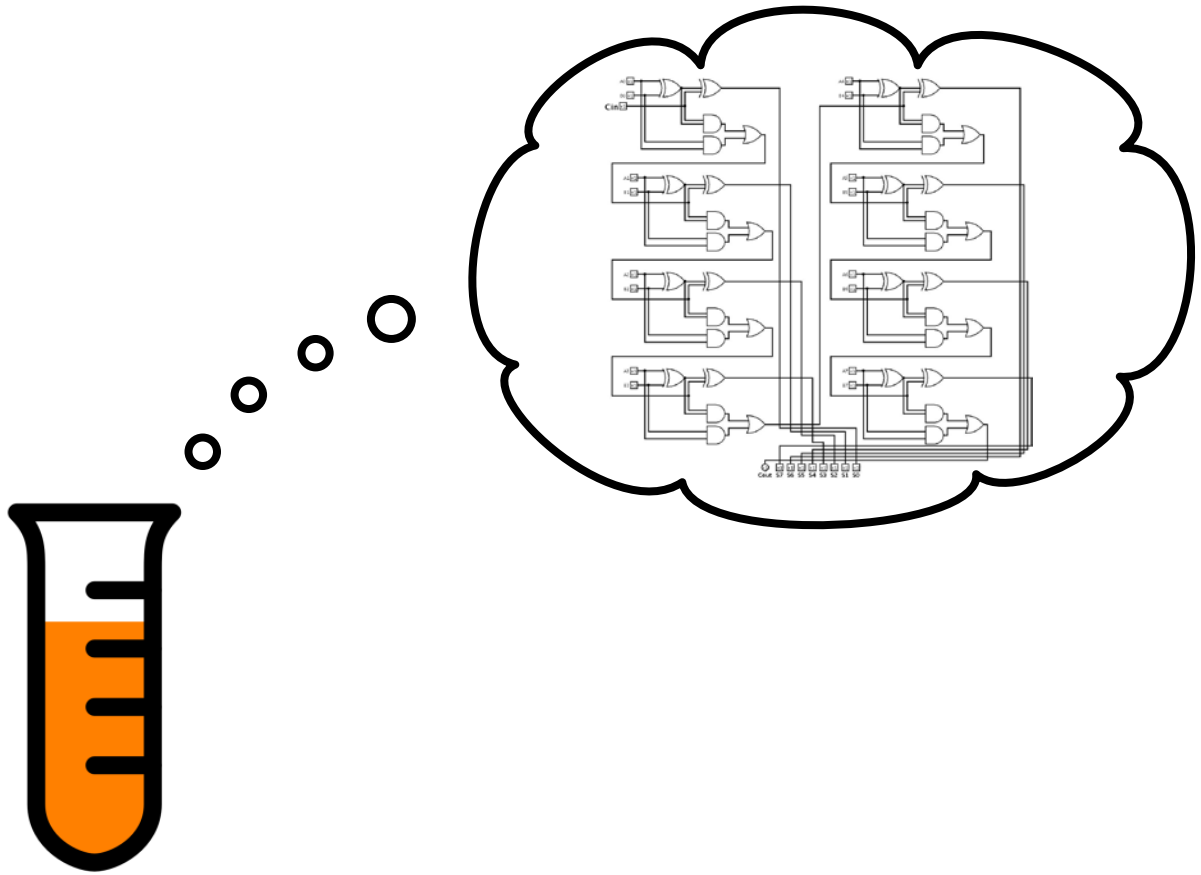
Goal

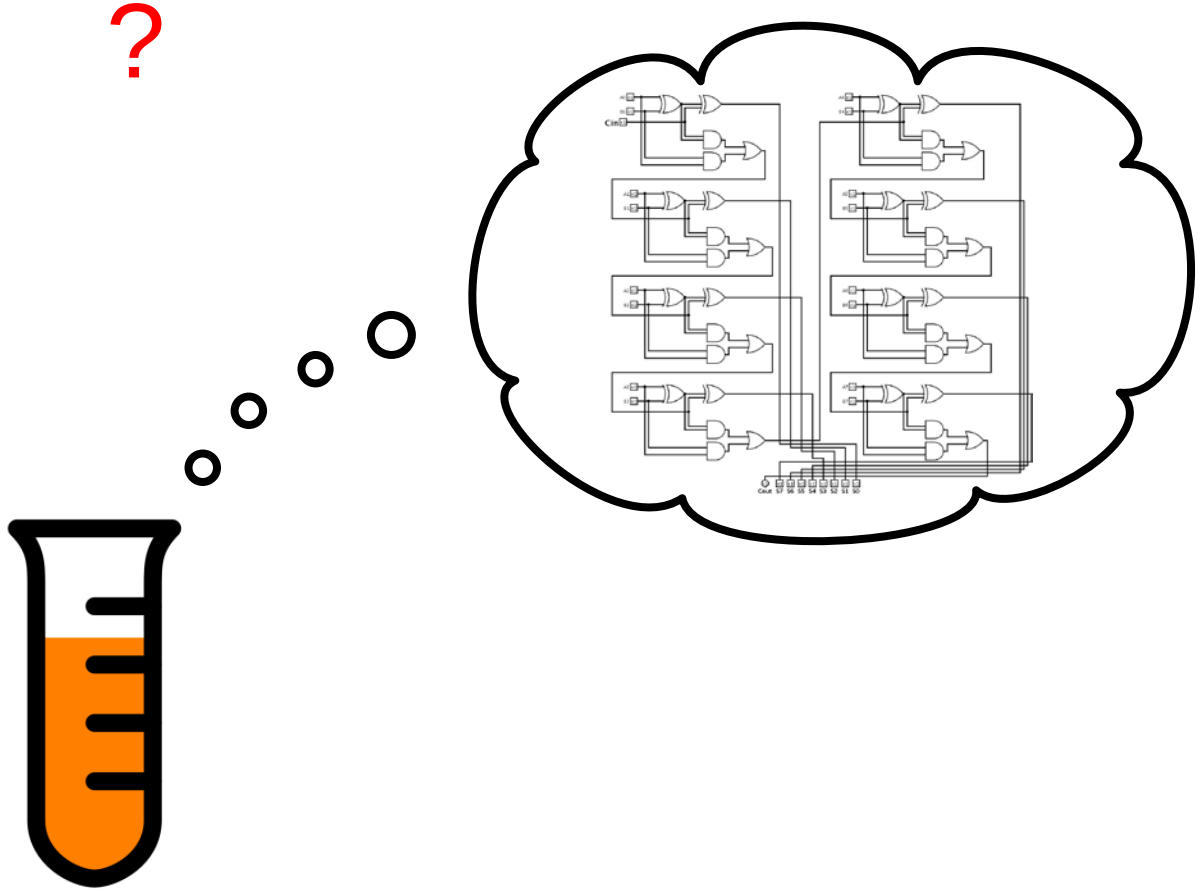
Build molecular computing systems that are reliable



Goal

Build molecular computing systems that are reliable

?



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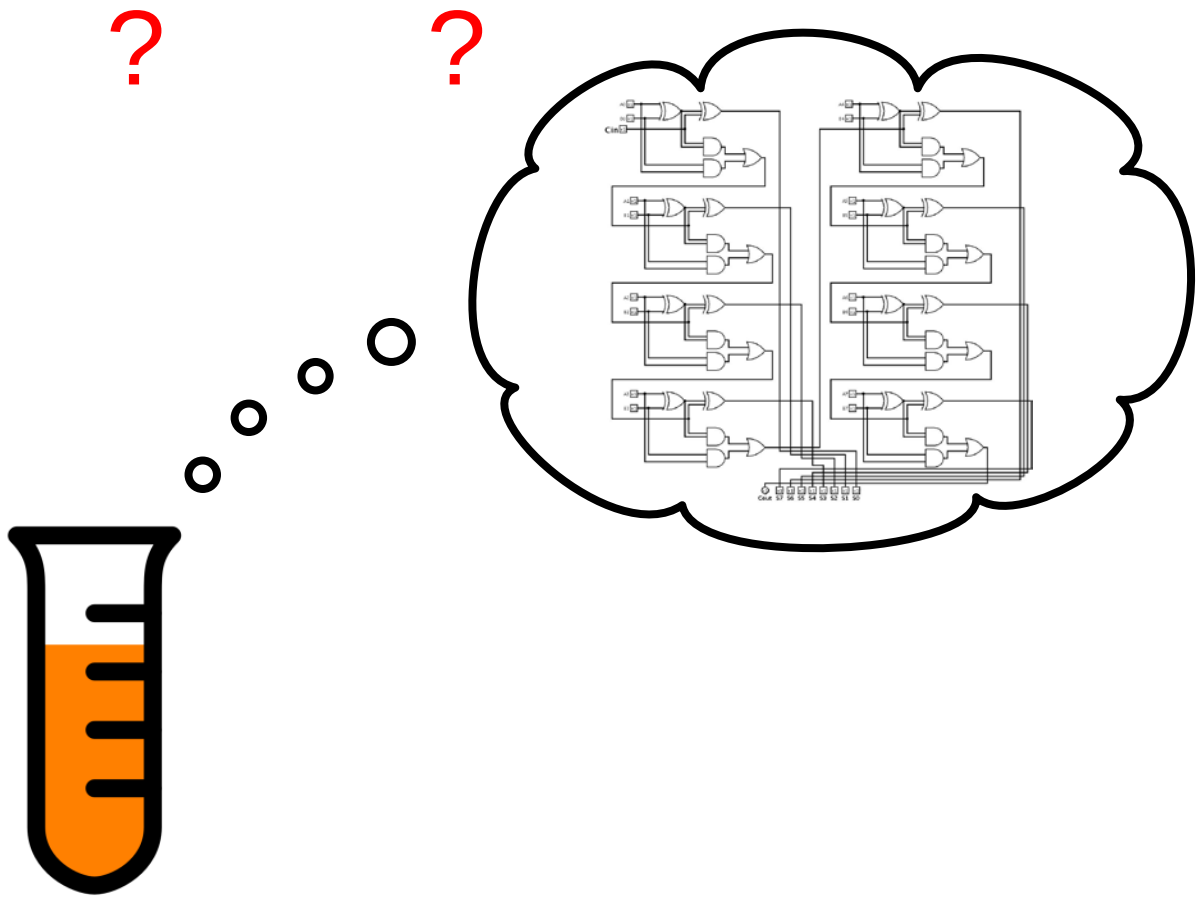
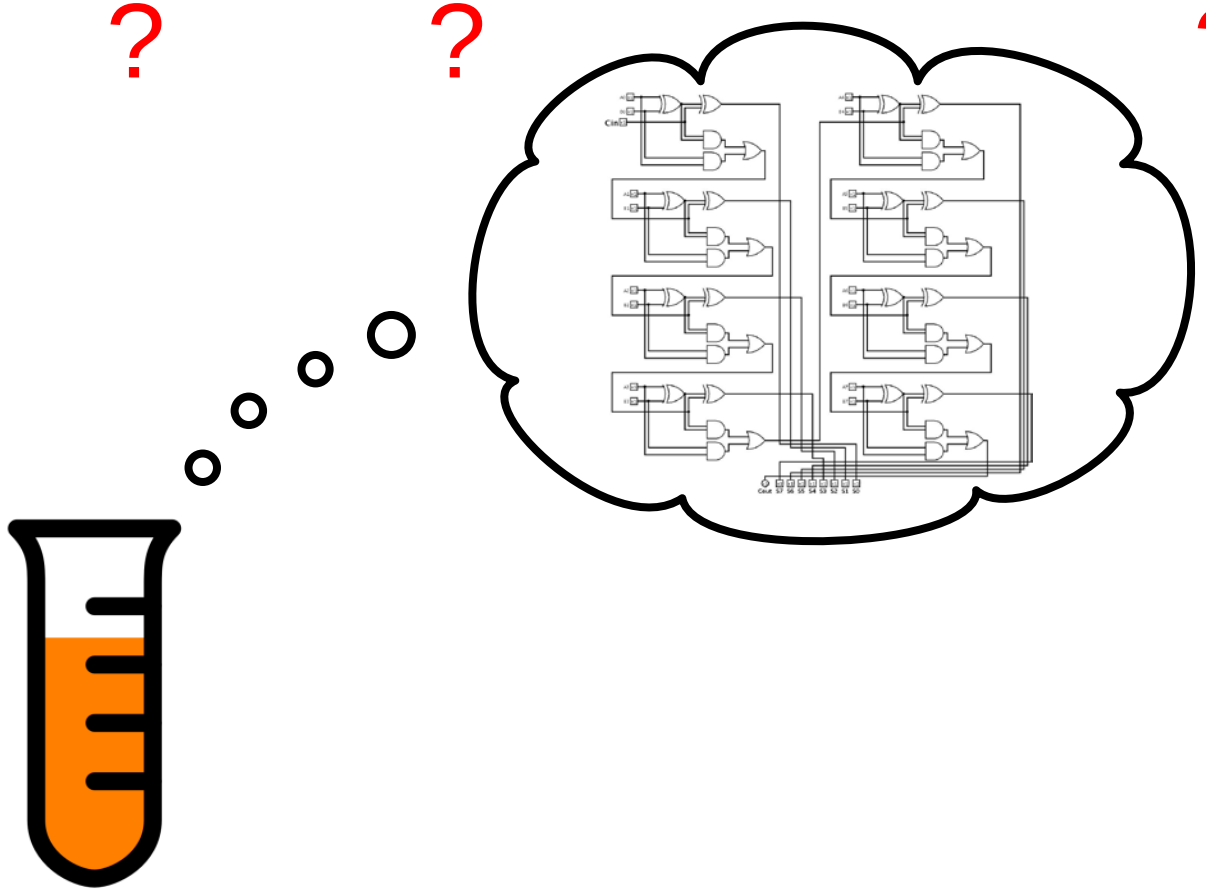
Build molecular computing systems that are reliable



Goal

Build molecular computing systems that are reliable

? ? ?!?

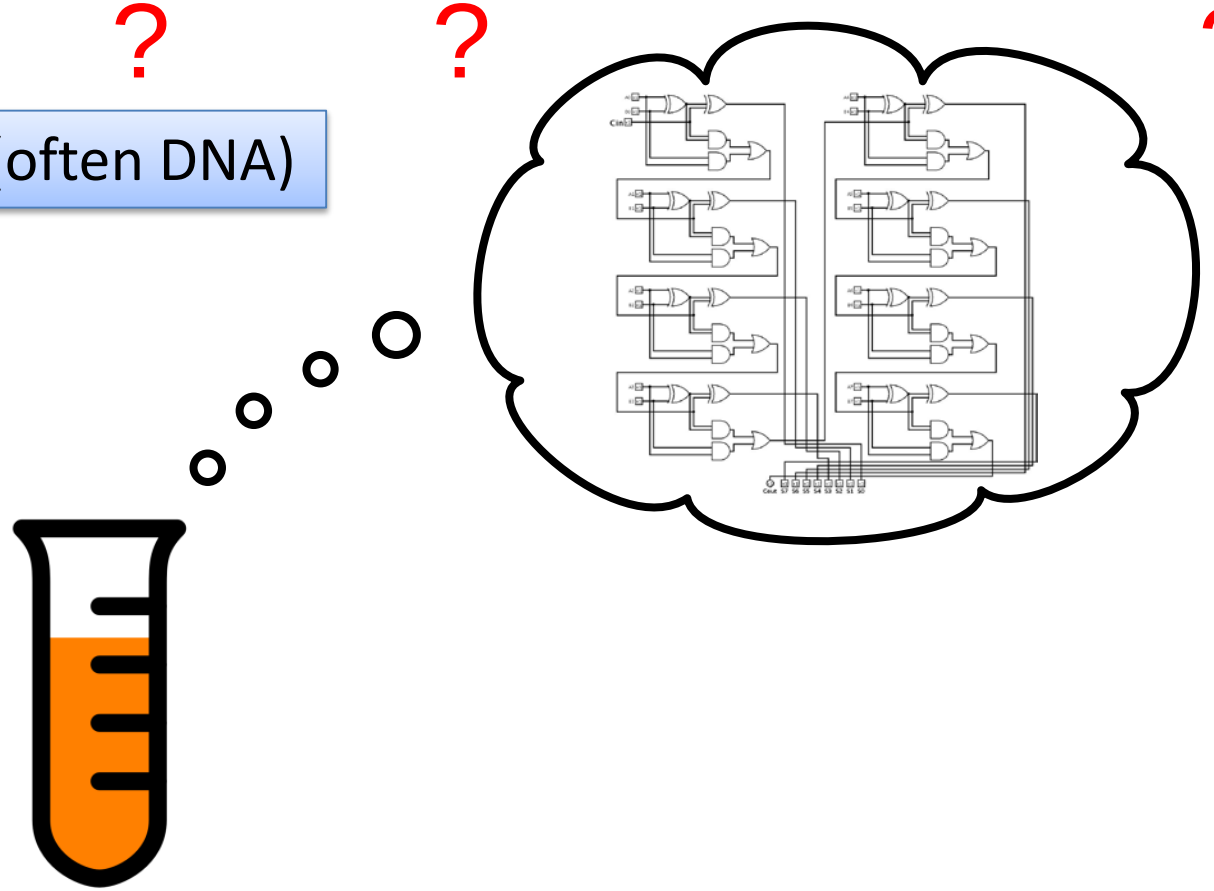


Goal

Build molecular computing systems that are reliable

? ? ?!?

(often DNA)



DNA nanotechnology applications

nonbiological:

- nanoscale resolution surface placement
- X-ray crystallization scaffolding
- molecular motors
- super-resolution imaging
- molecular circuits

biological:

- smart drugs
- mRNA detection
- cell surface marker detection
- genetically encoded structures

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- nanoscale resolution surface placement
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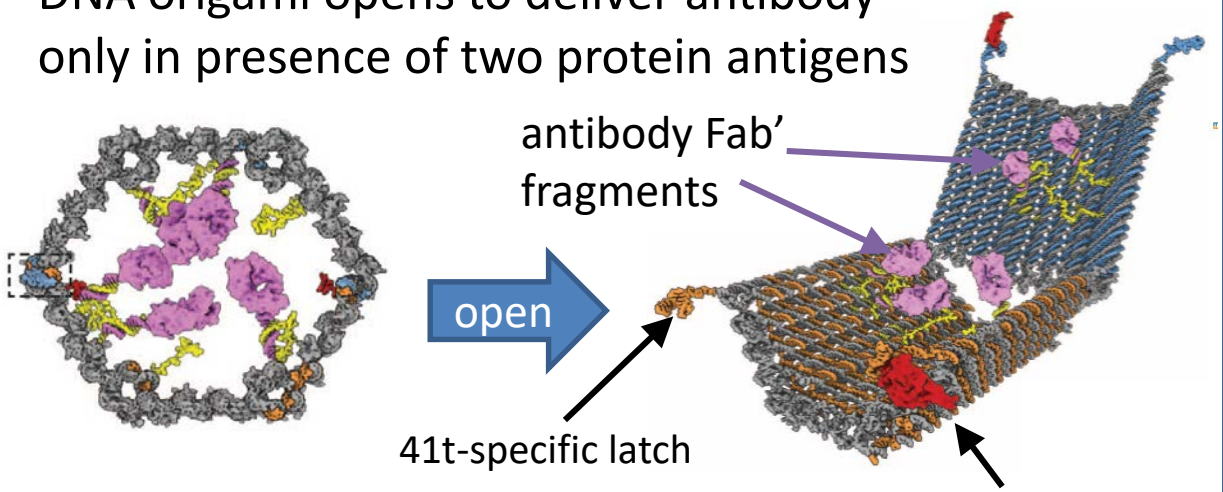
example

DNA origami opens to deliver antibody only in presence of two protein antigens

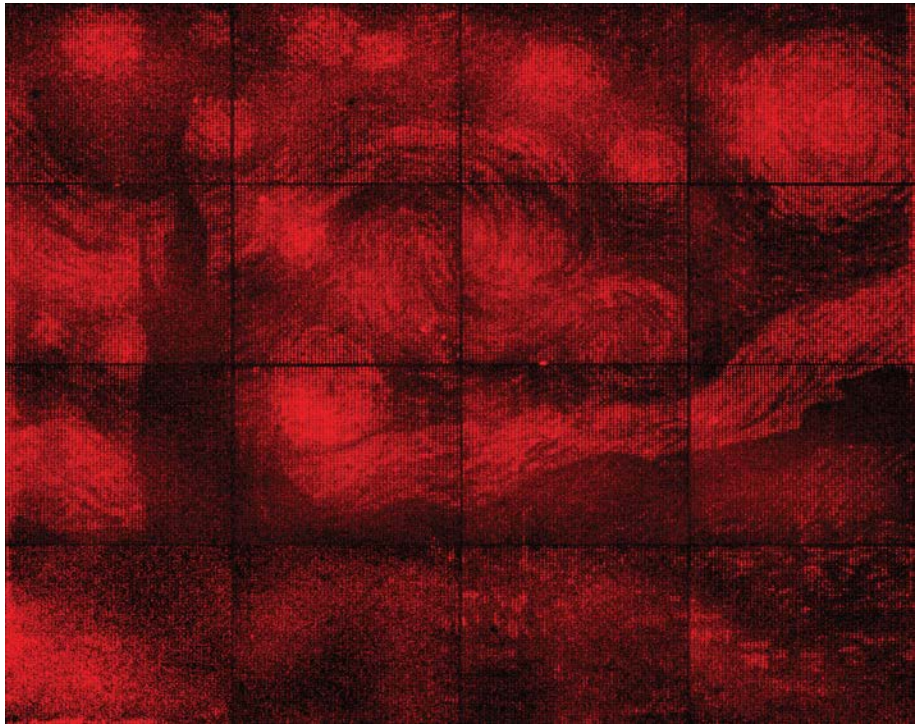


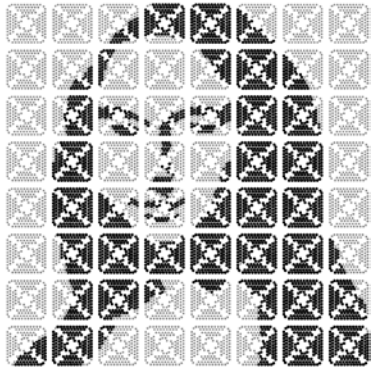
Shawn Douglas, Ido Bachelet, George Church, *A logic-gated nanorobot for targeted transport of molecular payloads*, Science 2012

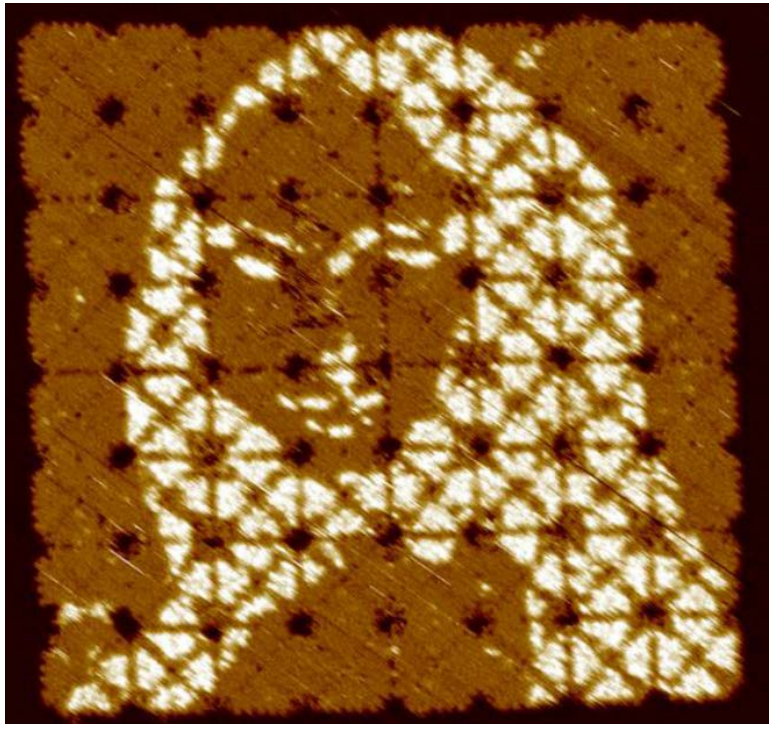
DNA nanotechnology applications

nonbiological:

- **art**





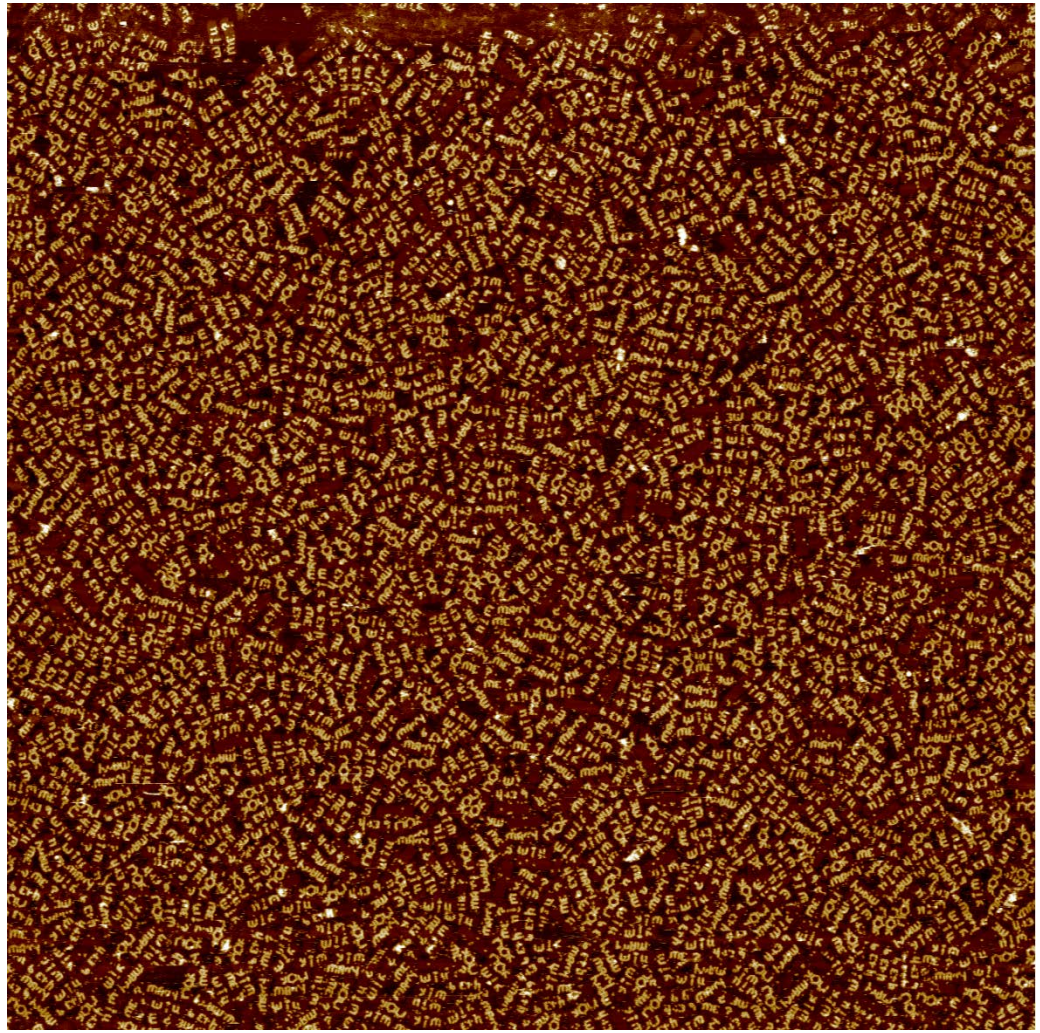


Ashwin Gopinath, Evan Miyazono, Andrei Faraon, Paul Rothemund, *Engineering and mapping nanocavity emission via precision placement of DNA origami*, Nature 2016

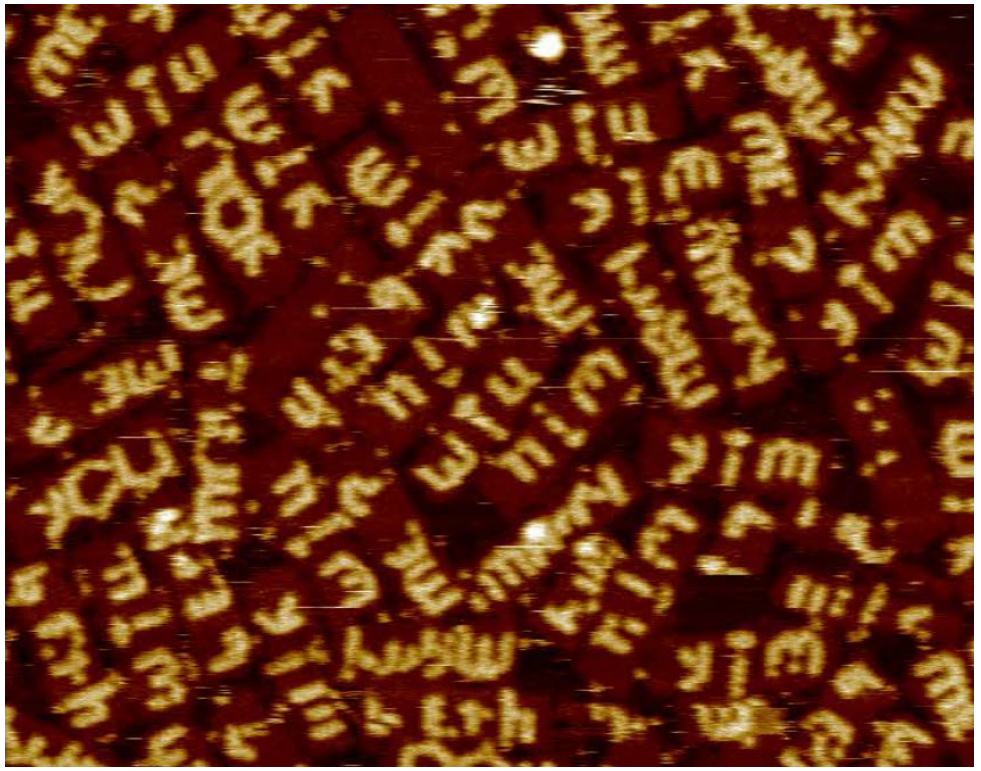
Grigory Tikhomirov, Philip Petersen, and Lulu Qian. *Fractal assembly of micrometre-scale DNA origami arrays with arbitrary patterns*. Nature 2017.

Other applications of DNA nanotechnology

4 μm wide scan



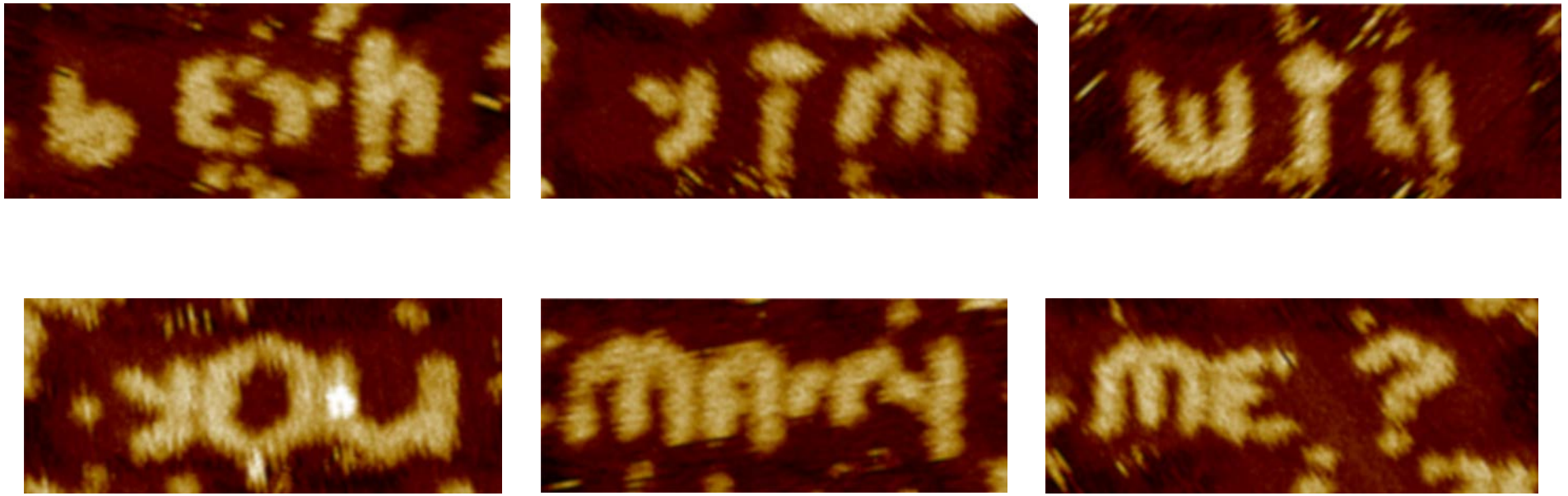
zoom in



Cherry-picked samples

Beth Yim

Cherry-picked samples



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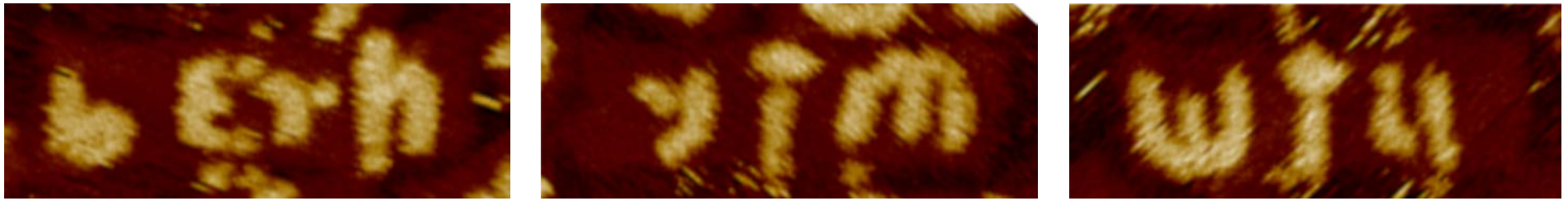
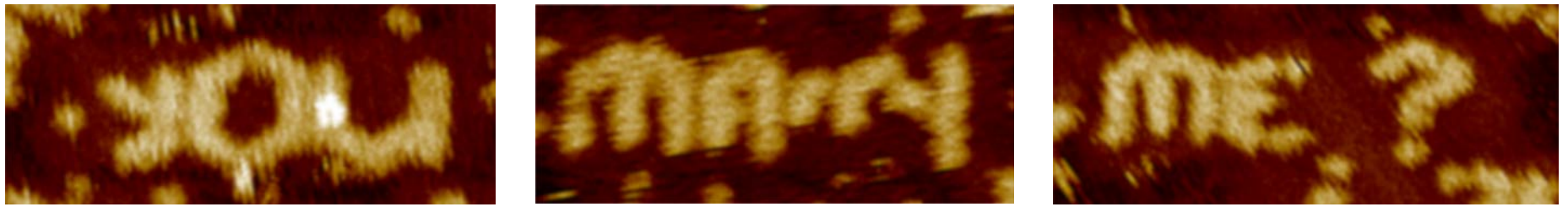
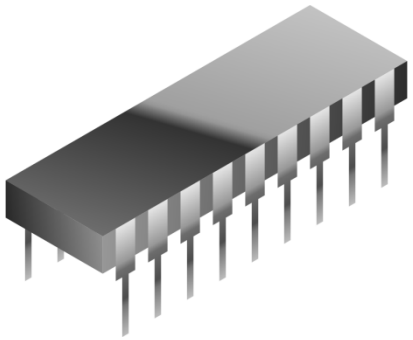
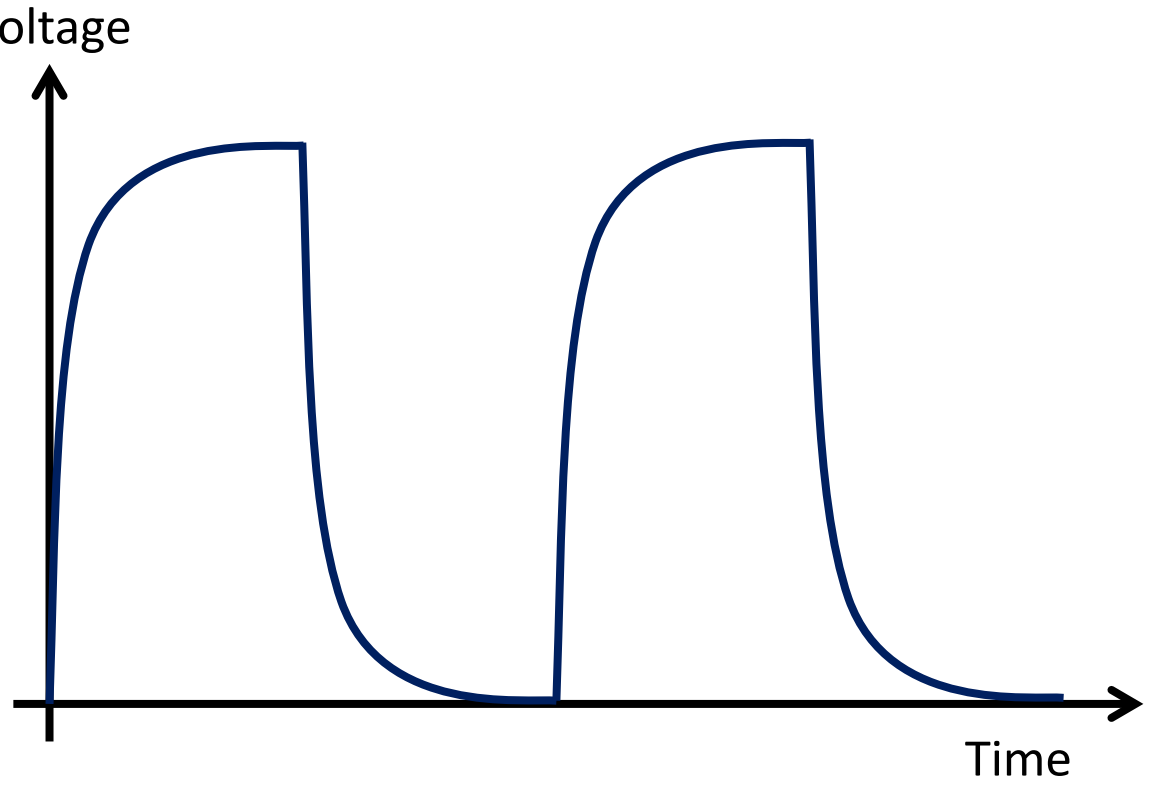




Beth Yim

Representing Information with Molecules

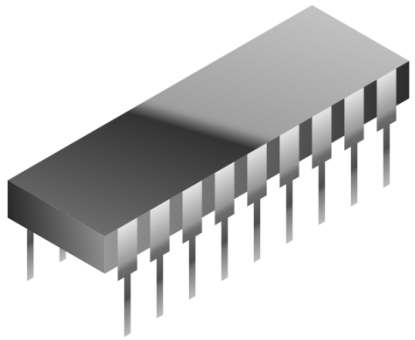


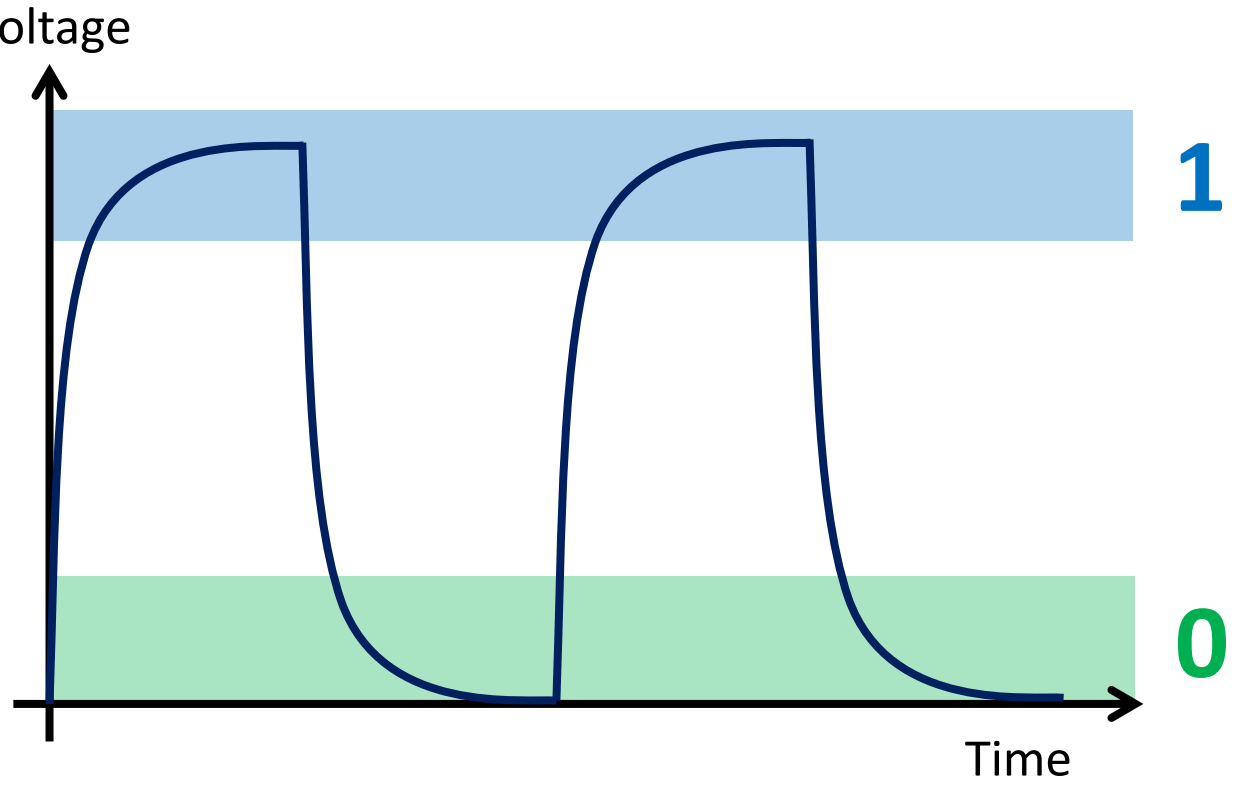


In an electronic circuit,

voltage can represent Boolean input

Representing Information with Molecules





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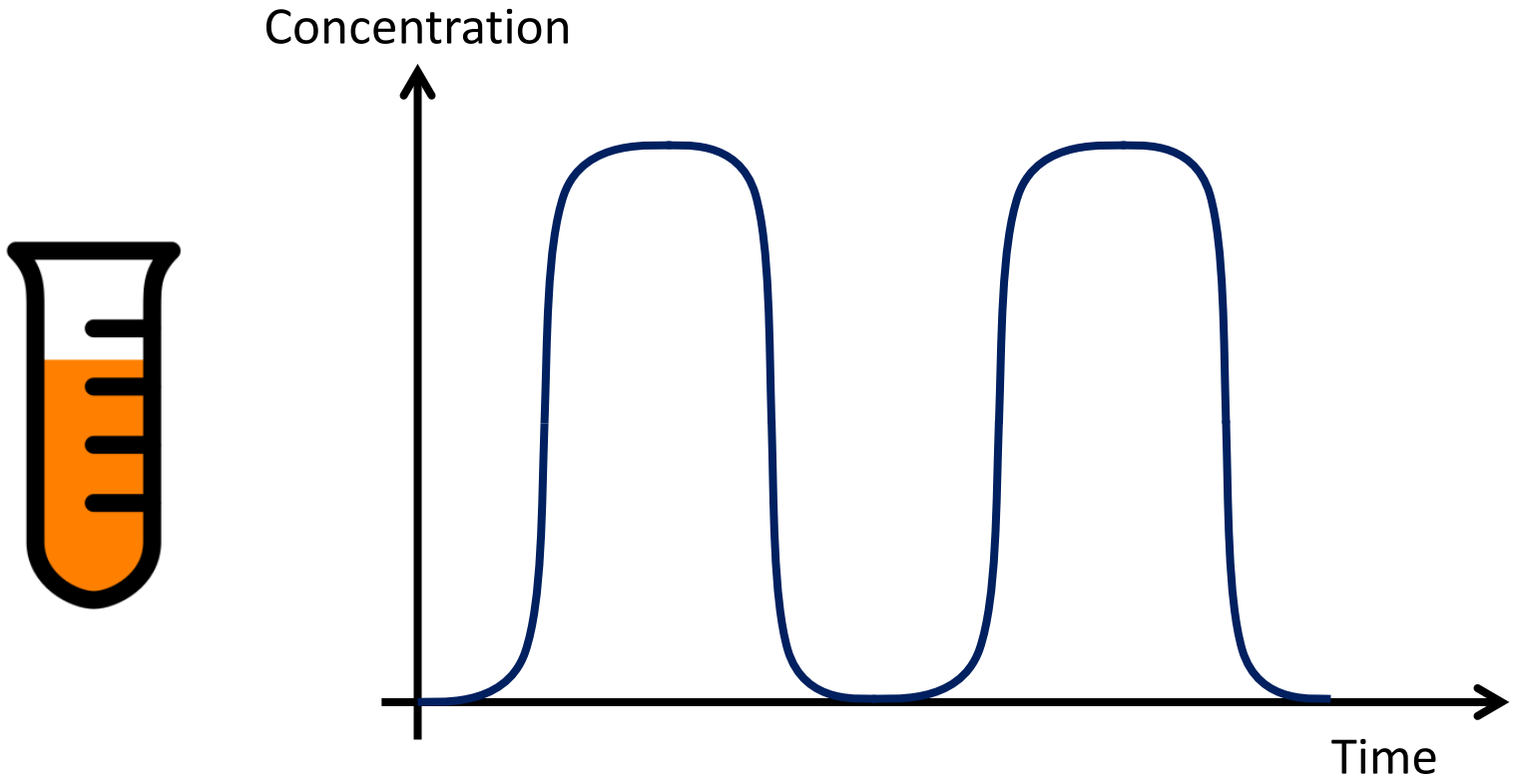
Representing Information with Molecules



