

# Polymers

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Homopolymer



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Homopolymer

-A-A-A-A-A-A-A-A-

Alternating copolymer

-A-B-A-B-A-B-A-B-

# Polymers

Homopolymer

-A-A-A-A-A-A-A-A-

Alternating copolymer

-A-B-A-B-A-B-A-B-

Statistical copolymer

-A-B-B-B-A-B-A-A-

# Polymers

Homopolymer	-A-A-A-A-A-A-A-A-
Alternating copolymer	-A-B-A-B-A-B-A-B-
Statistical copolymer	-A-B-B-B-A-B-A-A-
Block copolymer	-A-A-A-A-B-B-B-B-

# Polymers

Homopolymer	-A-A-A-A-A-A-A-A-
Alternating copolymer	-A-B-A-B-A-B-A-B-
Statistical copolymer	-A-B-B-B-A-B-A-A-
Block copolymer	-A-A-A-A-B-B-B-B-
<i>Complicated</i> copolymer	-A-A-C-C-B-B-D-D-

# Polymers

Homopolymer	-A-A-A-A-A-A-A-A-
Alternating copolymer	-A-B-A-B-A-B-A-B-
Statistical copolymer	-A-B-B-B-A-B-A-A-
Block copolymer	-A-A-A-A-B-B-B-B-
<i>Complicated</i> copolymer	-A-A-C-C-B-B-D-D-
<i>Really Complicated</i> copolymer	-A-B-C-D-A-B-C-D-

# Polymers

Homopolymer	-A-A-A-A-A-A-A-A-
Alternating copolymer	-A-B-A-B-A-B-A-B-
Statistical copolymer	-A-B-B-B-A-B-A-A-
Block copolymer	-A-A-A-A-B-B-B-B-
<i>Complicated</i> copolymer	-A-A-C-C-B-B-D-D-
<i>Really Complicated</i> copolymer	-A-B-C-D-A-B-C-D-
<i>Nobel prize 2100</i> copolymer	-A-B-C-D-E-F-G-H-



Polymerase

# Polymerase

-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-

DNA

# Self-Assembly

# Self-Assembly

-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-

# Self-Assembly

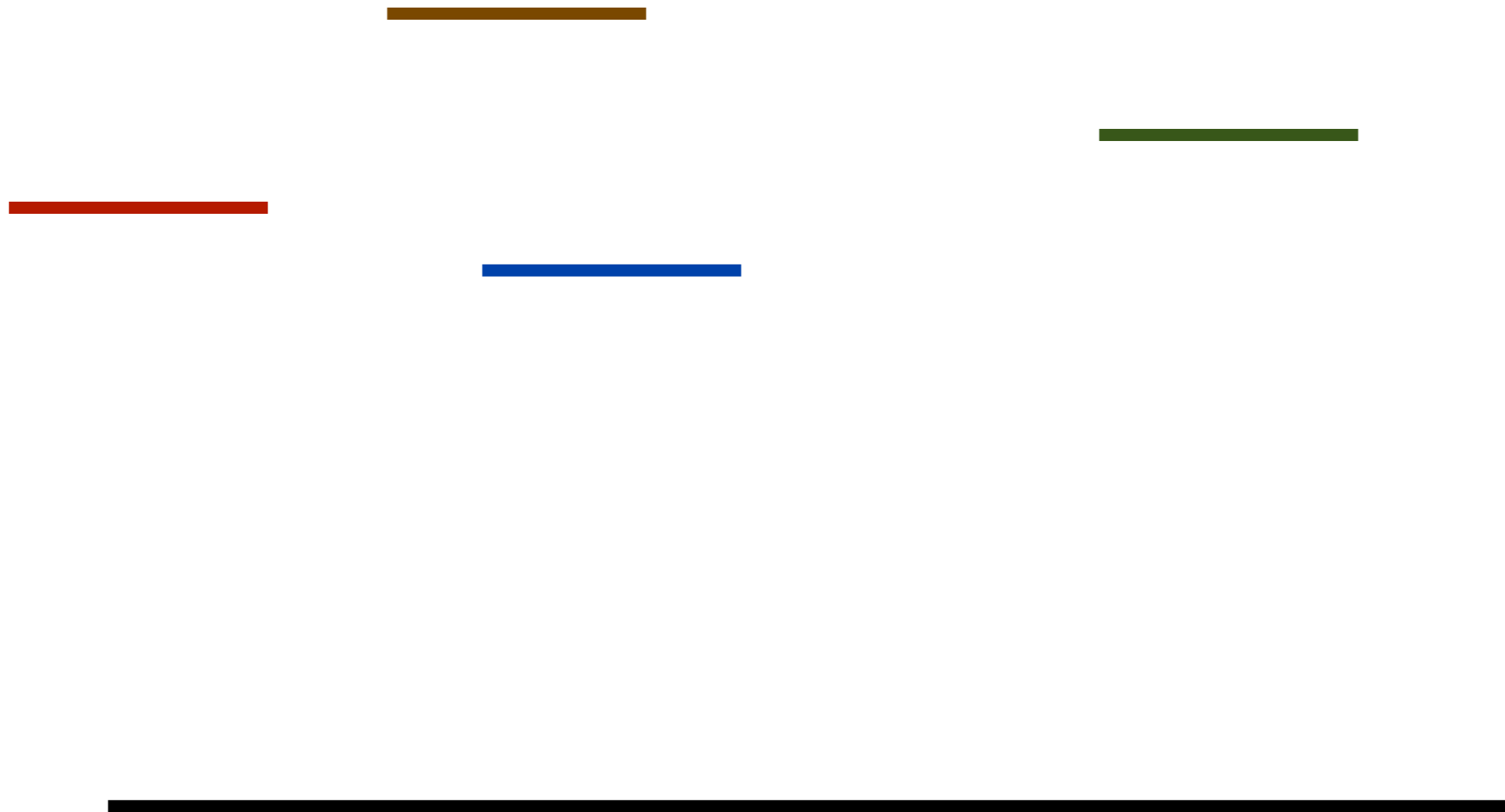
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-A-G-T-C-G-A-T-A-

# Self-Assembly

-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-  
-A-G-T-C-G-A-T-A-

# Programmed Assembly



# Programmed Assembly





# Programmed Assembly



# Programmed Assembly



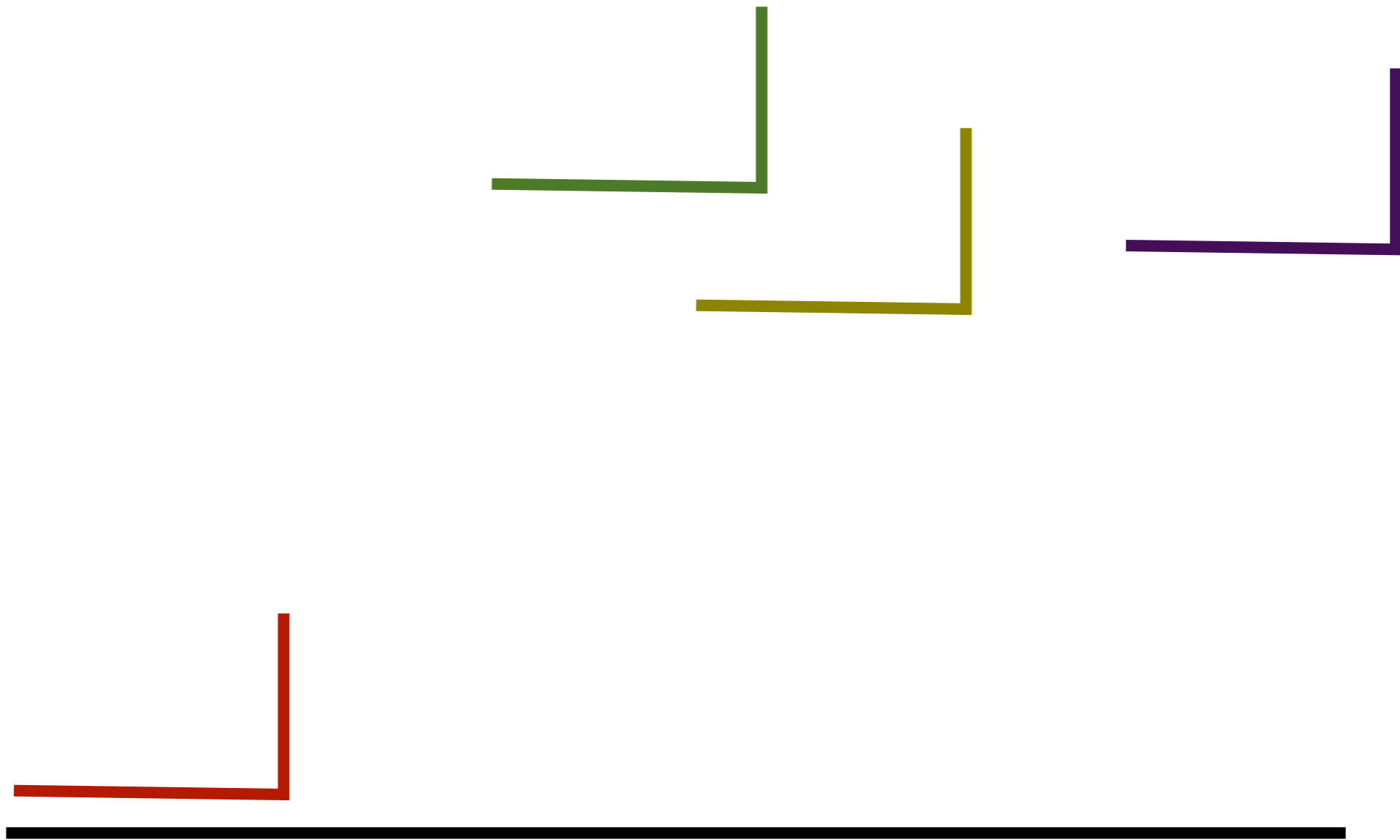
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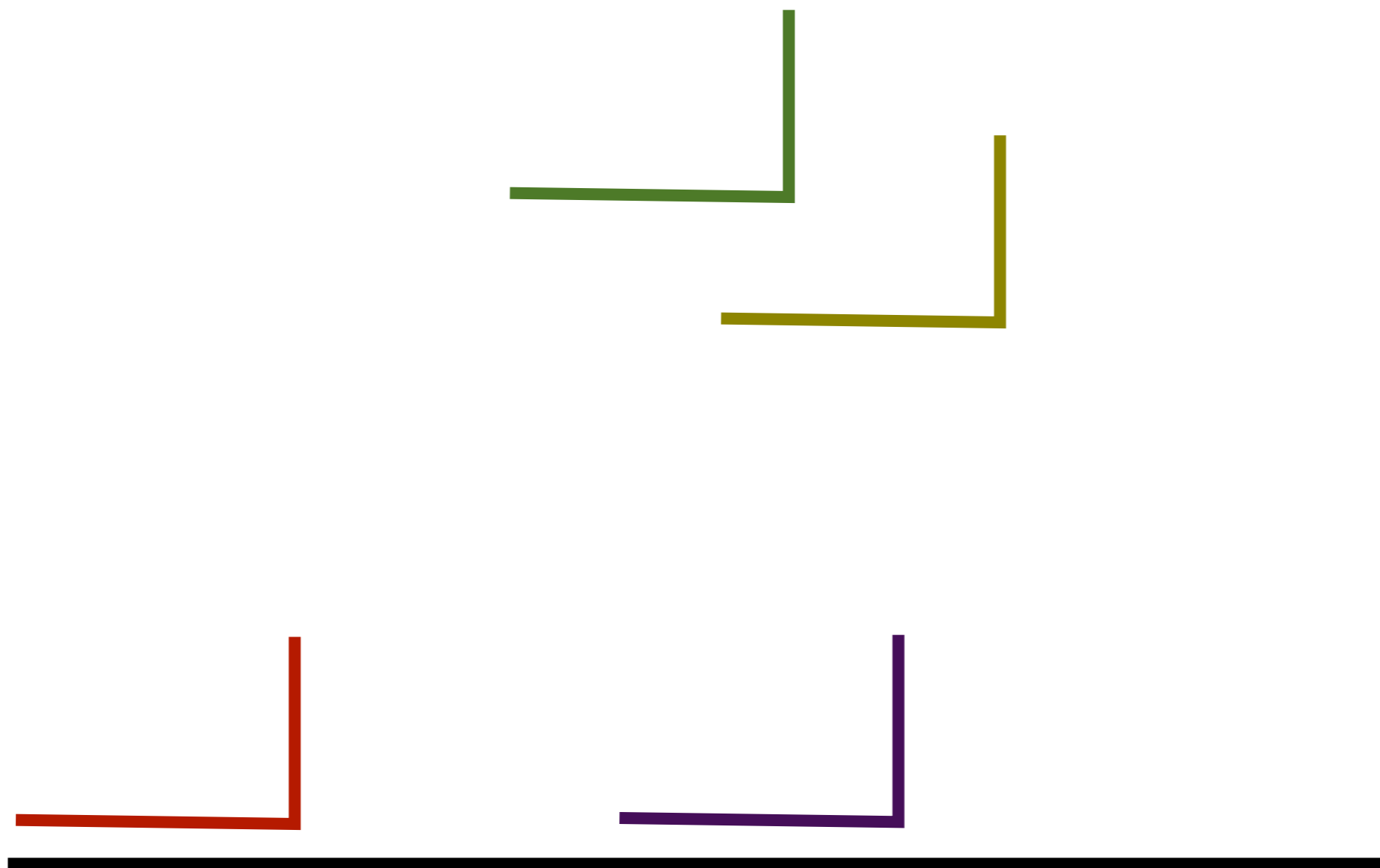
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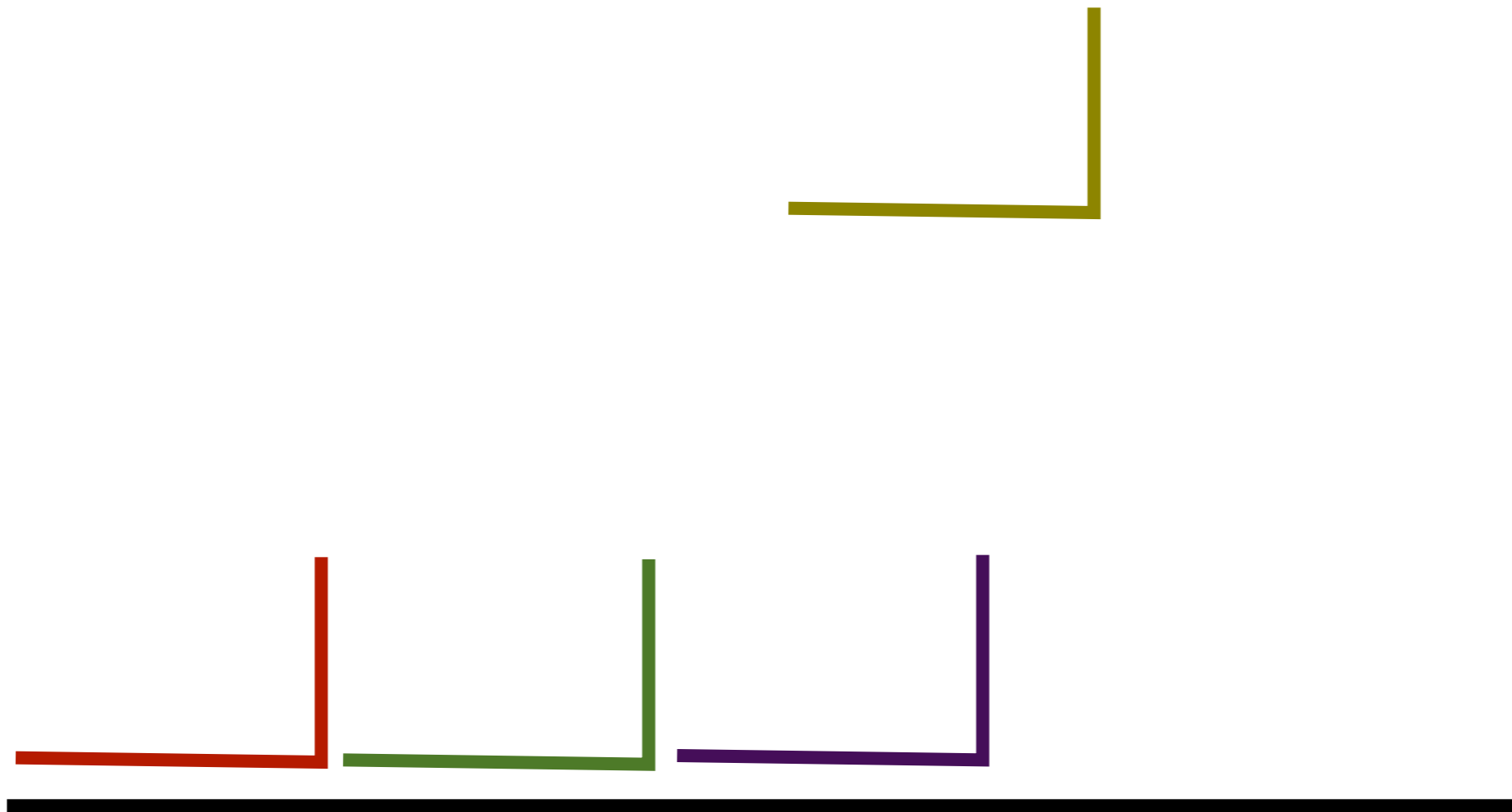
# Programmed Assembly