In a well-mixed solution,

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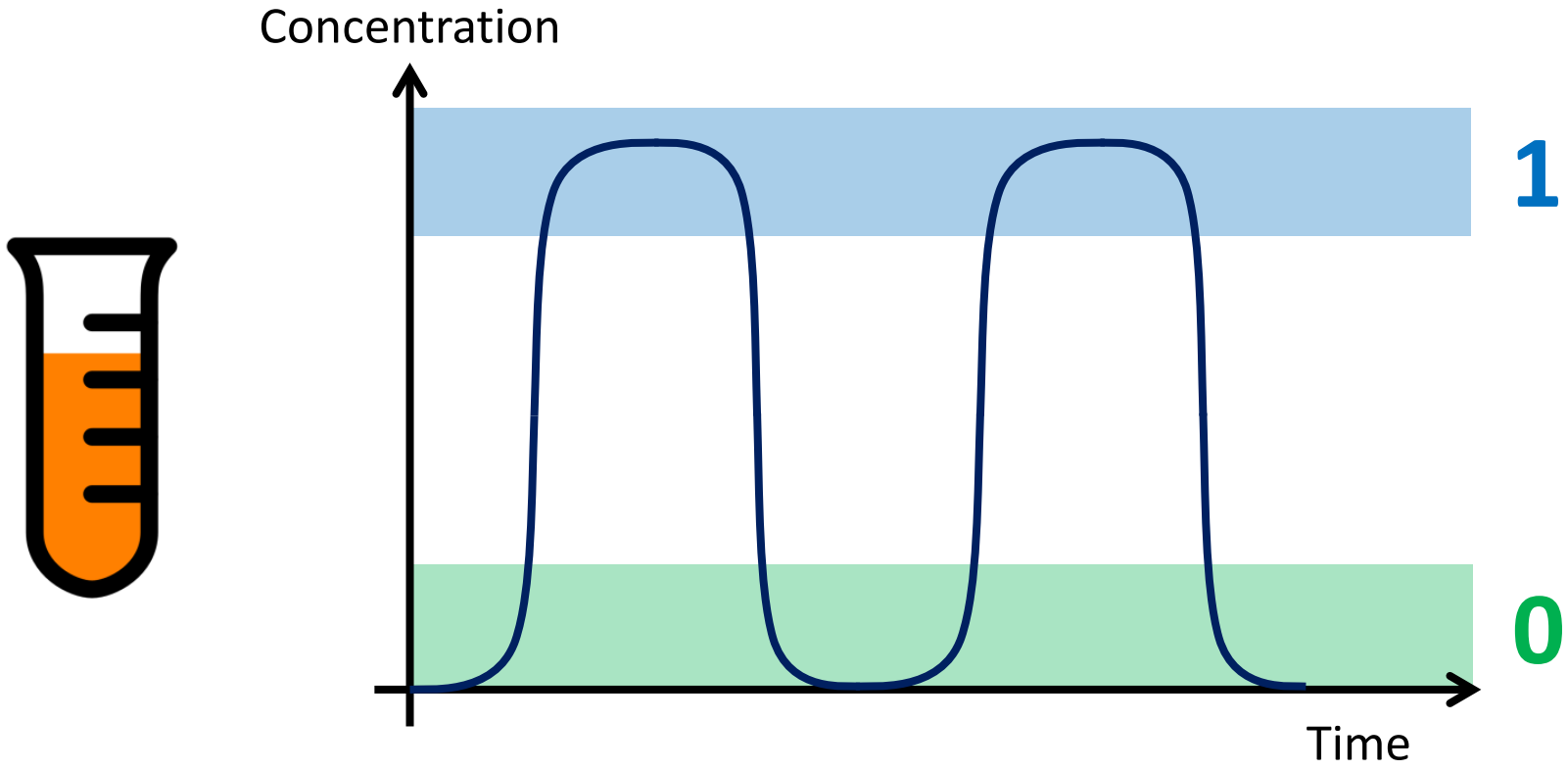
Representing Information with Molecules



In a well-mixed solution,

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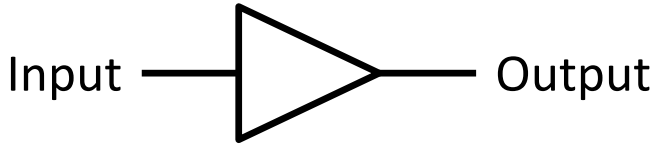
Chemical Identity Gate: Idealized vs. Actual Behavior



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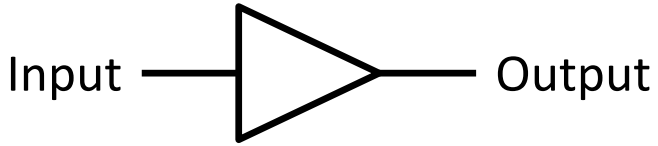
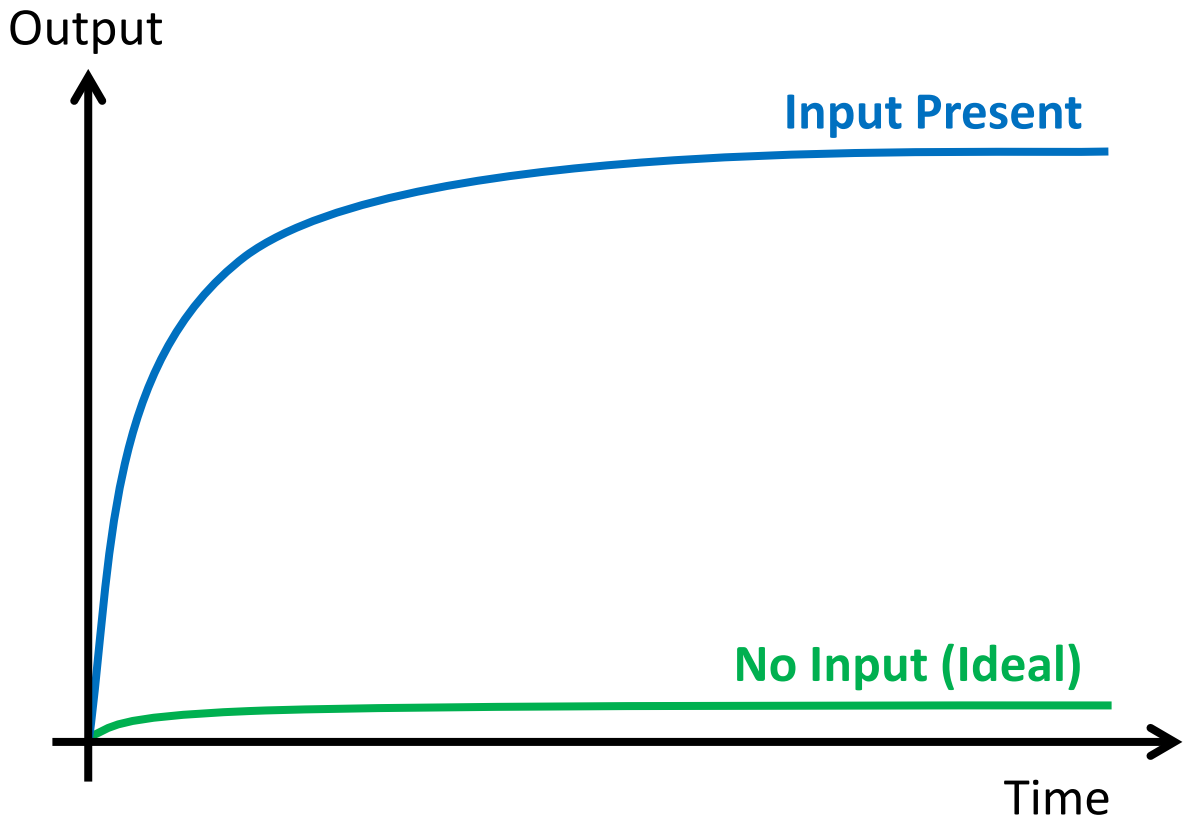
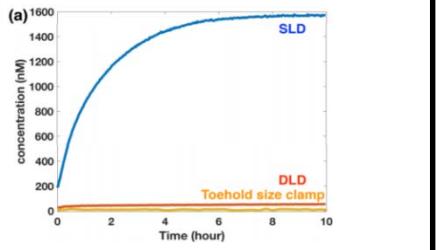


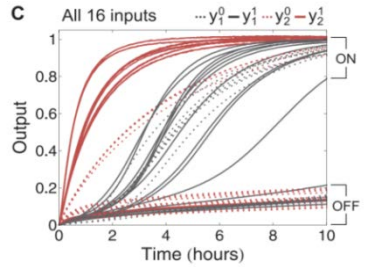


Chemical Identity Gate: Idealized vs. Actual Behavior

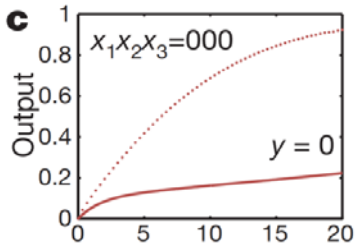
Experimental Implementation of Chemical Logic



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

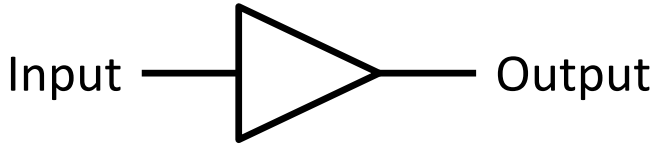


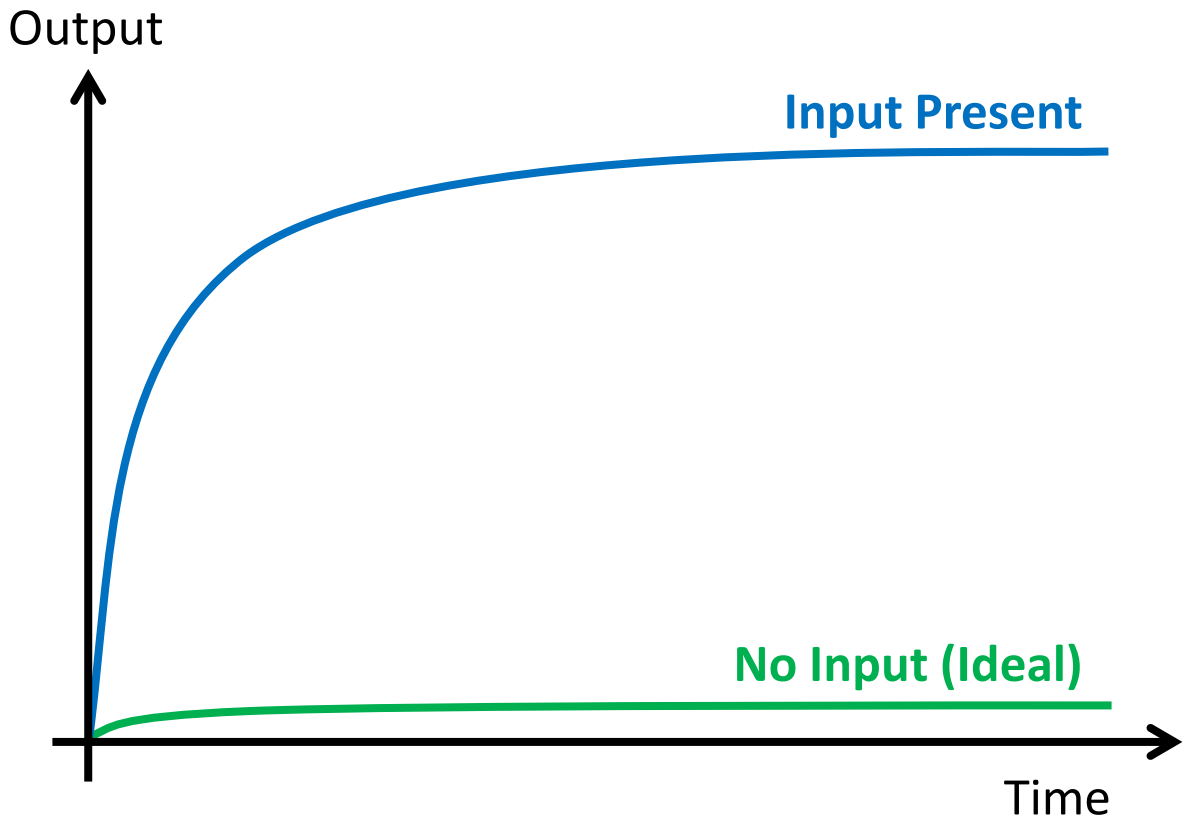
Qian et al. ***Science*** 332, 2011



Qian et al. ***Nature*** 475, 2011

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





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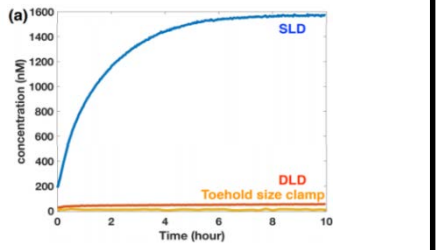

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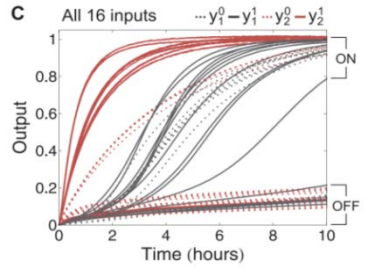

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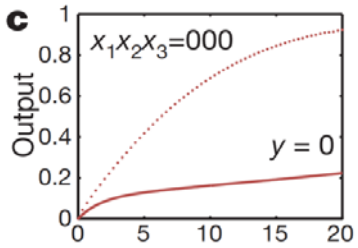

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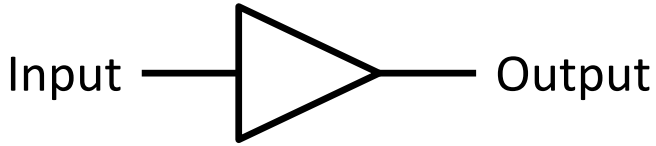

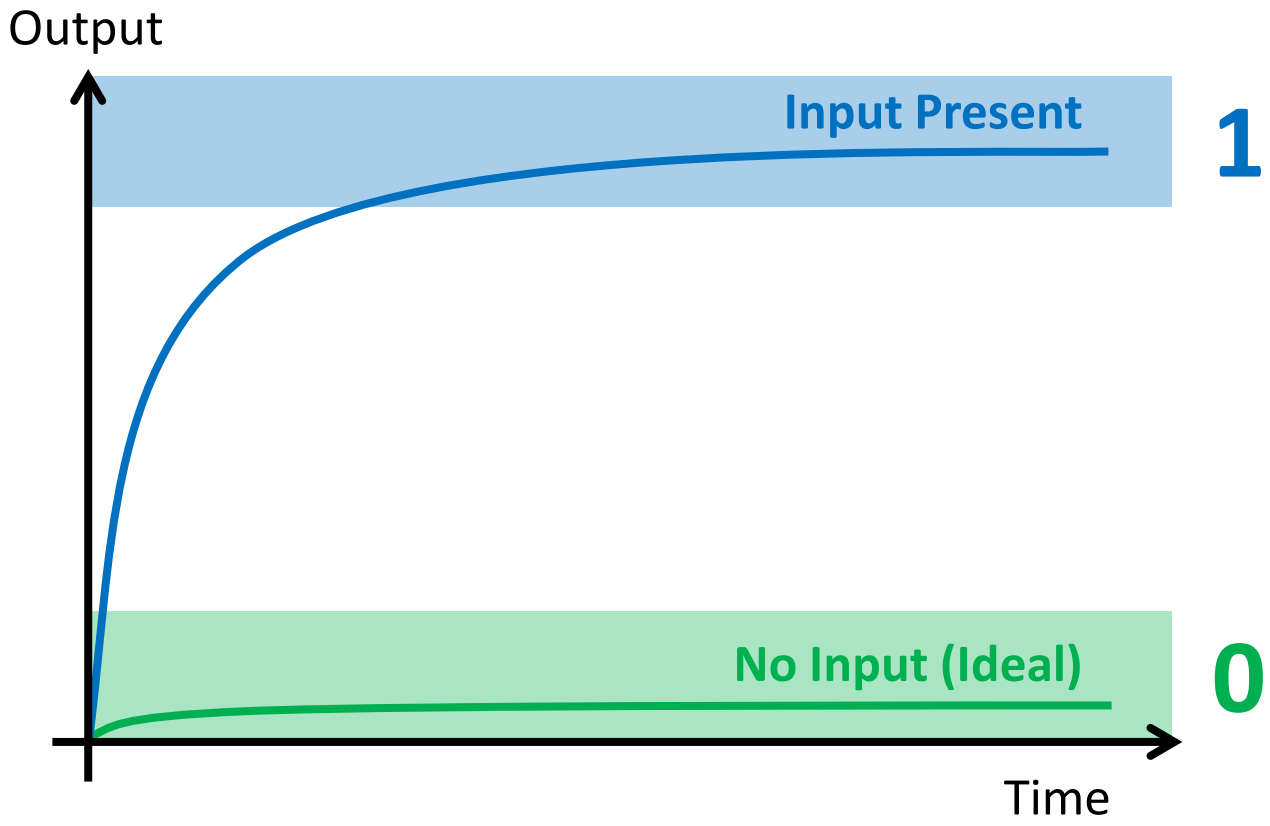

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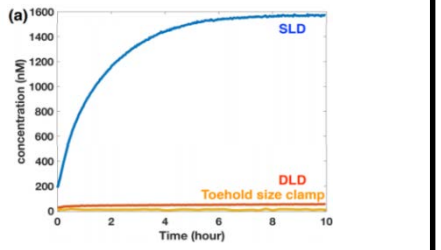

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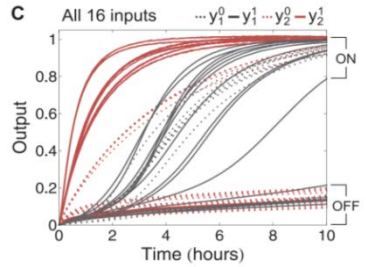

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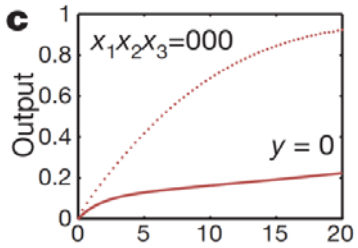

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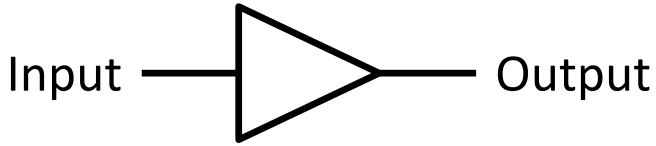
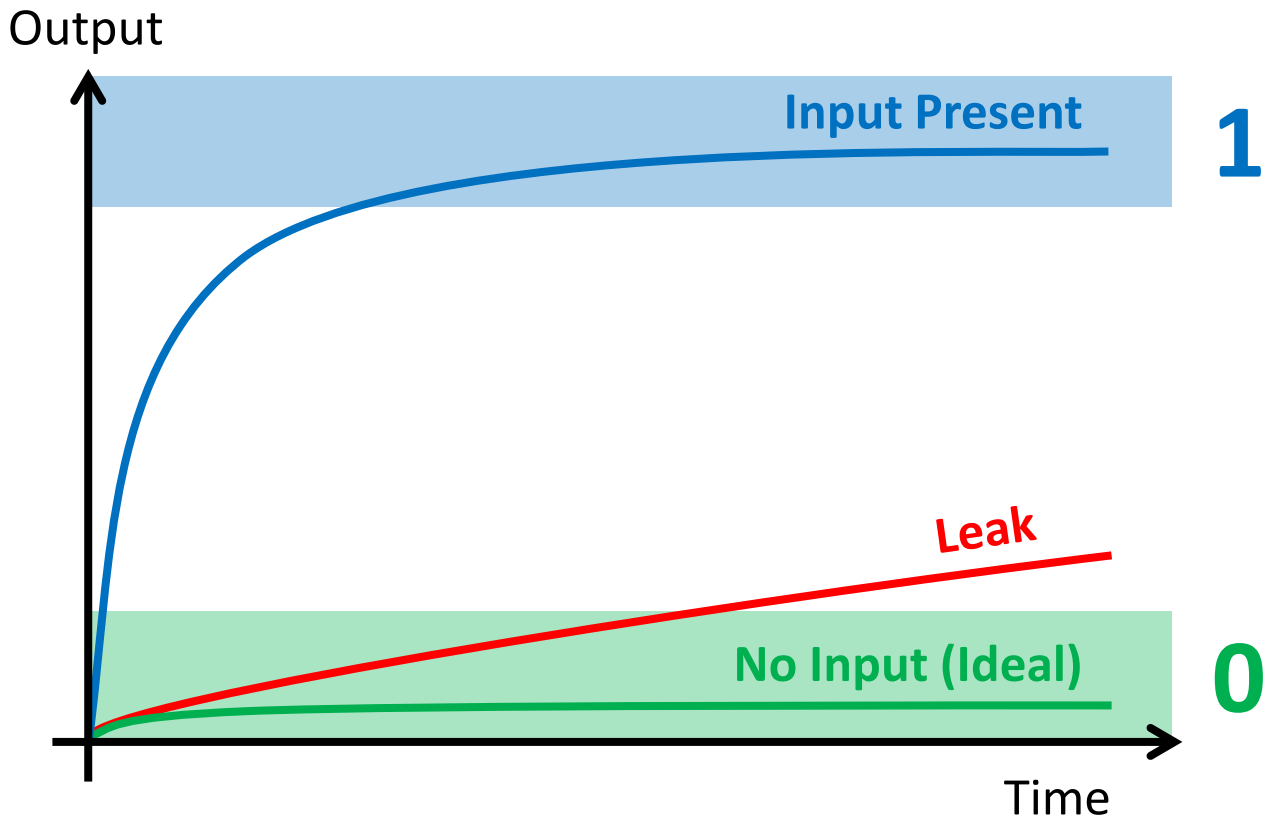




Levels of Abstraction

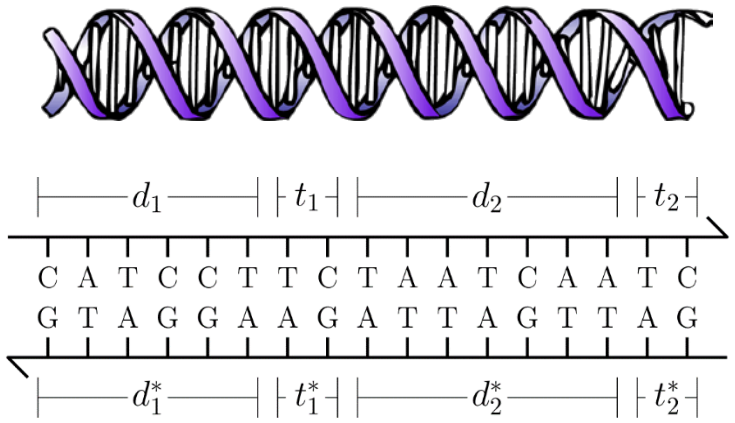
Levels of Abstraction

DNA

Levels of Abstraction

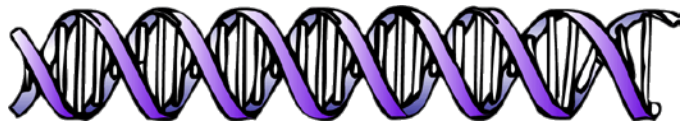
DNA

Base Pairs

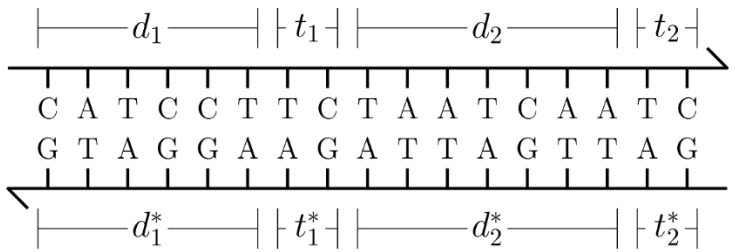


Levels of Abstraction

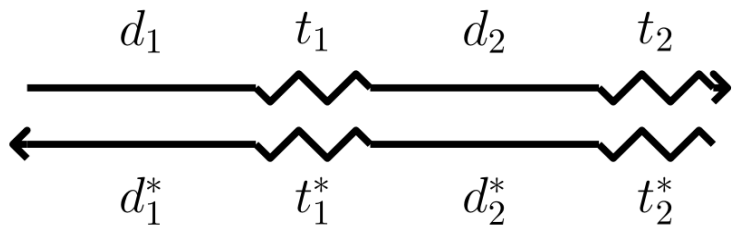
DNA



Base Pairs



Strands



Levels of Abstraction

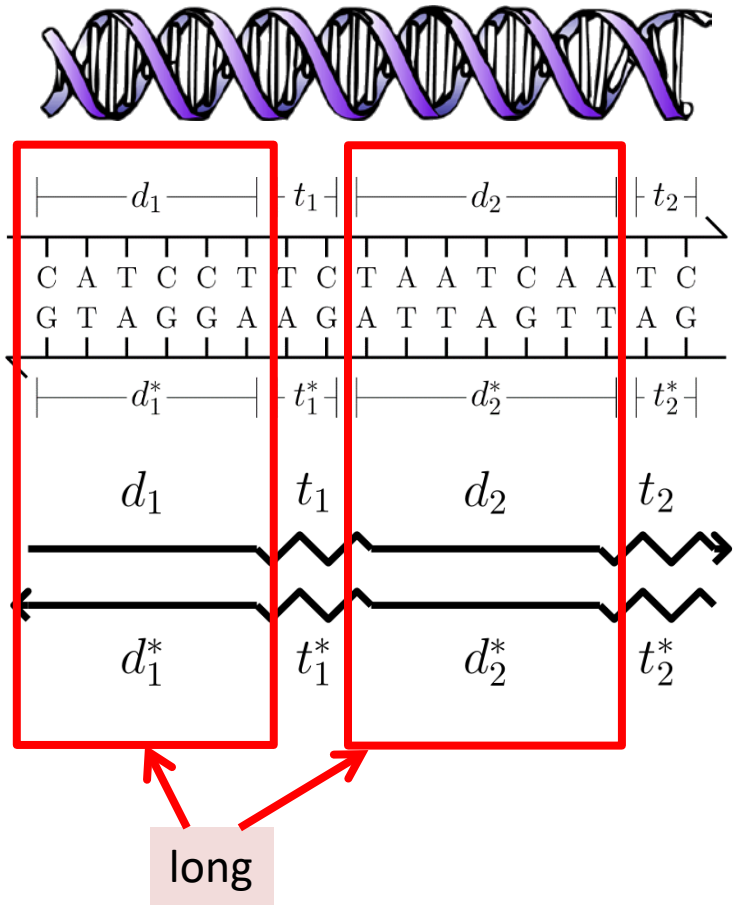
DNA

⬇

Base Pairs

⬇

Strands



Levels of Abstraction

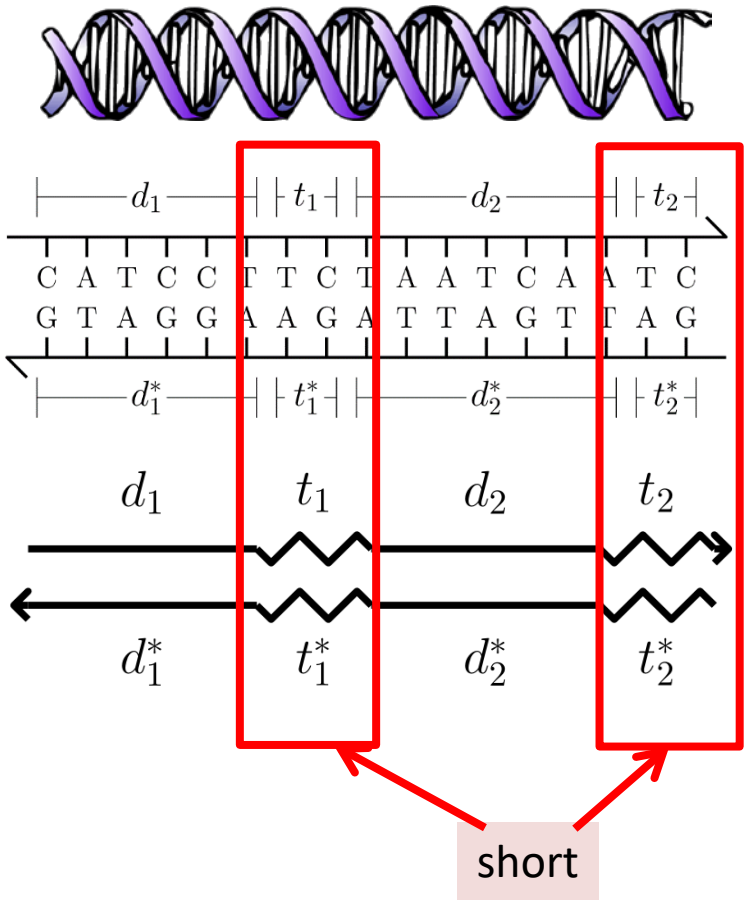
DNA

⬇

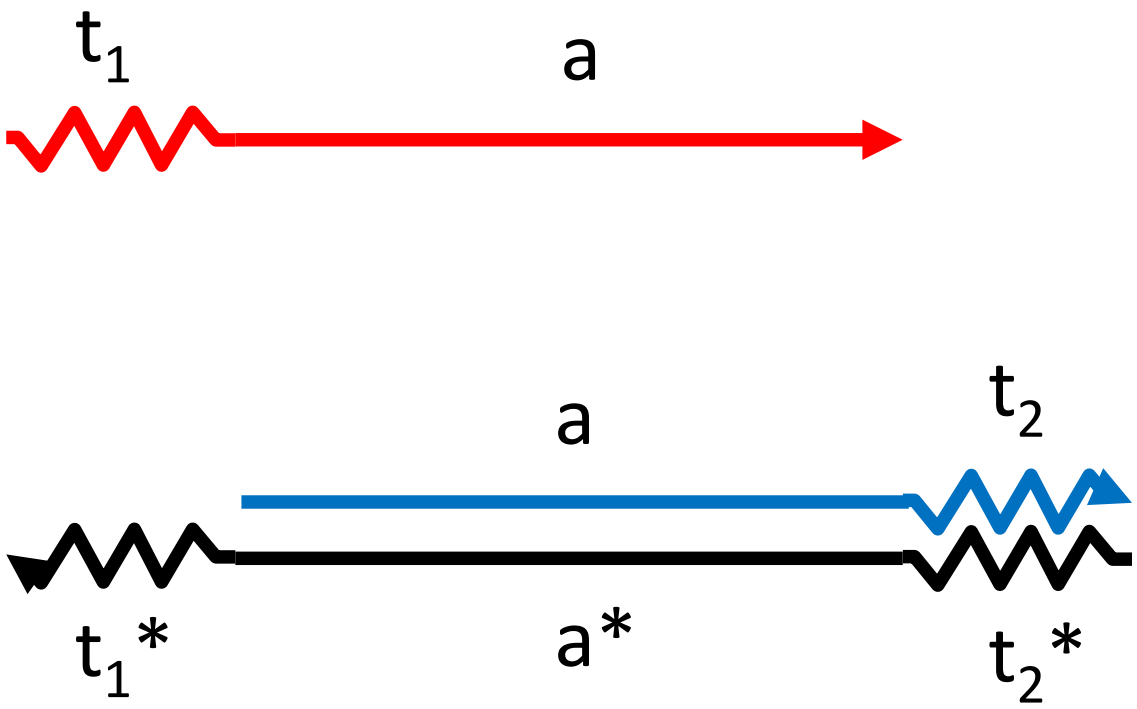
Base Pairs

⬇

Strands

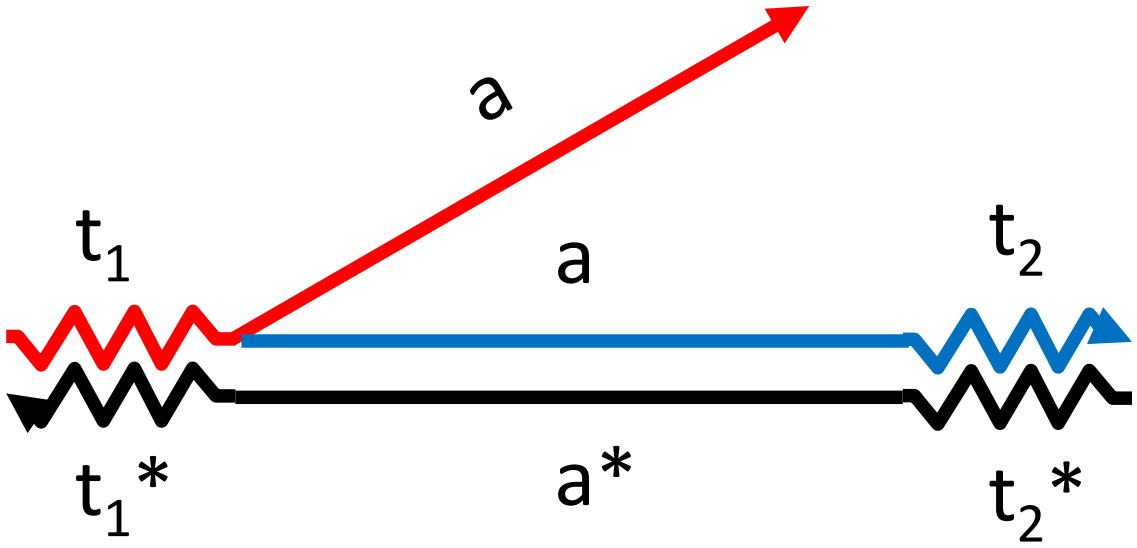


DNA strand displacement



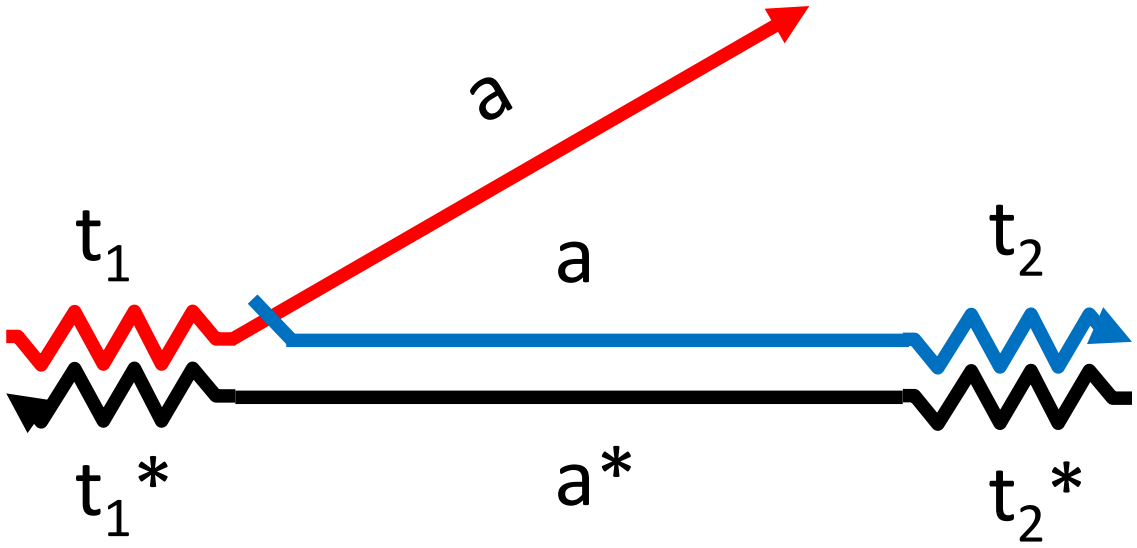
DNA strand displacement

Bind



DNA strand displacement

Bind



DNA strand displacement

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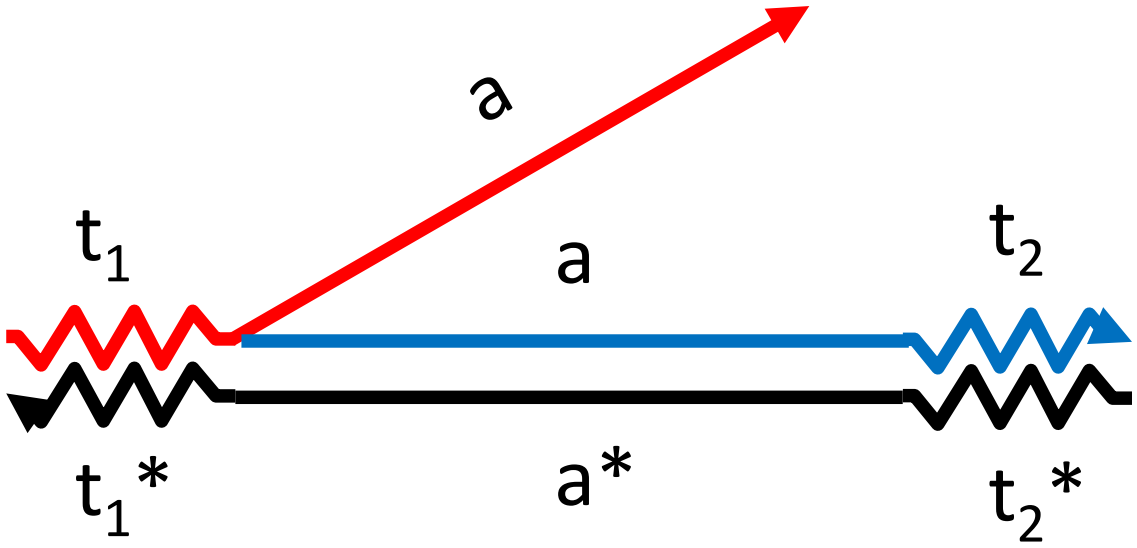
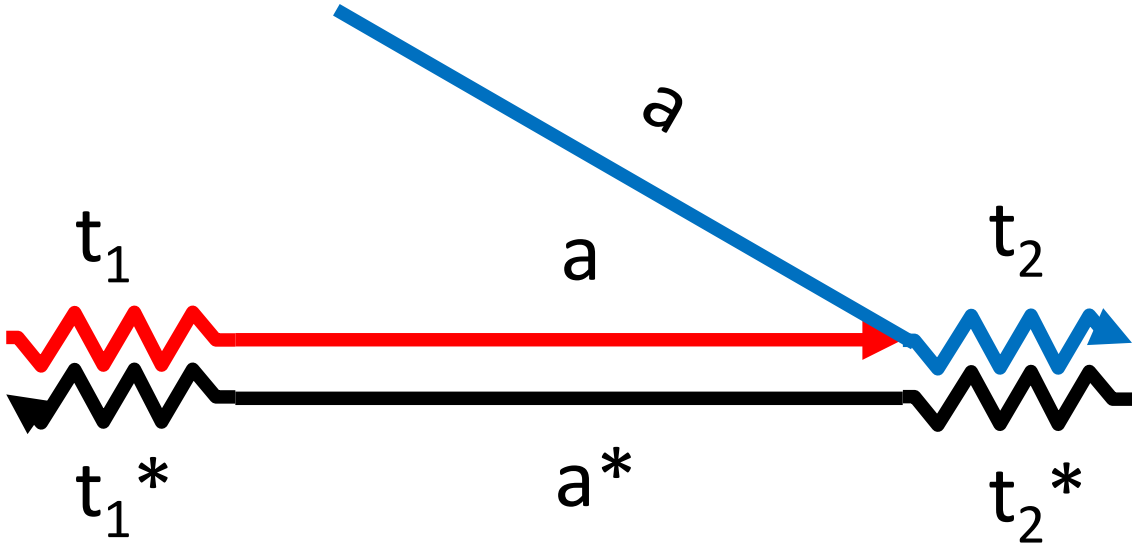