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# Programmed Assembly

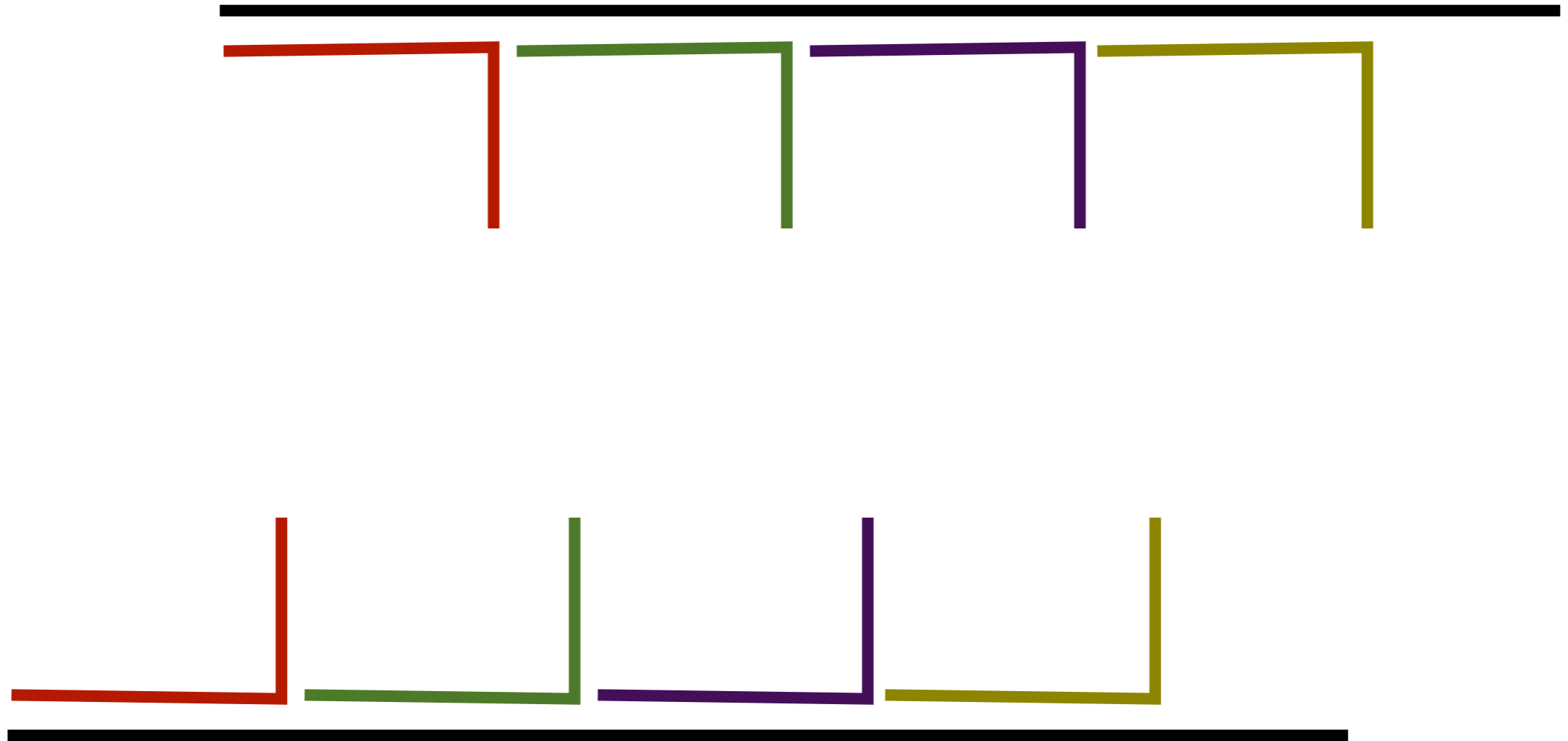


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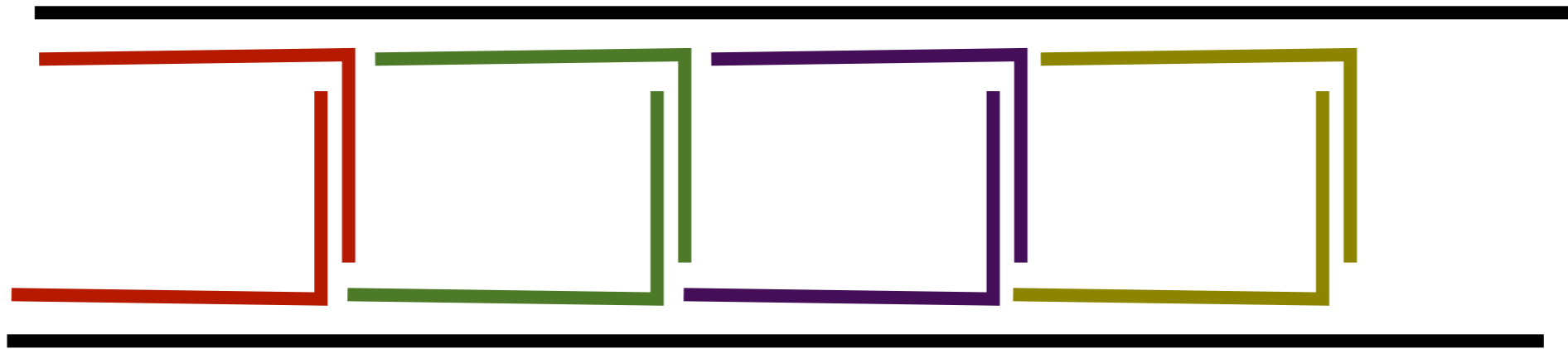




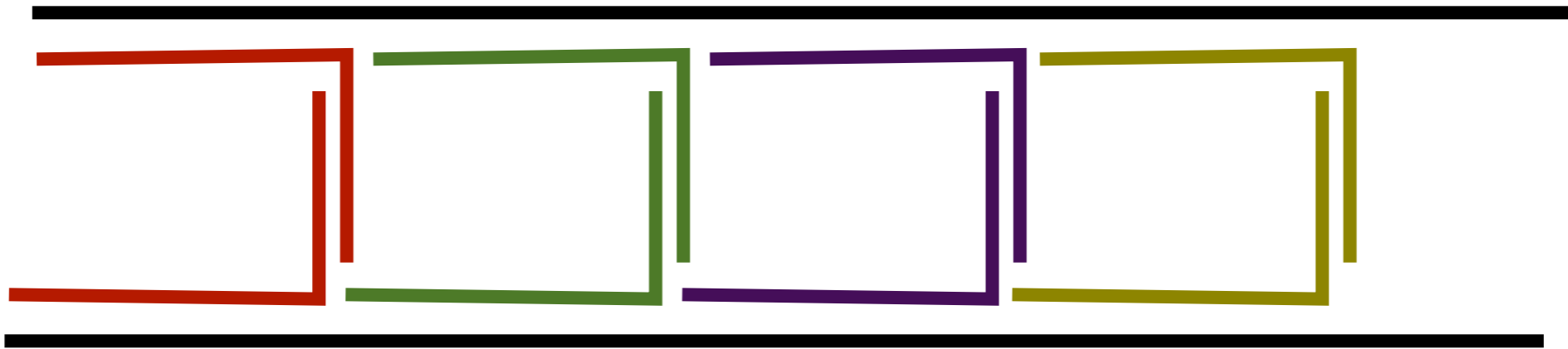
# Programmed Assembly



# Programmed Assembly

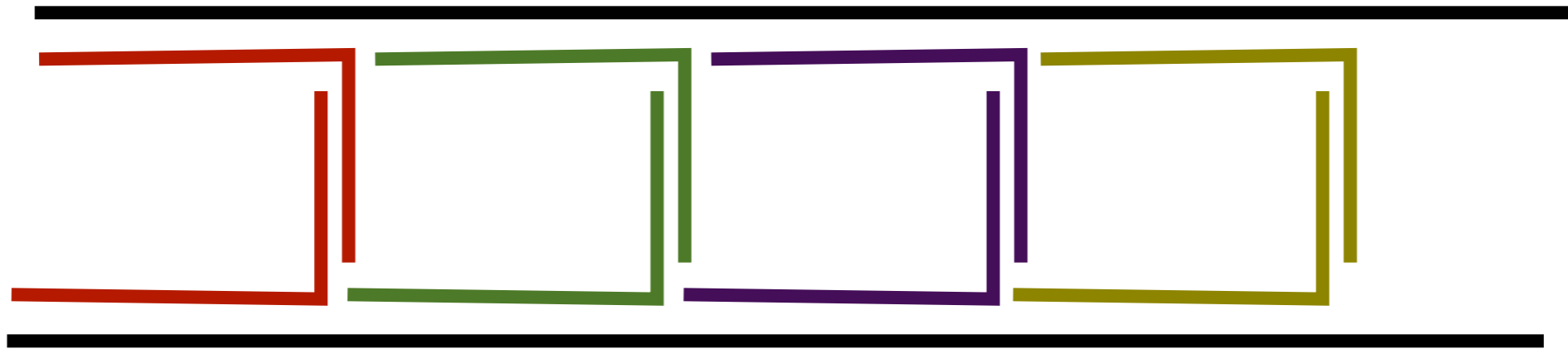


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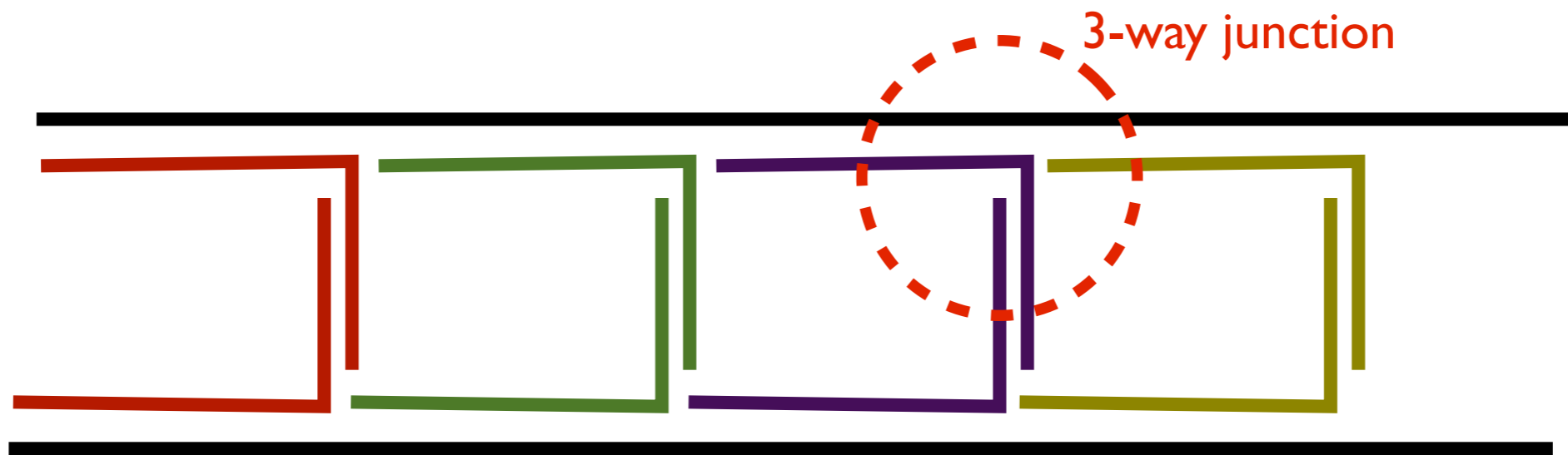
Distances programmable: 0.36 nm per base pair

# Programmed Assembly



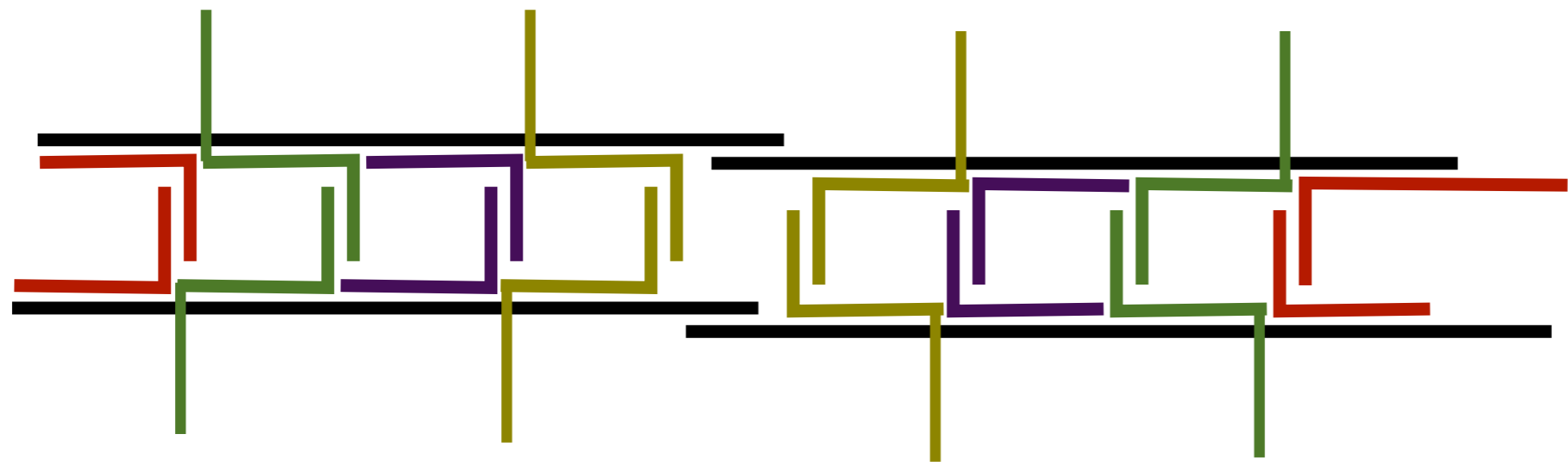
Distances programmable: 0.36 nm per base pair  
Helices are rigid (persistence length of  $\approx 15$  nm)

# Programmed Assembly

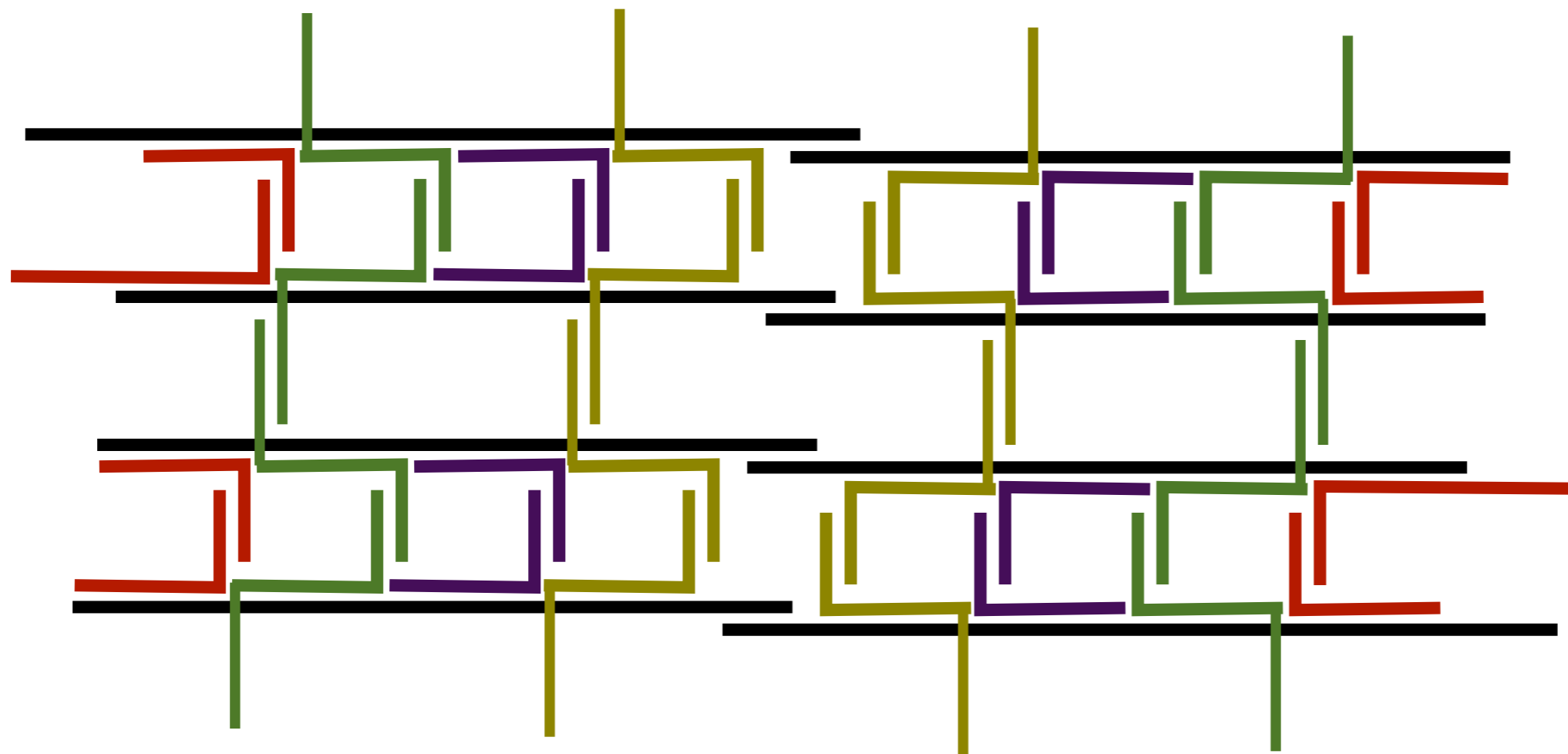


Distances programmable: 0.36 nm per base pair  
Helices are rigid (persistence length of  $\approx 15$  nm)  
Can make 3, or even 4-way junctions

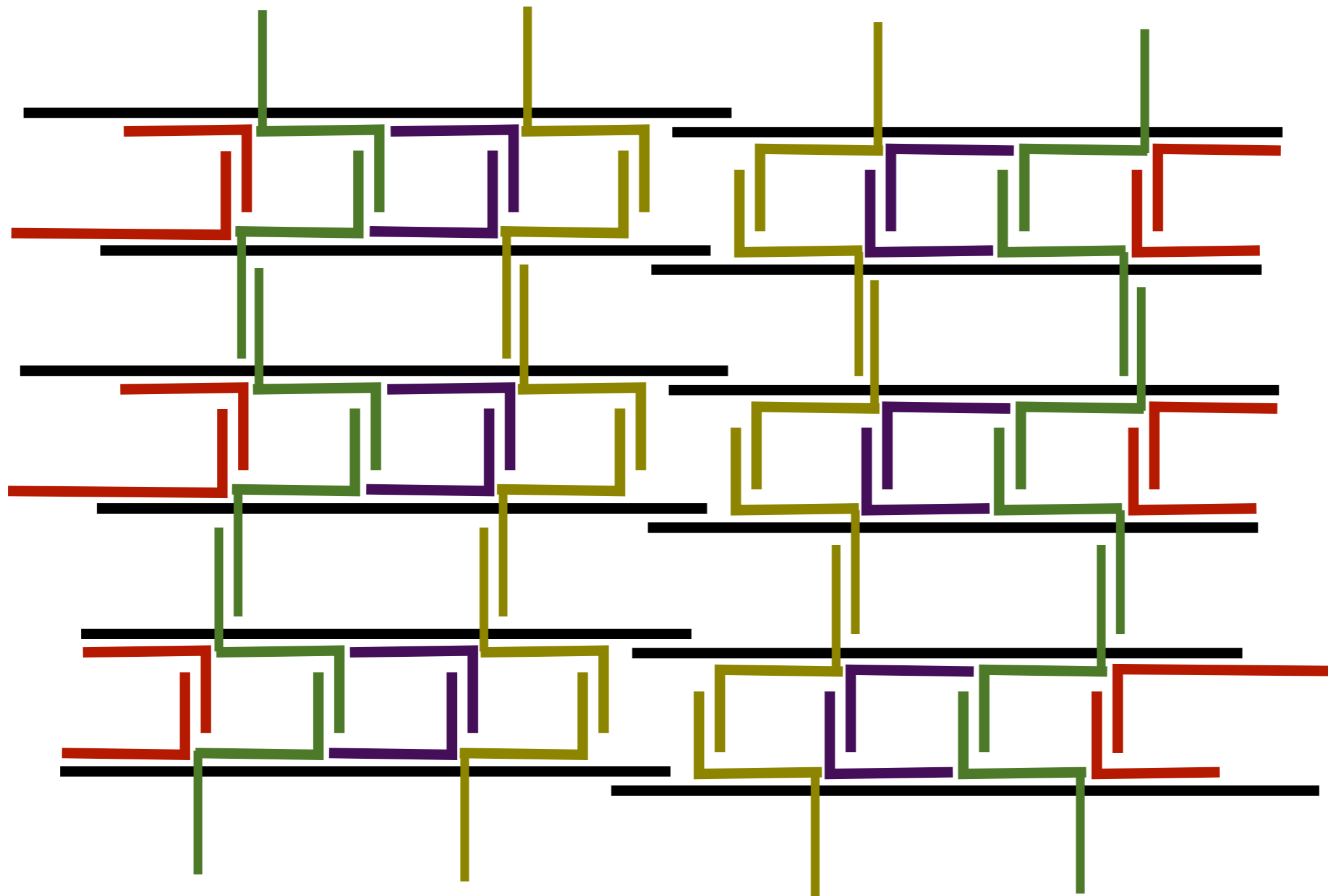
# Programmed Assembly



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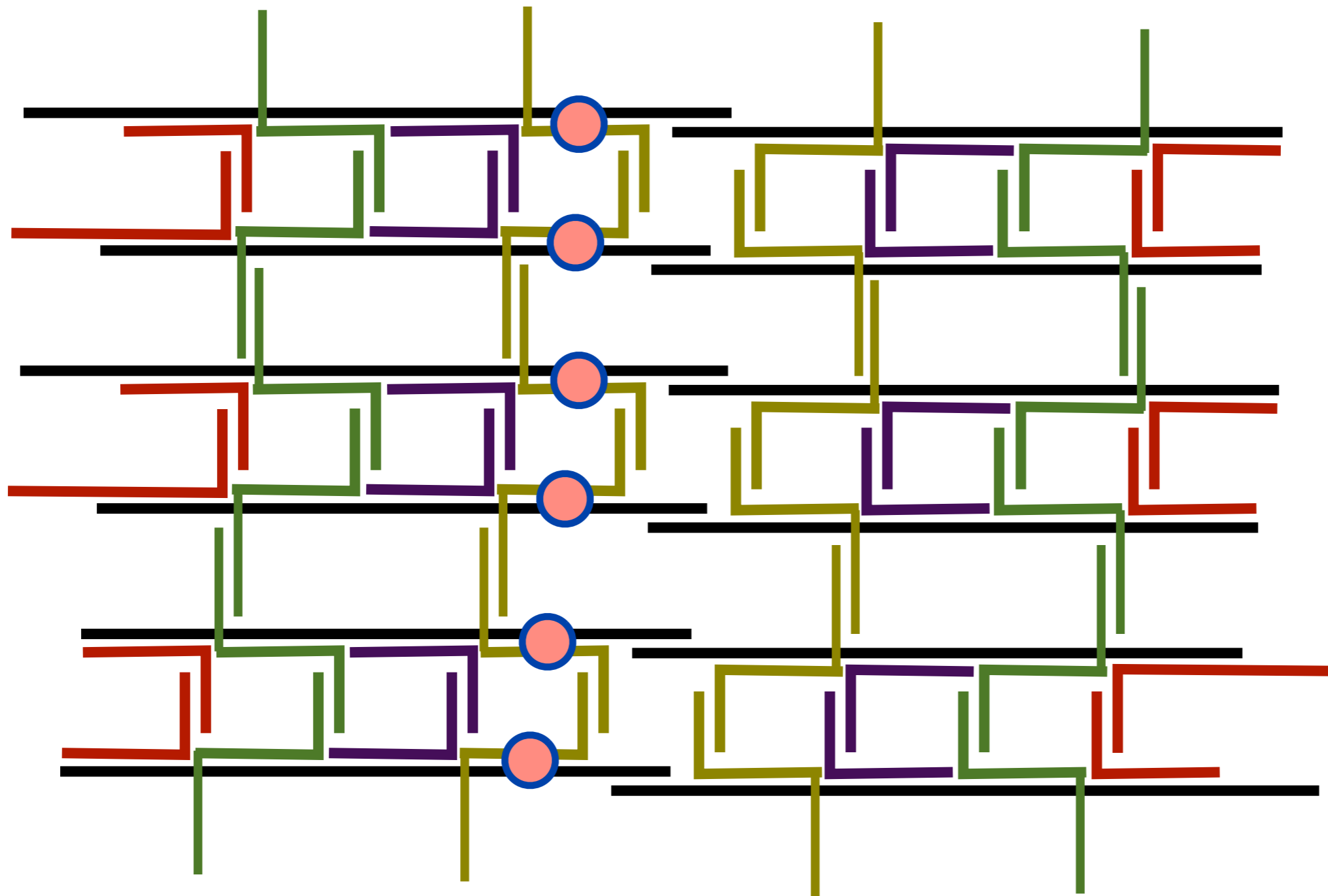