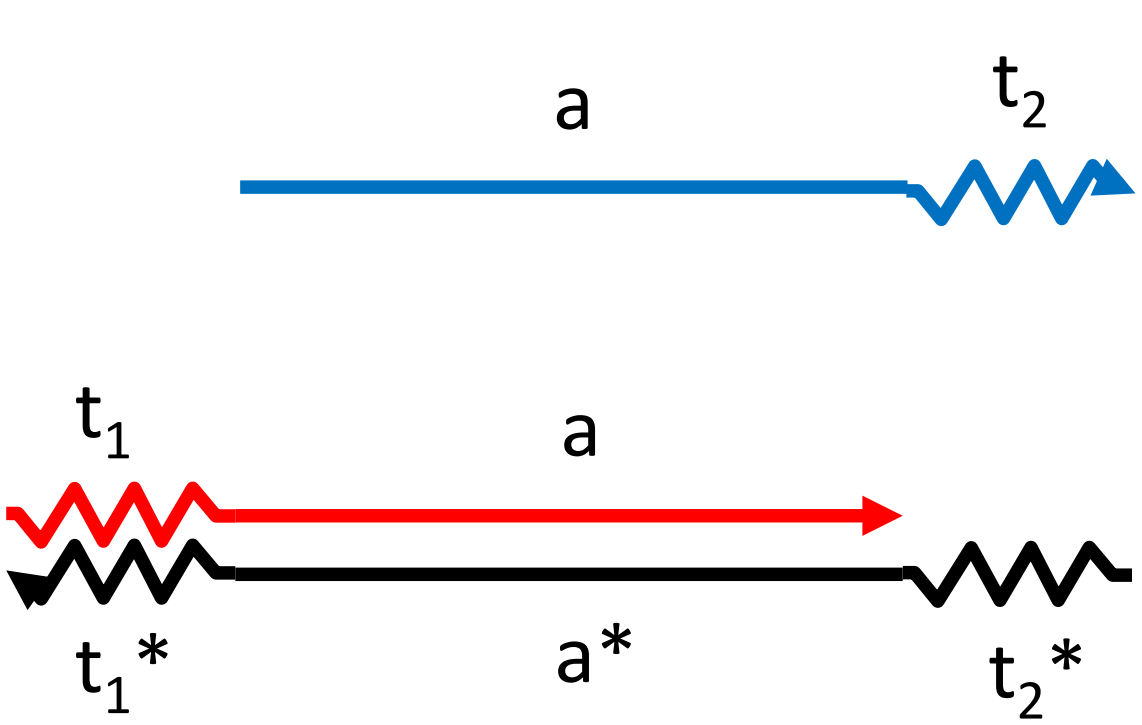
DNA strand displacement



Bind

Displace

DNA strand displacement



Bind

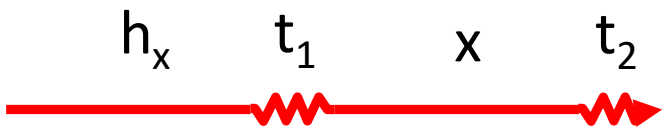
Displace

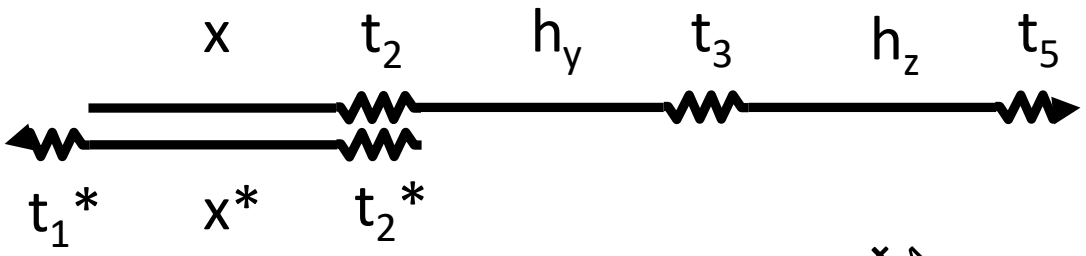
Release

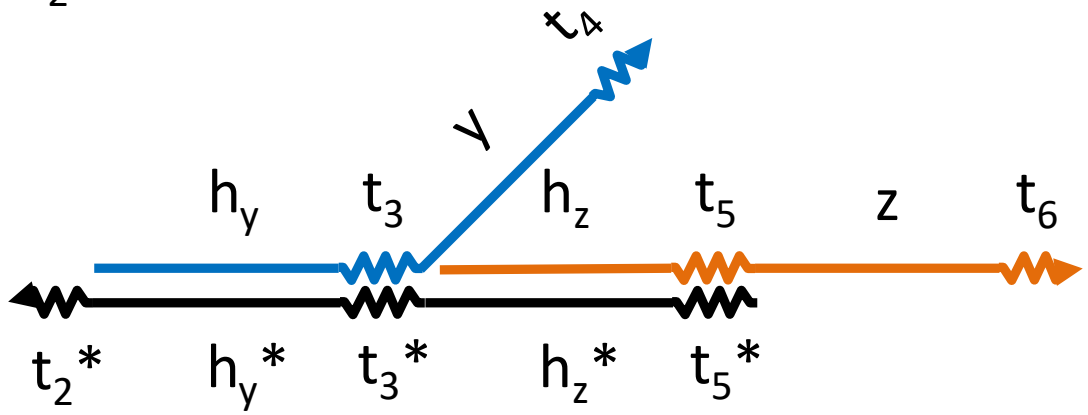
DNA strand displacement implementing A+B → C

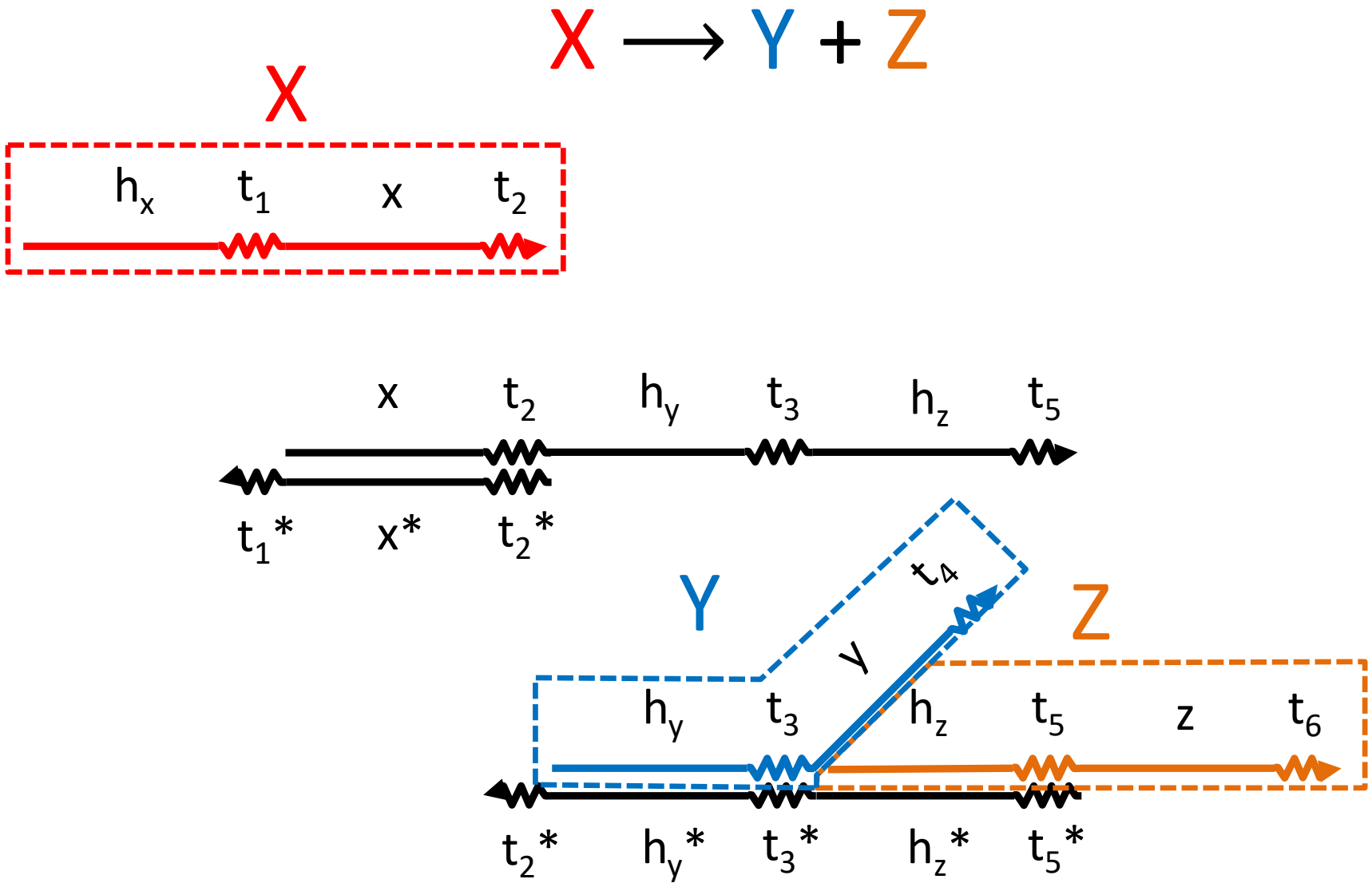
video: Microsoft Research Cambridge

$$X \longrightarrow Y + Z$$

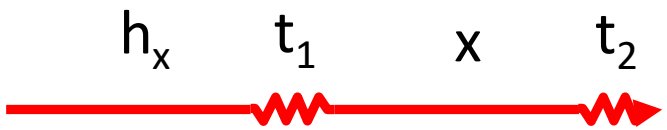


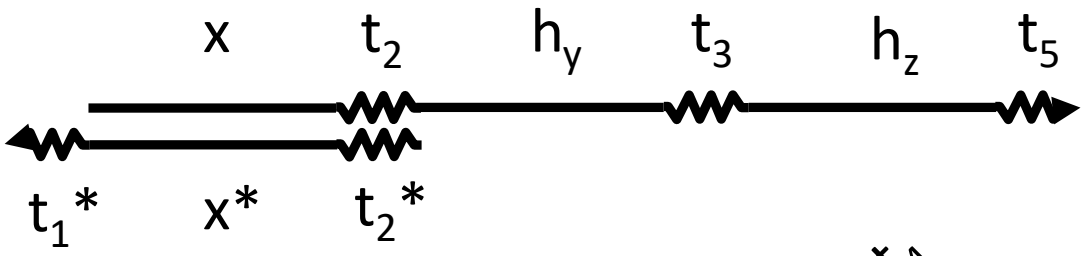


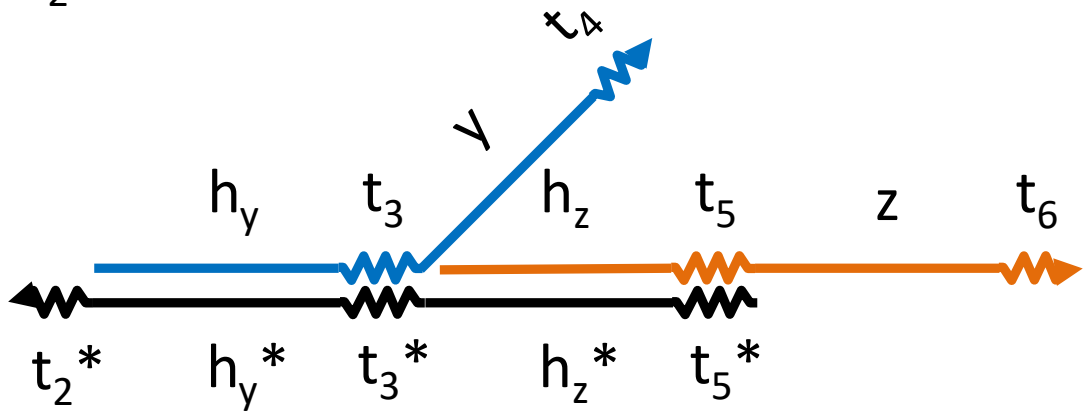



X ⟶ Y + Z
X
h_x
t_1
x
t_2
x
t_2
h_y
t_3
h_z
t_5
t_1*
x*
t_2*
Y
t_4
Z
y
h_y
t_3
h_z
t_5
z
t_6
t_2*
h_y*
t_3*
h_z*
t_5*

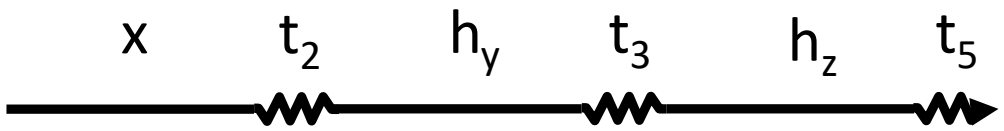
$$X \longrightarrow Y + Z$$

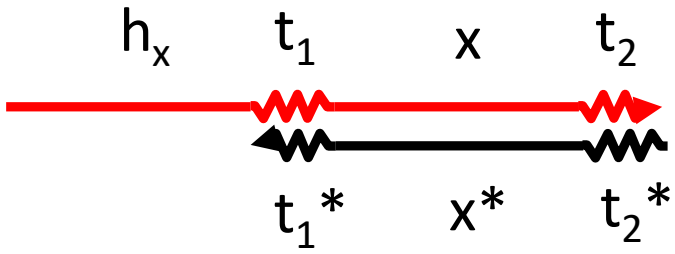


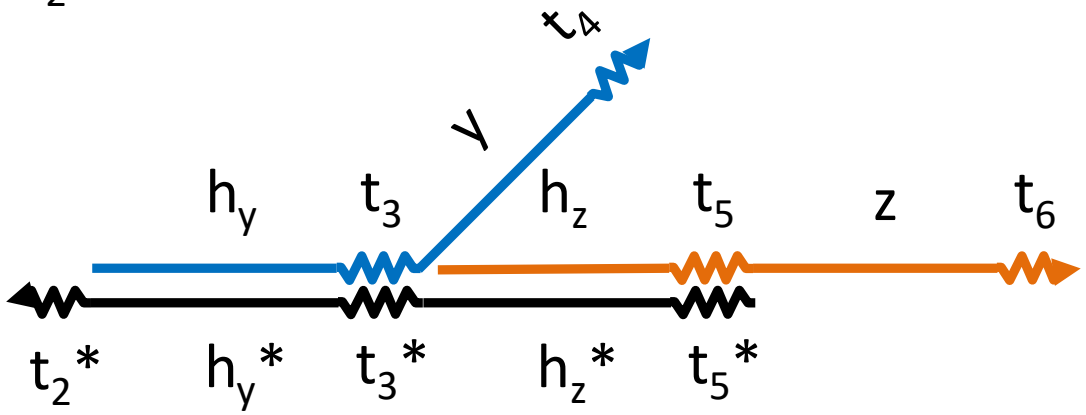


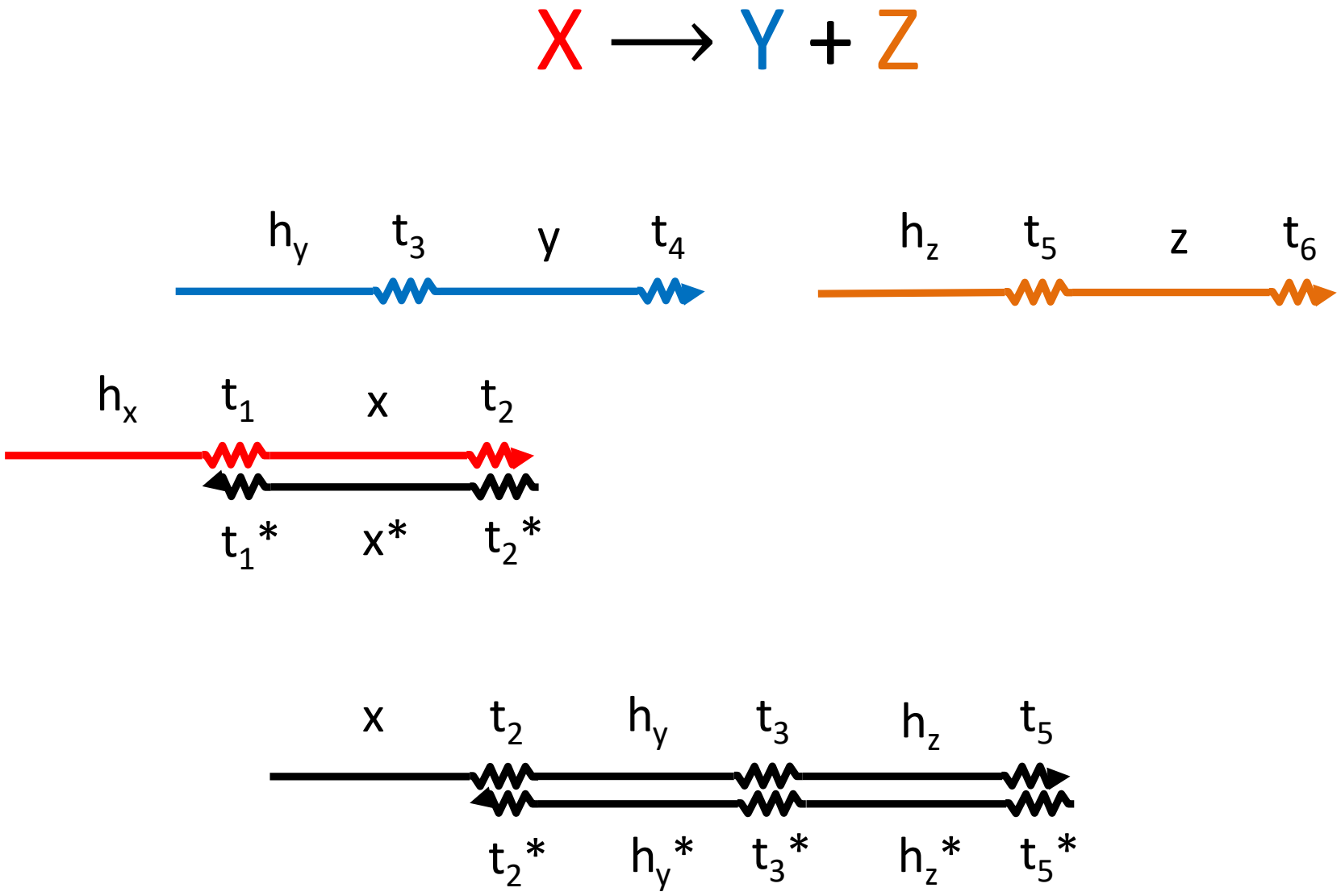


$$X \longrightarrow Y + Z$$

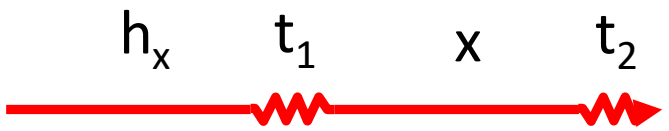


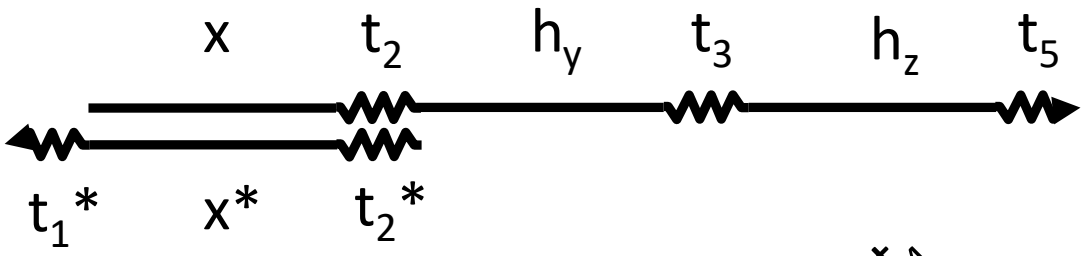


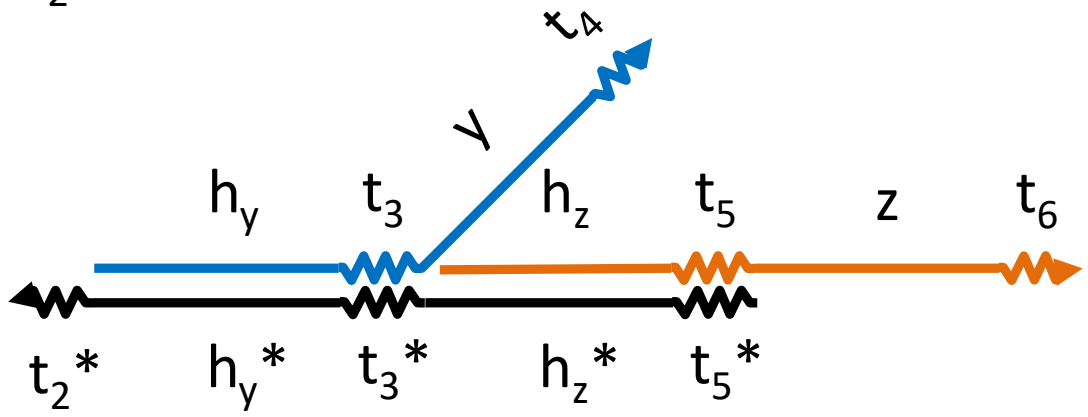



X ⟶ Y + Z
h_y t_3 y t_4
h_z t_5 z t_6
h_x t_1 x t_2
t_1* x* t_2*
x t_2 h_y t_3 h_z t_5
t_2* h_y* t_3* h_z* t_5*

$$X \longrightarrow Y + Z$$

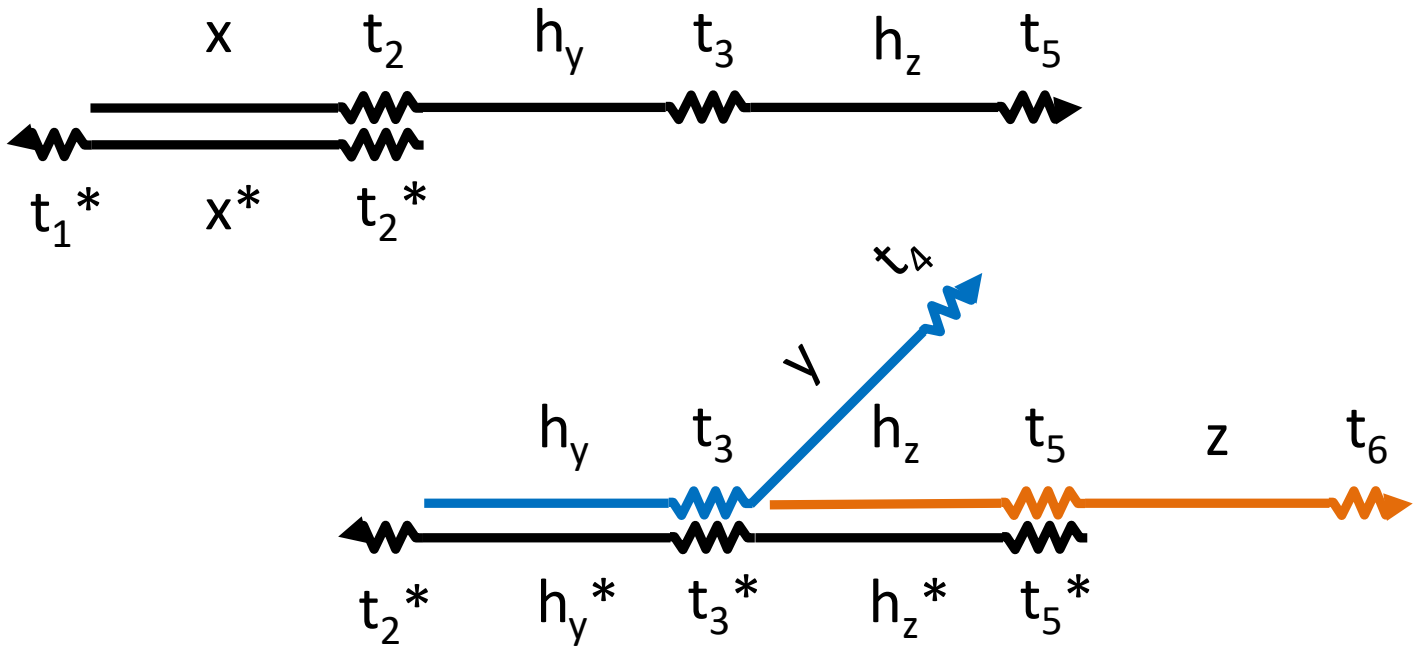






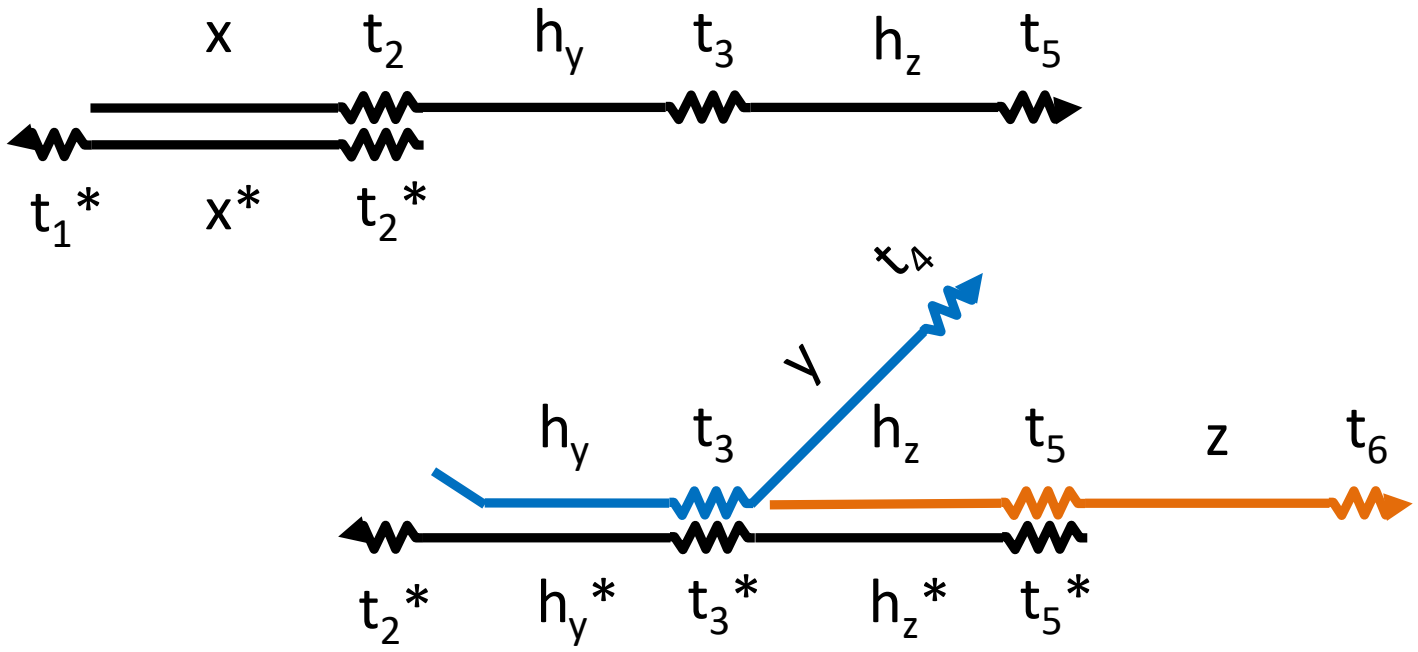
Leak: A Source of Error

$$\emptyset \longrightarrow Y + Z$$



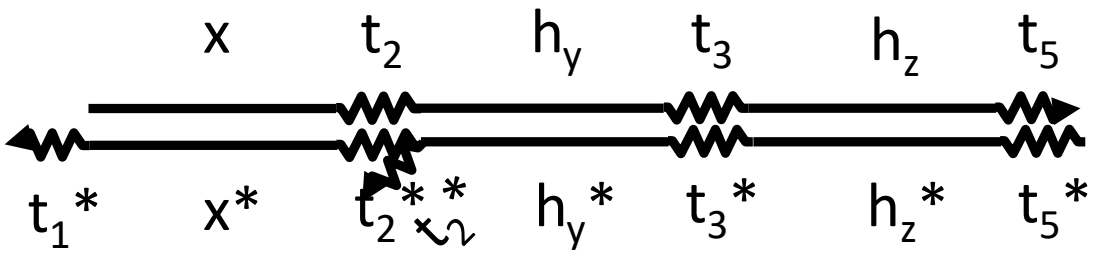
Leak: A Source of Error

$$\emptyset \longrightarrow Y + Z$$



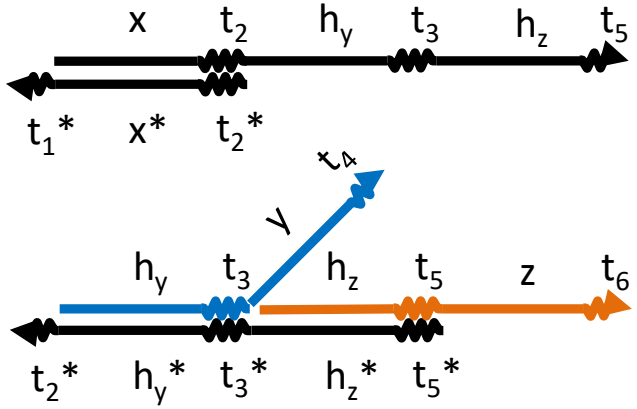
Leak: A Source of Error

$$\emptyset \longrightarrow Y + Z$$

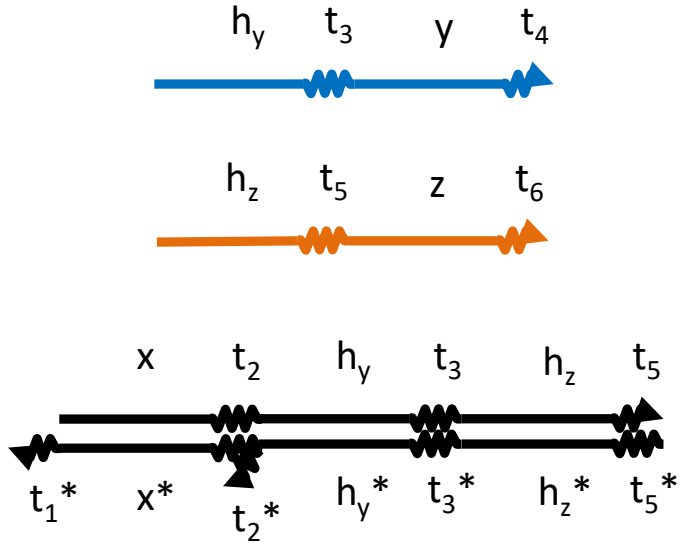


A Driving Force for Leak

Before:

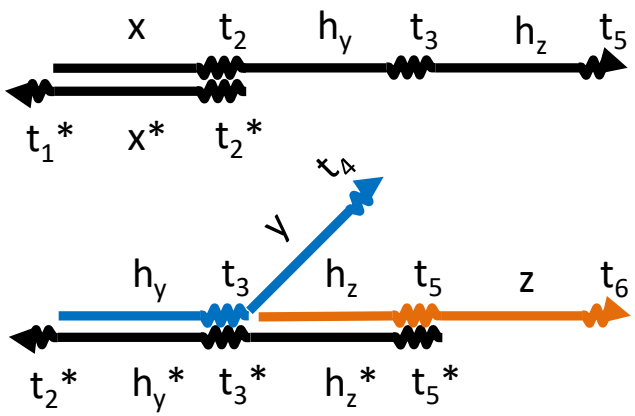


After:



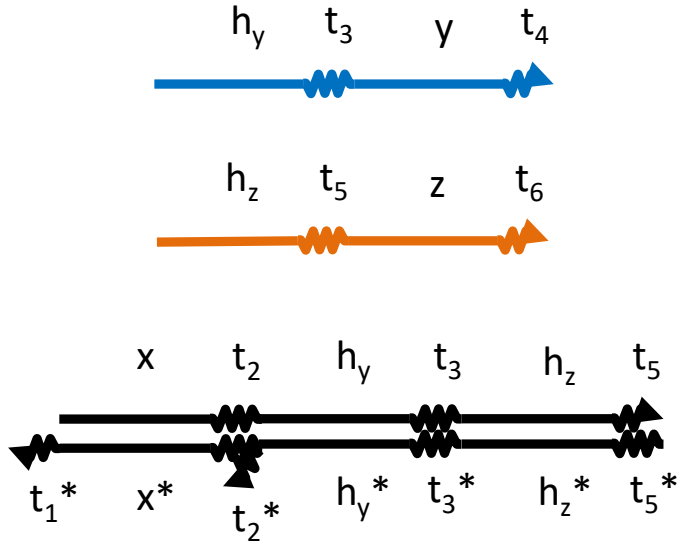
A Driving Force for Leak

Before:



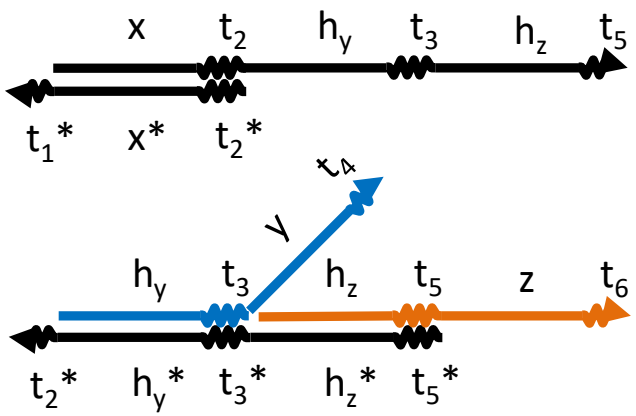
slow

After:



A Driving Force for Leak

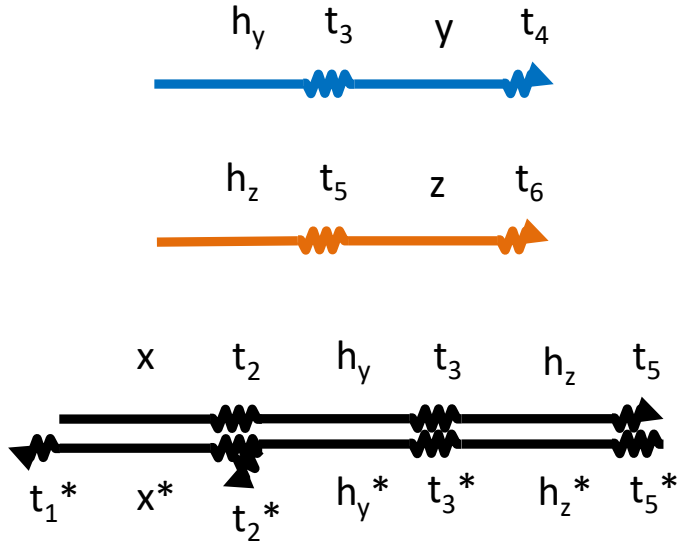
Before:



slow

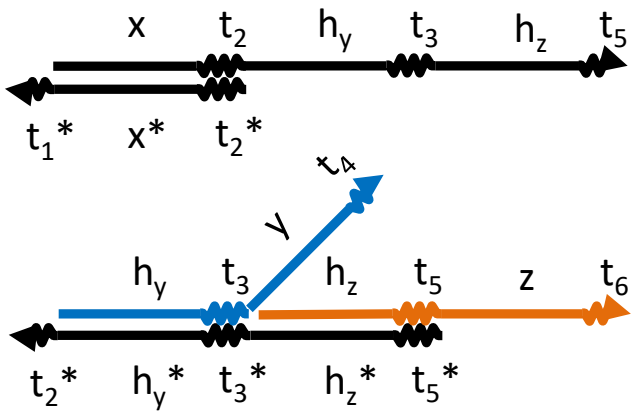
very slow

After:



A Driving Force for Leak

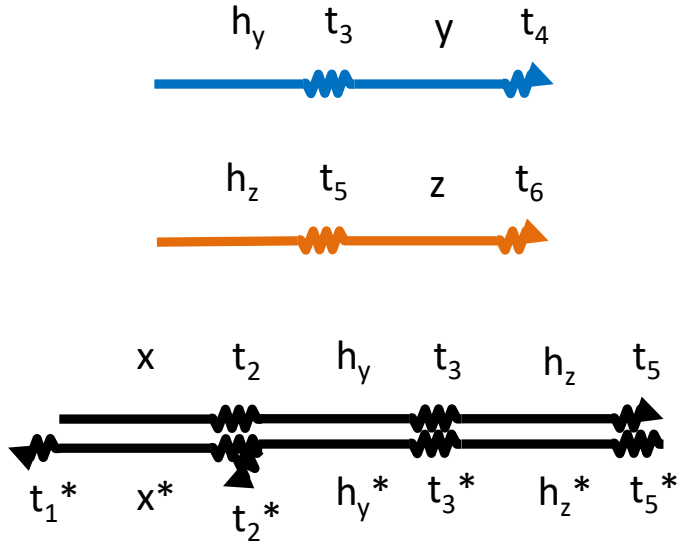
Before:



slow

very slow

After:

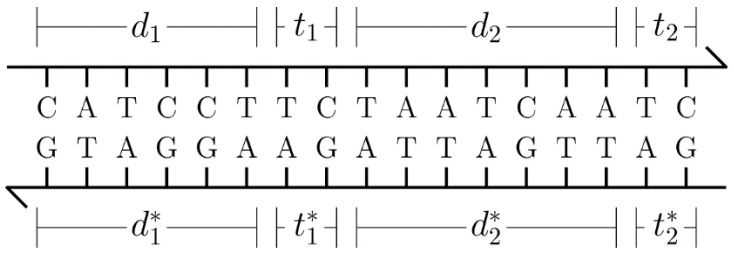


less favorable

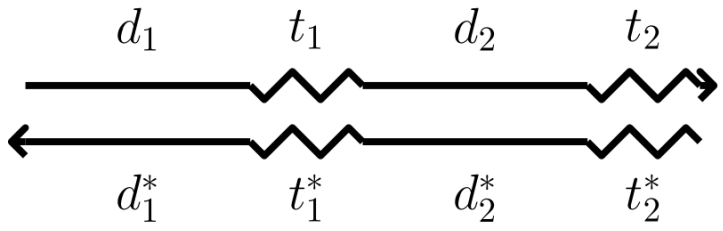
more favorable

Levels of Abstraction

DNA



Base Pairs

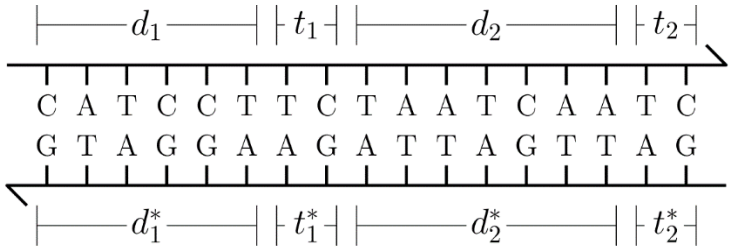


Strands

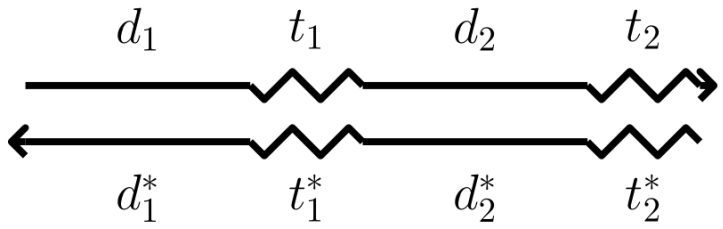
Levels of Abstraction

DNA

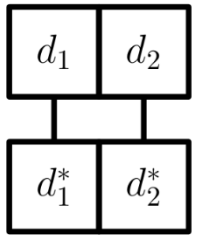
Base Pairs



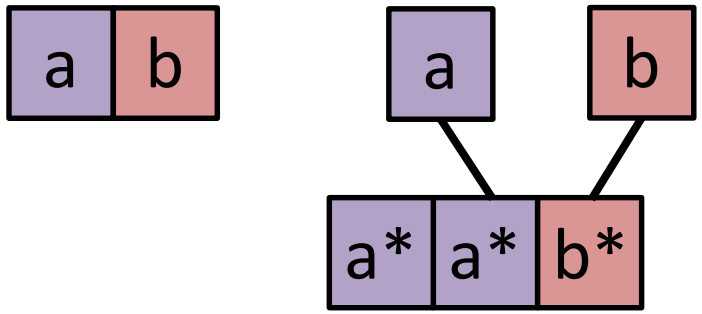
Strands



Thermodynamic Binding Network



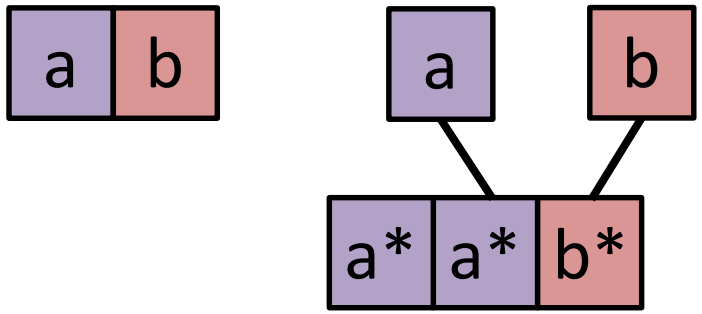
Thermodynamic Binding Networks



Monomer = collection of domains

Configuration = how monomers are bound

Thermodynamic Binding Networks



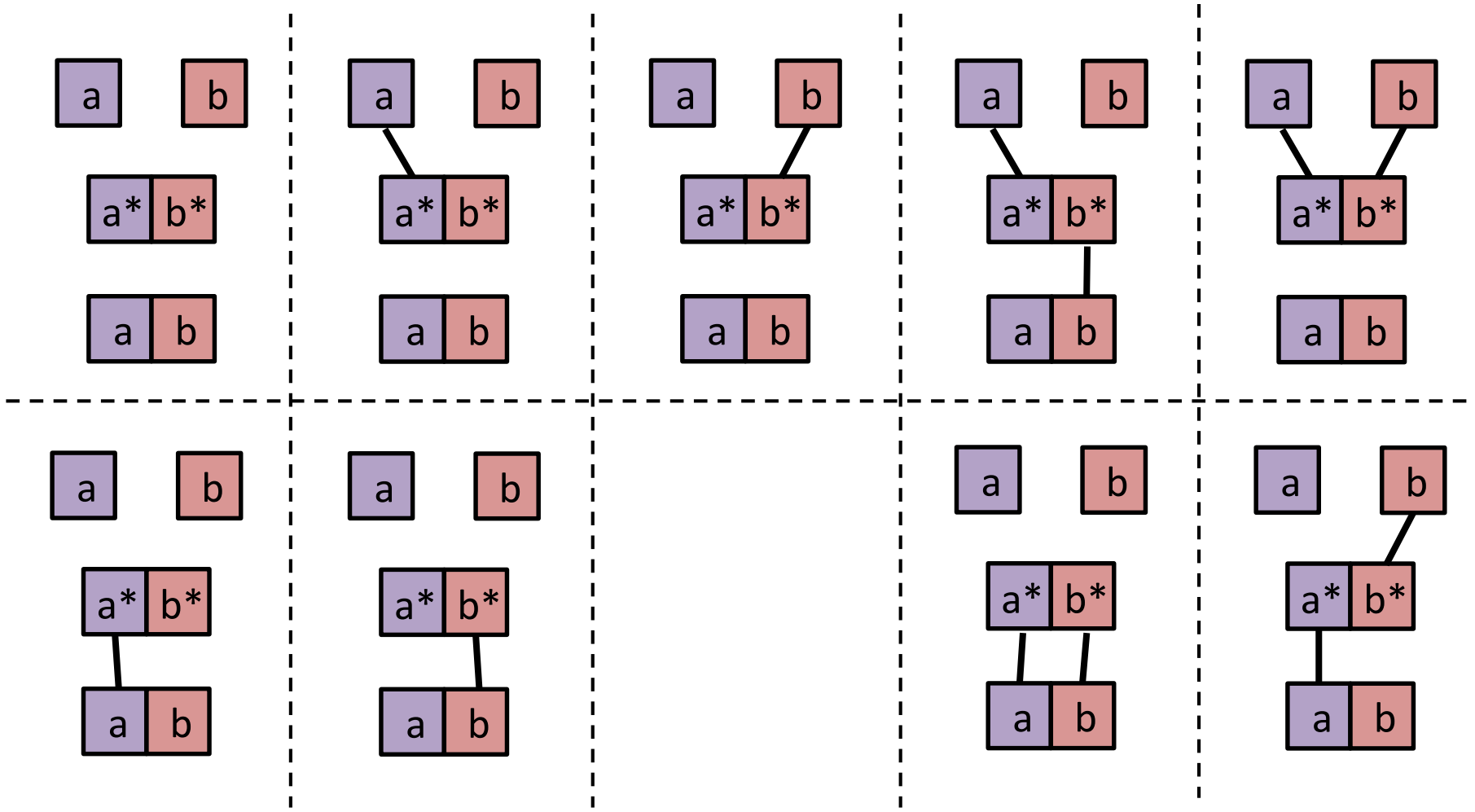
Geometry-Free Model:

The domains within a monomer are unordered

Monomer = collection of domains

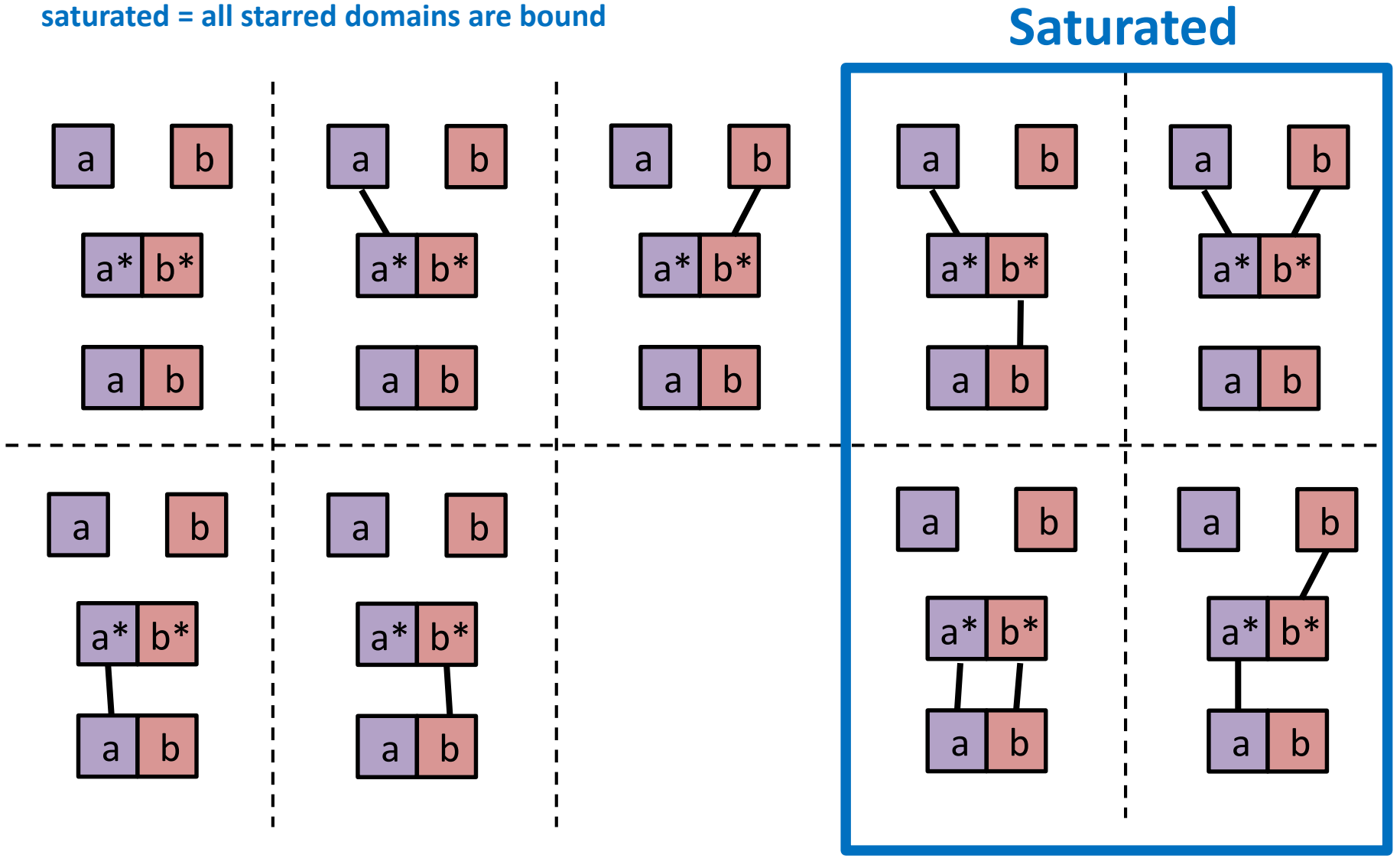
Configuration = how monomers are bound

Thermodynamic Binding Networks



Thermodynamic Binding Networks

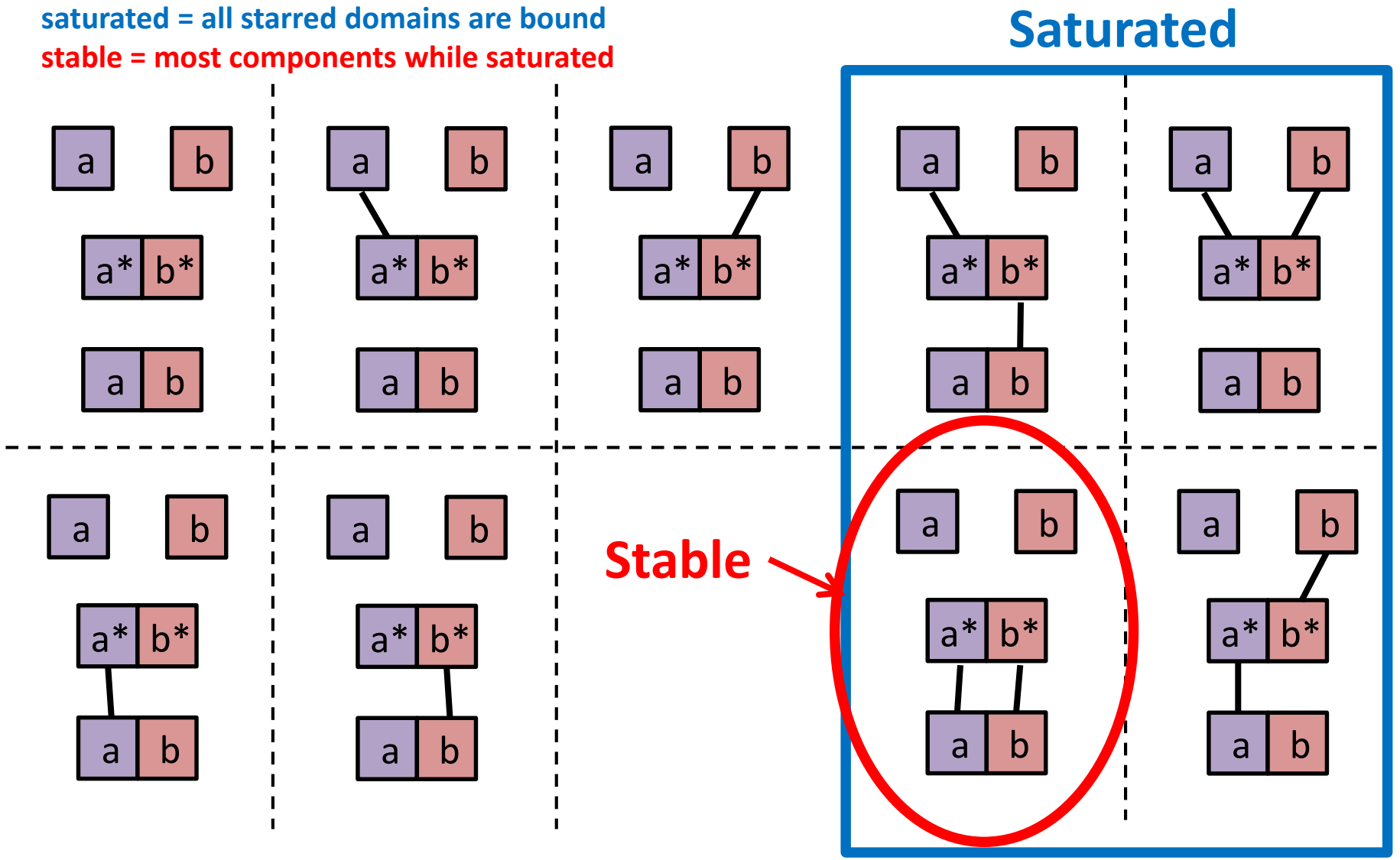
saturated = all starred domains are bound



Thermodynamic Binding Networks

saturated = all starred domains are bound

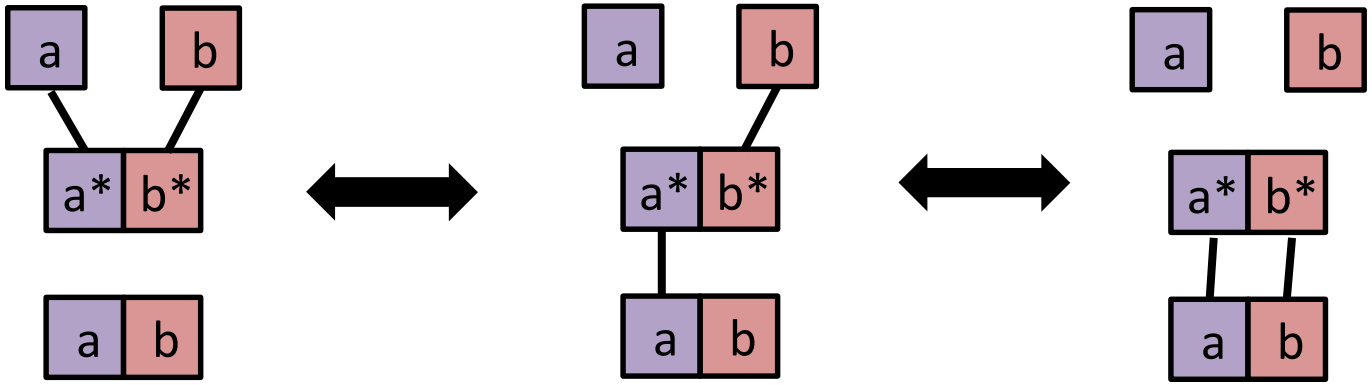
stable = most components while saturated



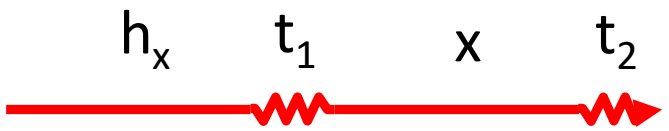
Pathways

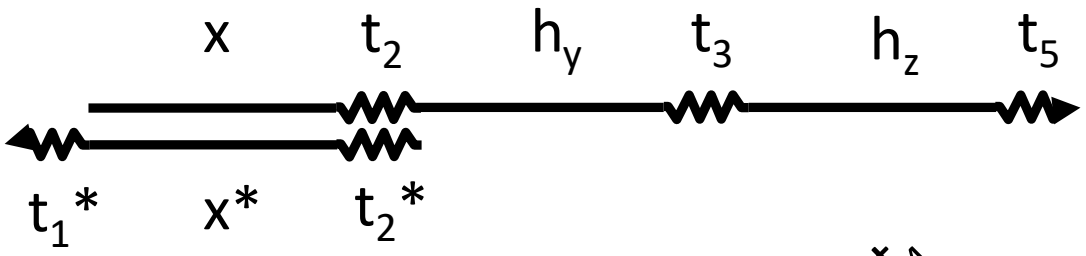
Thermodynamics: Which configurations are energetically favorable

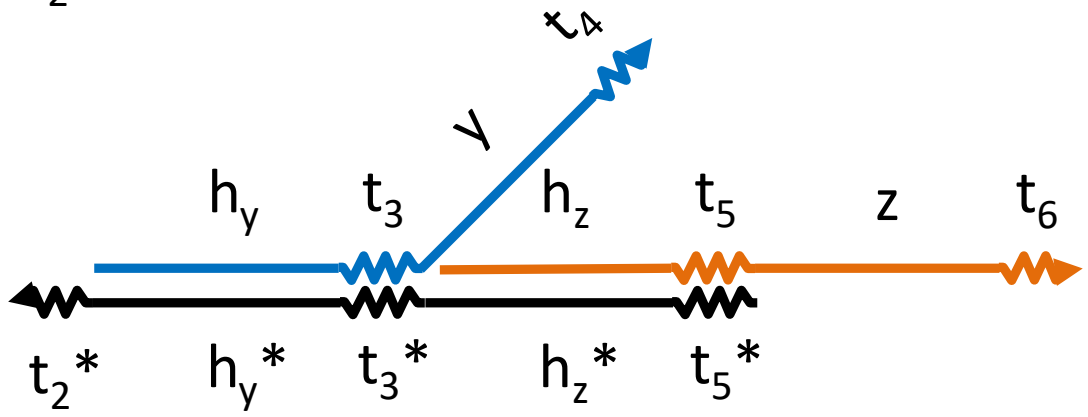
Kinetics: How a system moves between configurations over time



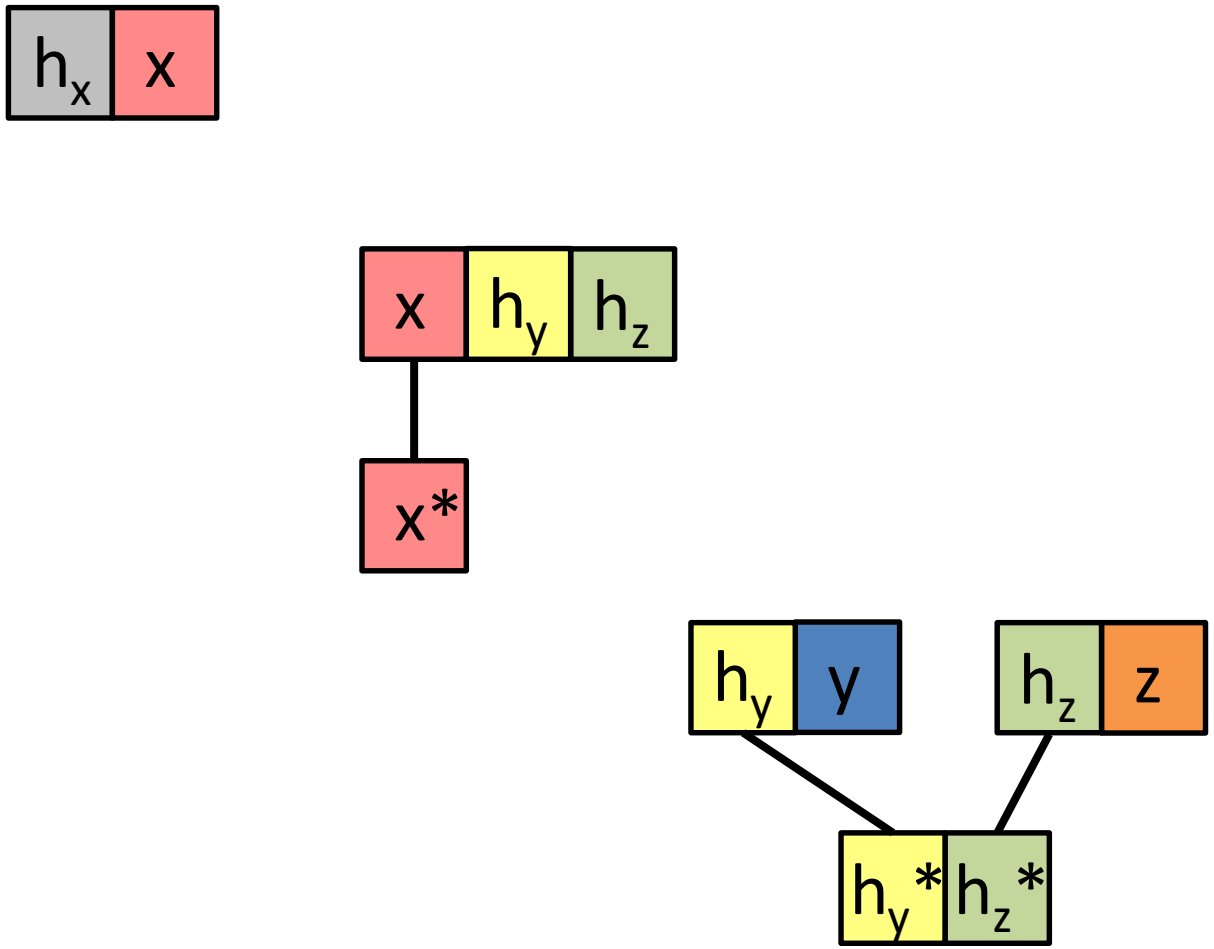
$$X \longrightarrow Y + Z$$

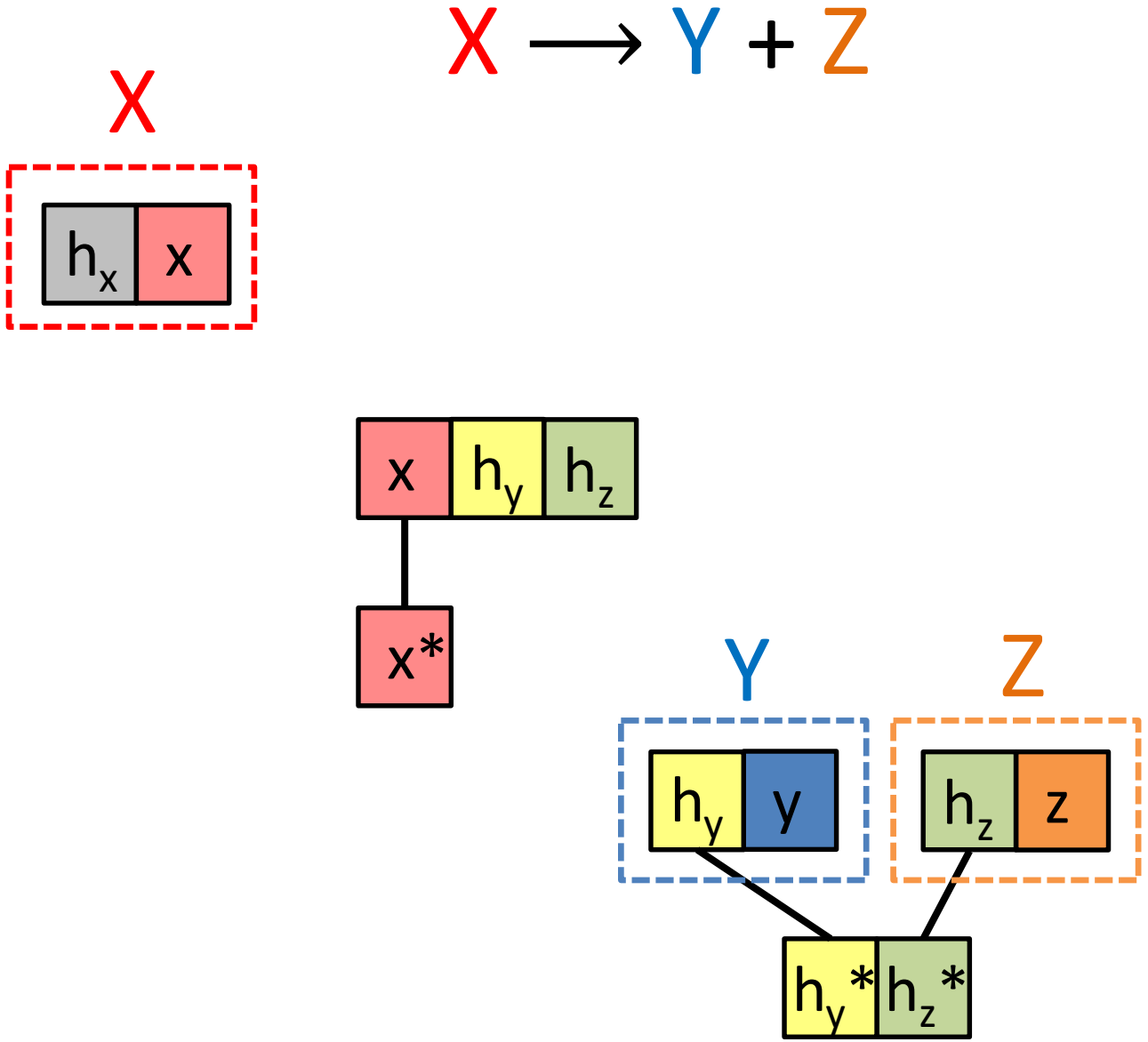




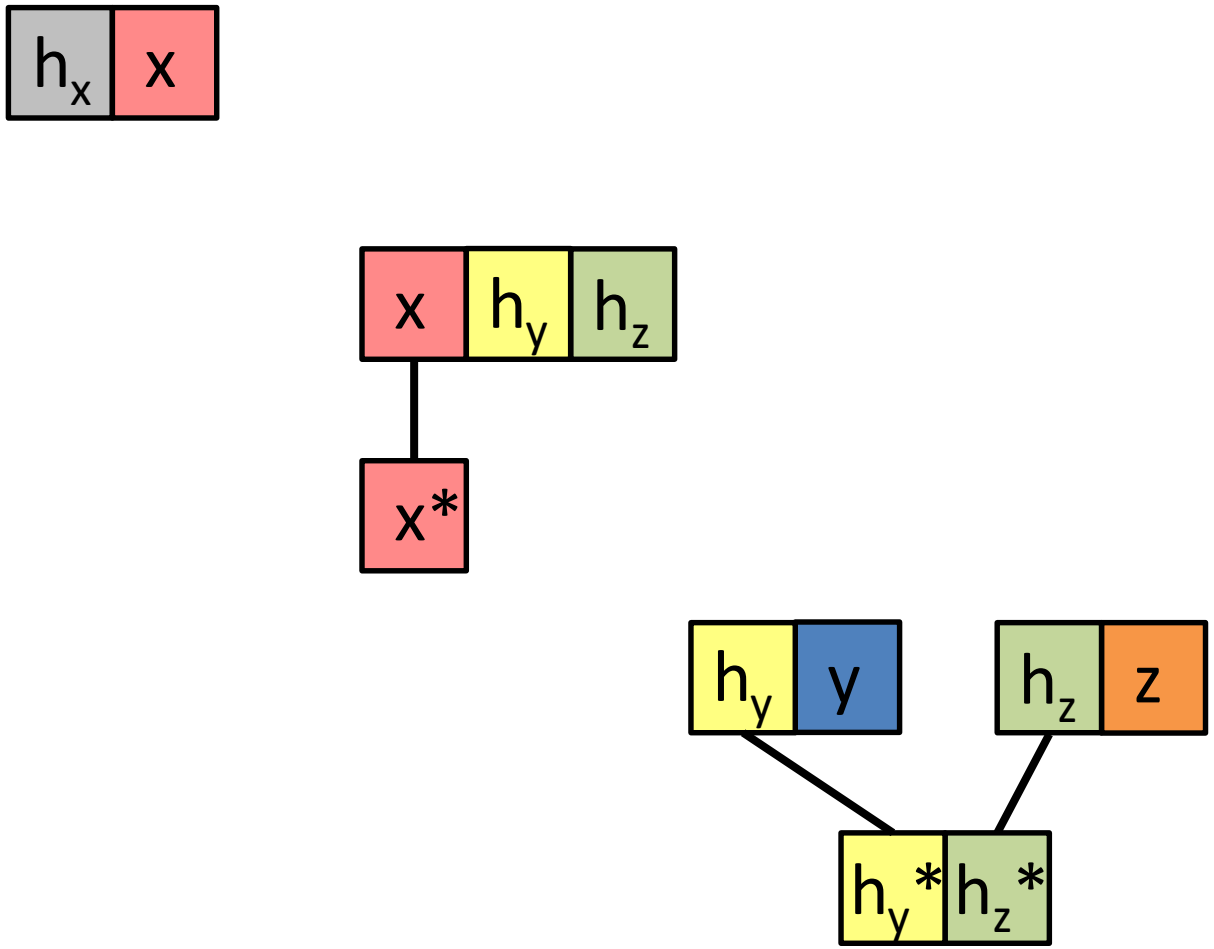


$$X \longrightarrow Y + Z$$

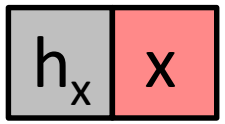


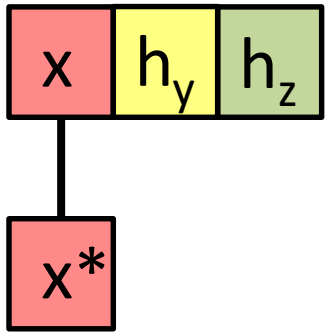

X ⟶ Y + Z
X
h_x
x
x
h_y
h_z
x*
Y
Z
h_y
y
h_z
z
h_y*
h_z*

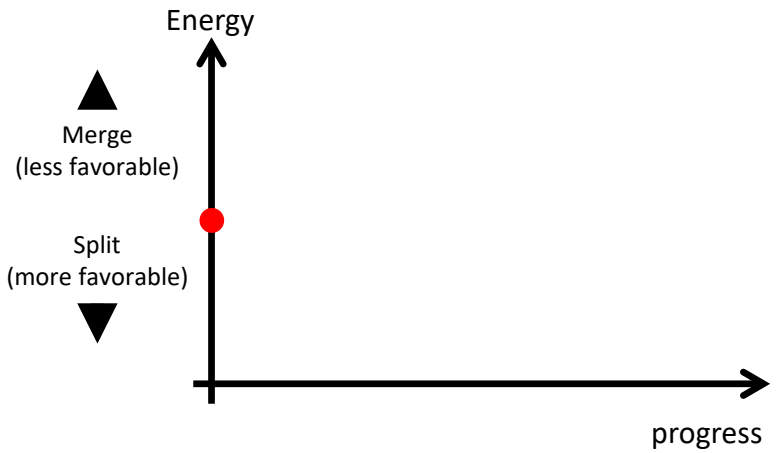
$$X \longrightarrow Y + Z$$

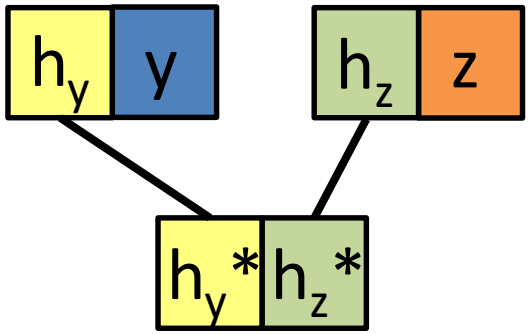


$$X \longrightarrow Y + Z$$

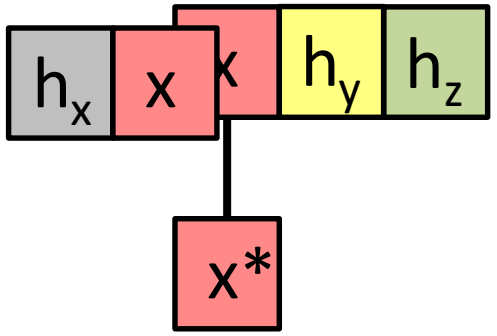


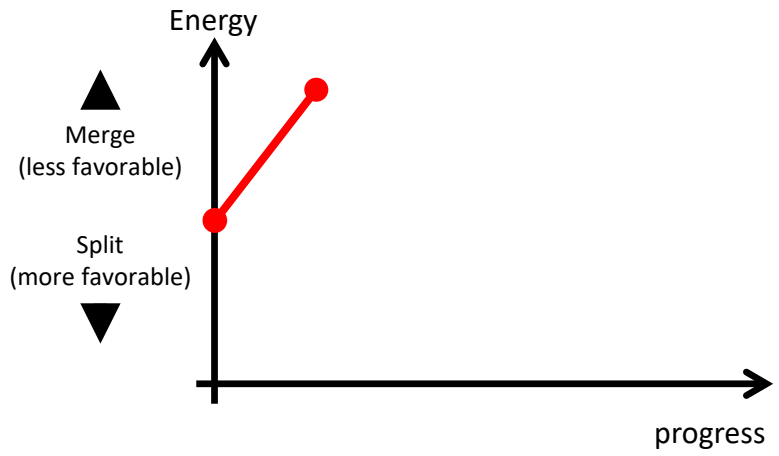


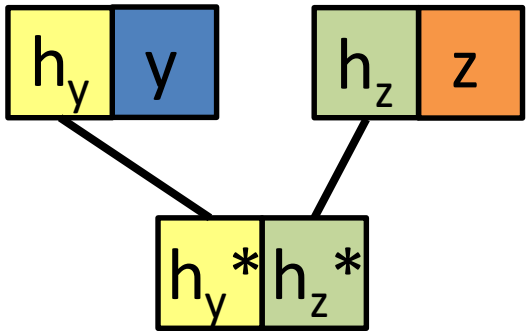




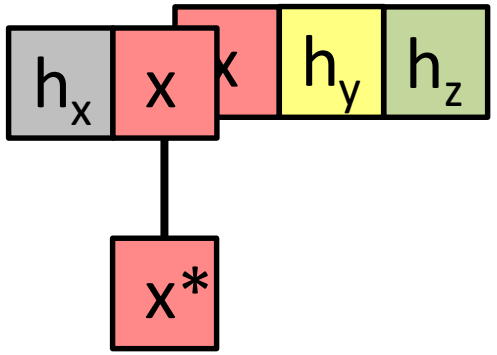
$$X \longrightarrow Y + Z$$

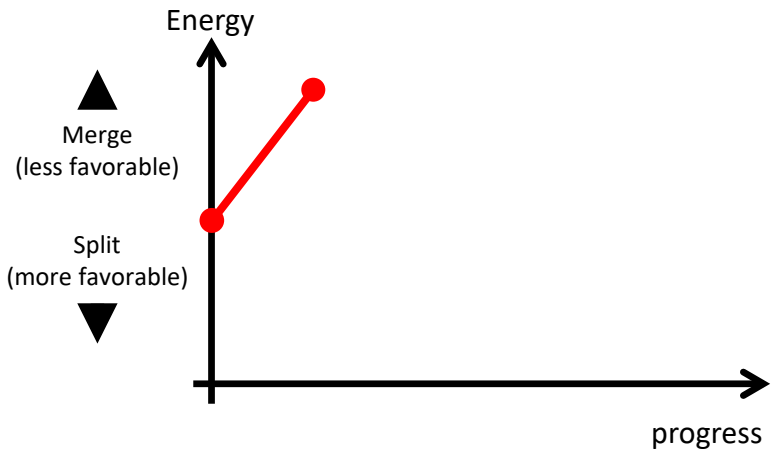


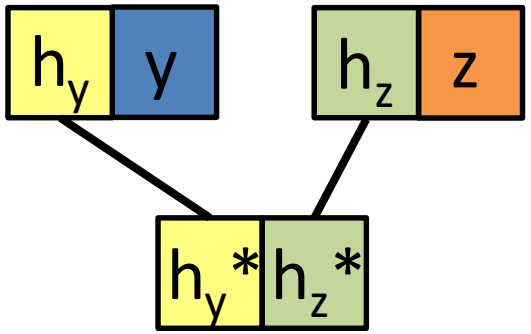




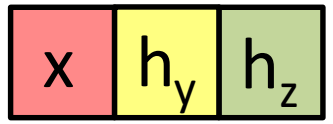
$$X \longrightarrow Y + Z$$

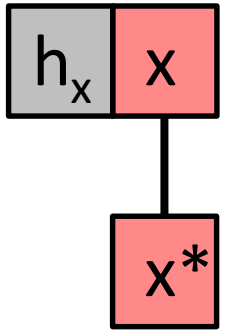


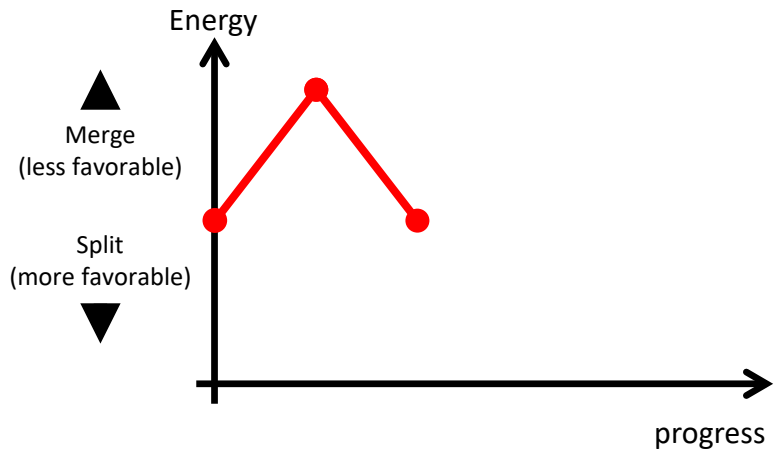


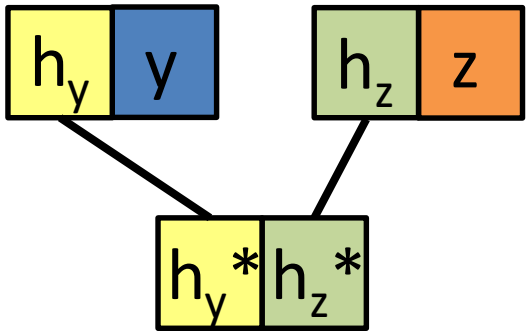


$$X \longrightarrow Y + Z$$

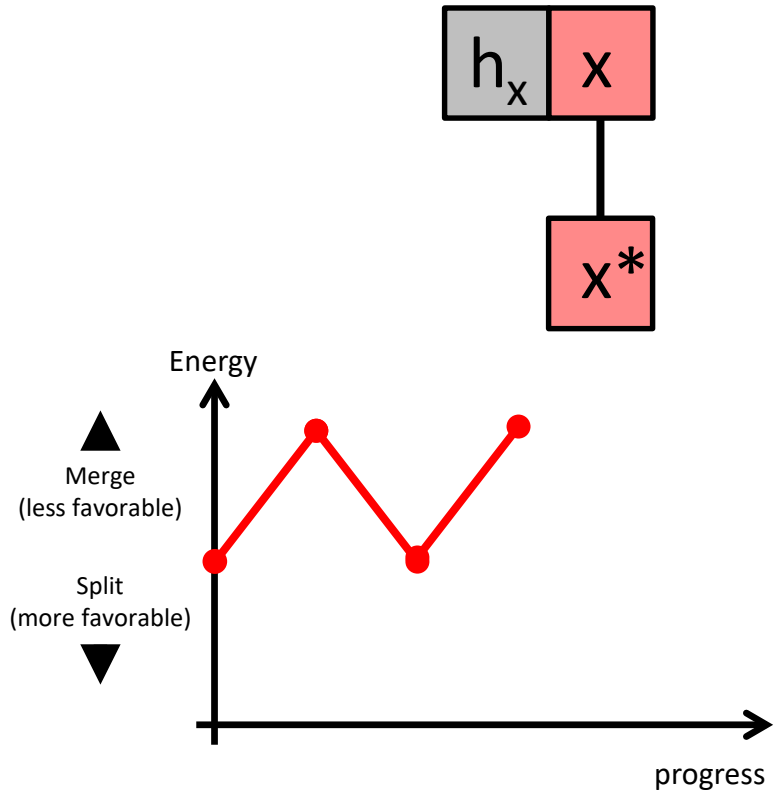


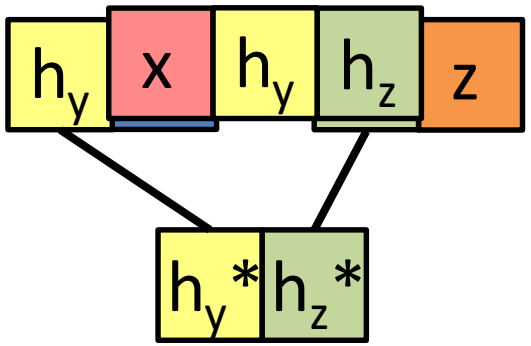






$$X \longrightarrow Y + Z$$





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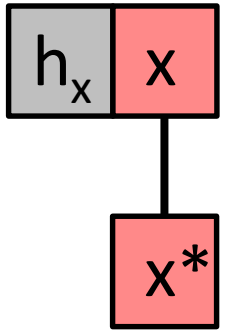

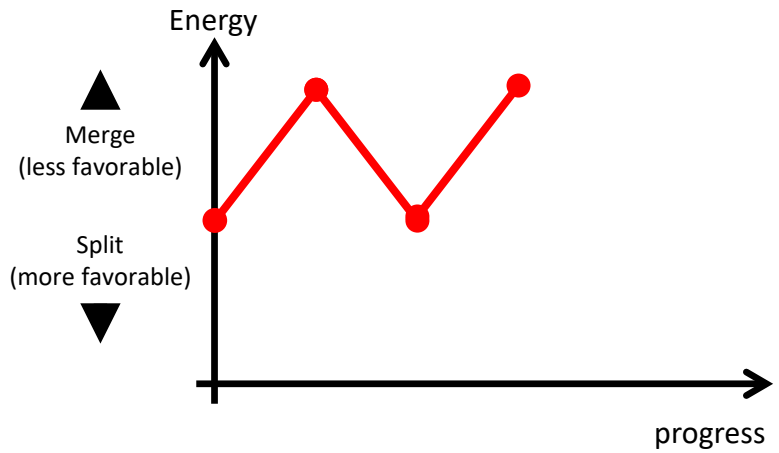

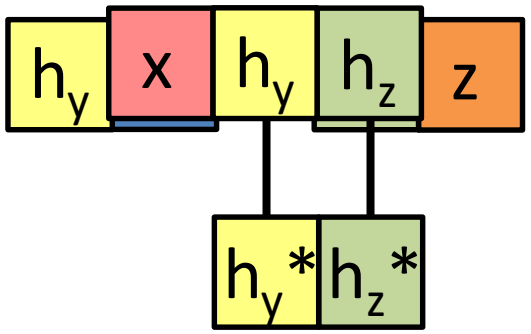

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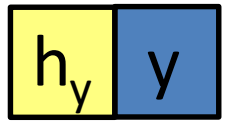

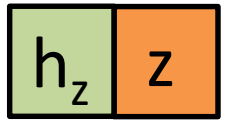

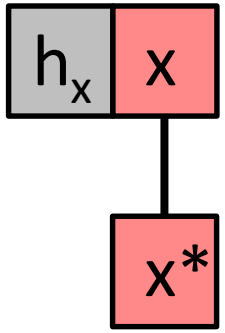

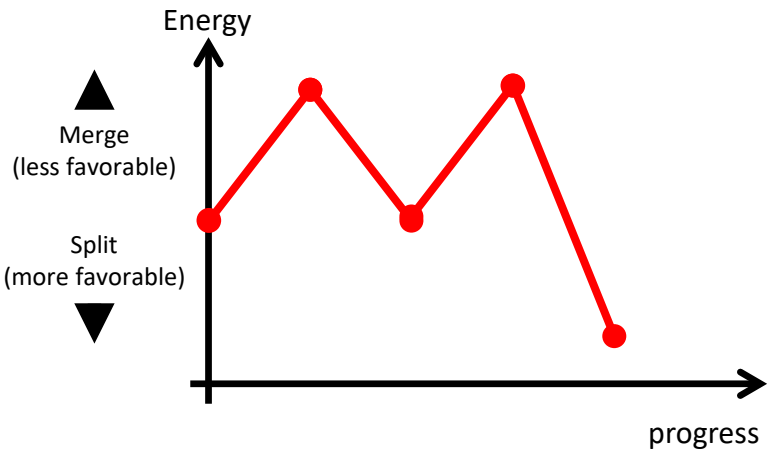

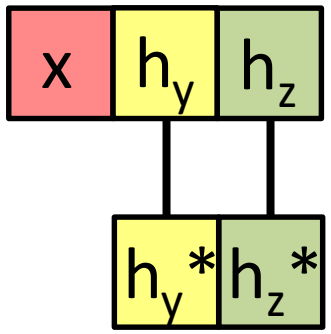

Leak: A Source of Error

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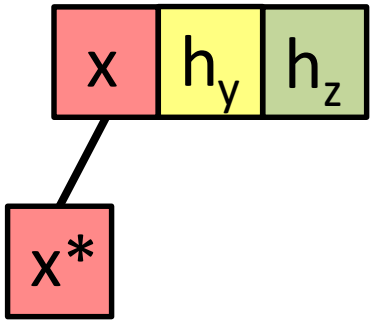

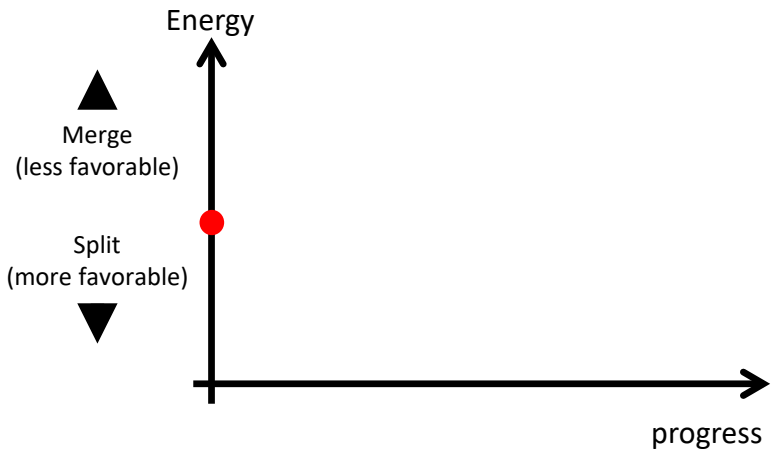

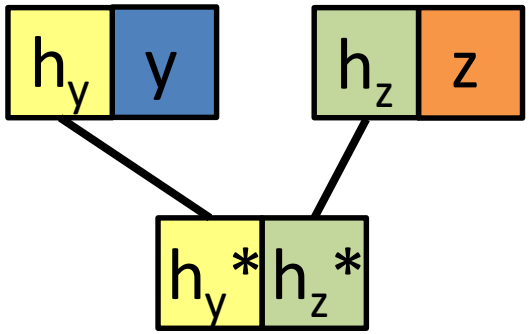

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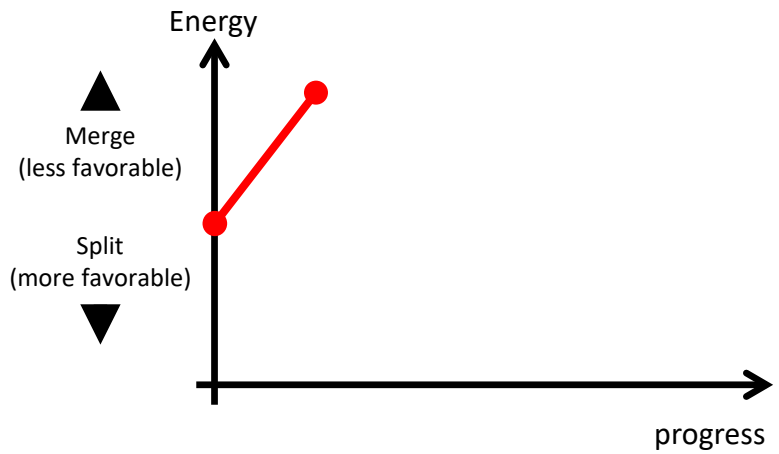