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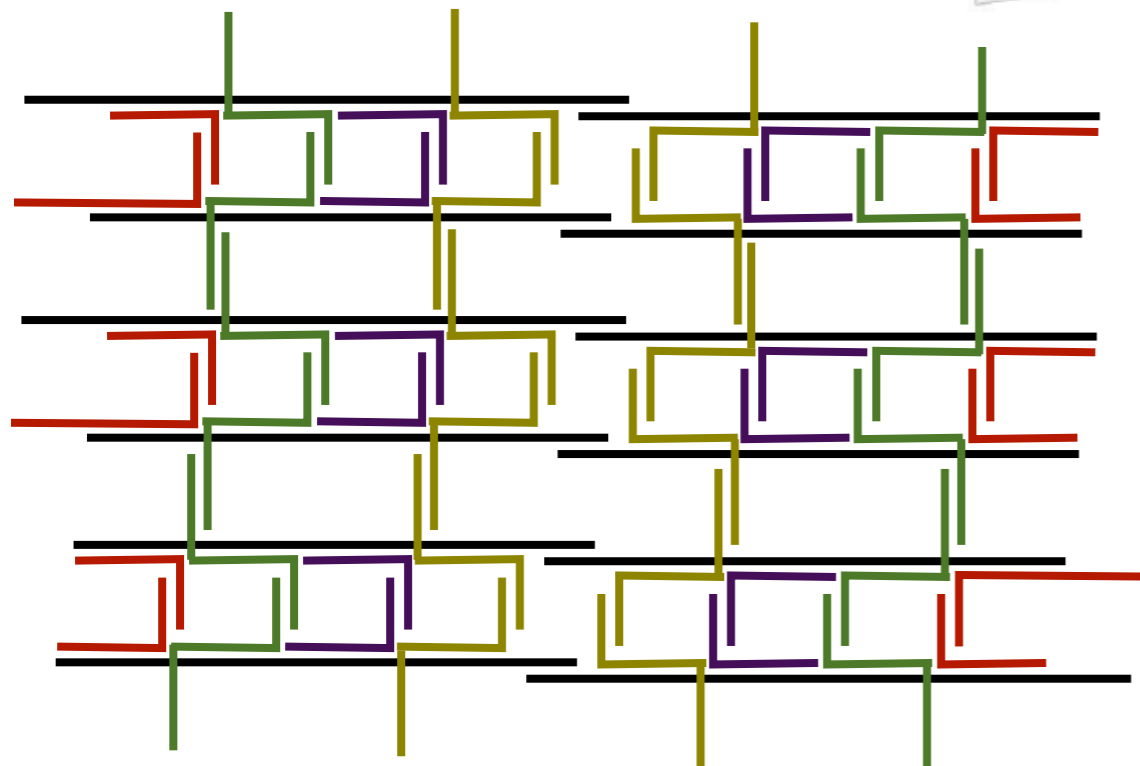
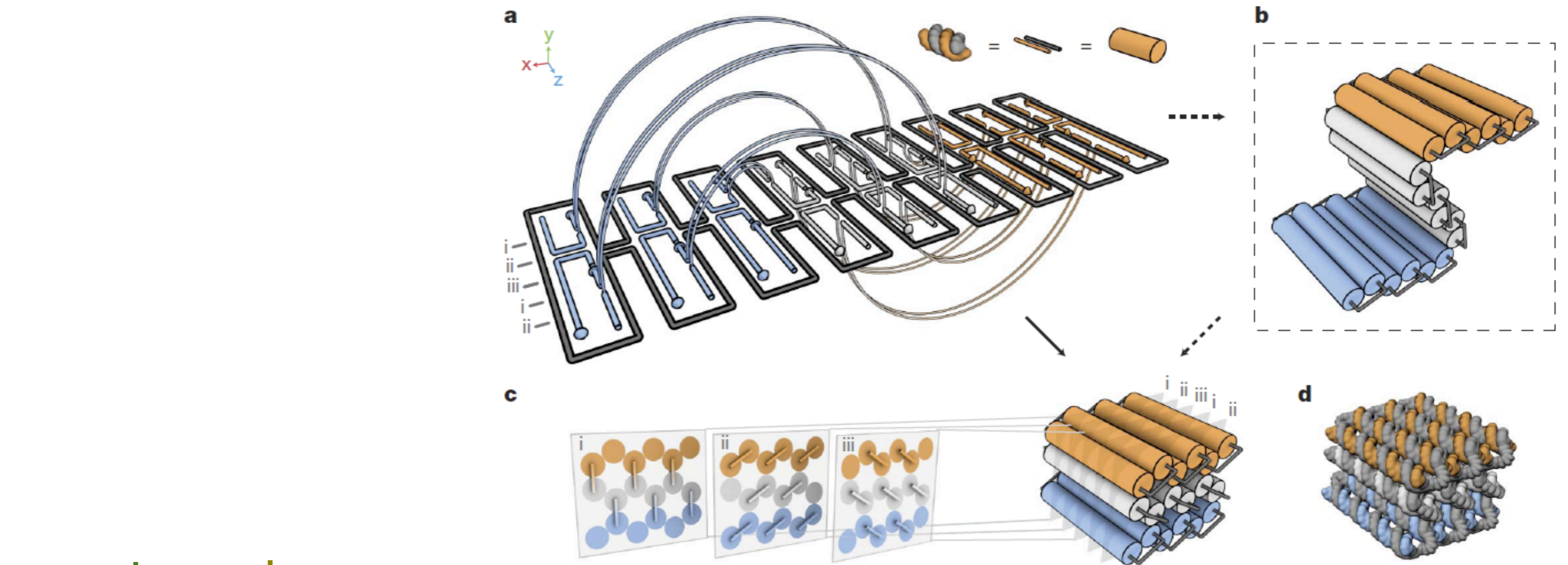




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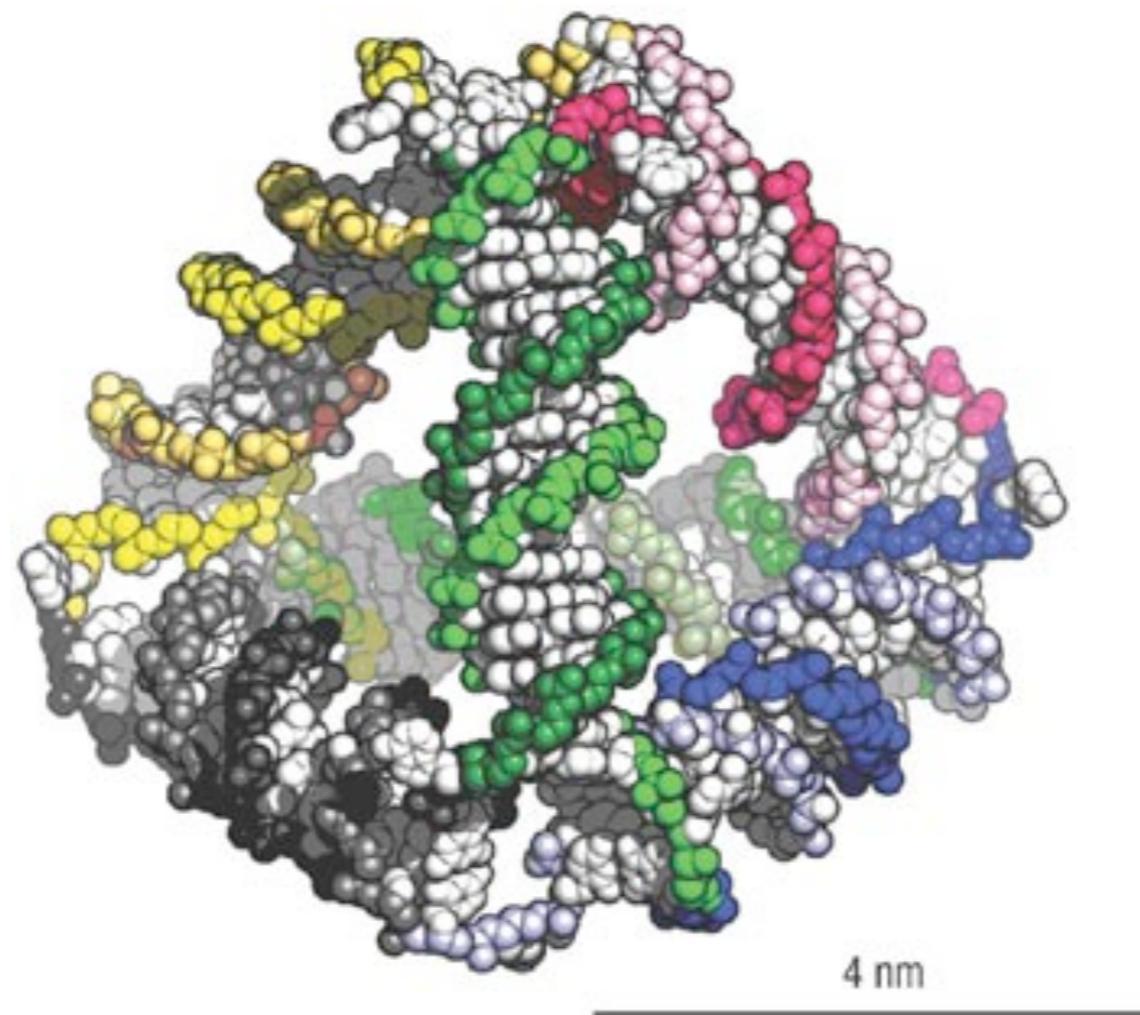