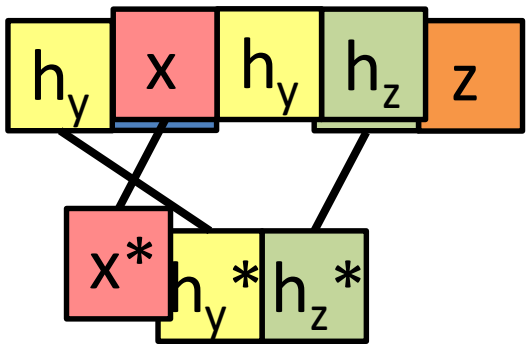

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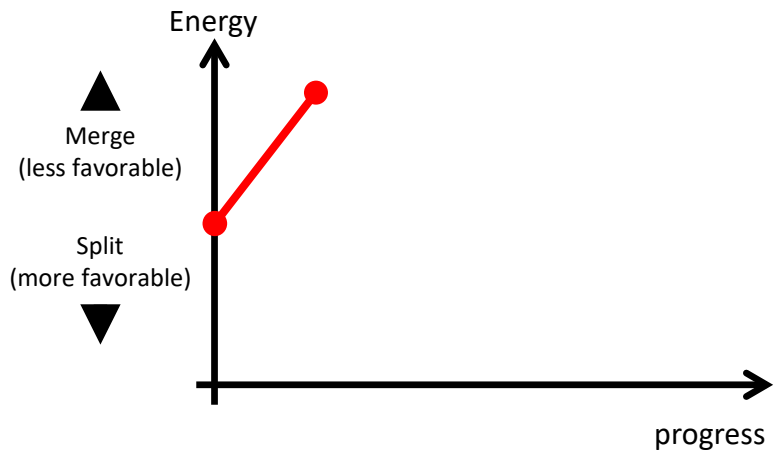

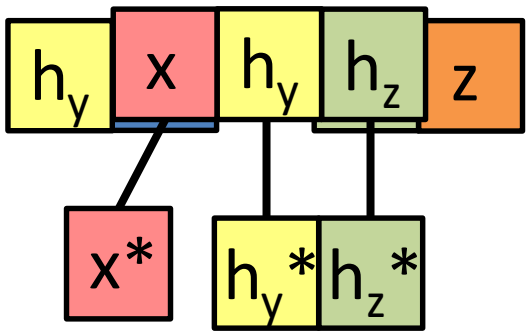

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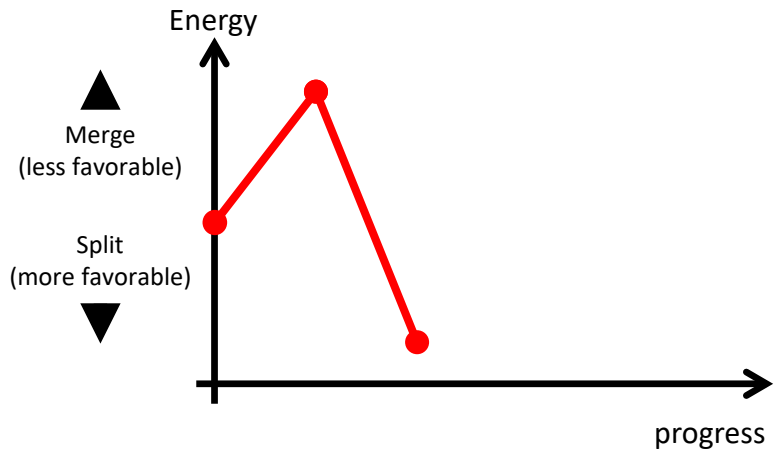

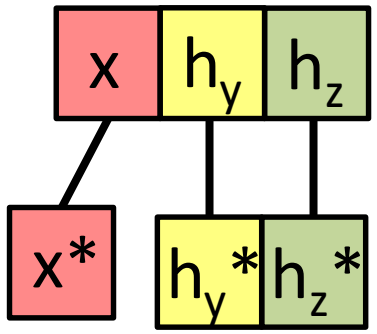

Kinetic Binding Networks

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- Favorability is a combination of bond count and component count

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<u>Weighted average:</u>

Energy := $-w_H(\#\text{ bonds}) - (\#\text{ components})$

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[2]Keenan Breik, Cameron Chalk, David Doty, David Haley, David Soloveichik. *Programming Substrate-Independent Kinetic Barriers with Thermodynamic Binding Networks*. CMSB 2018

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

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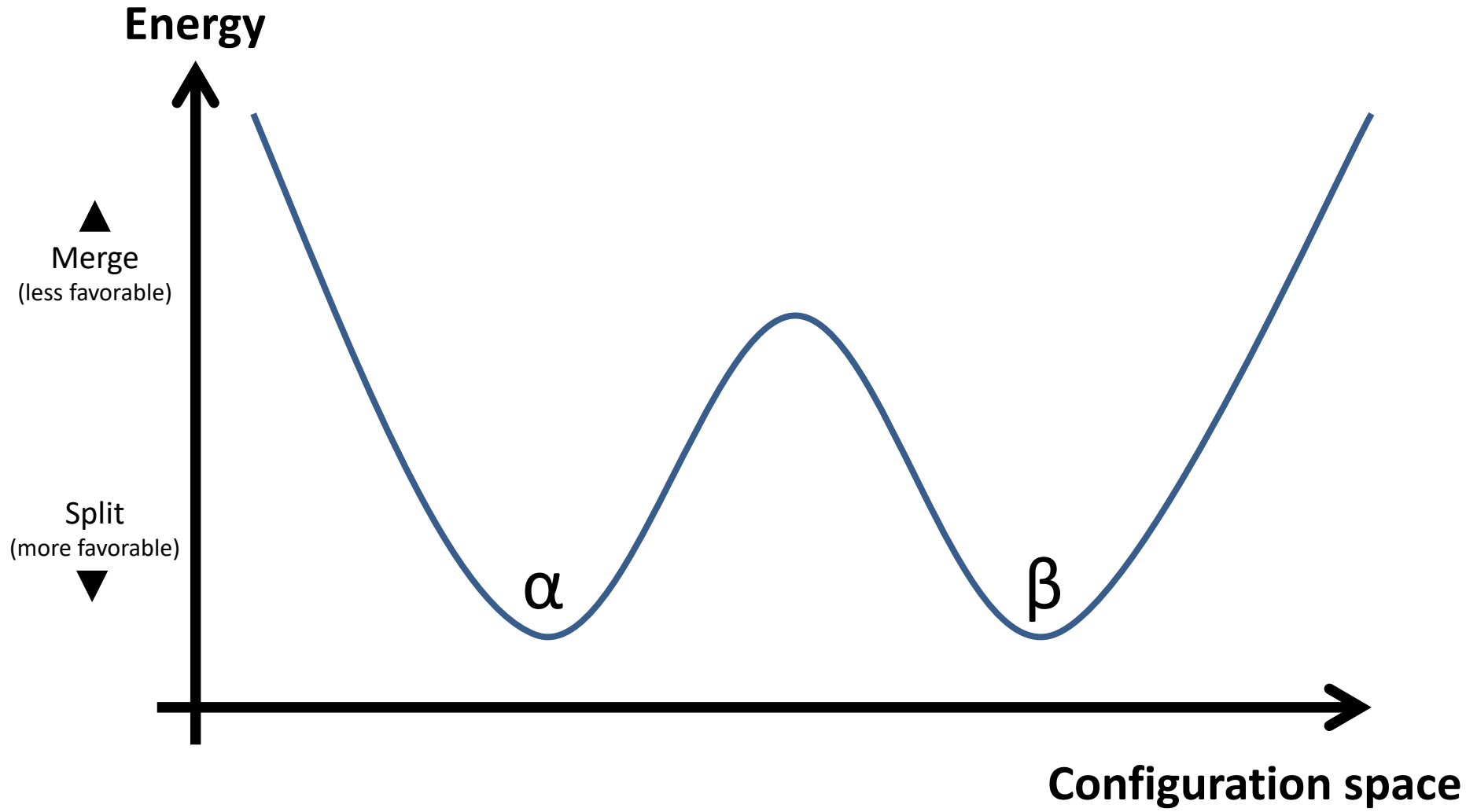
Large Energy Barriers



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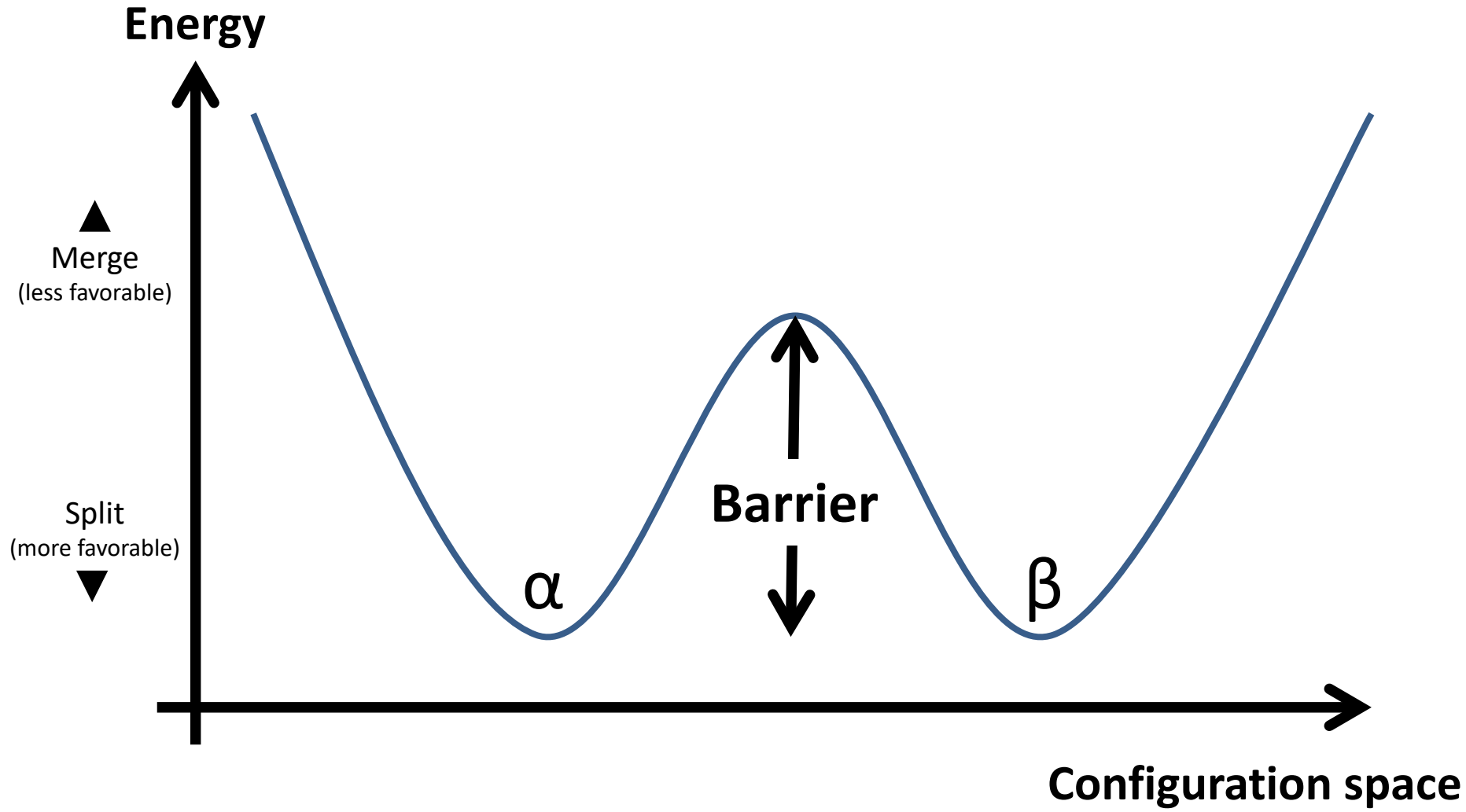

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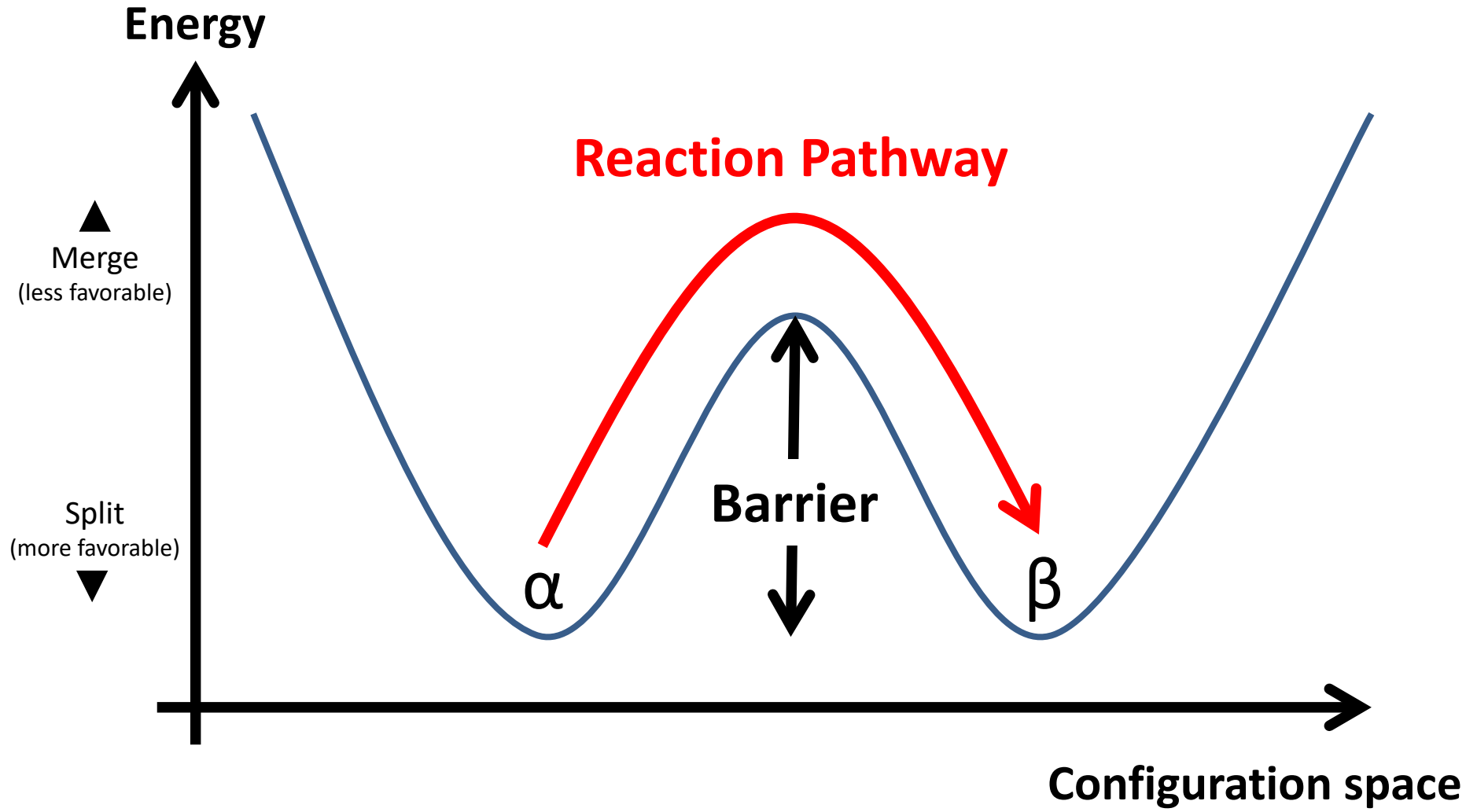
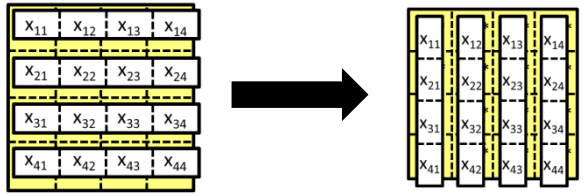
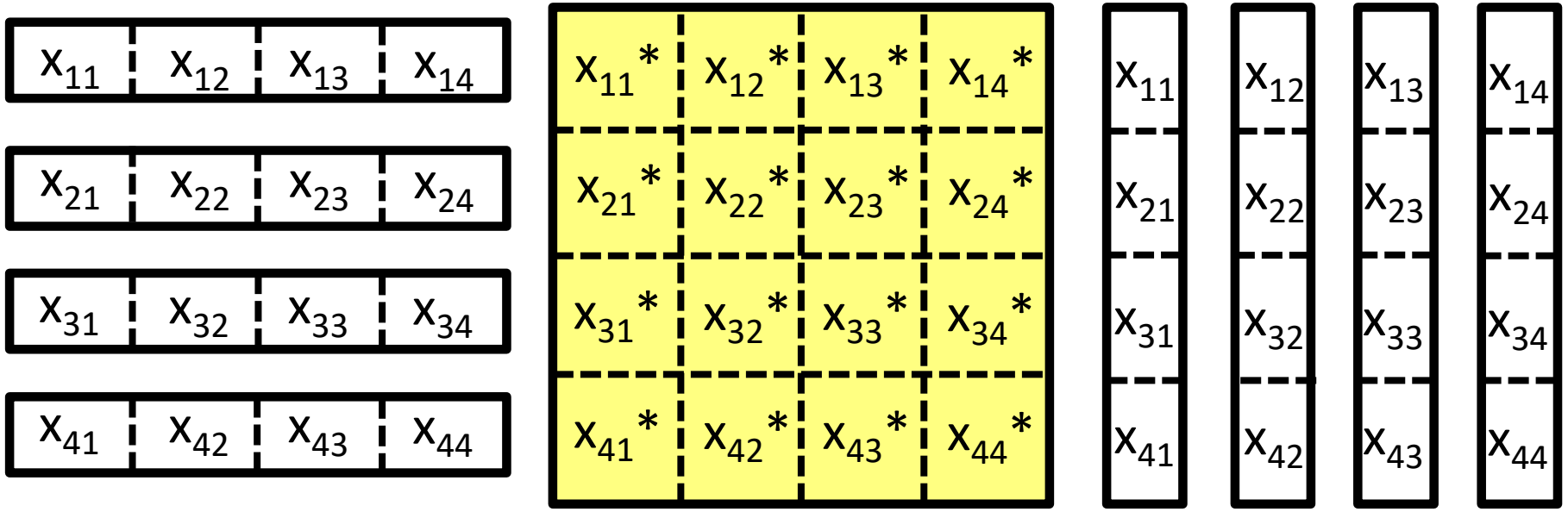


A Network with a Programmable Energy Barrier





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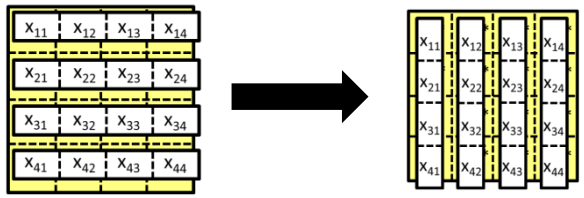

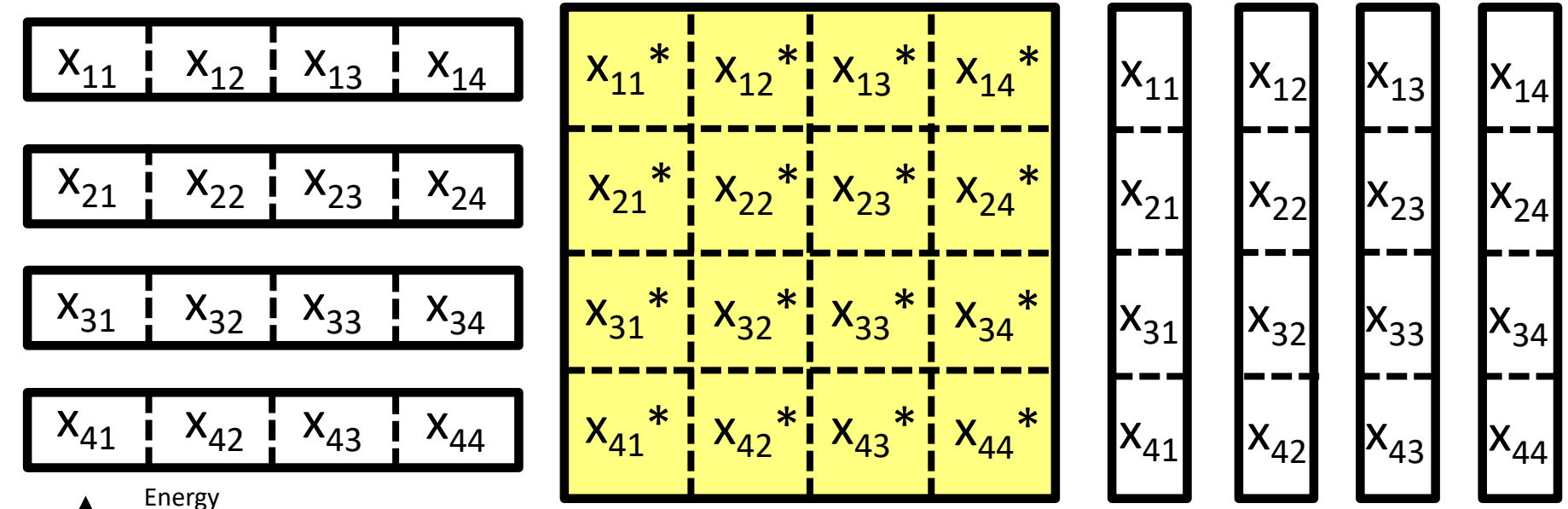

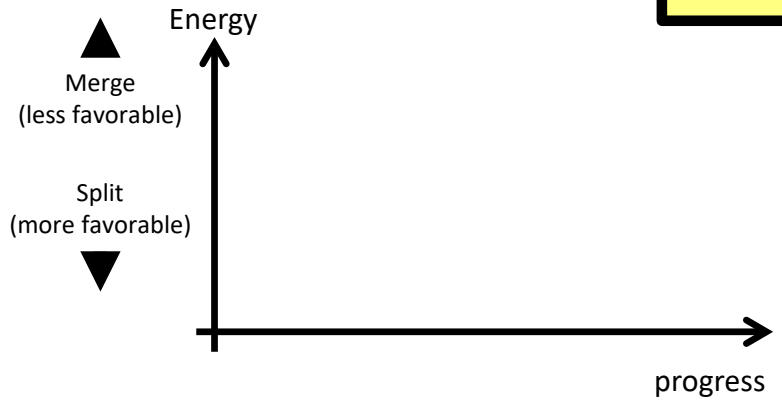

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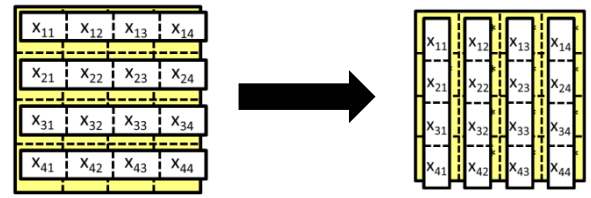

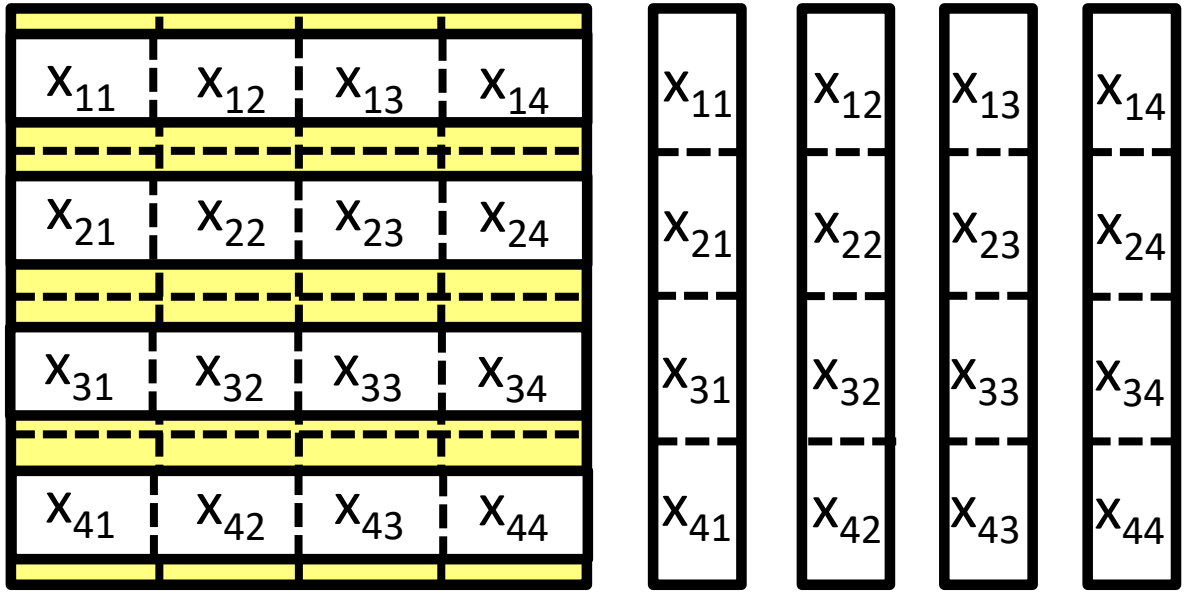

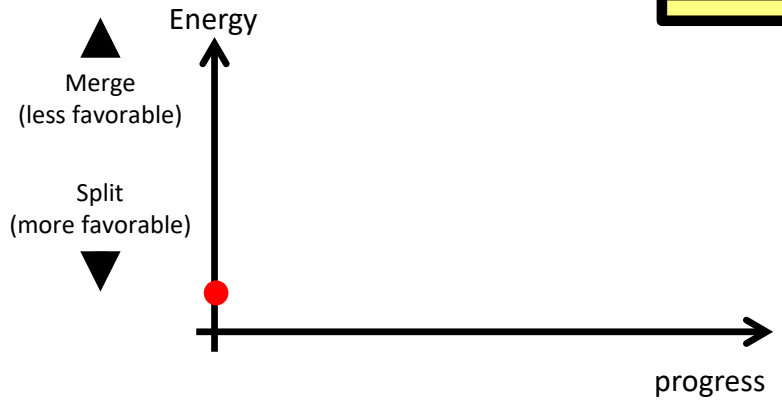

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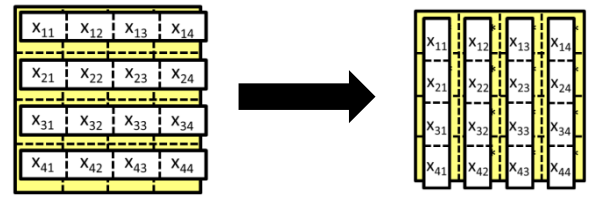

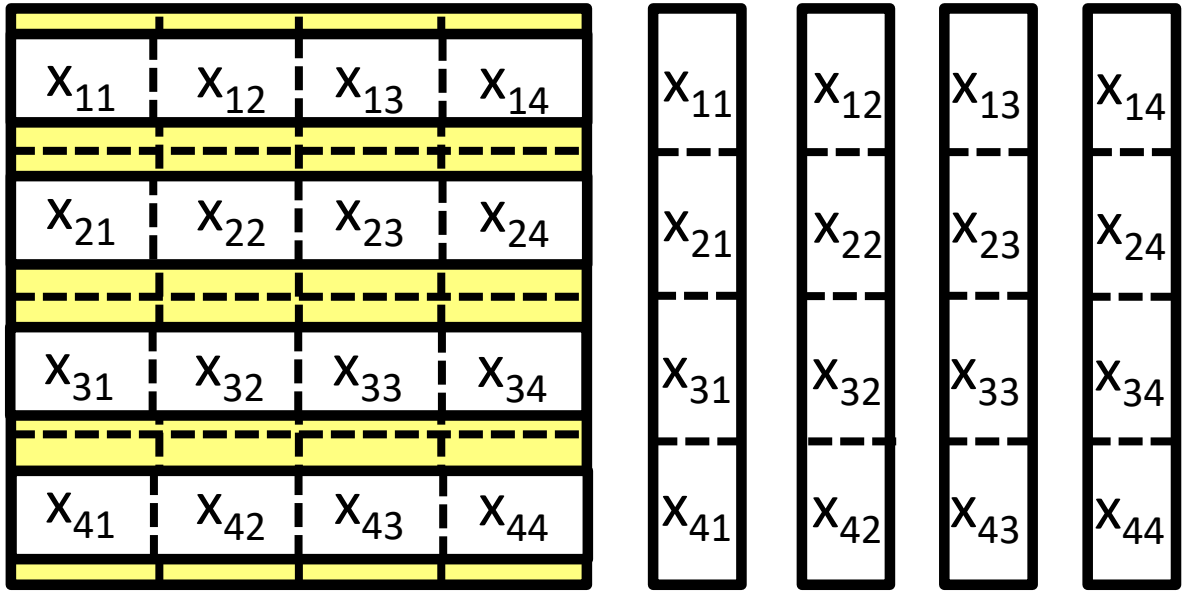

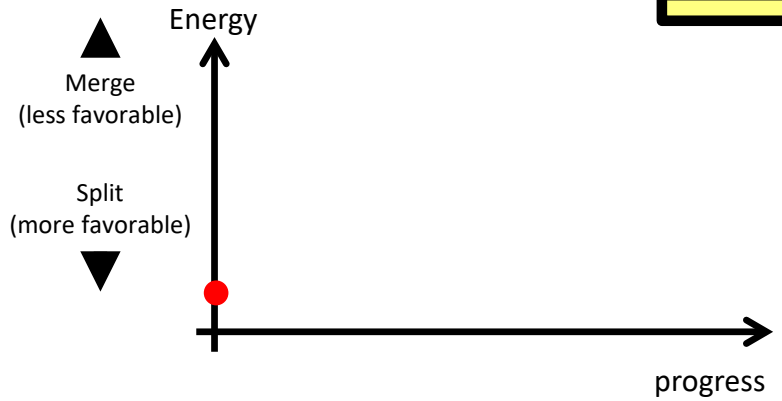

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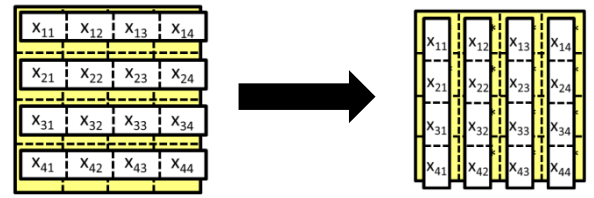

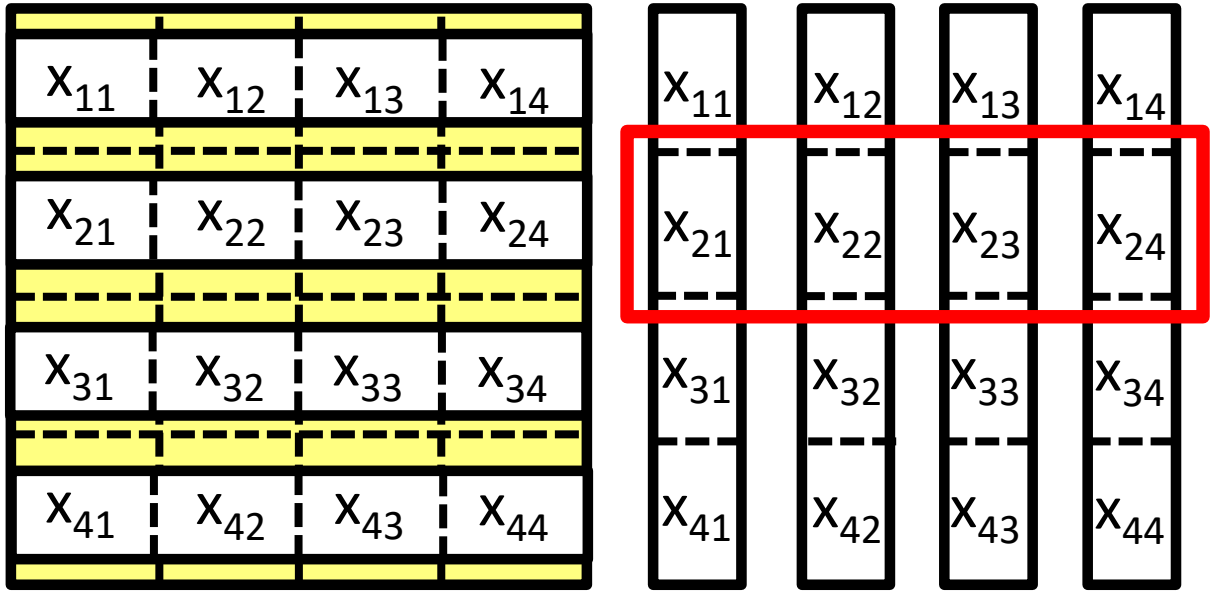

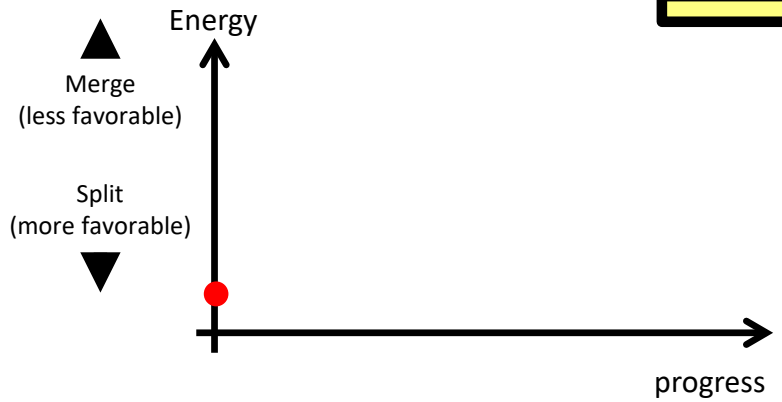

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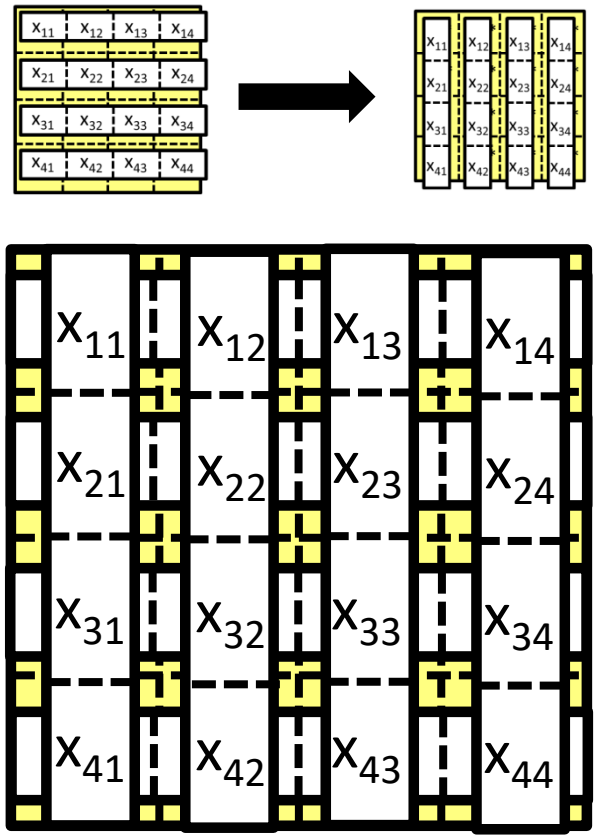

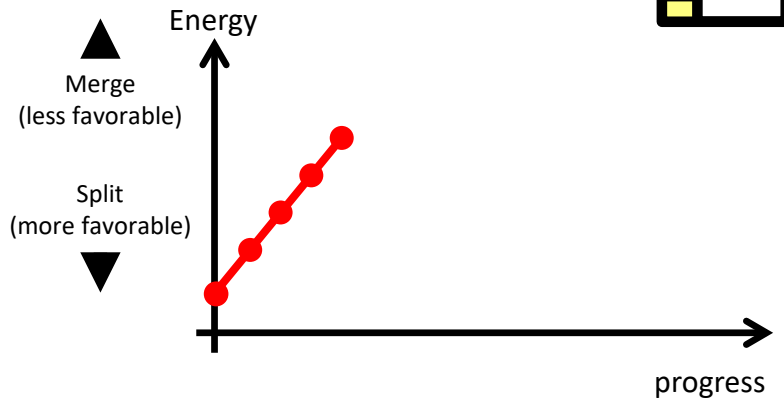

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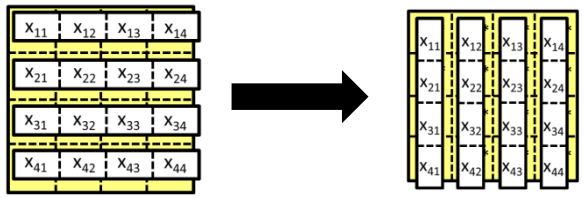
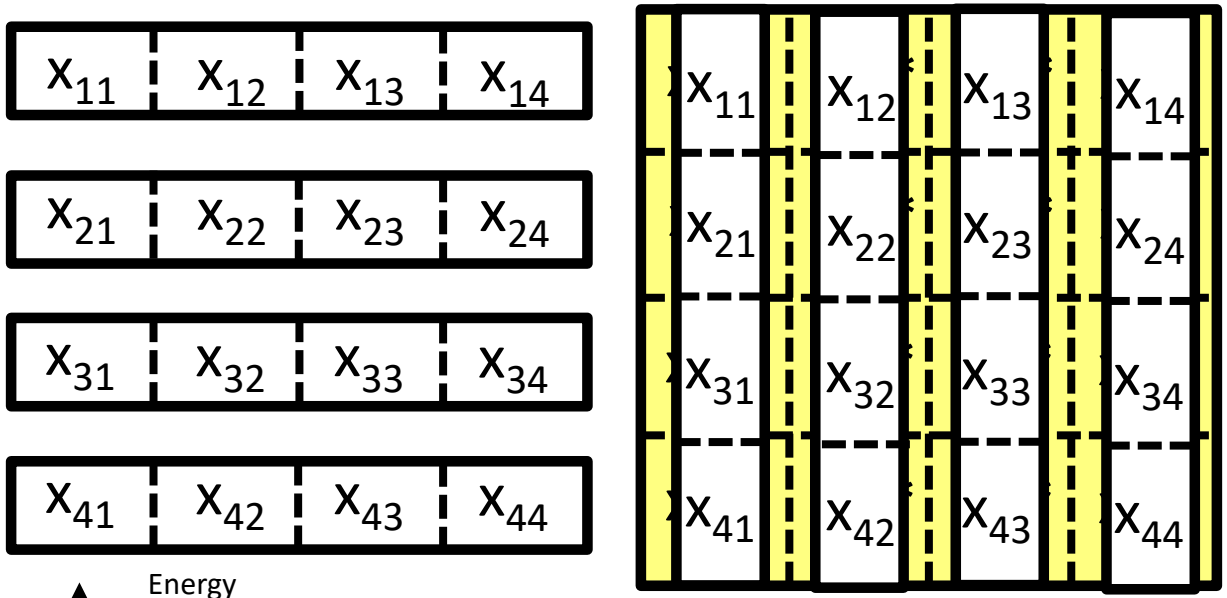
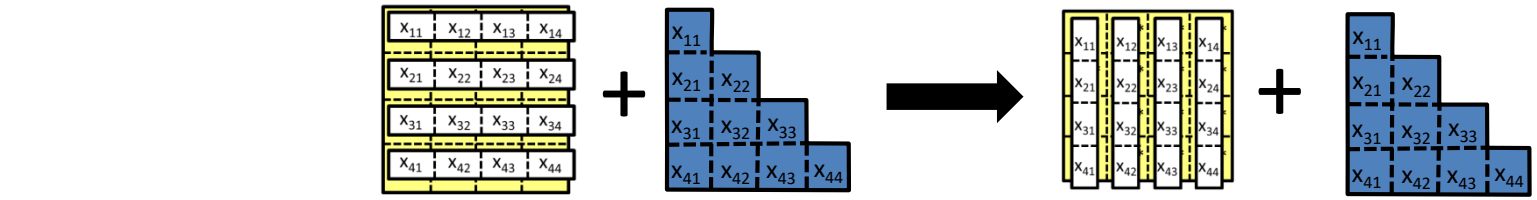
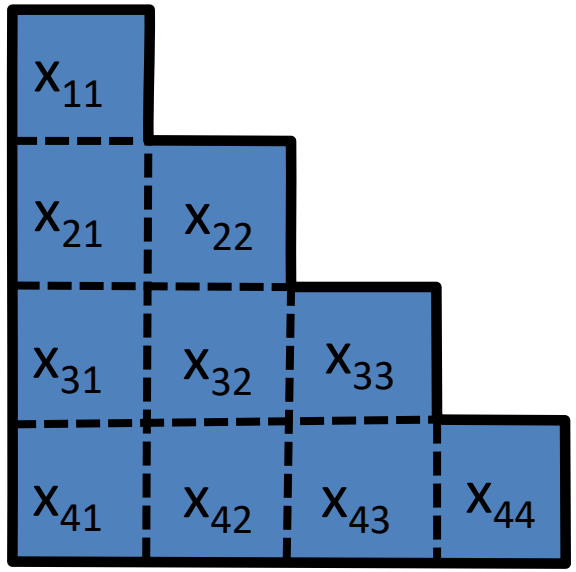




Catalysis


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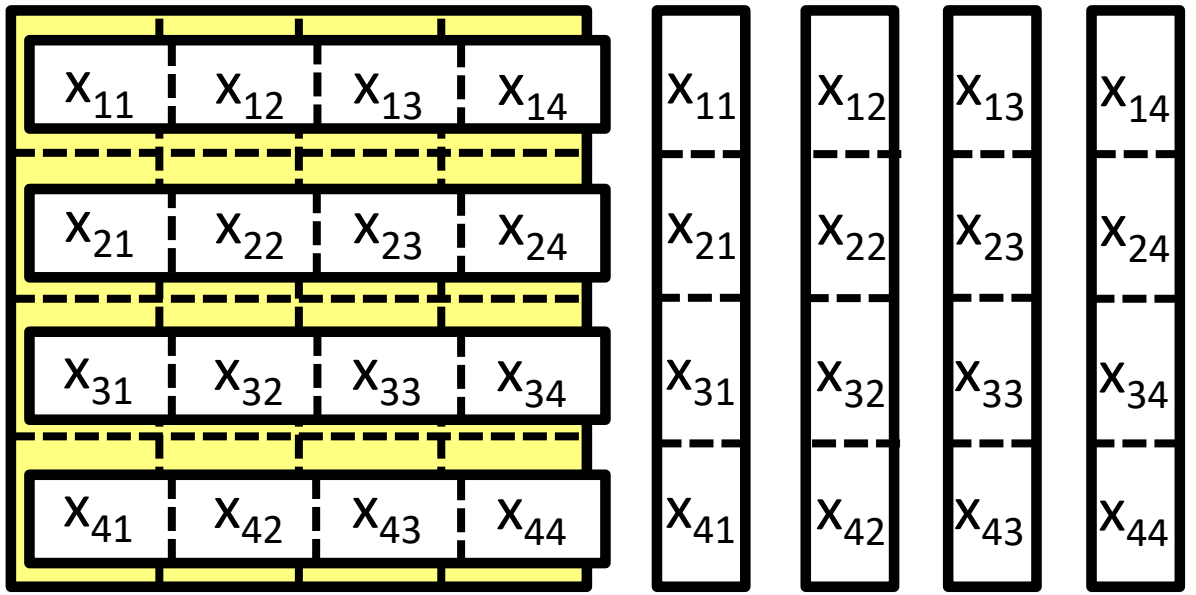
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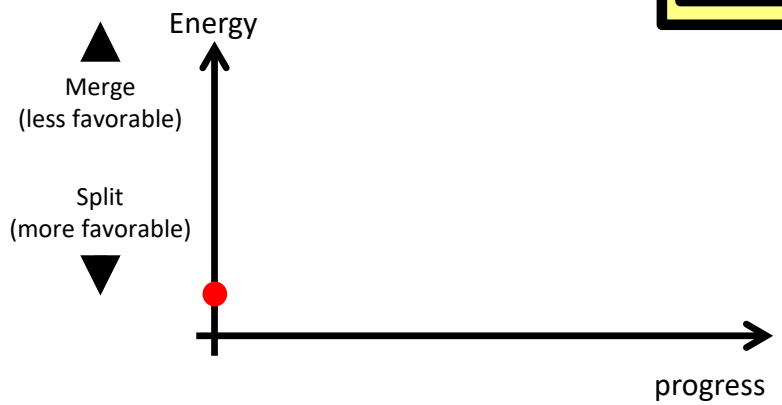
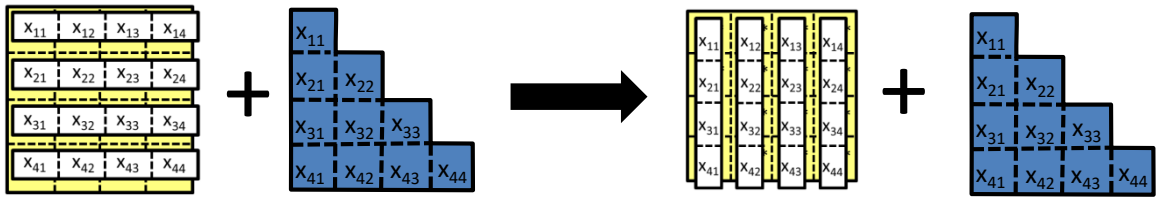

Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis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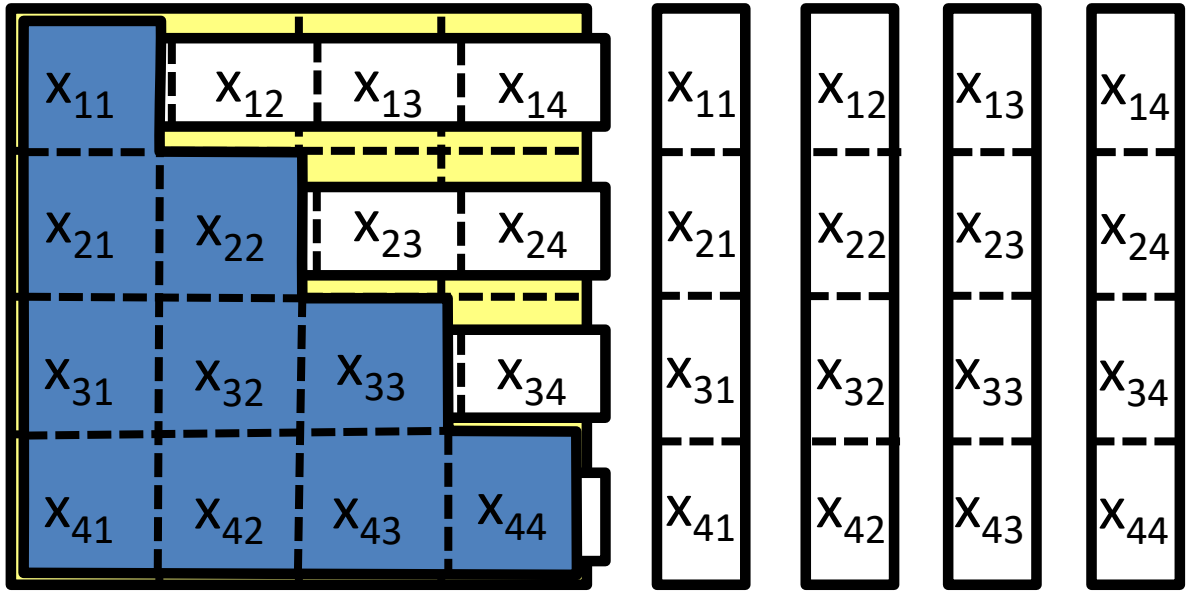
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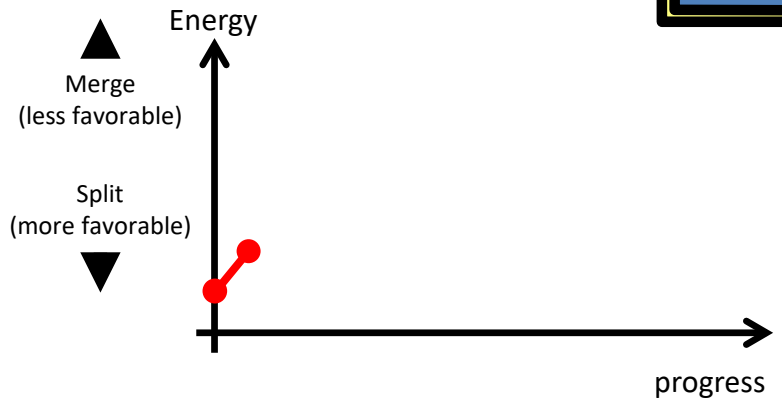
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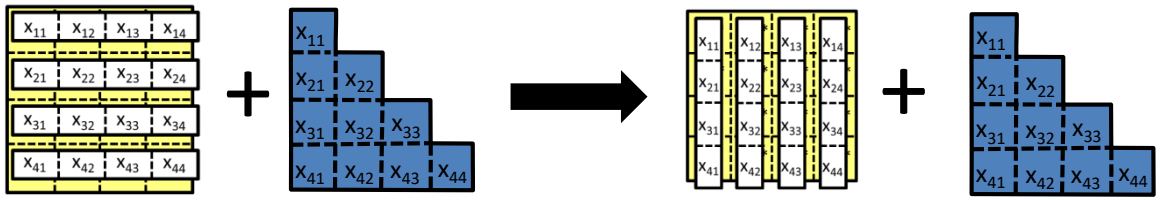
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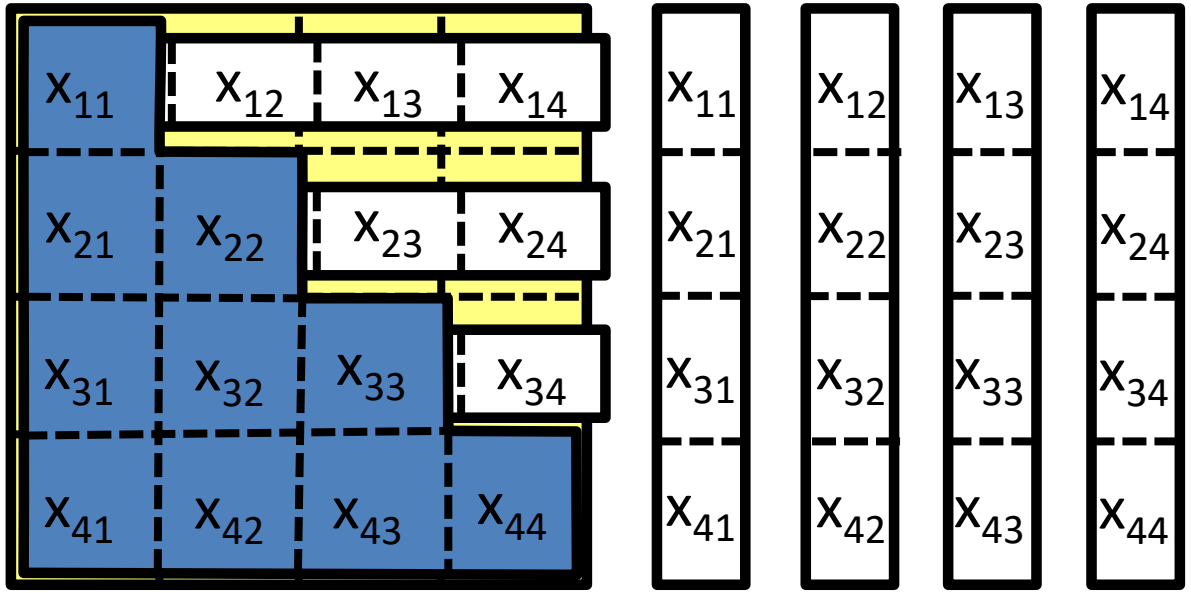
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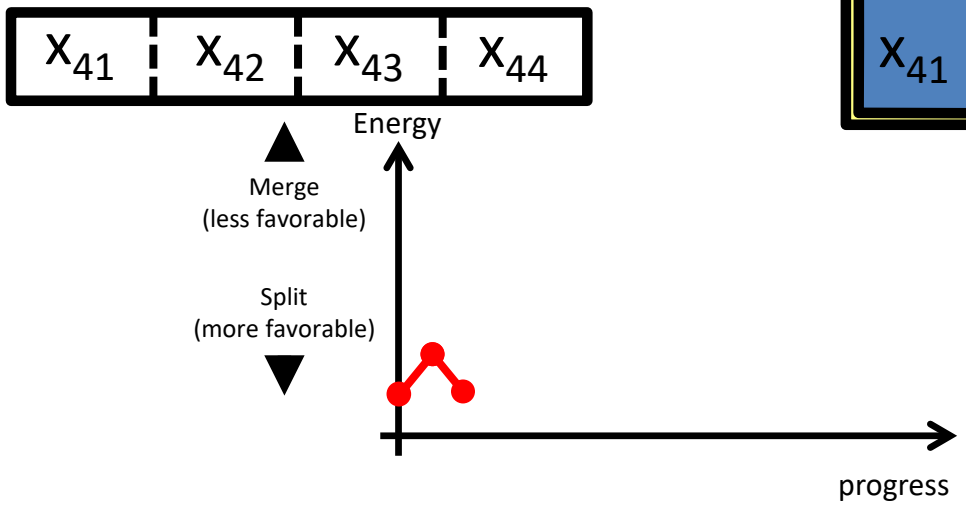
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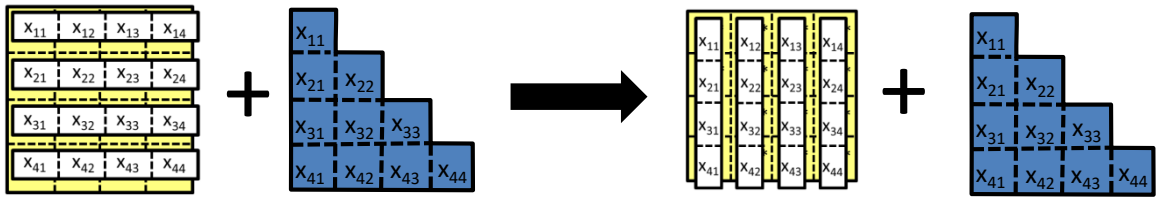
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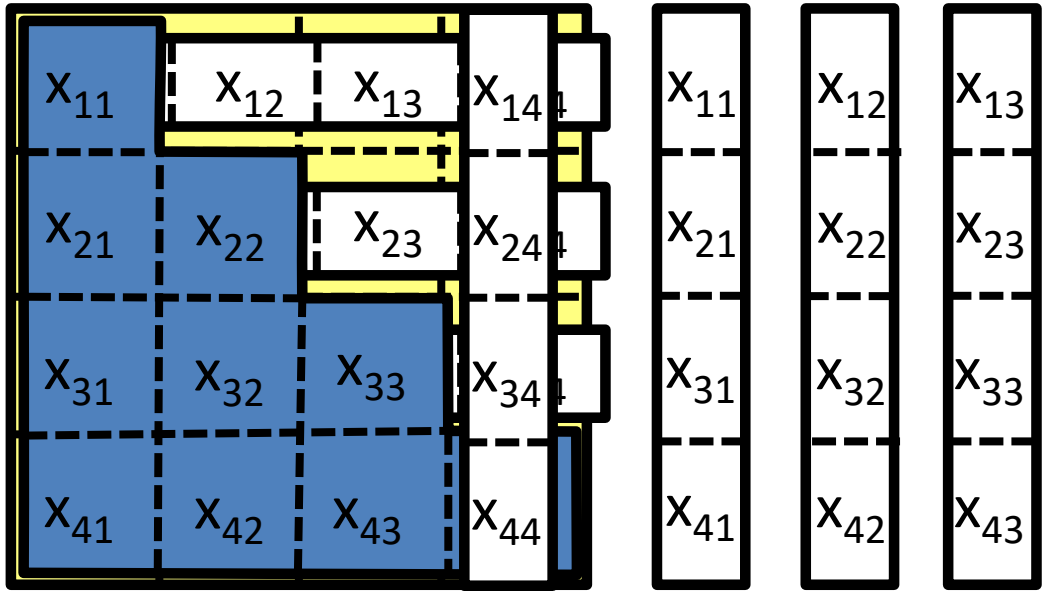
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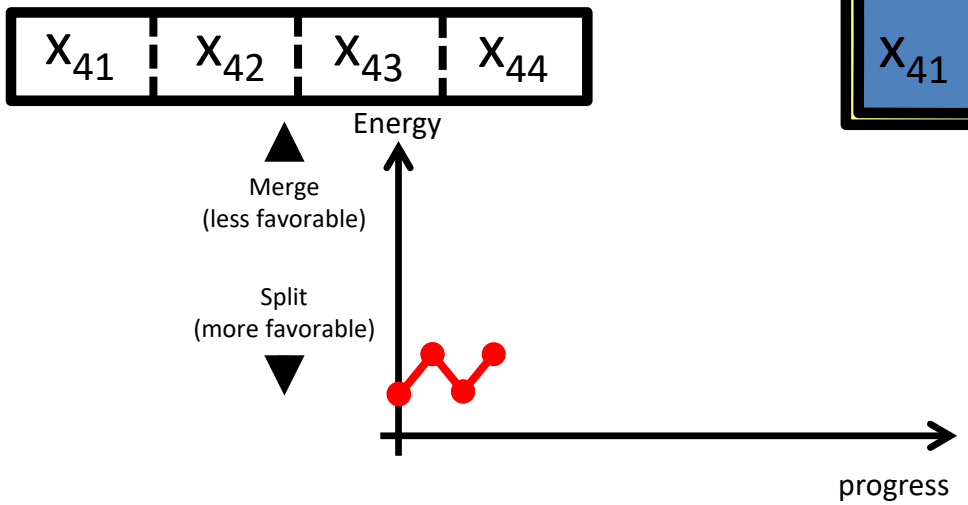
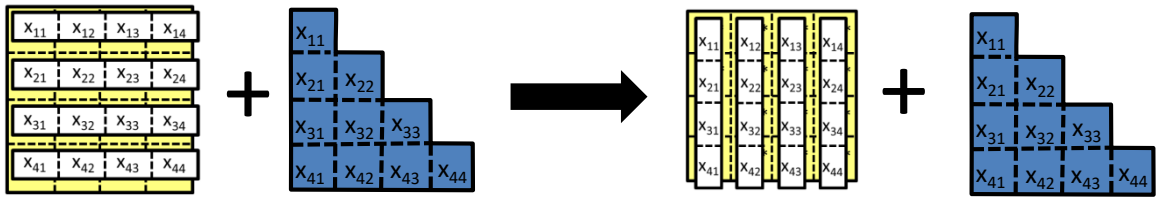
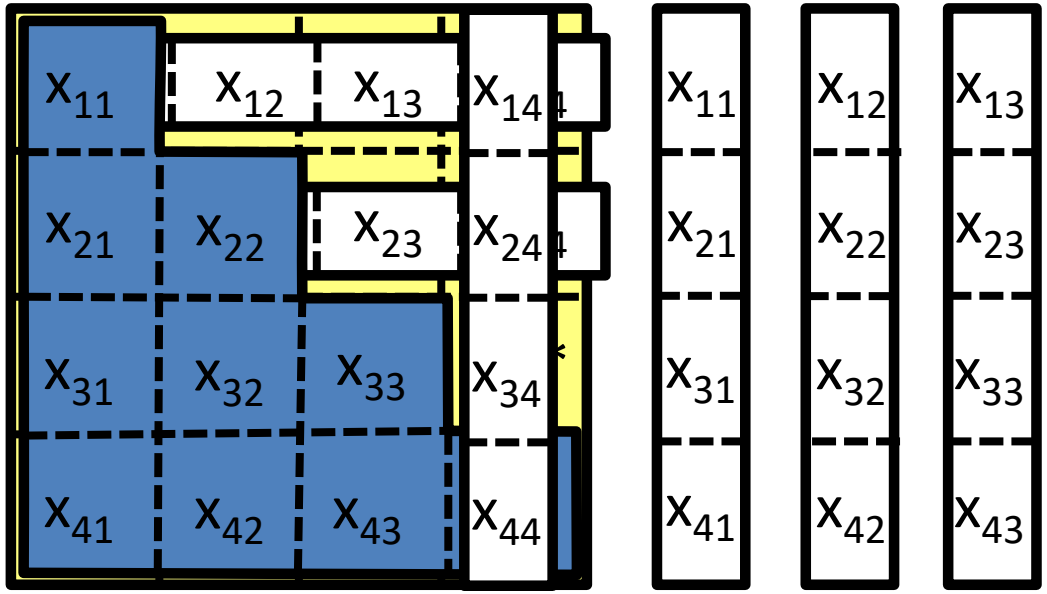
x41 x42 x43 x44
x11 x12 x13
x21 x22 x23
x31 x32 x33
x41 x42 x43
x44
x11 x21 x31 x41
x12 x22 x32 x42
x13 x23 x33 x43


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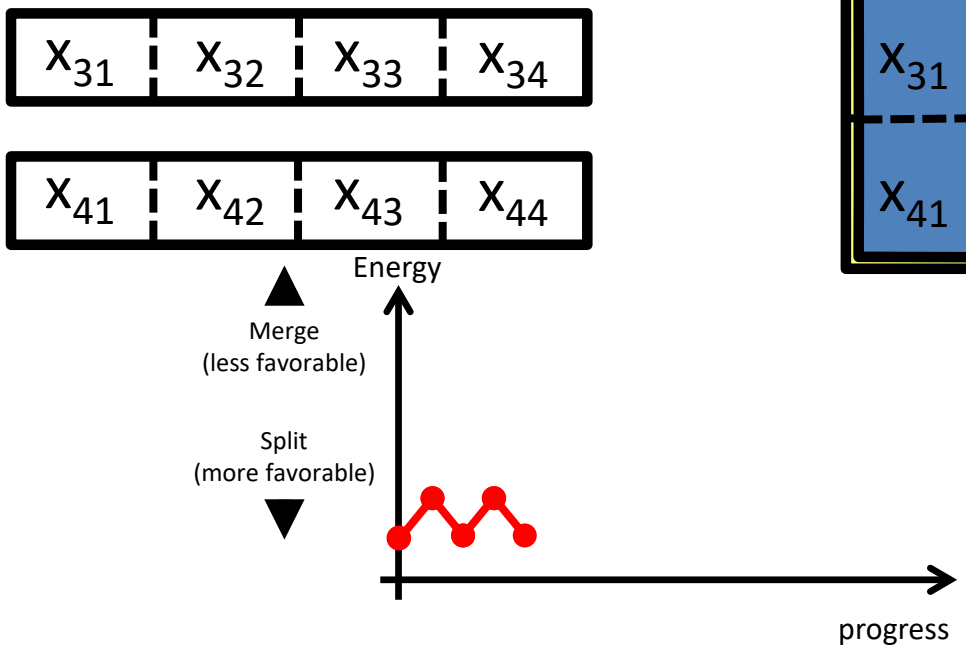
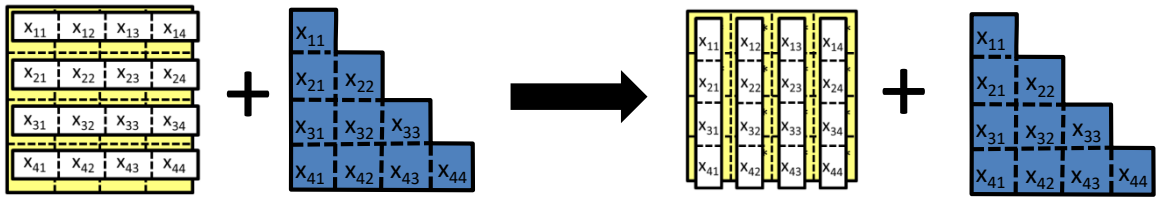
x41 x42 x43 x44
x11 x12 x13
x21 x22 x23
x31 x32 x33
x41 x42 x43


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

Catalysis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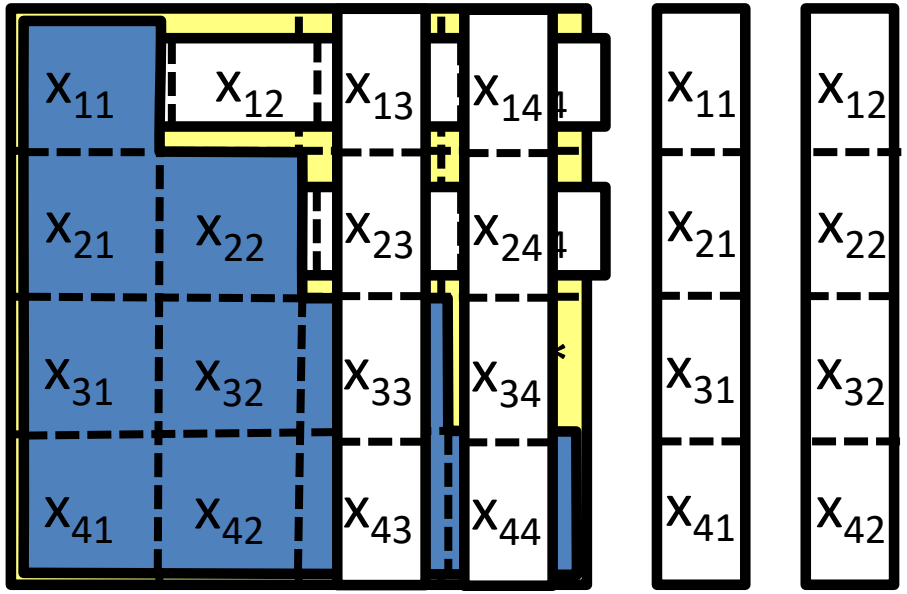
x11 x12 x13 x14
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x41 x42 x43 x44
x11 x12
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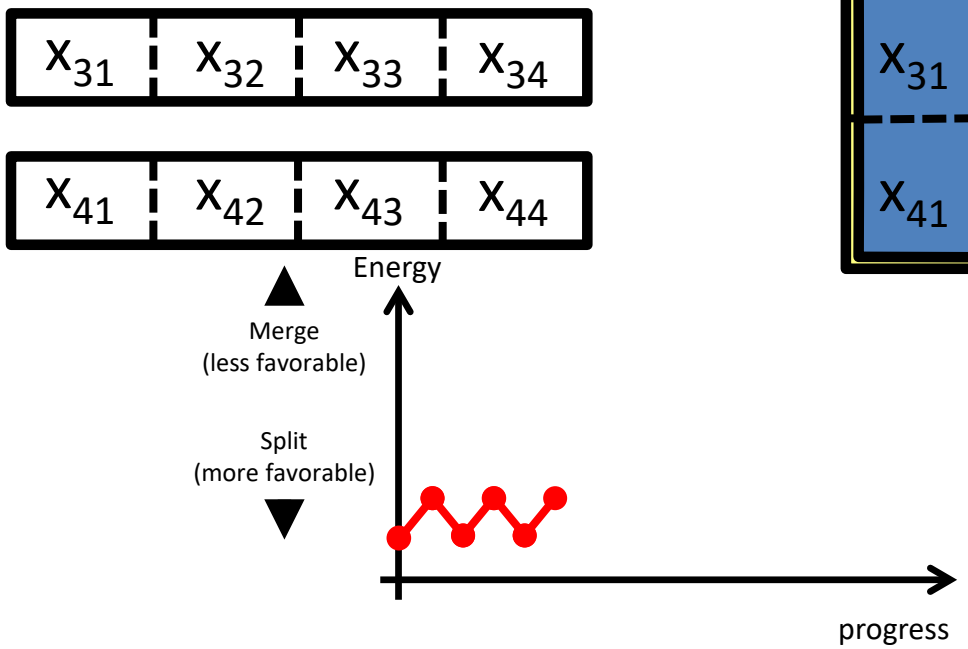
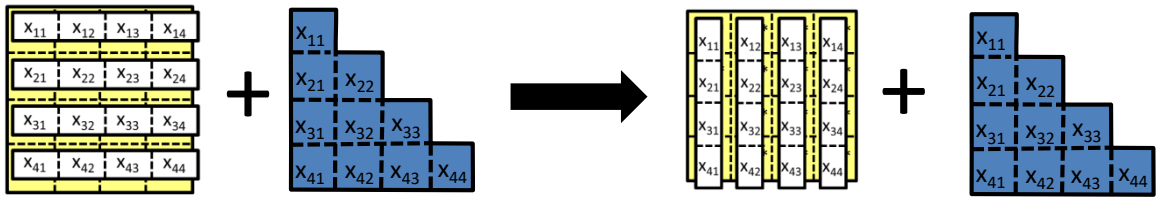
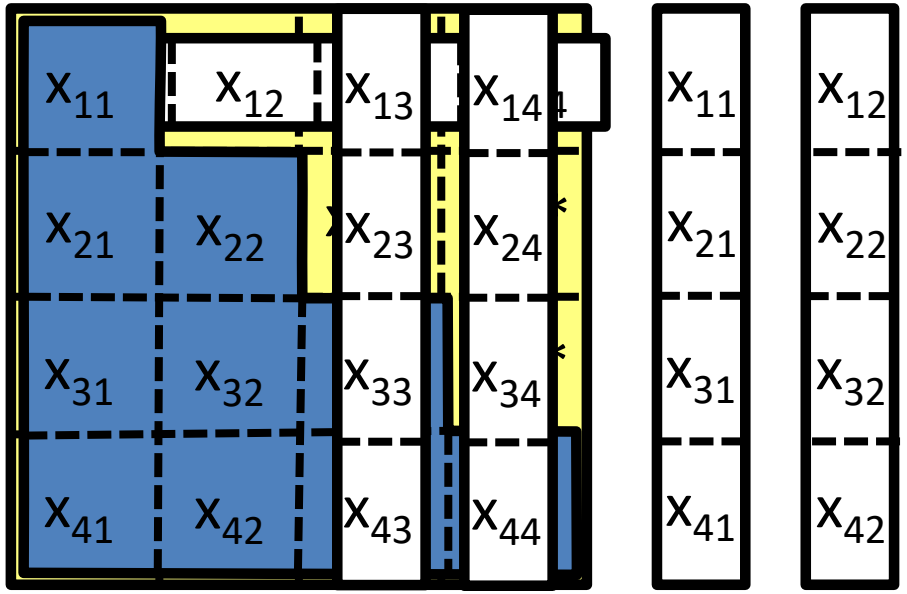
x31 x32
x41 x42


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
x21 x22 x23 x24
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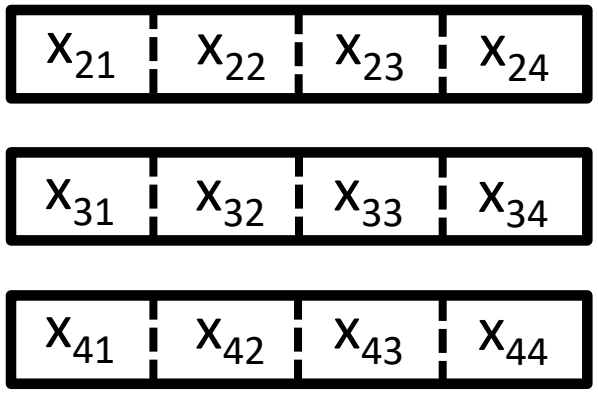
x11 x12
x21 x22
x31 x32
x41 x42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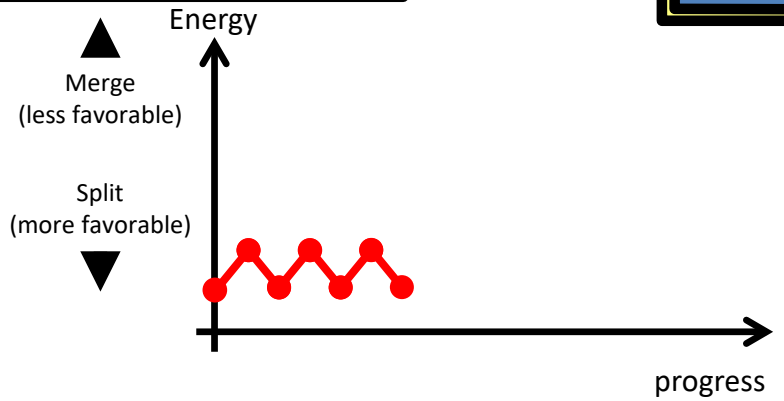
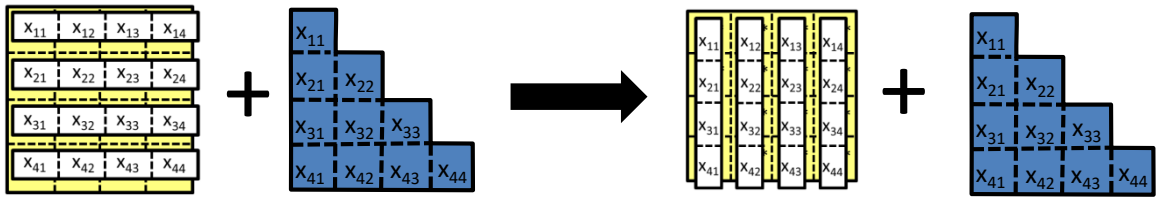

Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis


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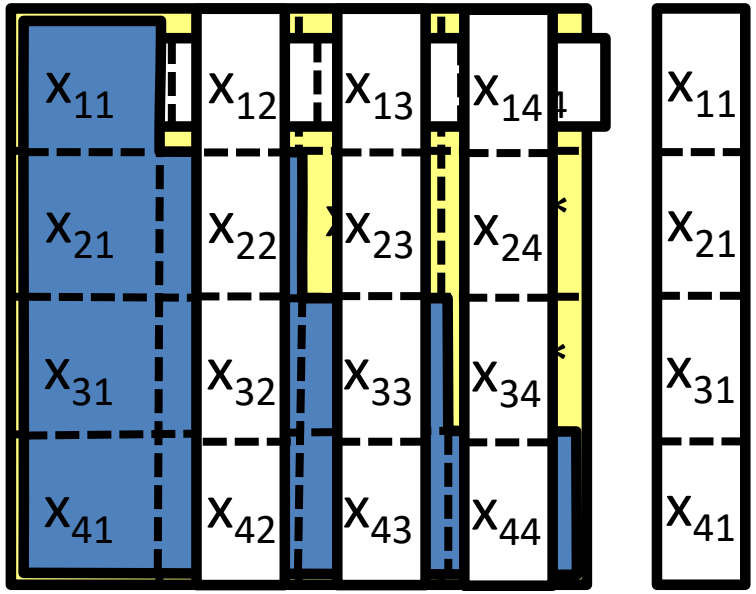
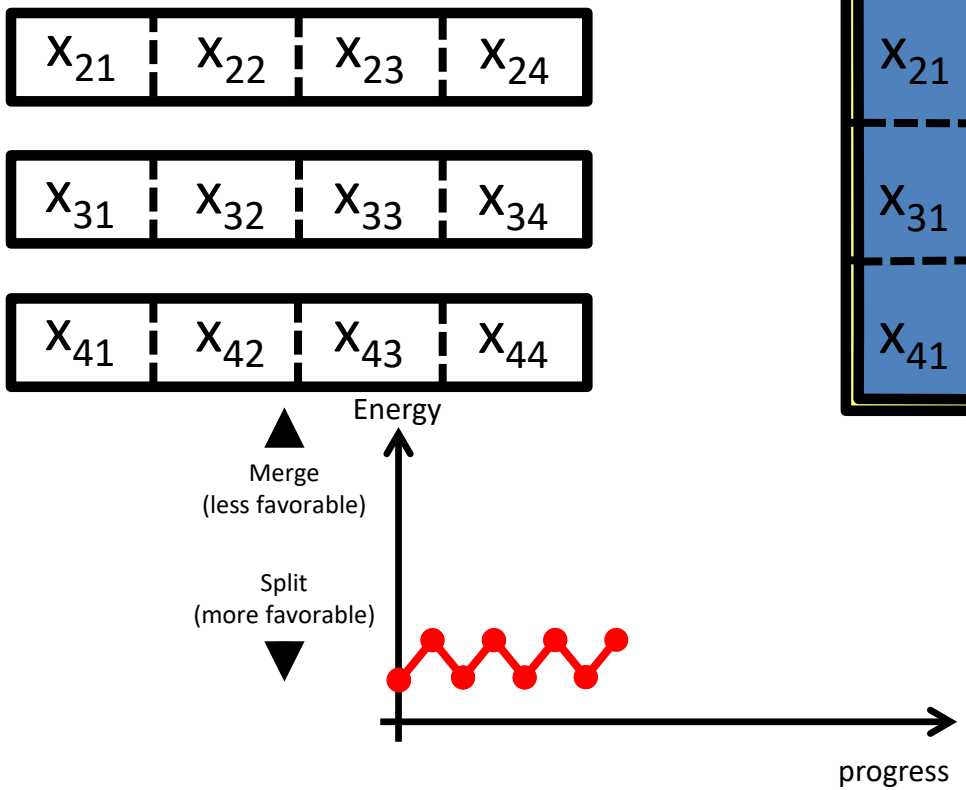
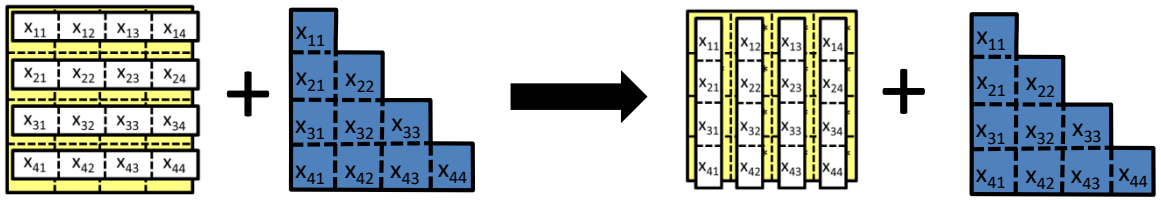
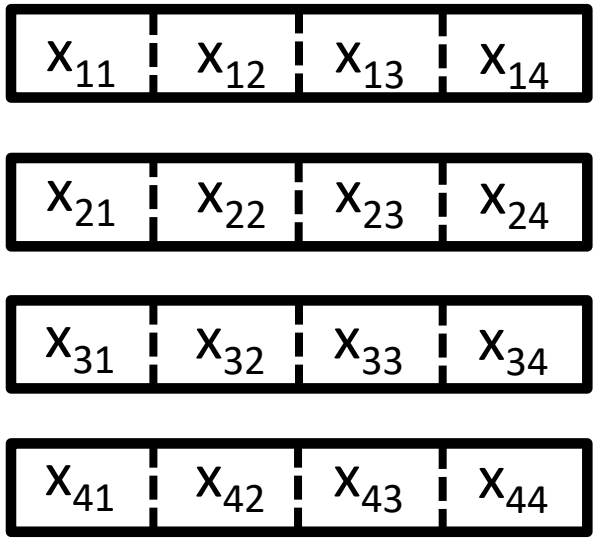
x41 x42 x43 x44


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
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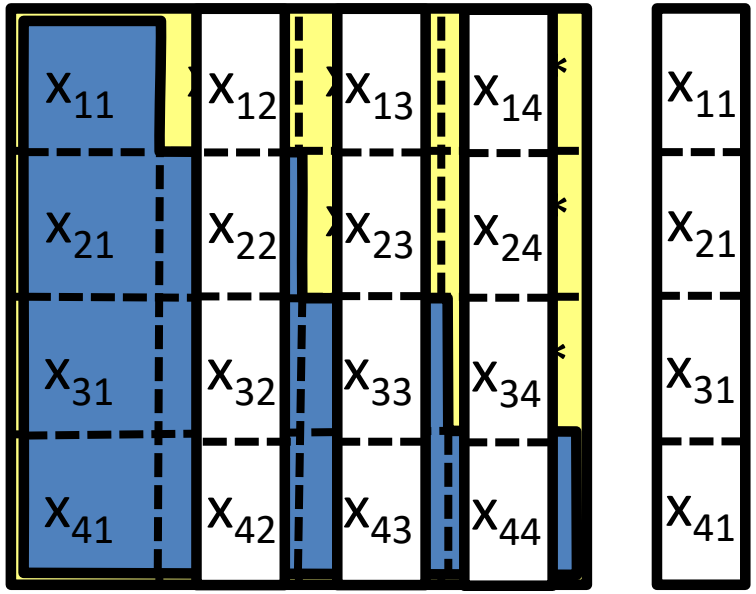
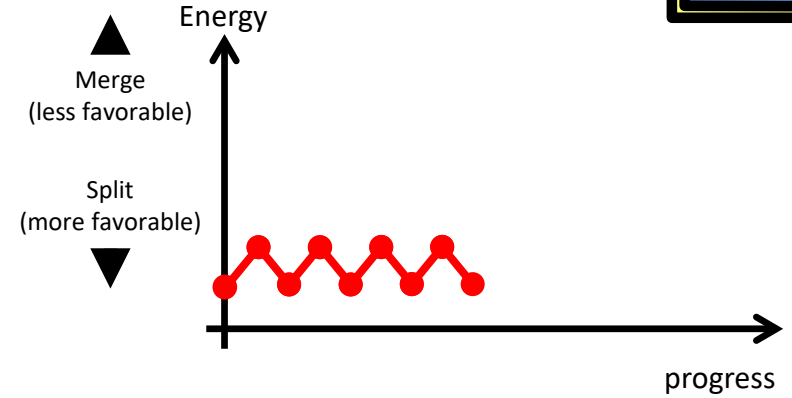
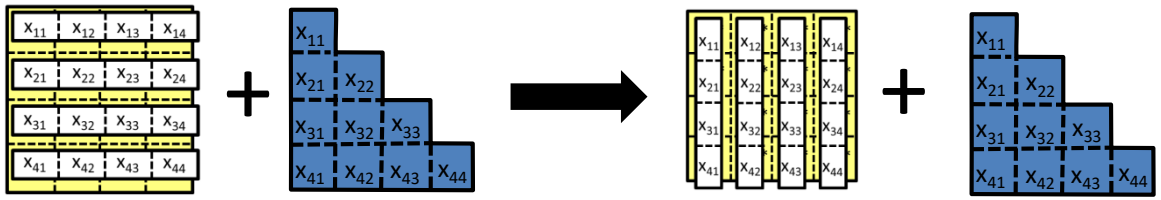
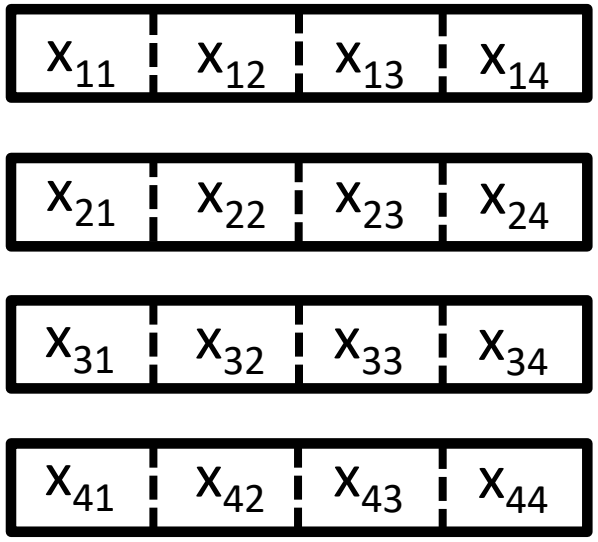

x11 x12 x13 x14
x21 x22 x23 x24
x31 x32 x33 x34
x41 x42 x43 x44
x11
x21
x31
x41


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
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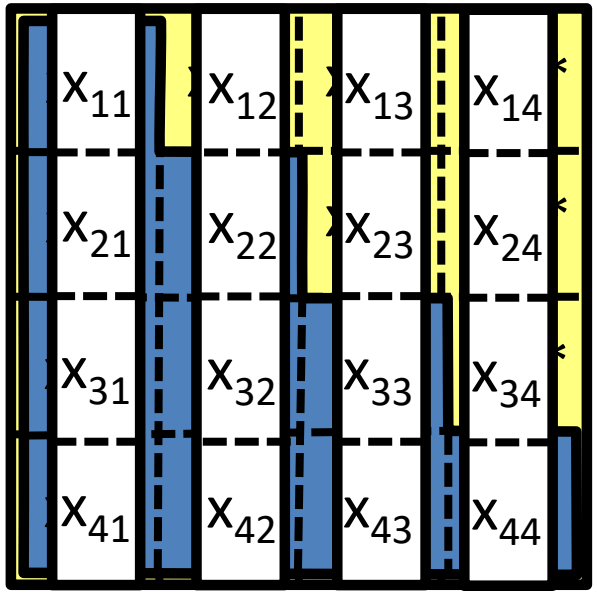
x11 x12 x13 x14
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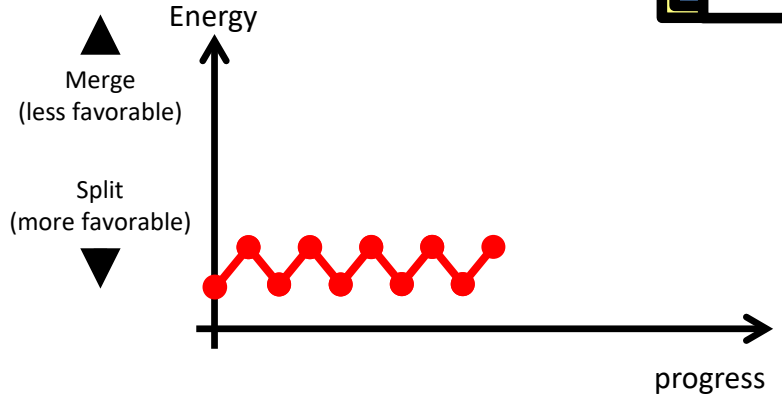
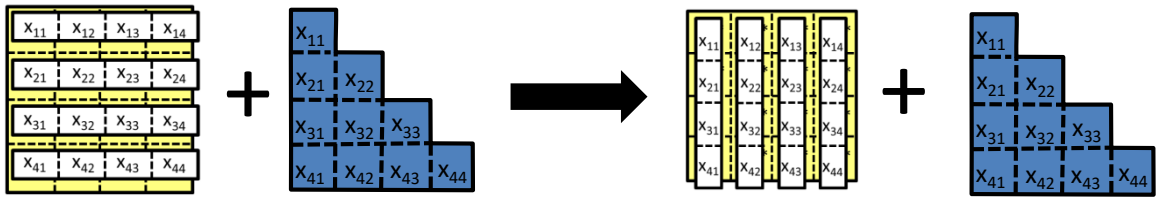