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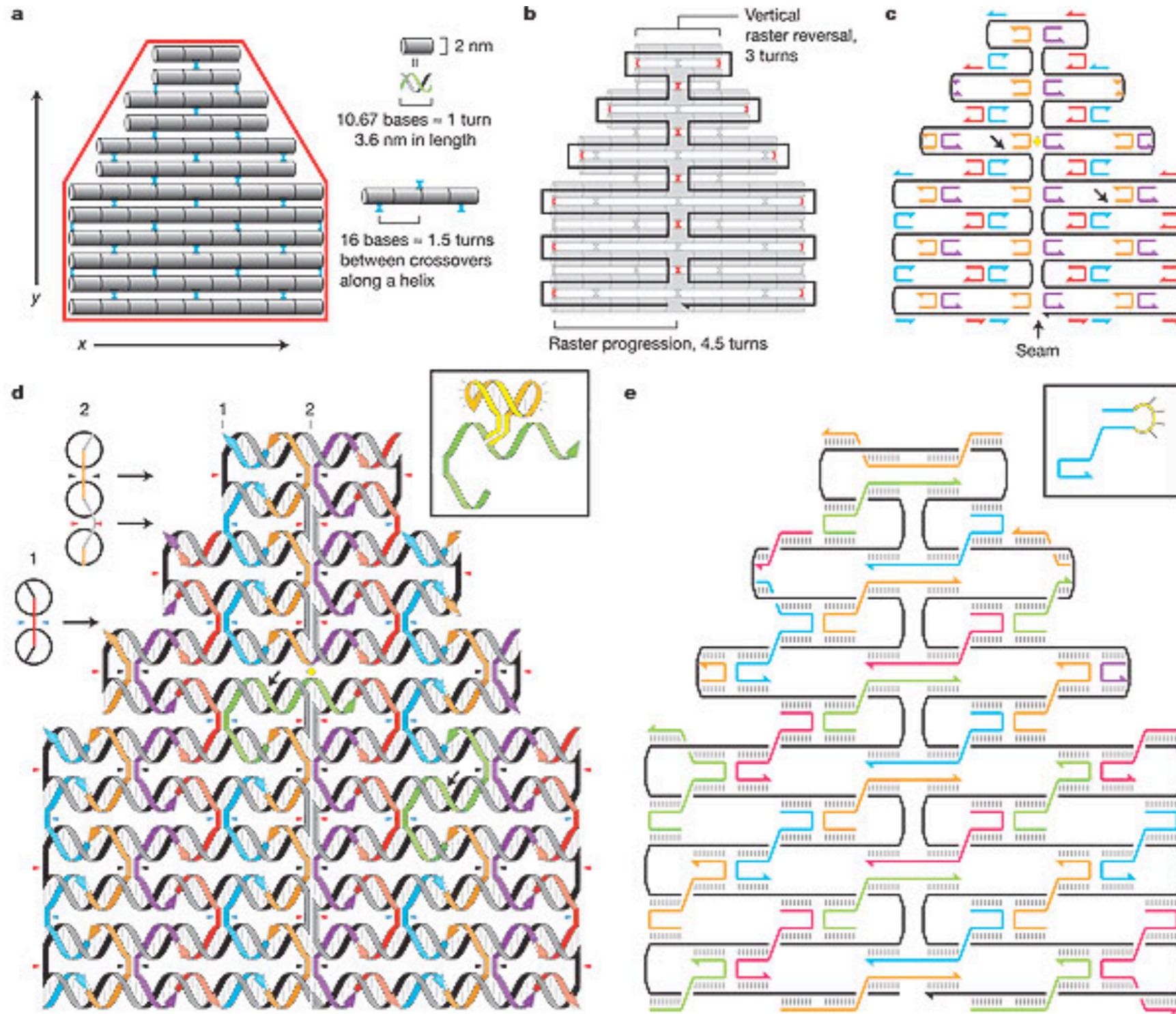


Assembly in 3 dimensions

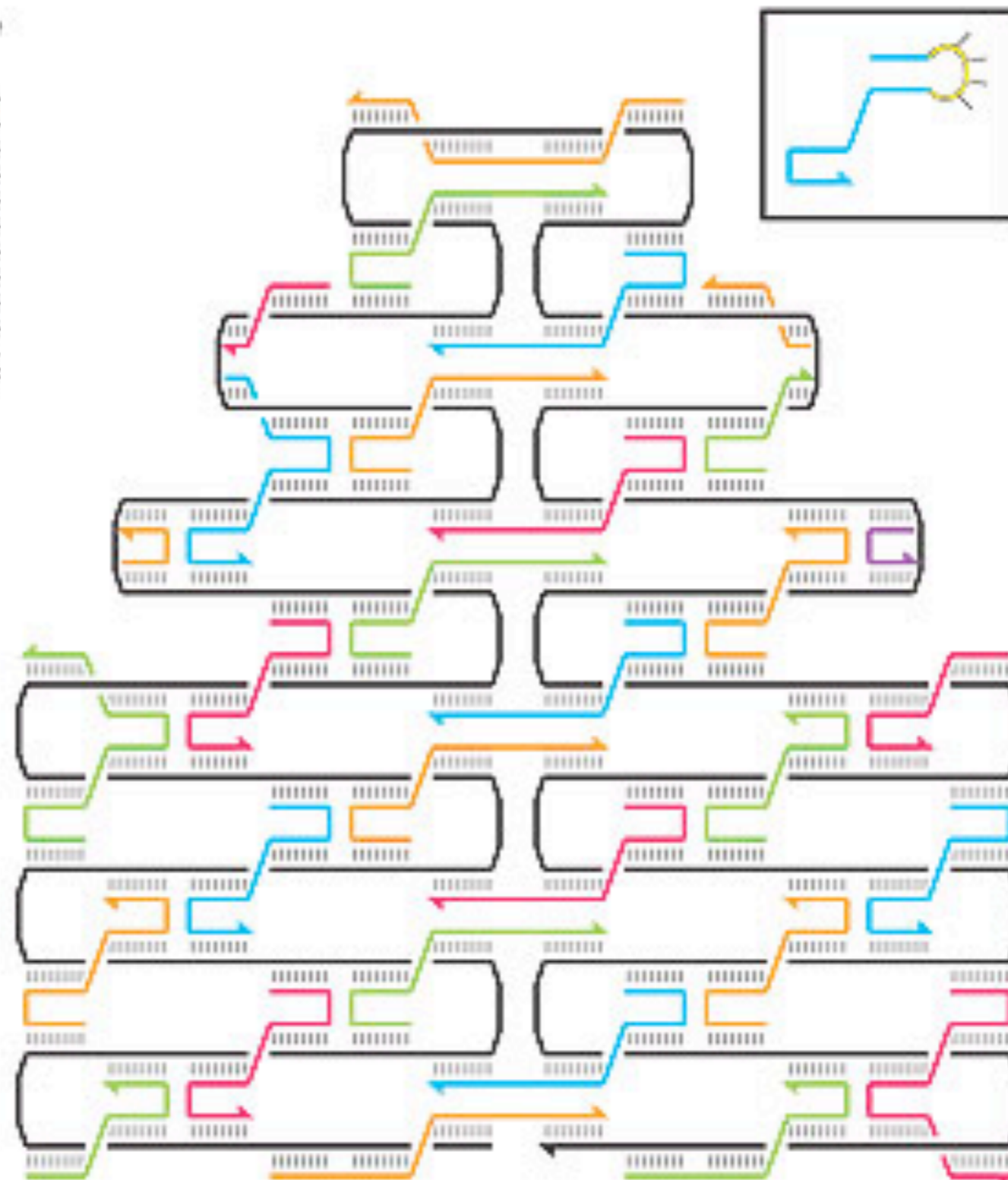
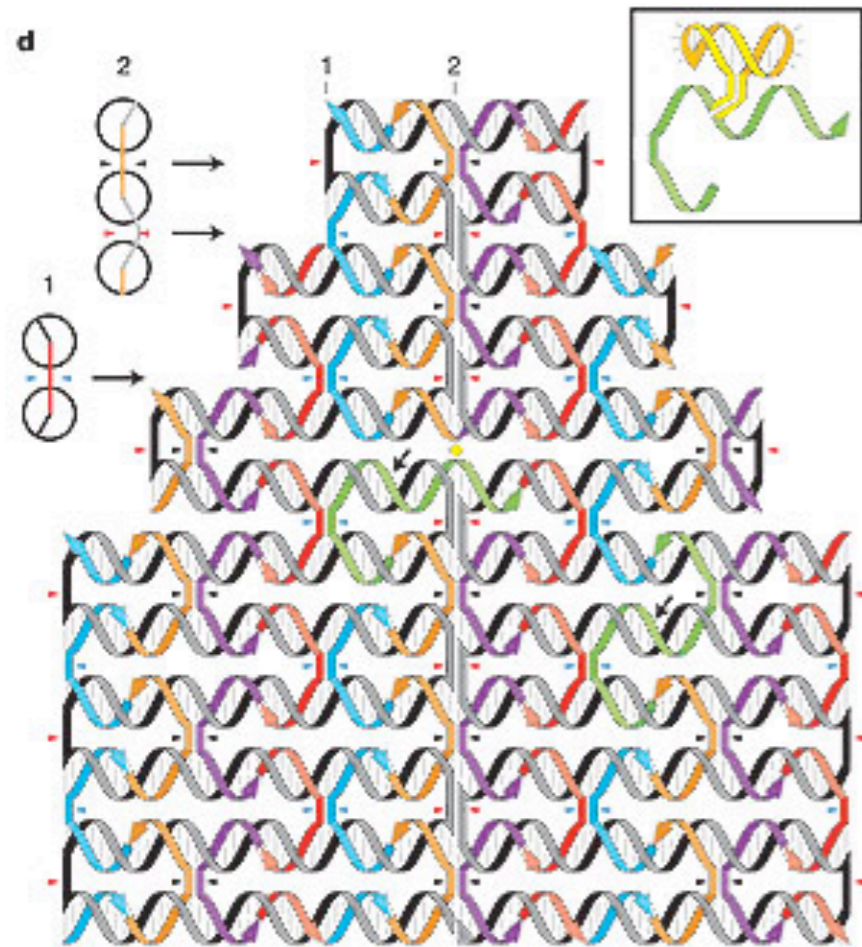
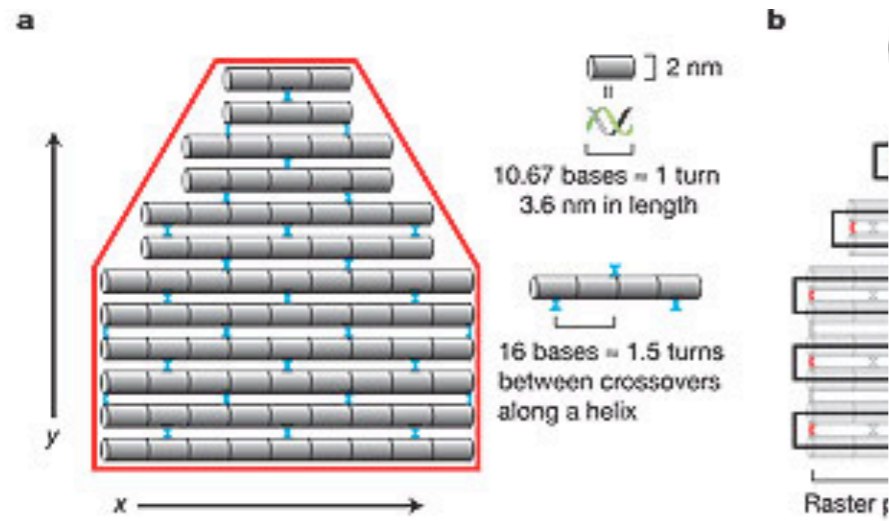
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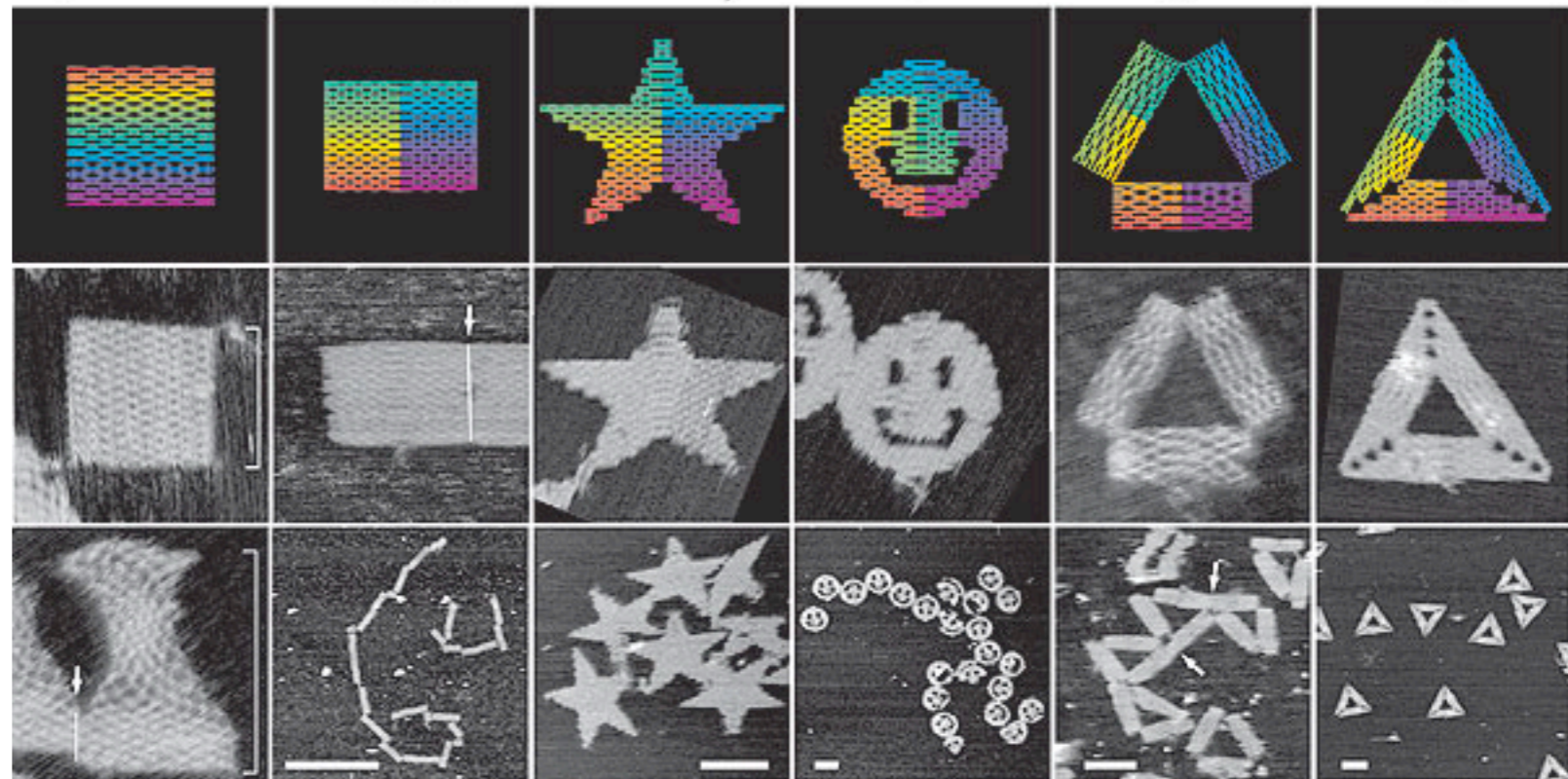
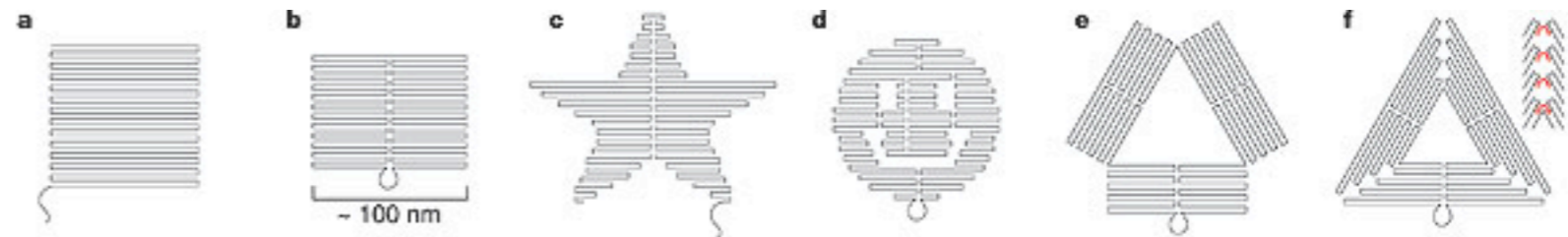
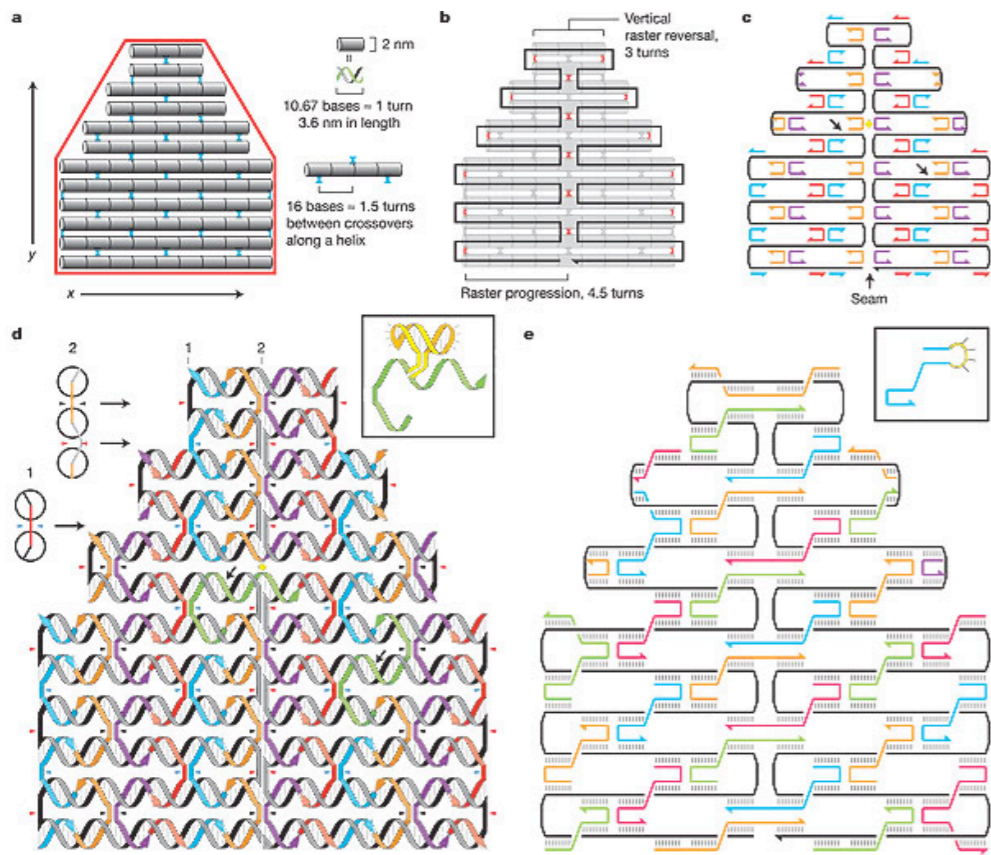
# Programmed Assembly