Energy
Merge
(less favorable)
Split
(more favorable)
progress

Catalysis


x11 x12 x13 x14
x21 x22 x23 x24
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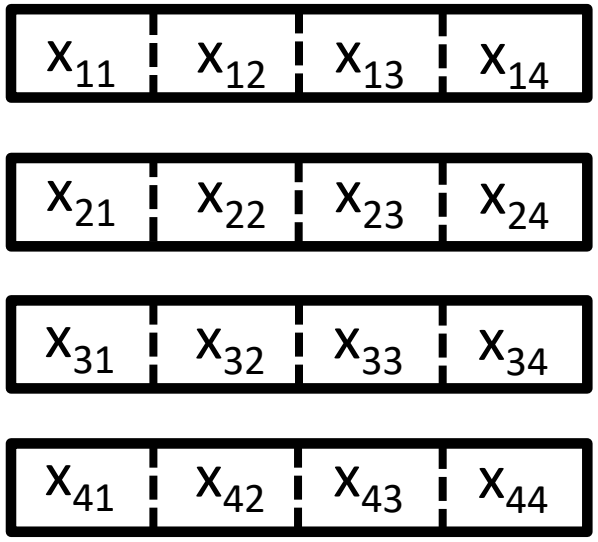
x11 x12 x13 x14
x21 x22 x23 x24
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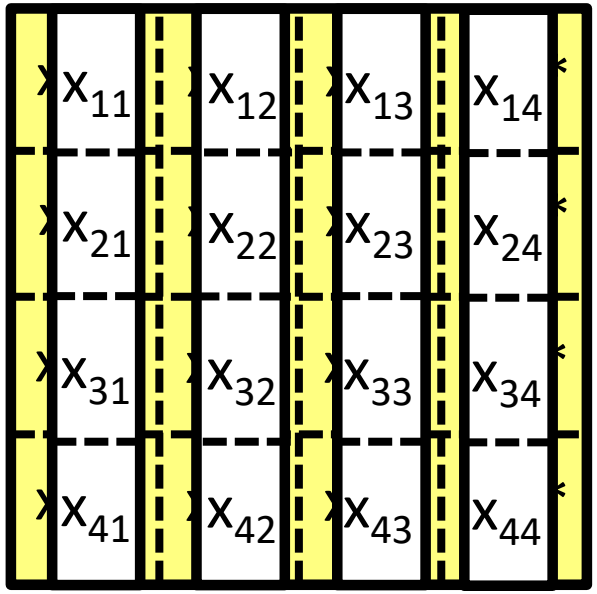
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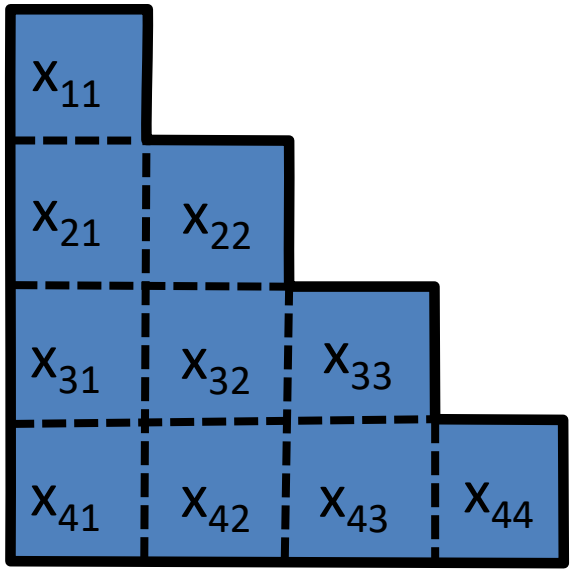
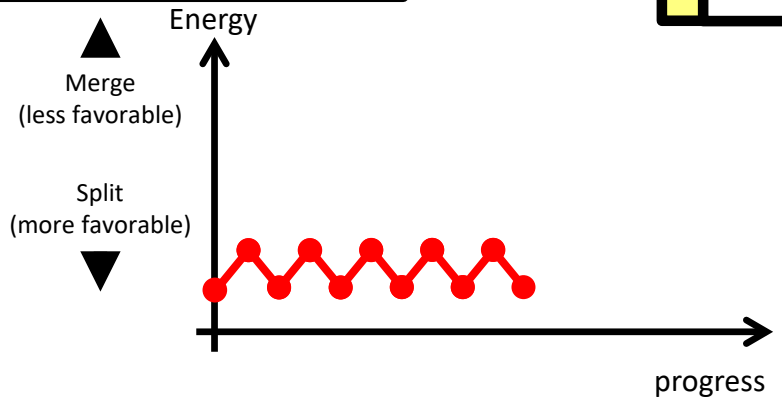
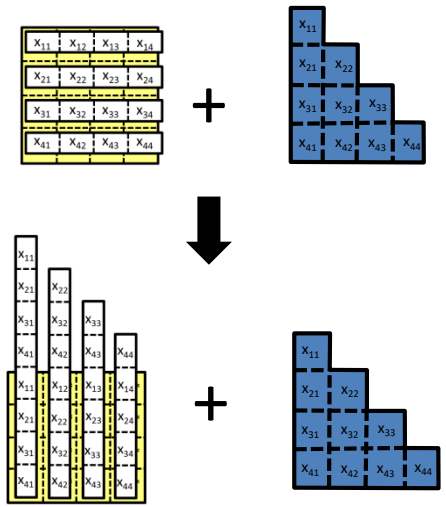
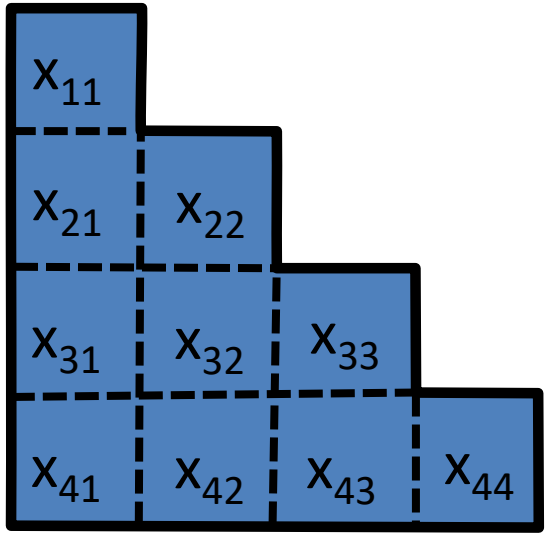
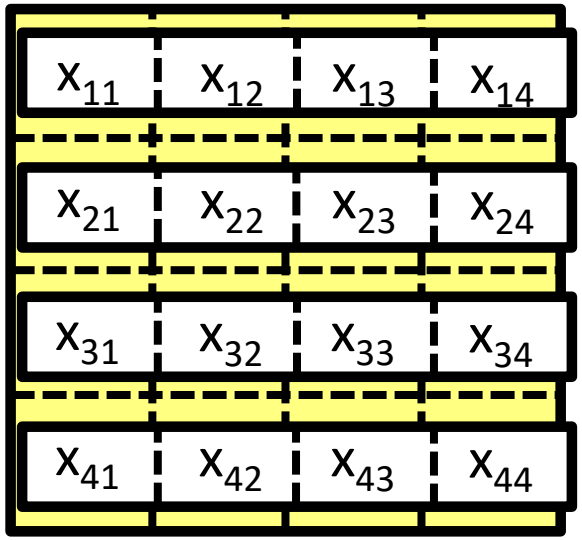

x11
x21 x22
x31 x32 x33
x41 x42 x43 x44

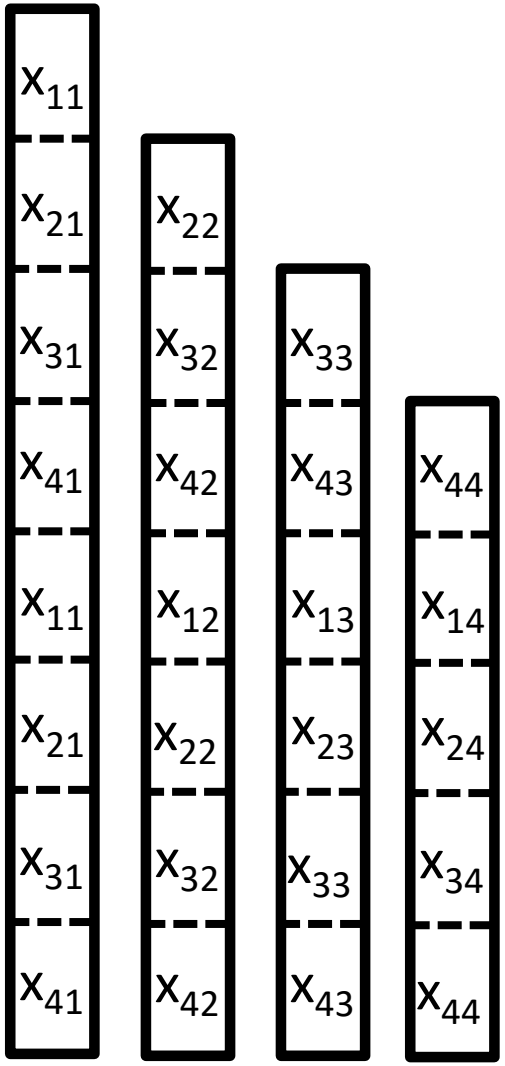

Energy
Merge
(less favorable)
Split
(more favorable)
progress

Autocatalysis

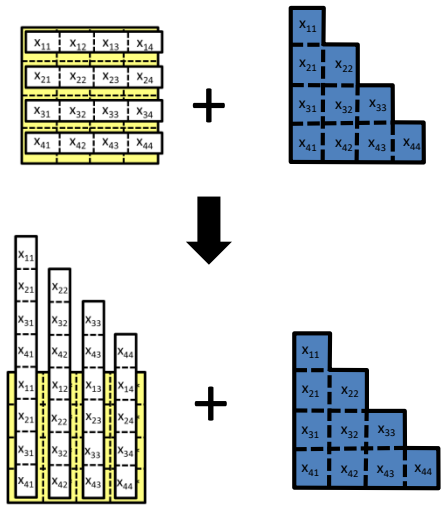


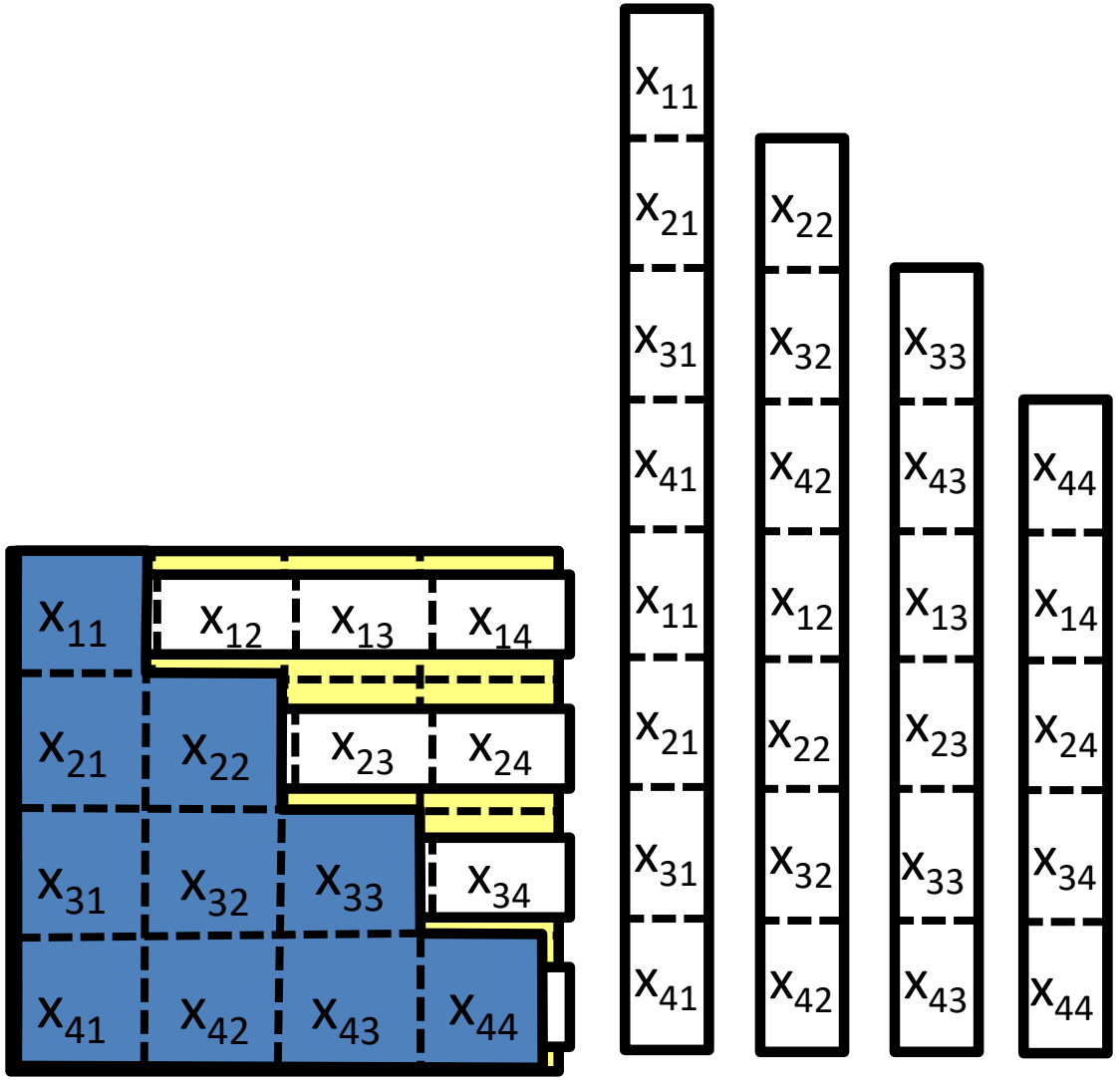




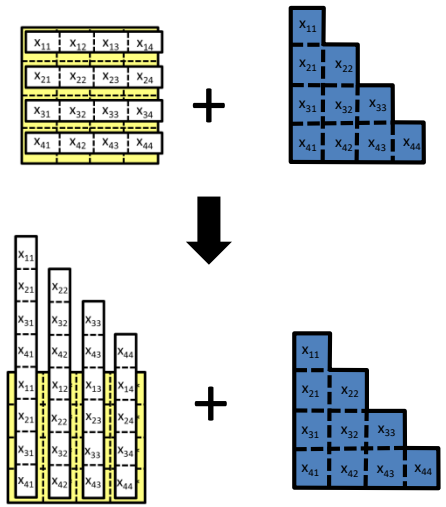


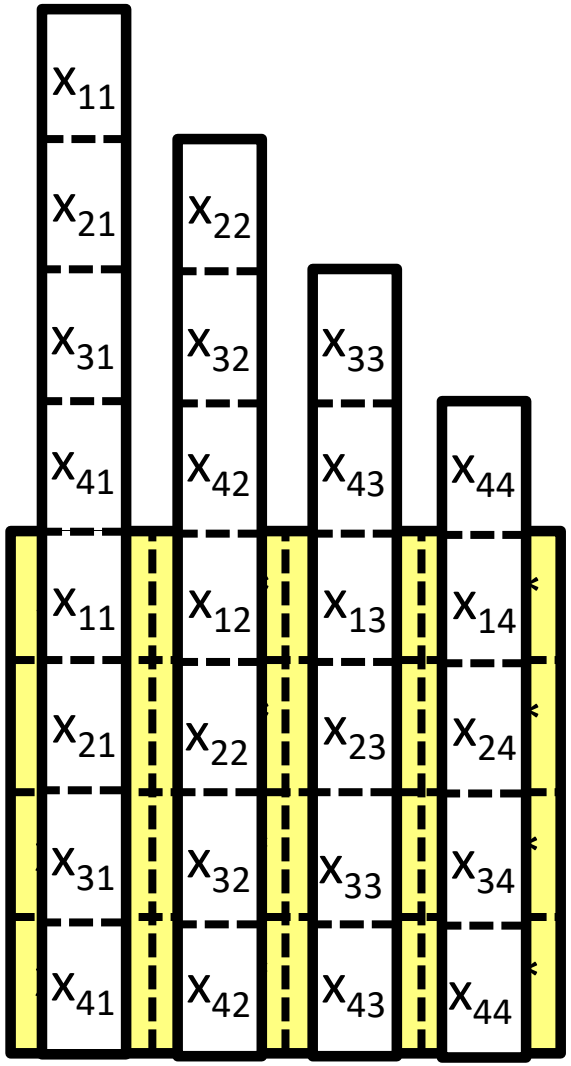
Autocatalysis

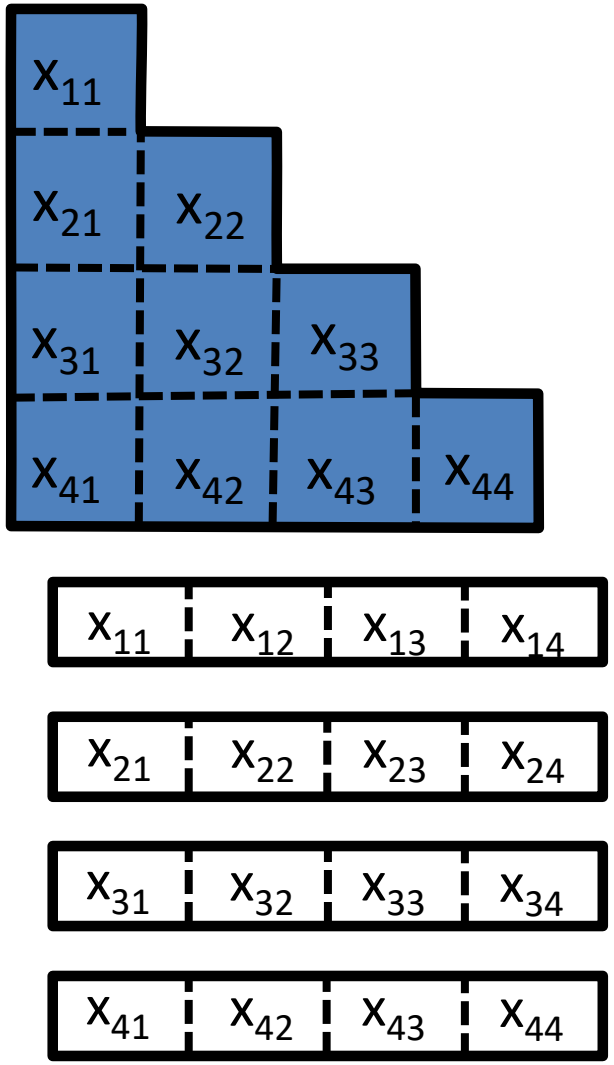




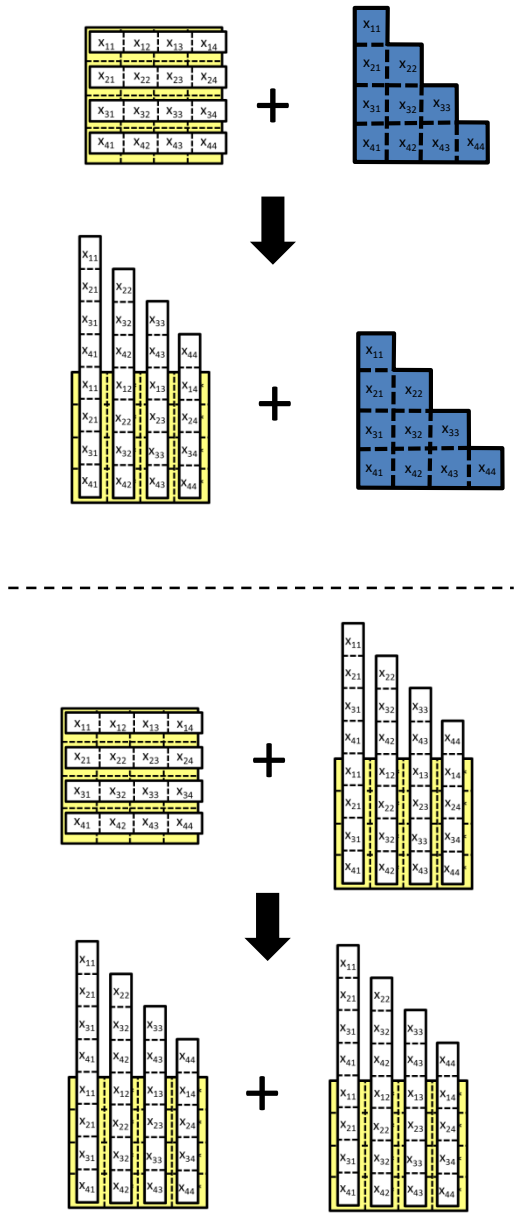
Autocatalysis

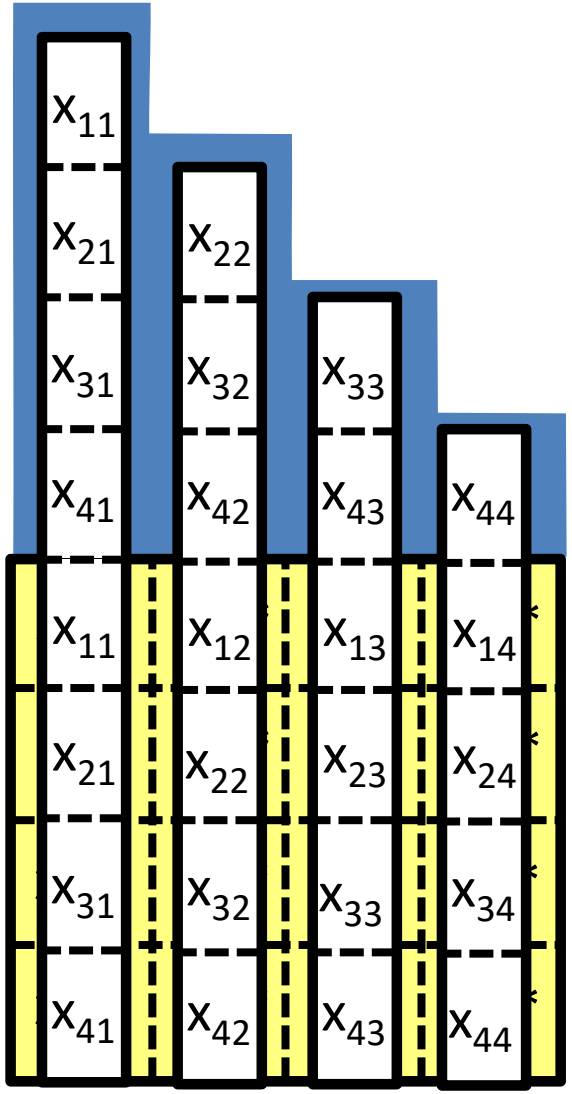


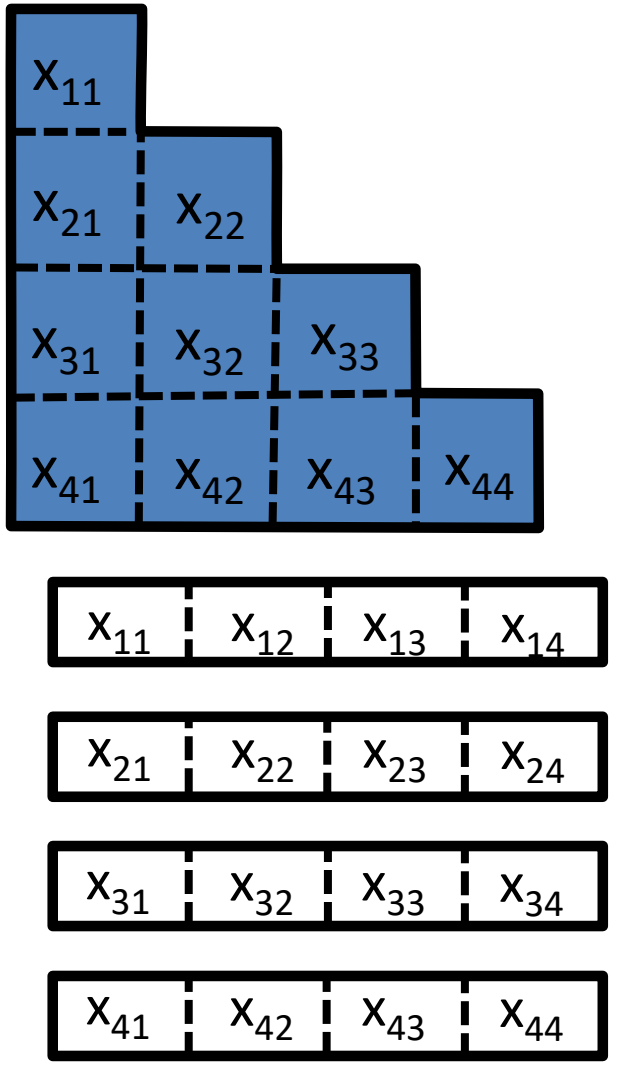




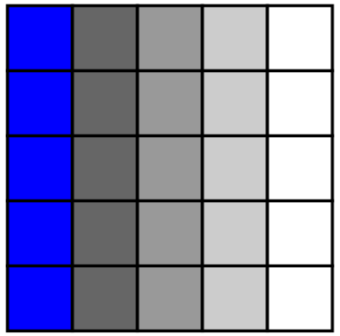
Autocatalysis

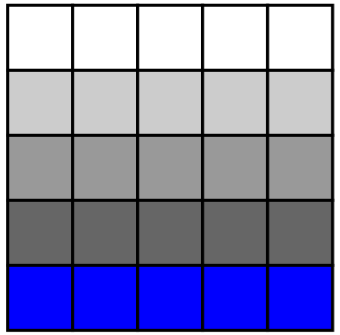




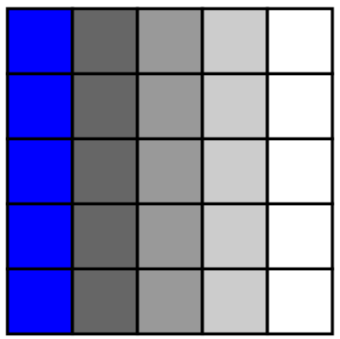


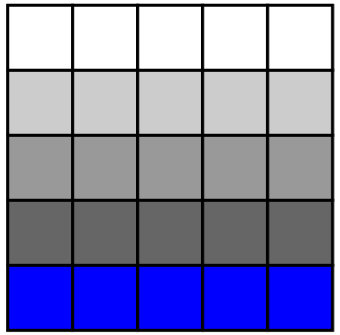
Multiple Stable Configurations

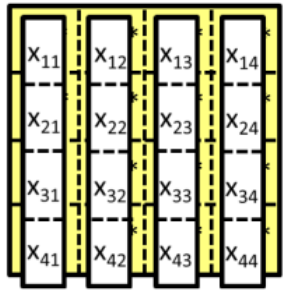


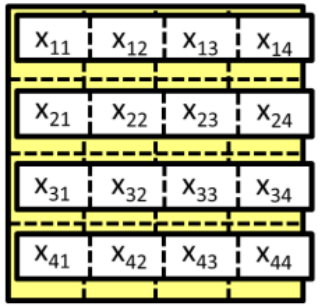


Multiple Stable Configurations

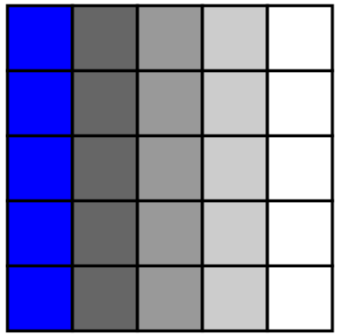


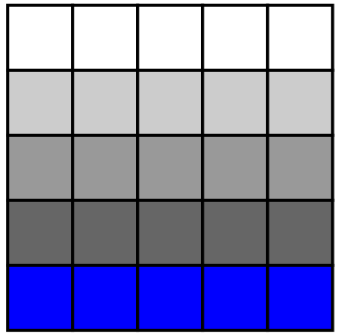




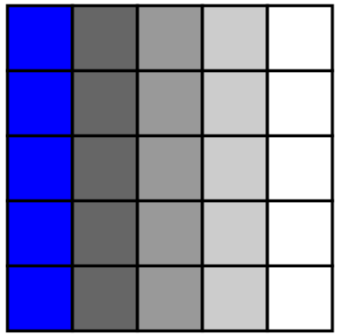


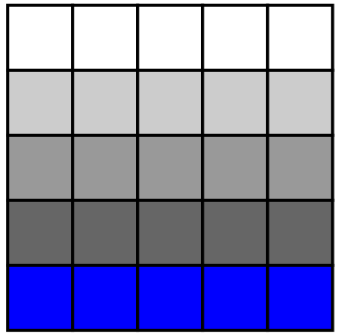
Multiple Stable Configurations

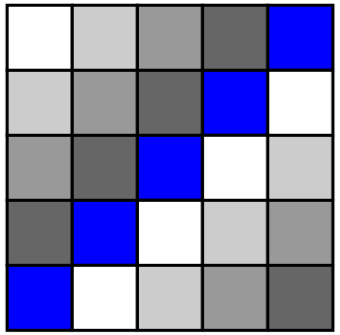




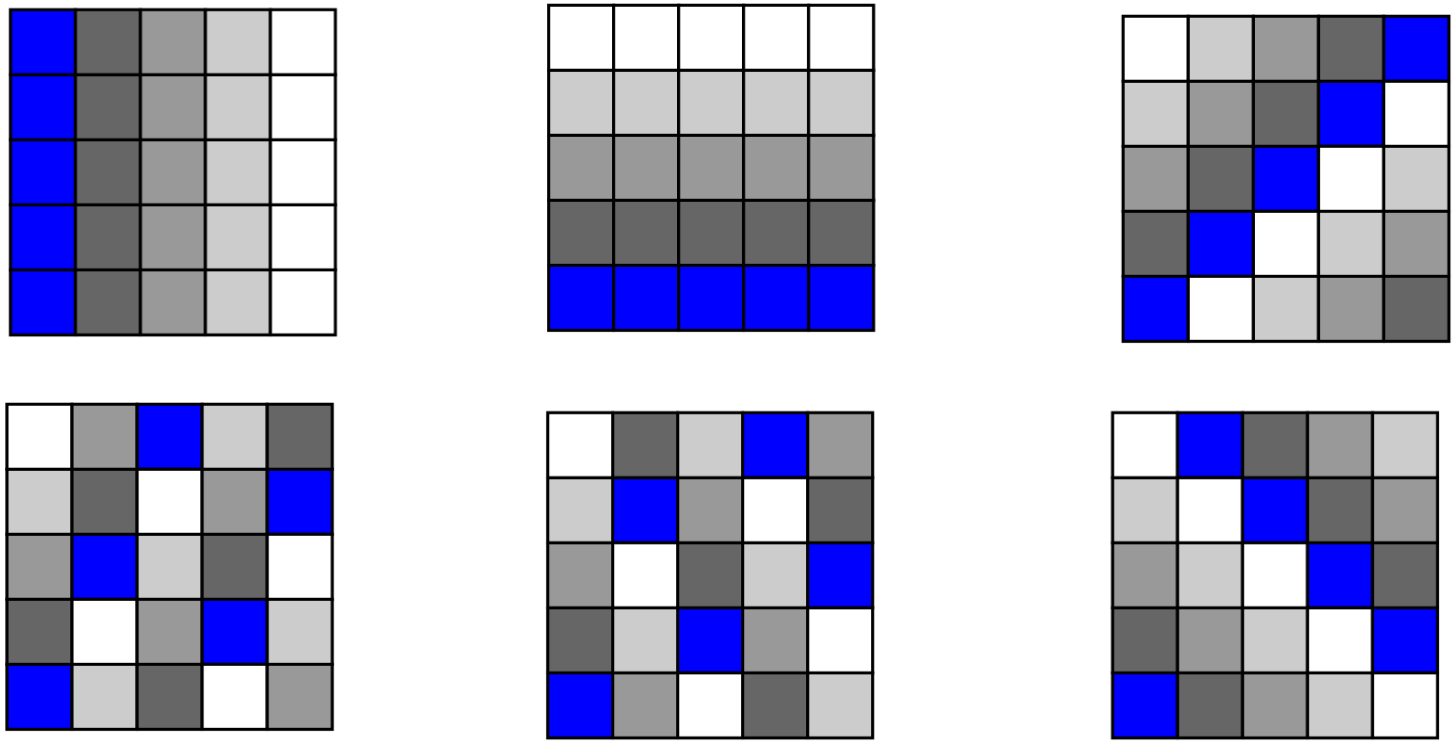
Multiple Stable Configurations





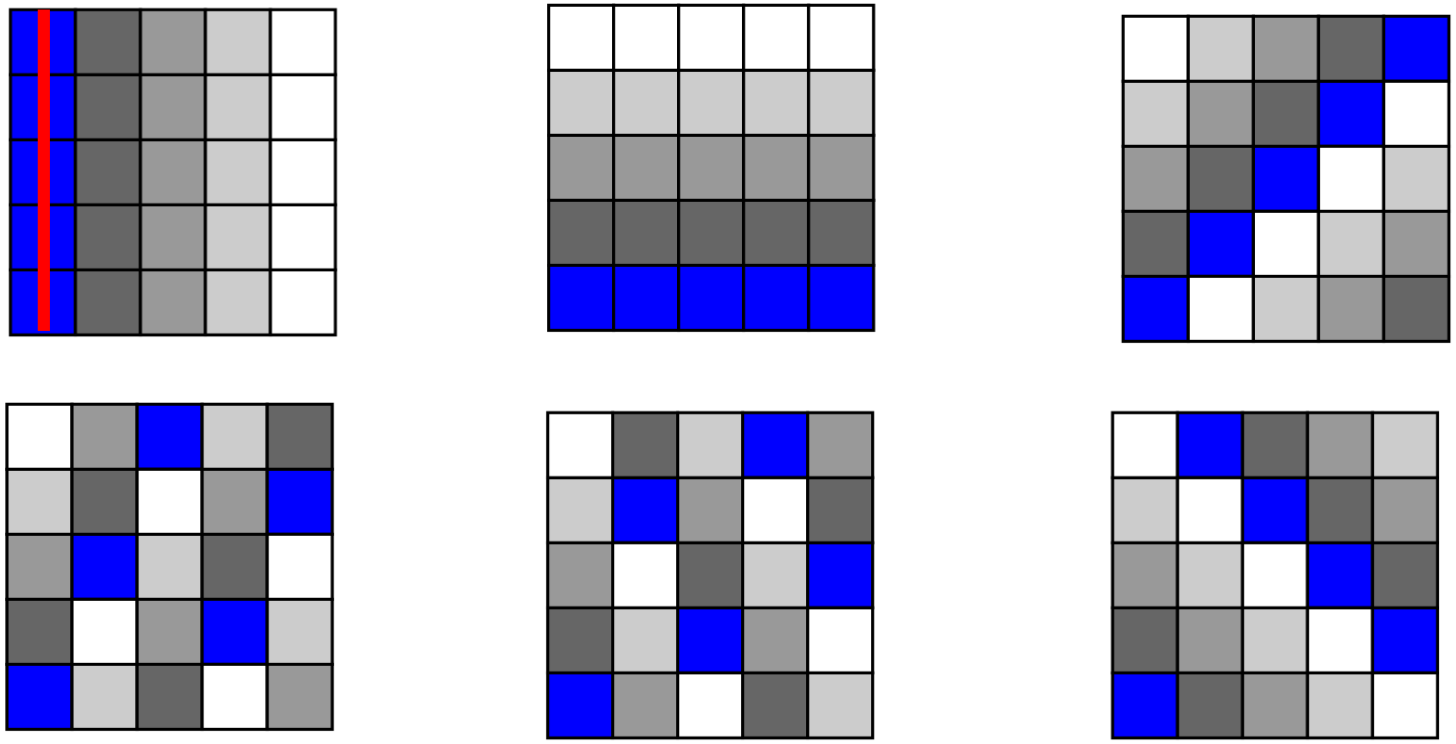


Multiple Stable Configurations



For a grid of 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 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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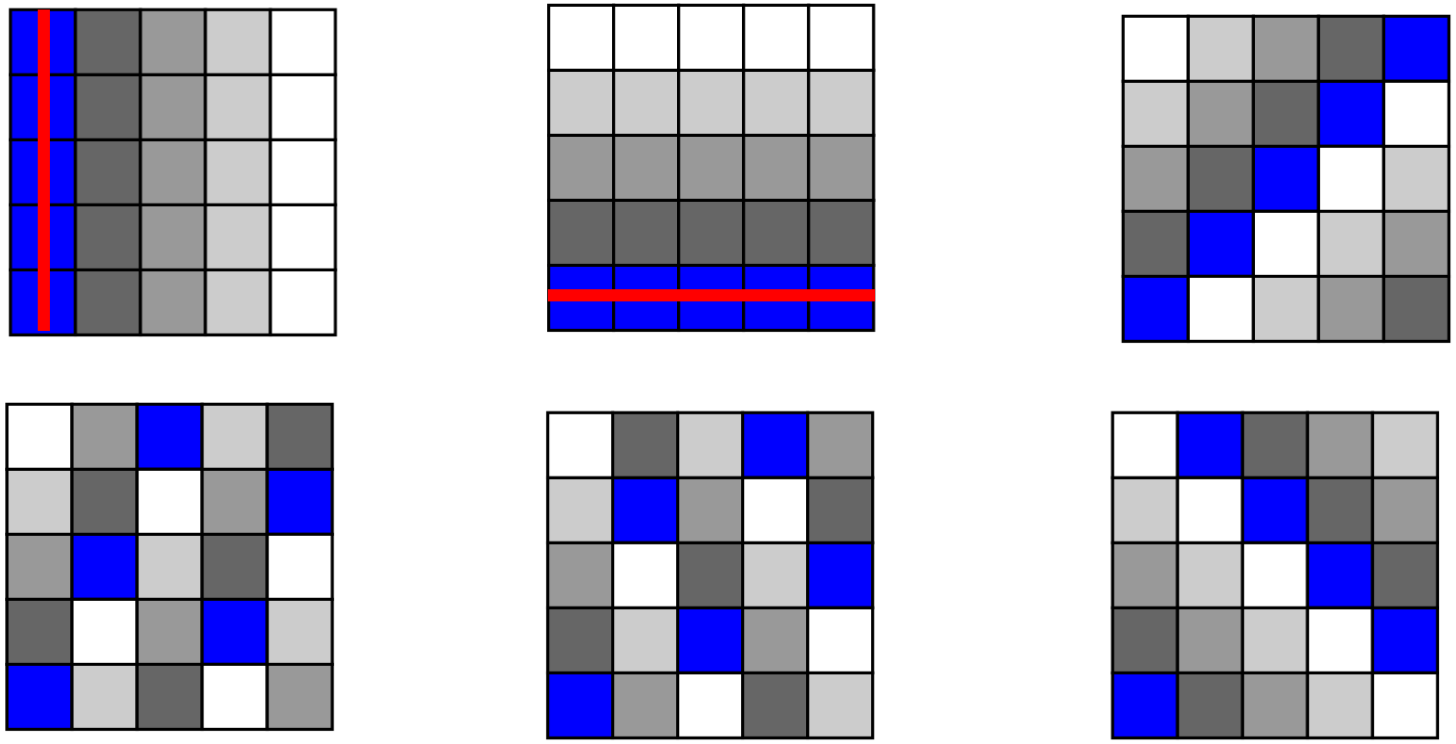

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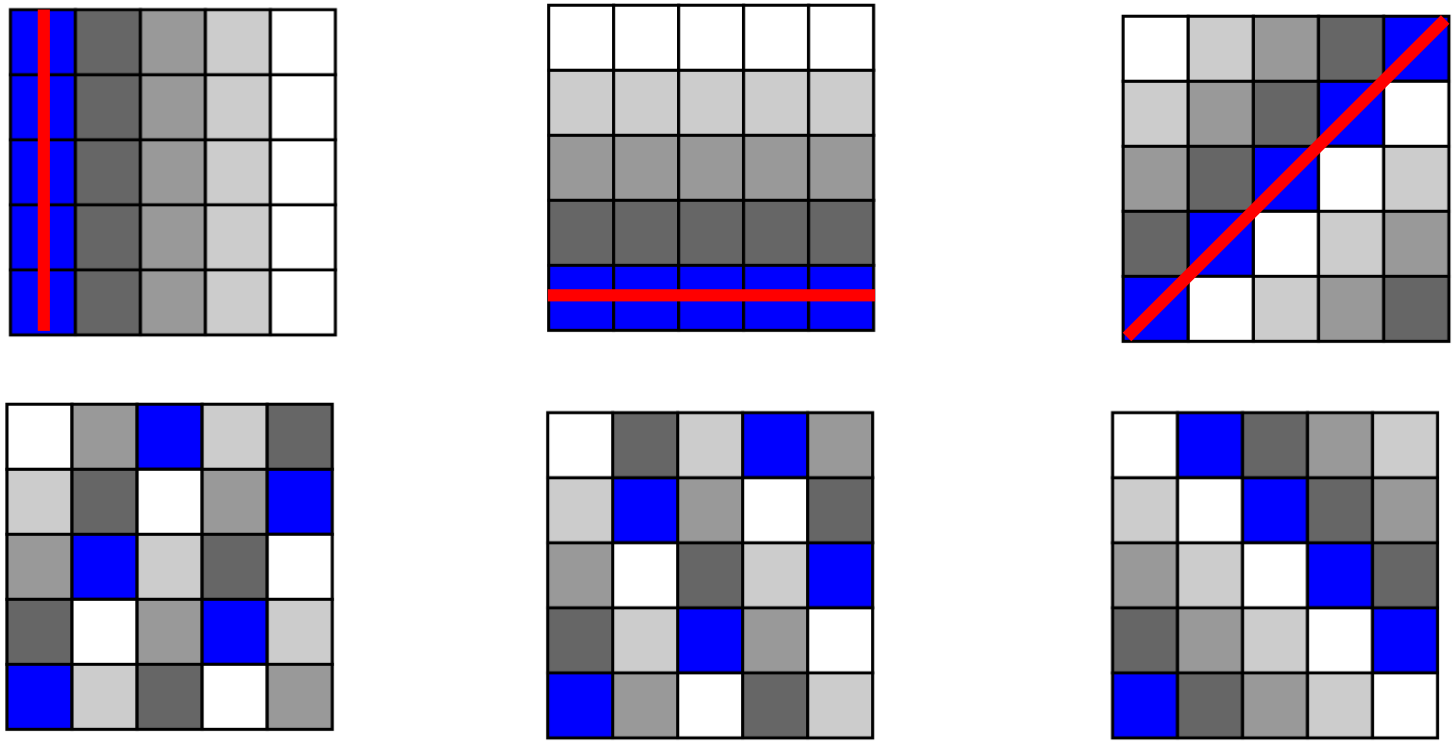

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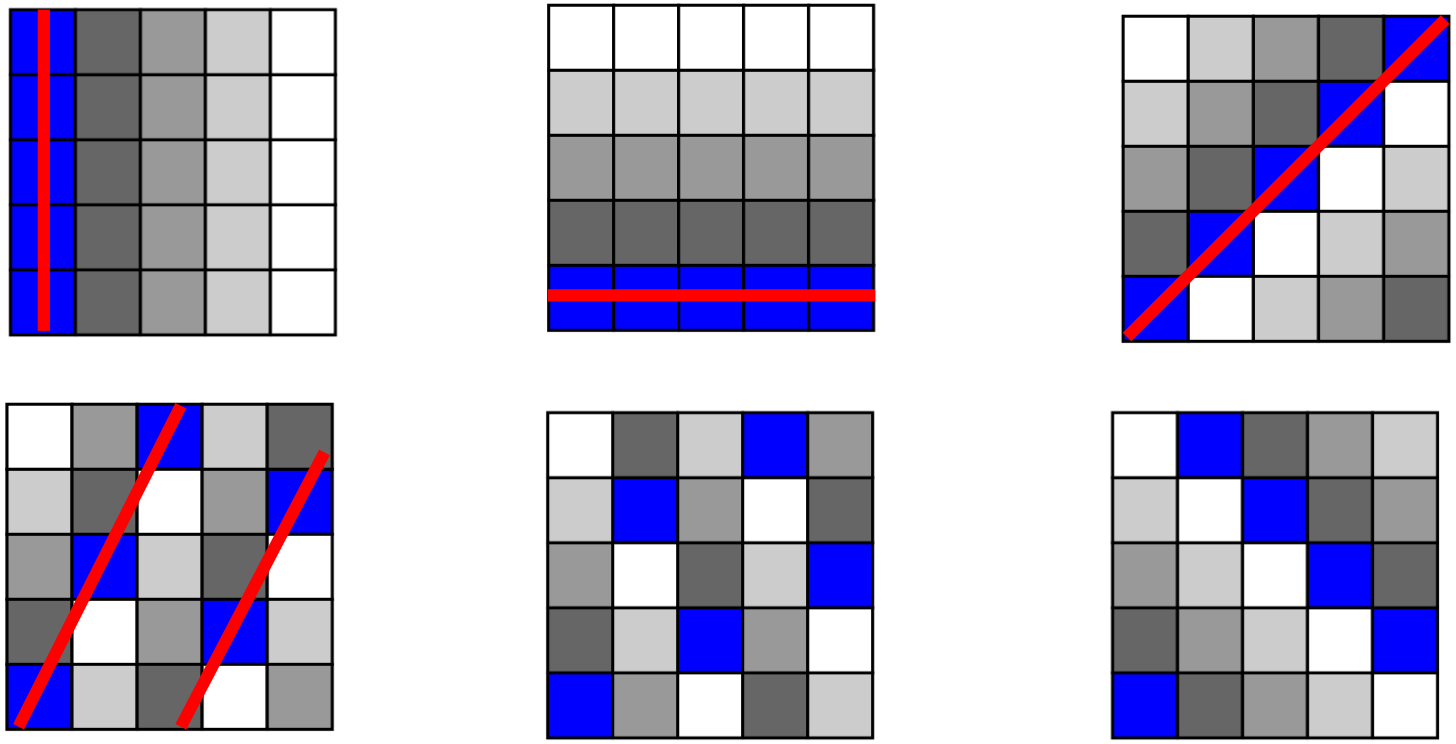

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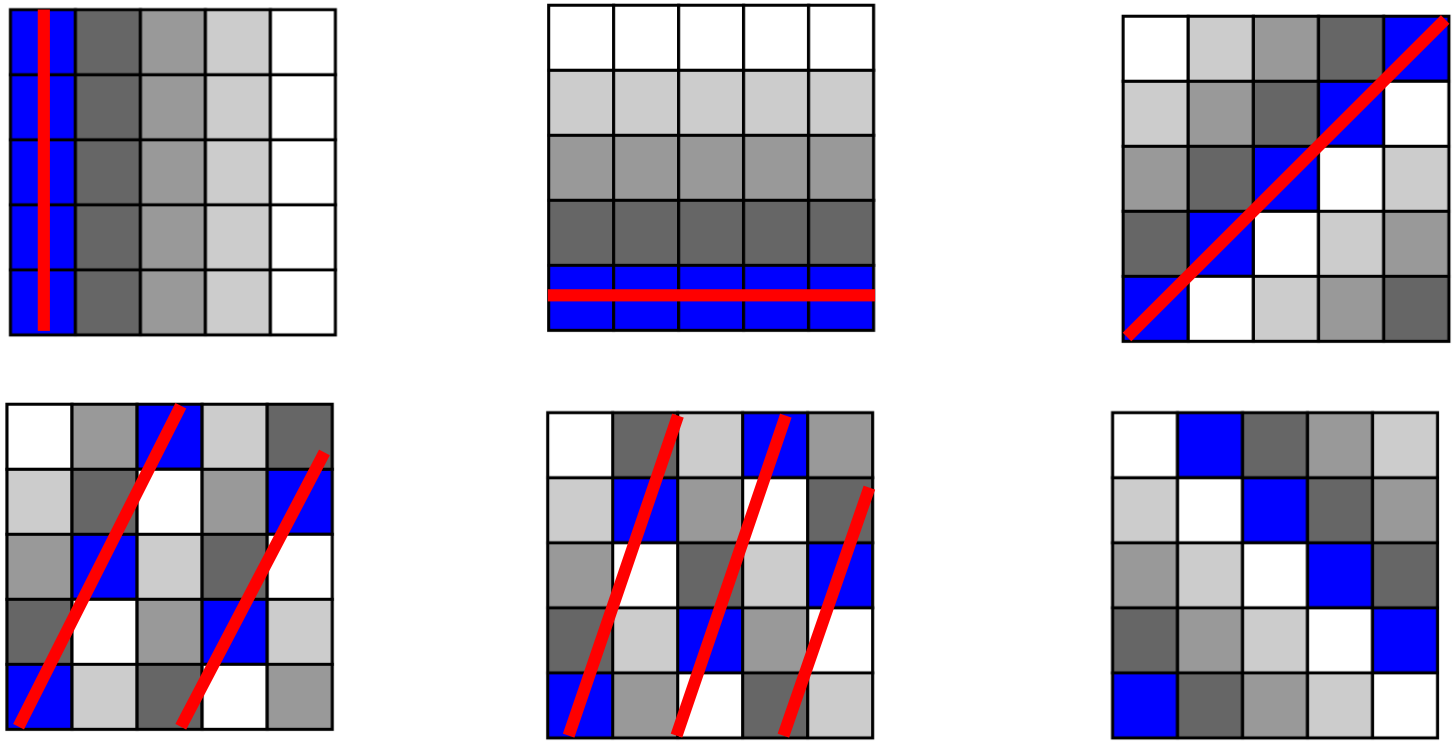

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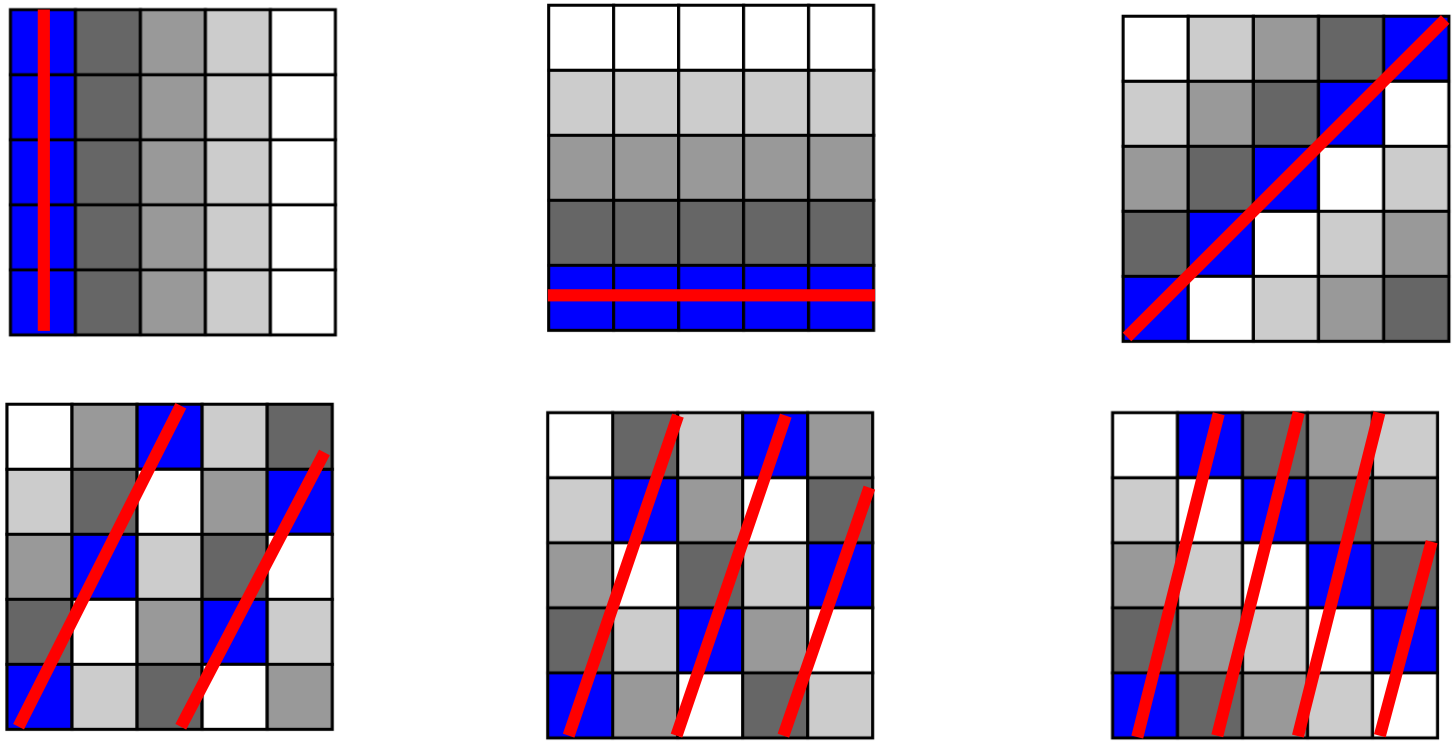

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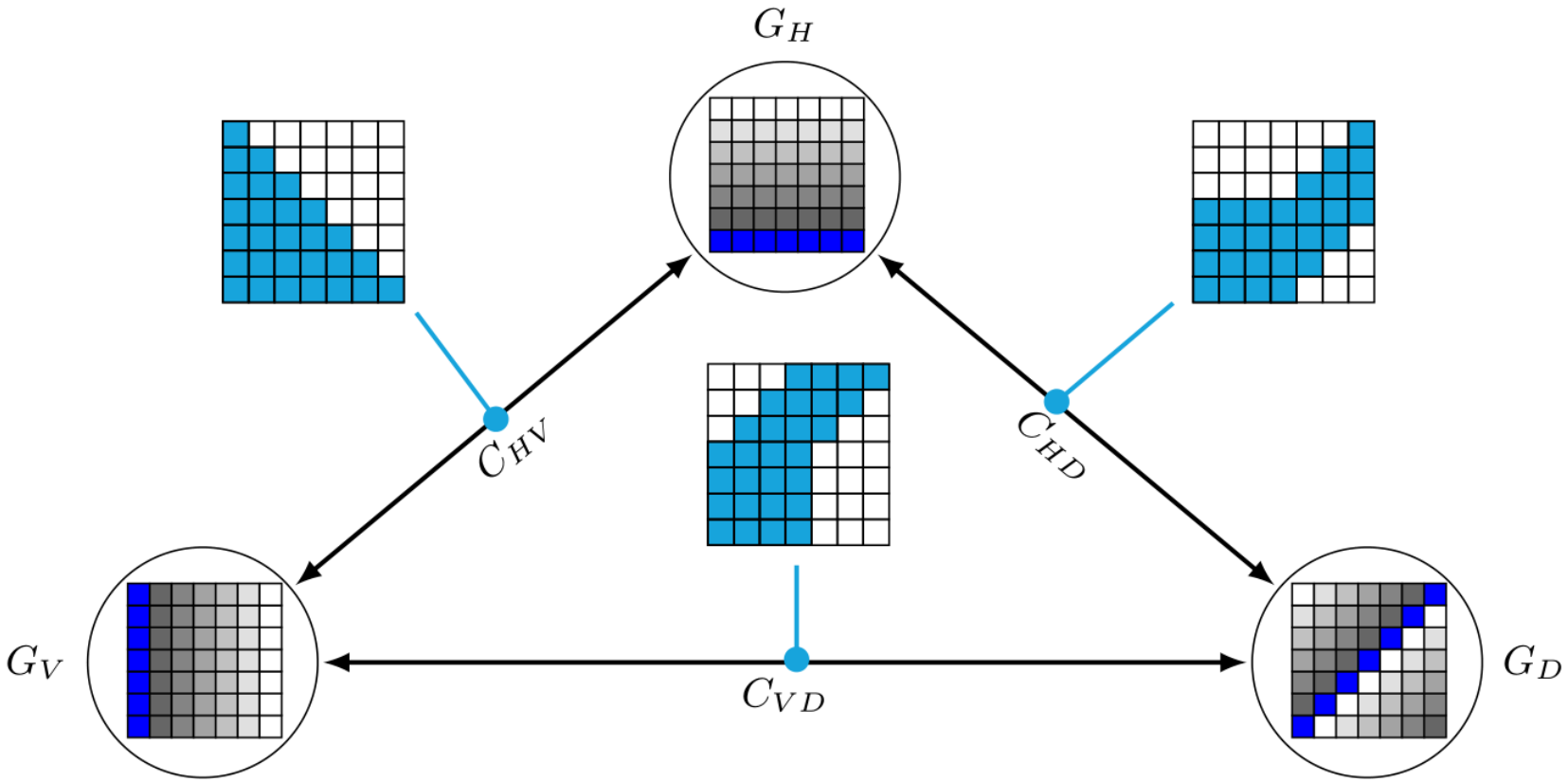
- Unknown for next prime power n=10:
  - trivial upper bound is 11 days
  - best known lower bound is 3

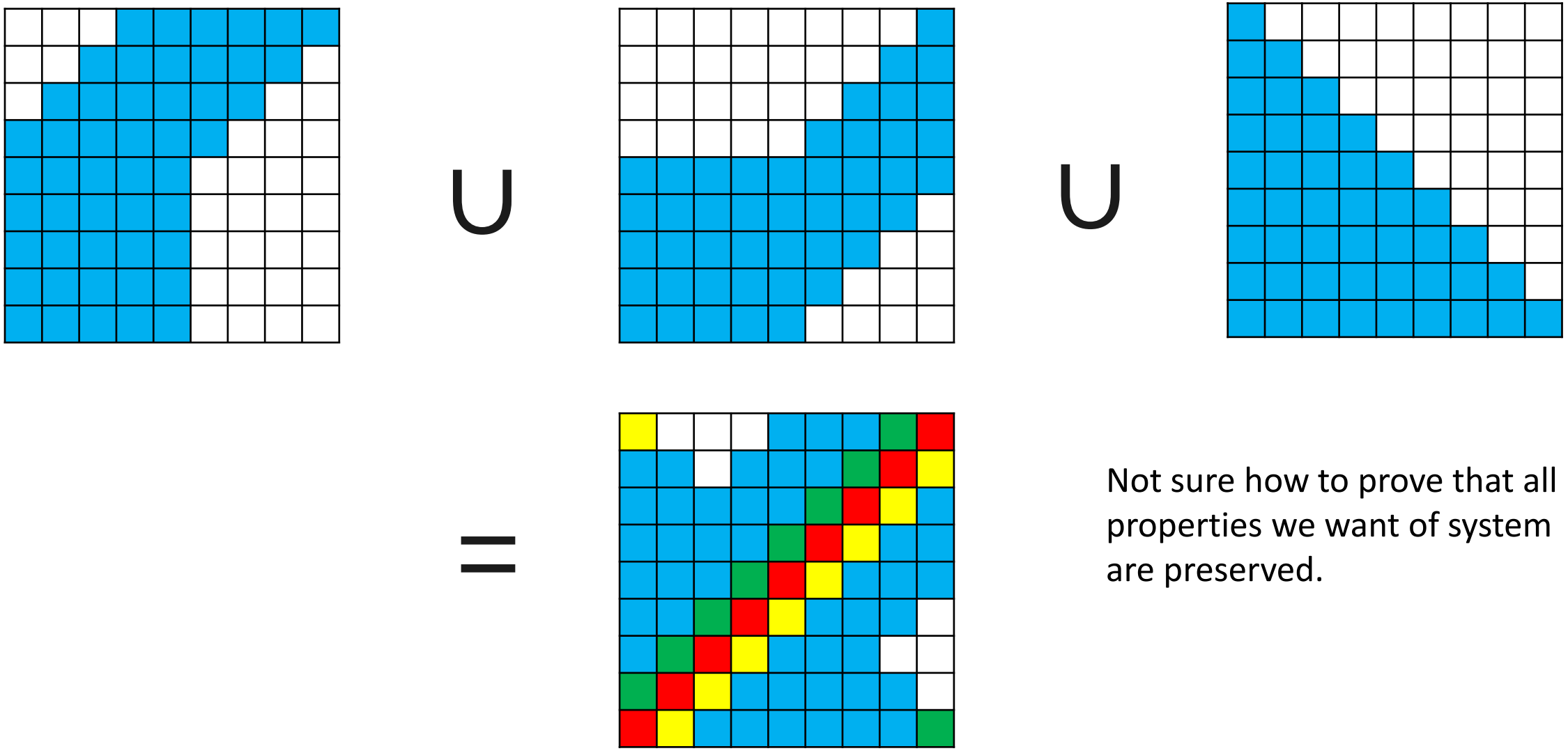
Directed Catalysis



Along a catalyzed pathway, the barrier is 1

Otherwise the barrier is $n/2$

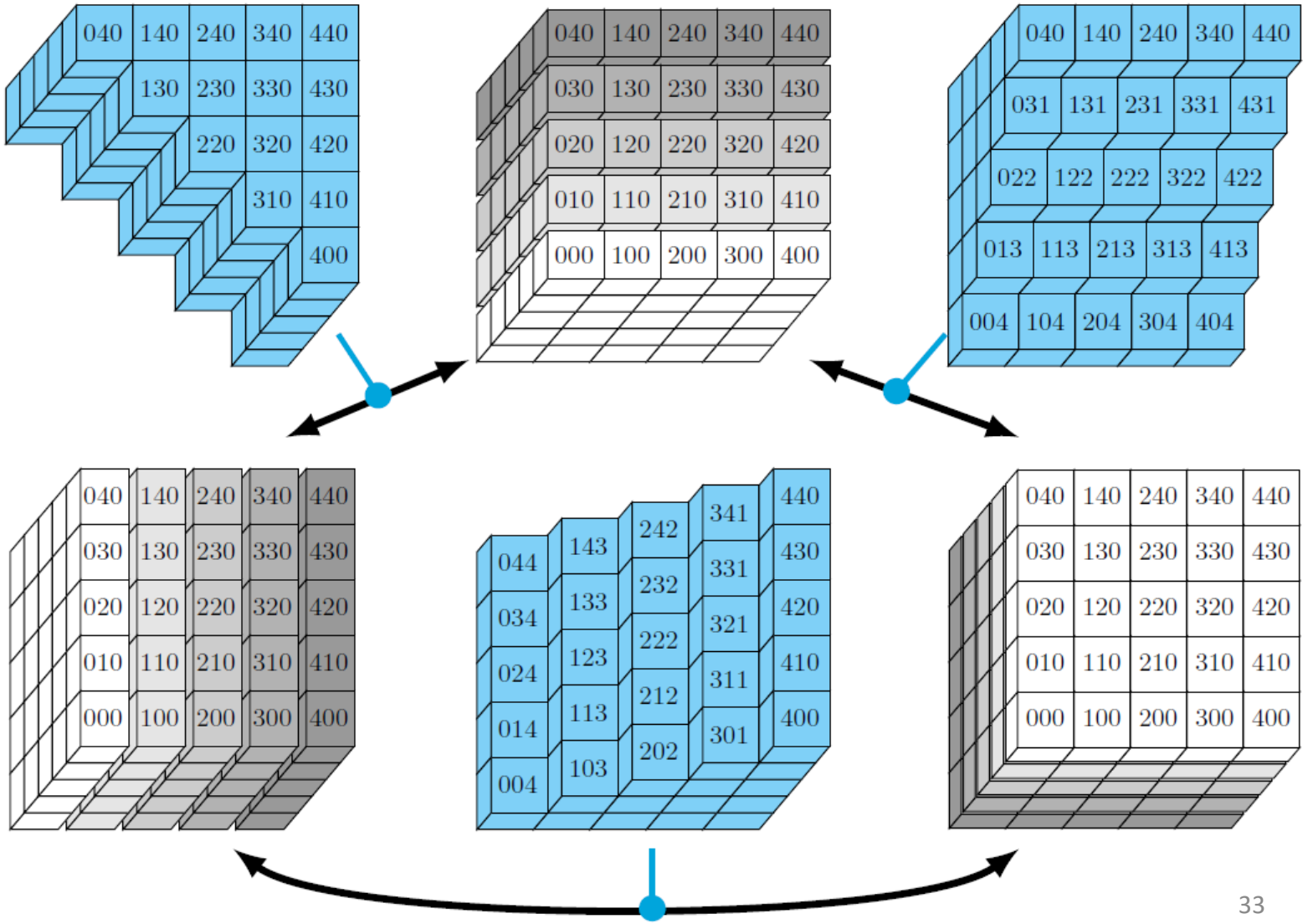
Allowing more than one catalyst at once



Not sure how to prove that all properties we want of system are preserved.

Allowing more than one catalyst at once

- To have *d* stable states, set of domains is discrete *d*-dimensional hypercube.
- Each monomer is (*d*-1)-dimensional hyperplane
- Maintains energy barrier *n*, not just Ω(*n*).



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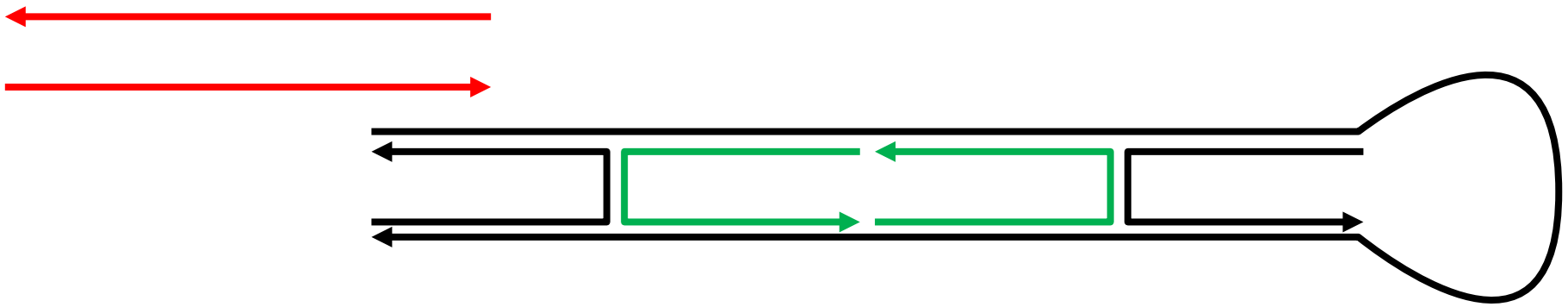
- Minimum number of domain types to be robust to varying relative amounts of the monomers
- Constrained catalytic networks using overhangs

Thank you!

Feasible DNA implementation



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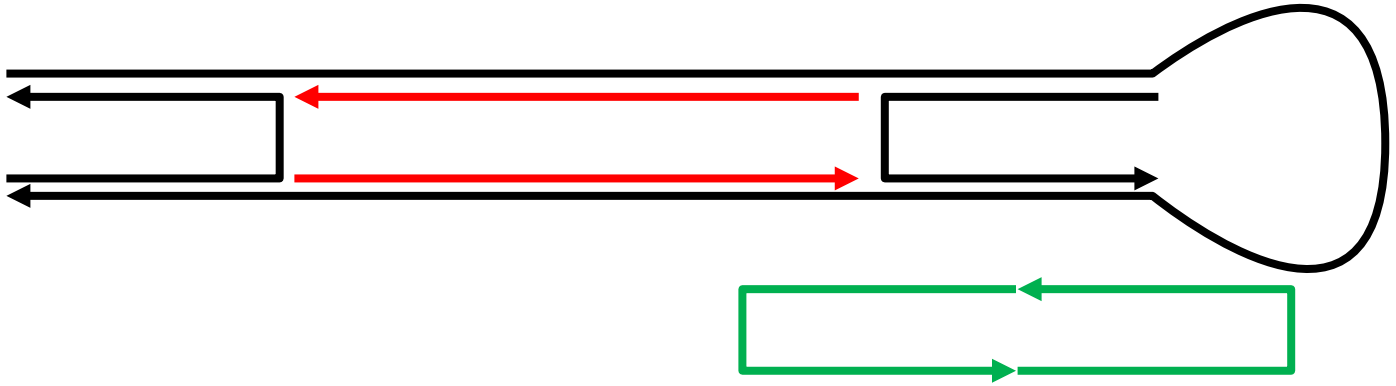

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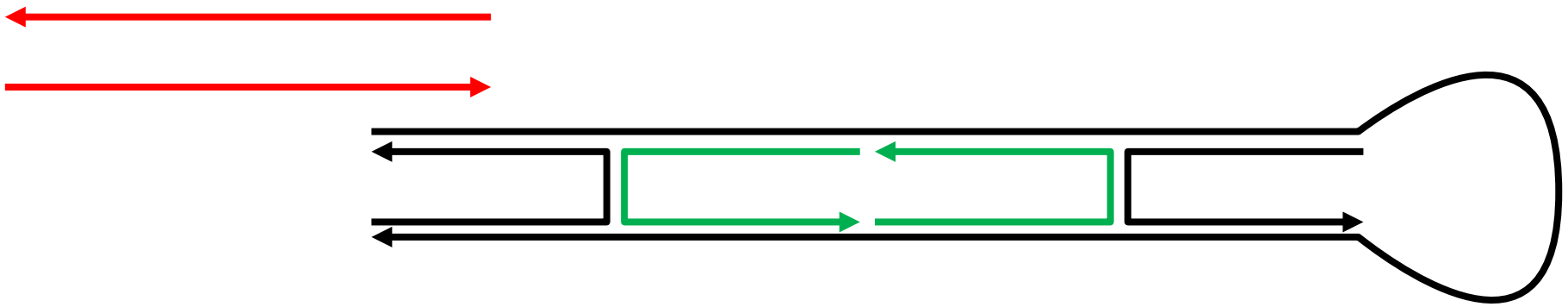

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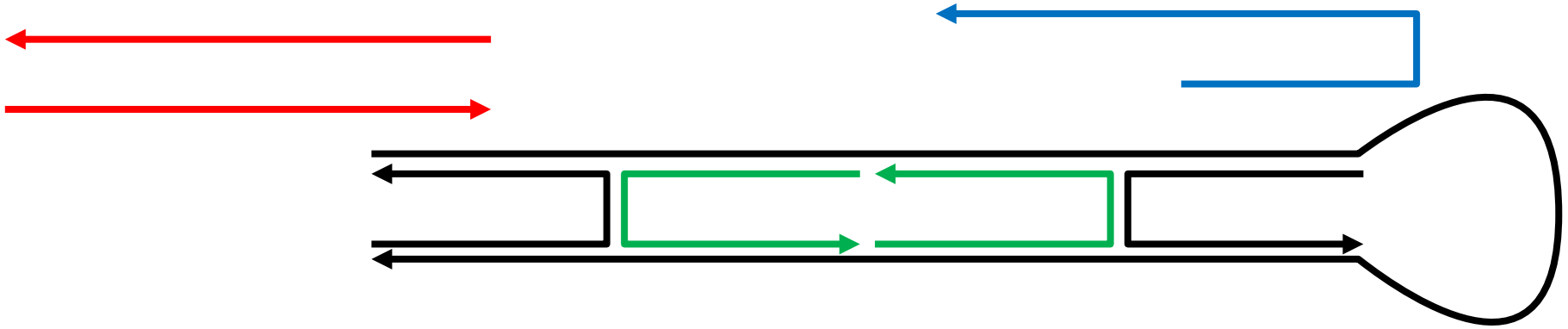

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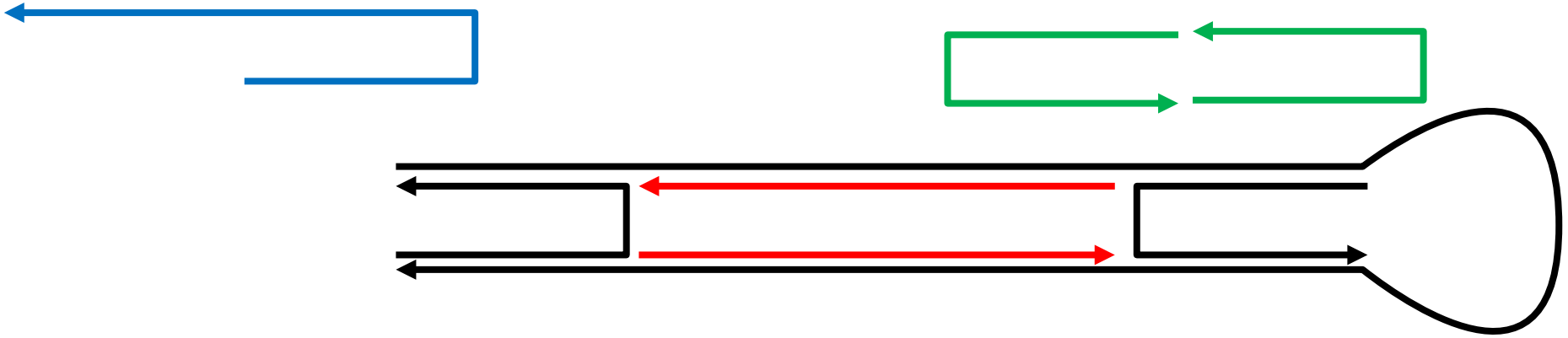

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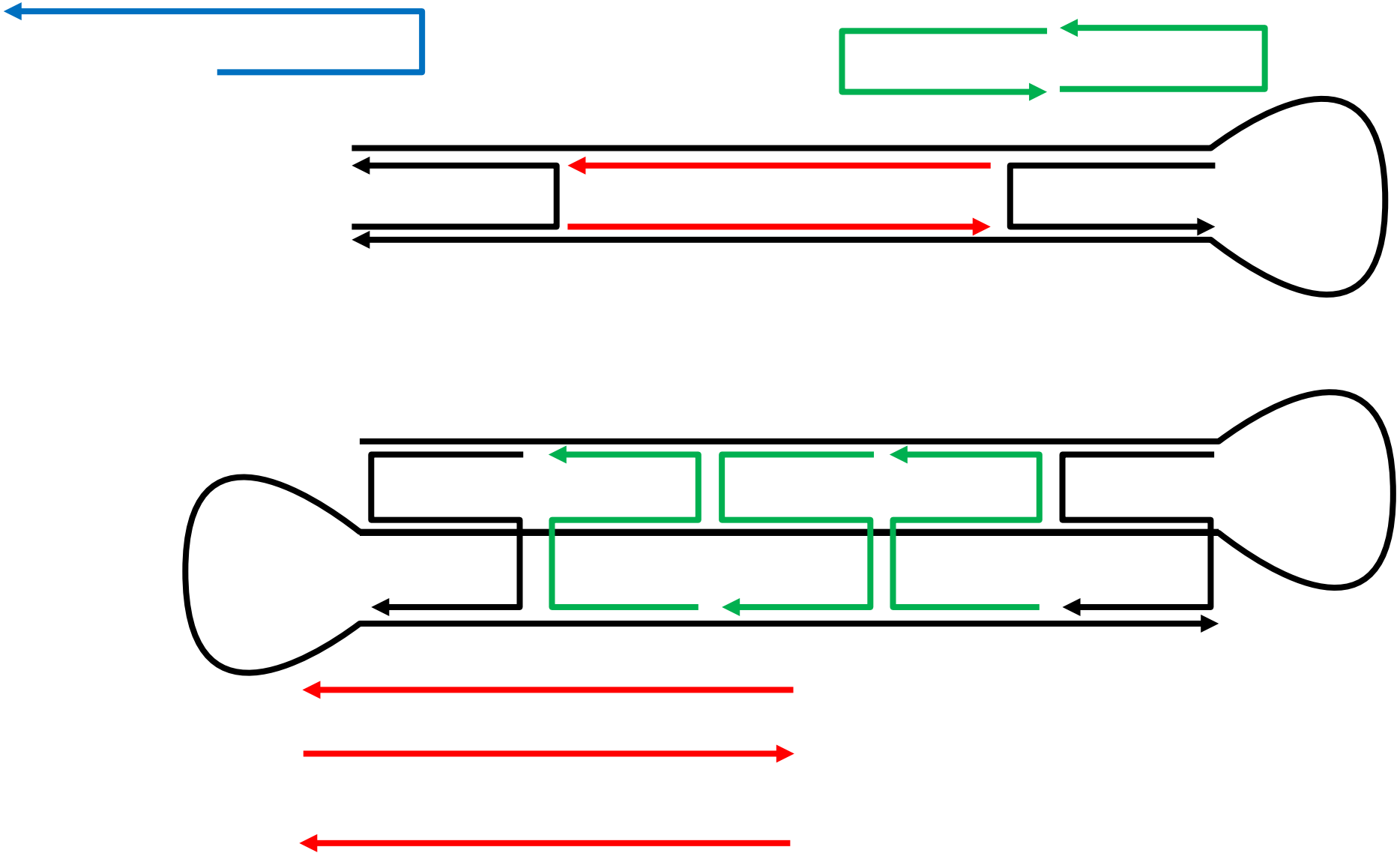

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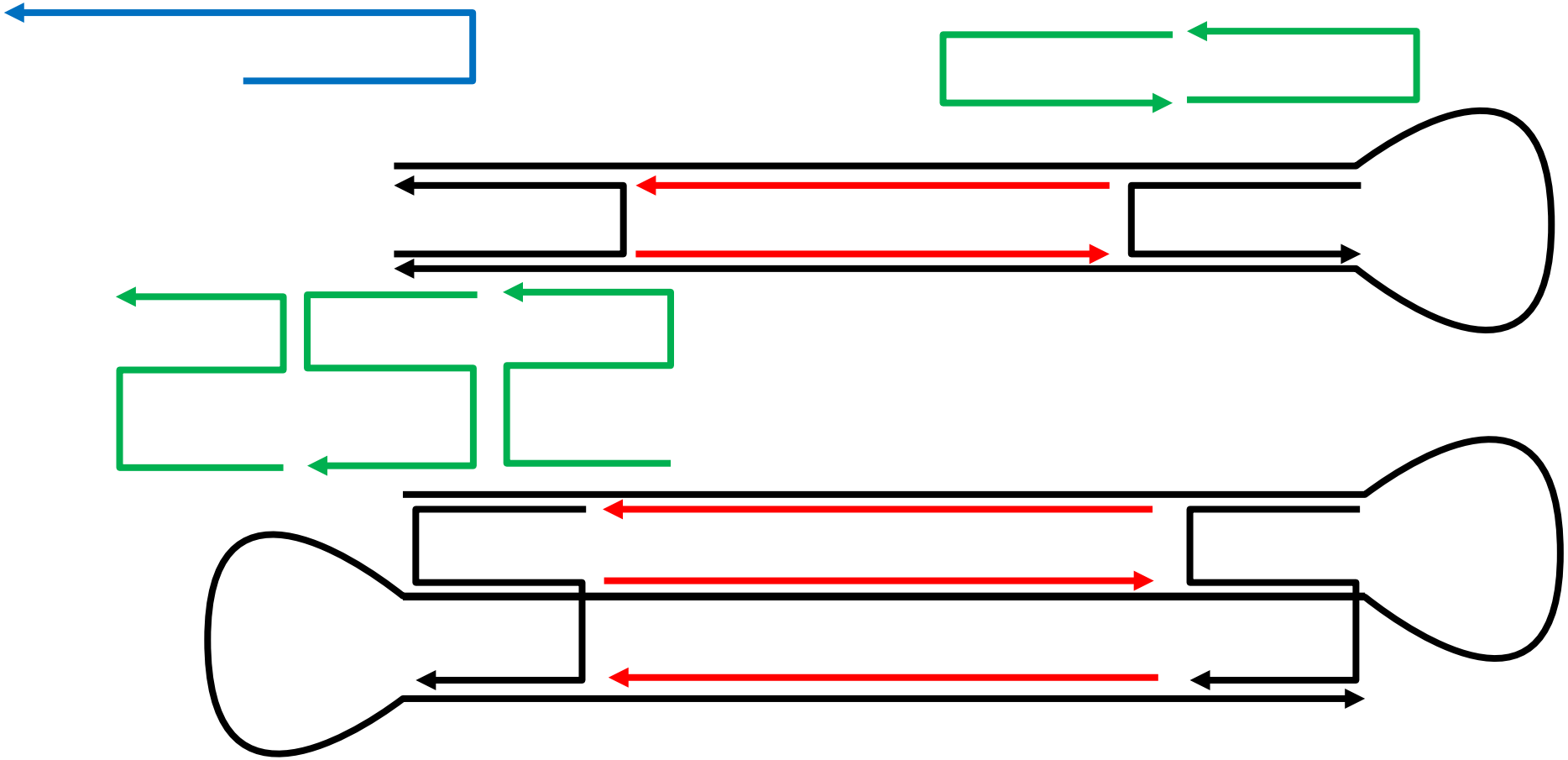

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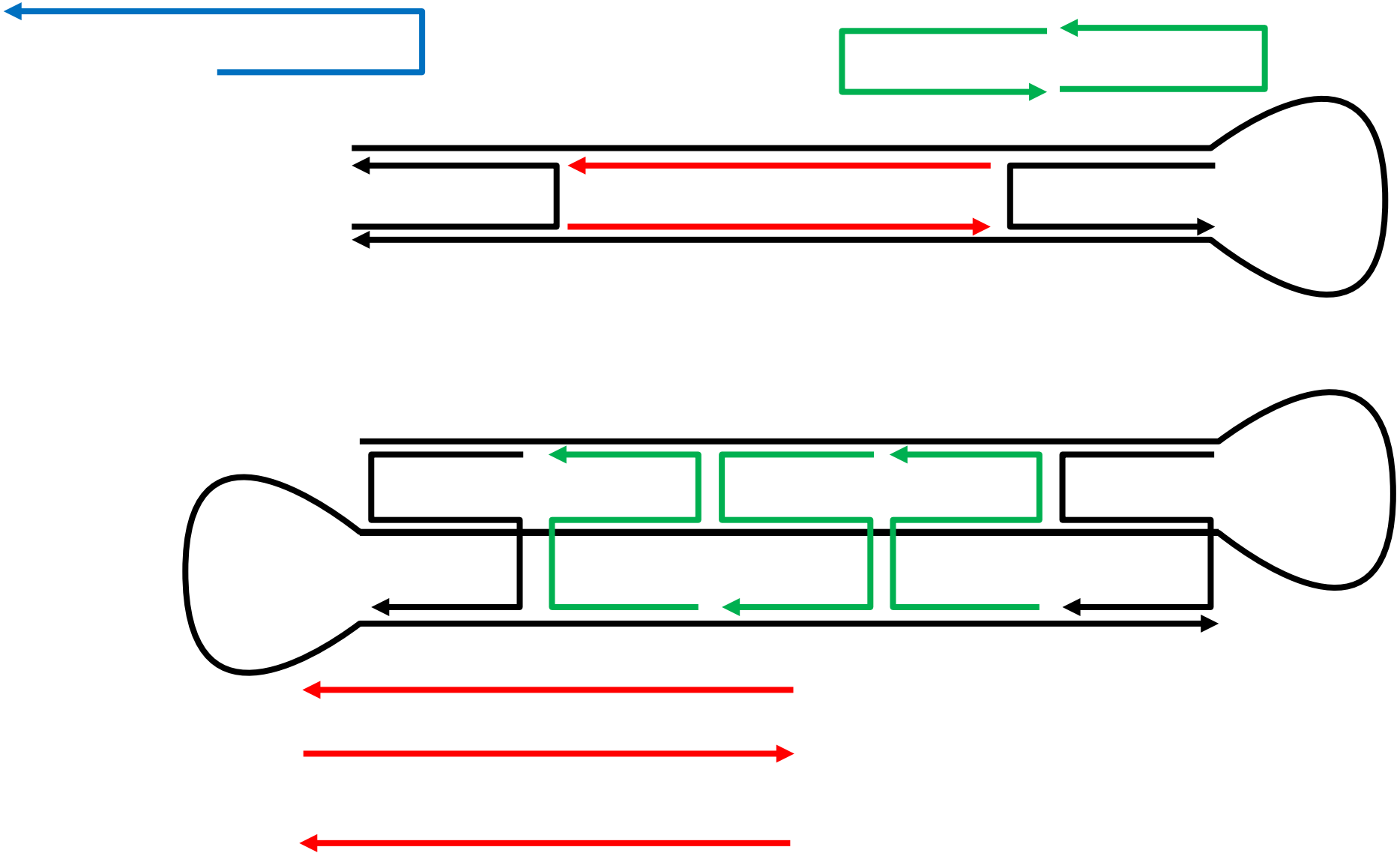

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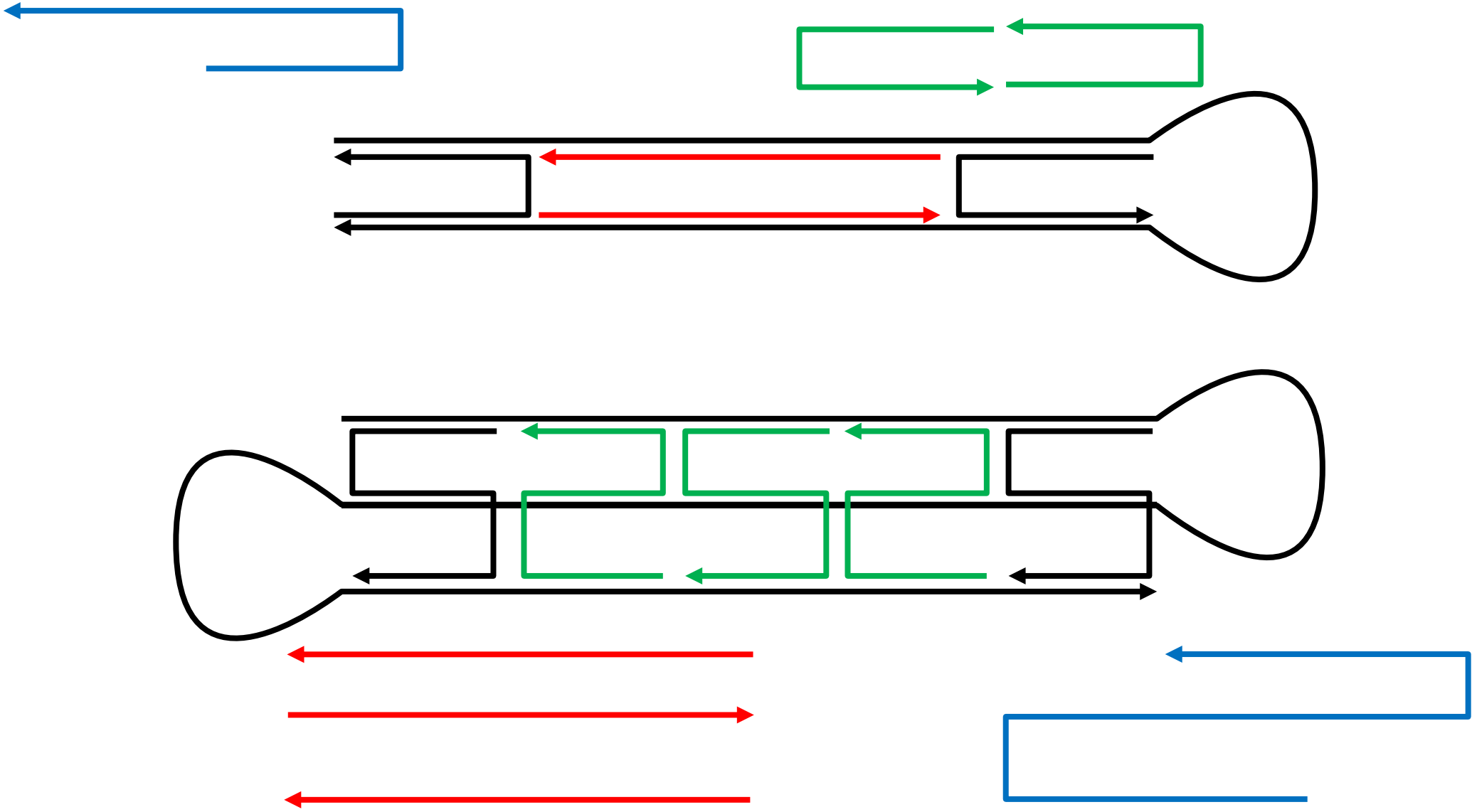

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