# Programmed Assembly

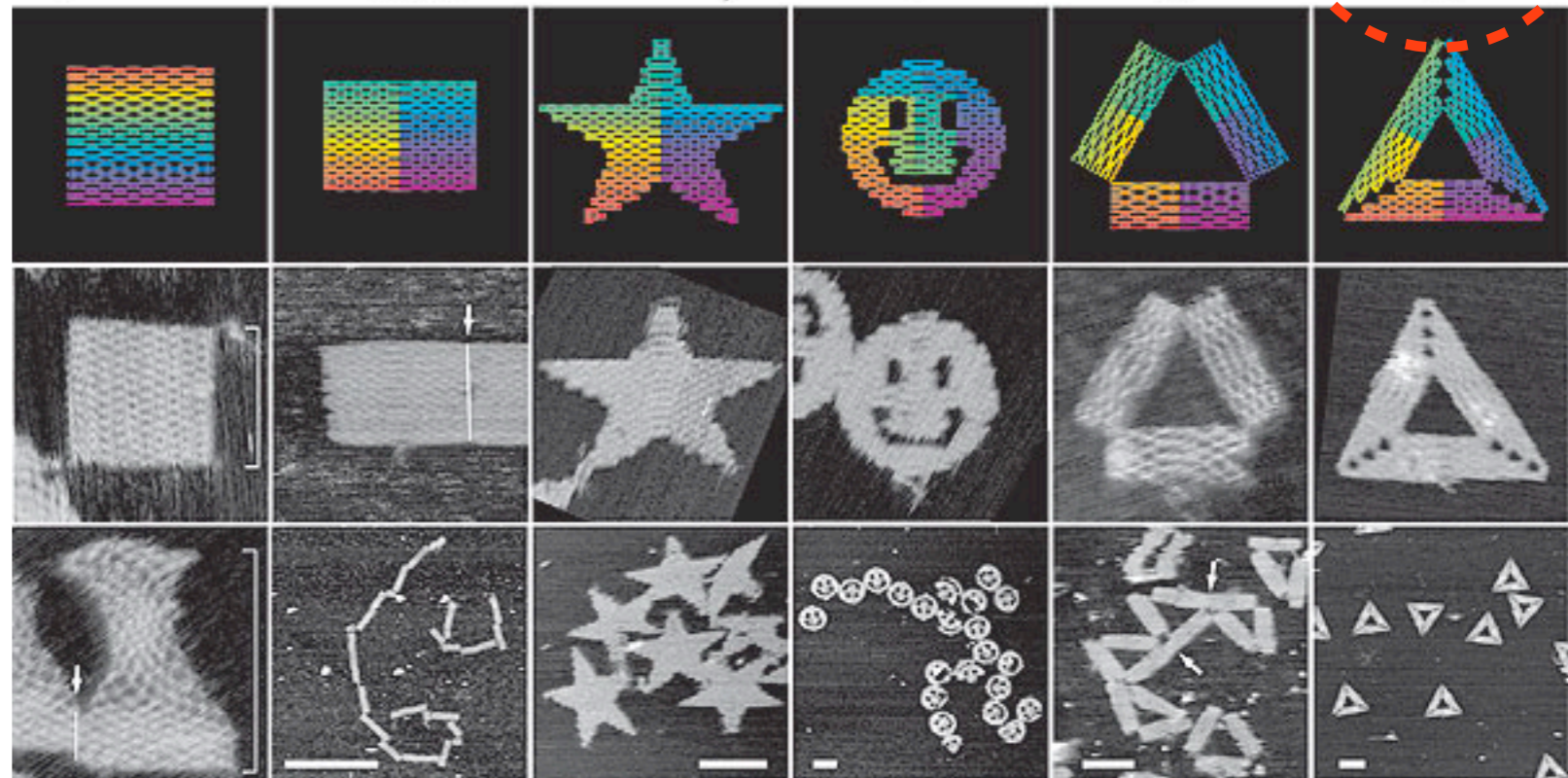
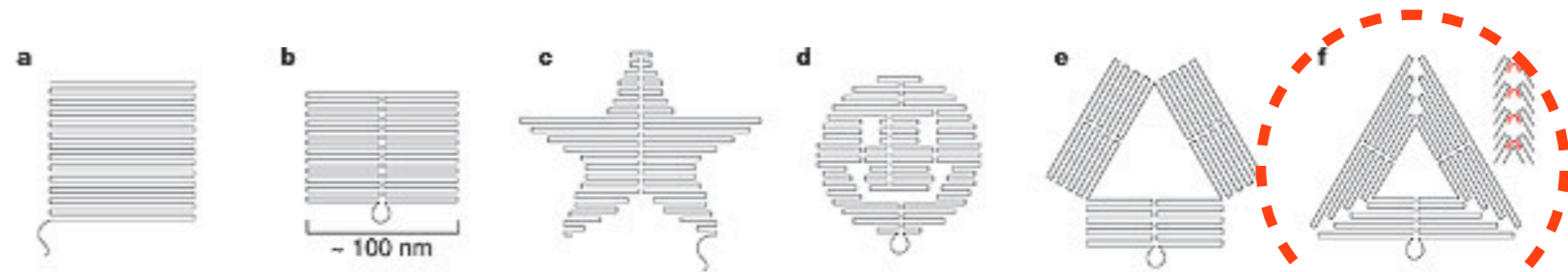
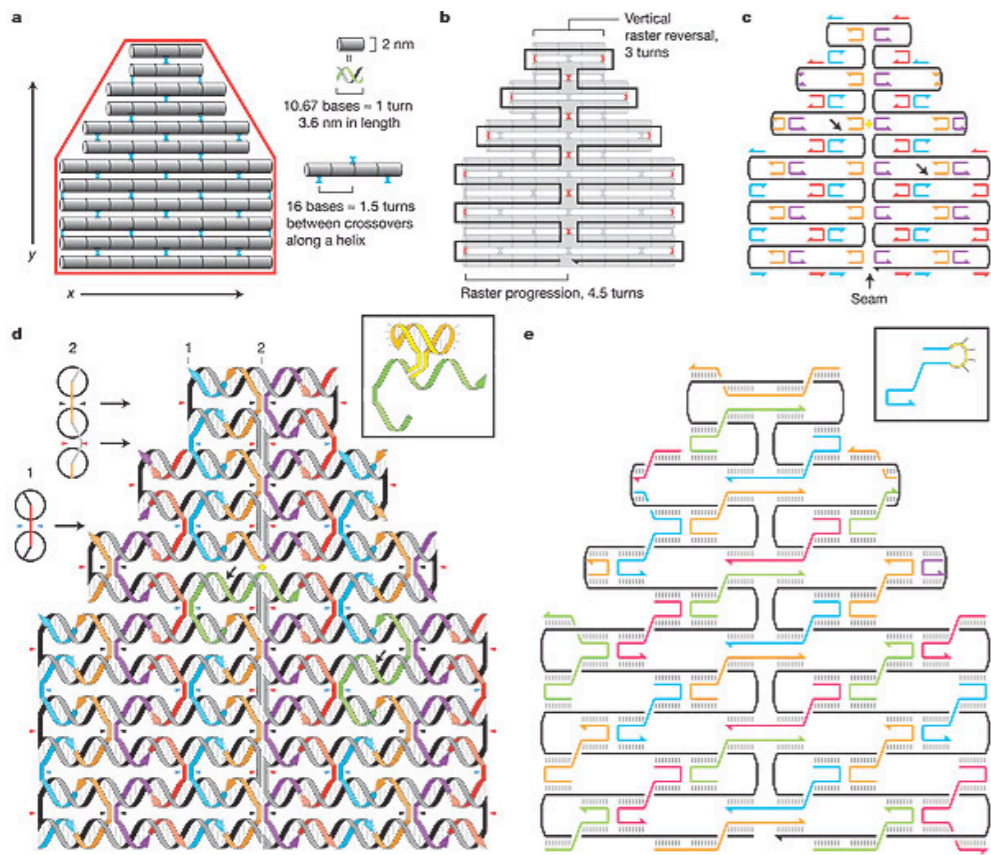


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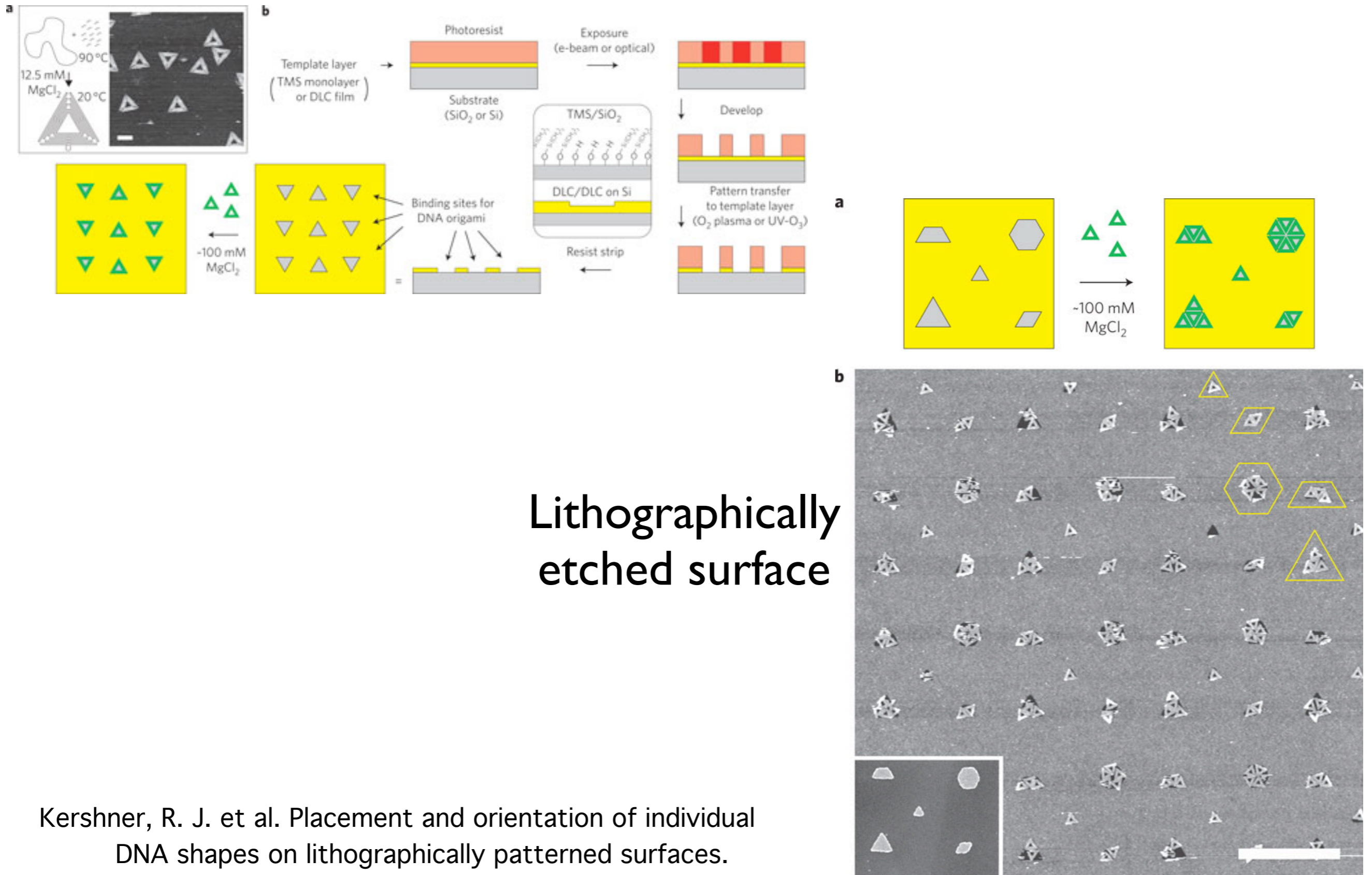
Rothemund, P. W. Folding DNA to create nanoscale shapes and patterns. Nature 440, 297-302 (2006).

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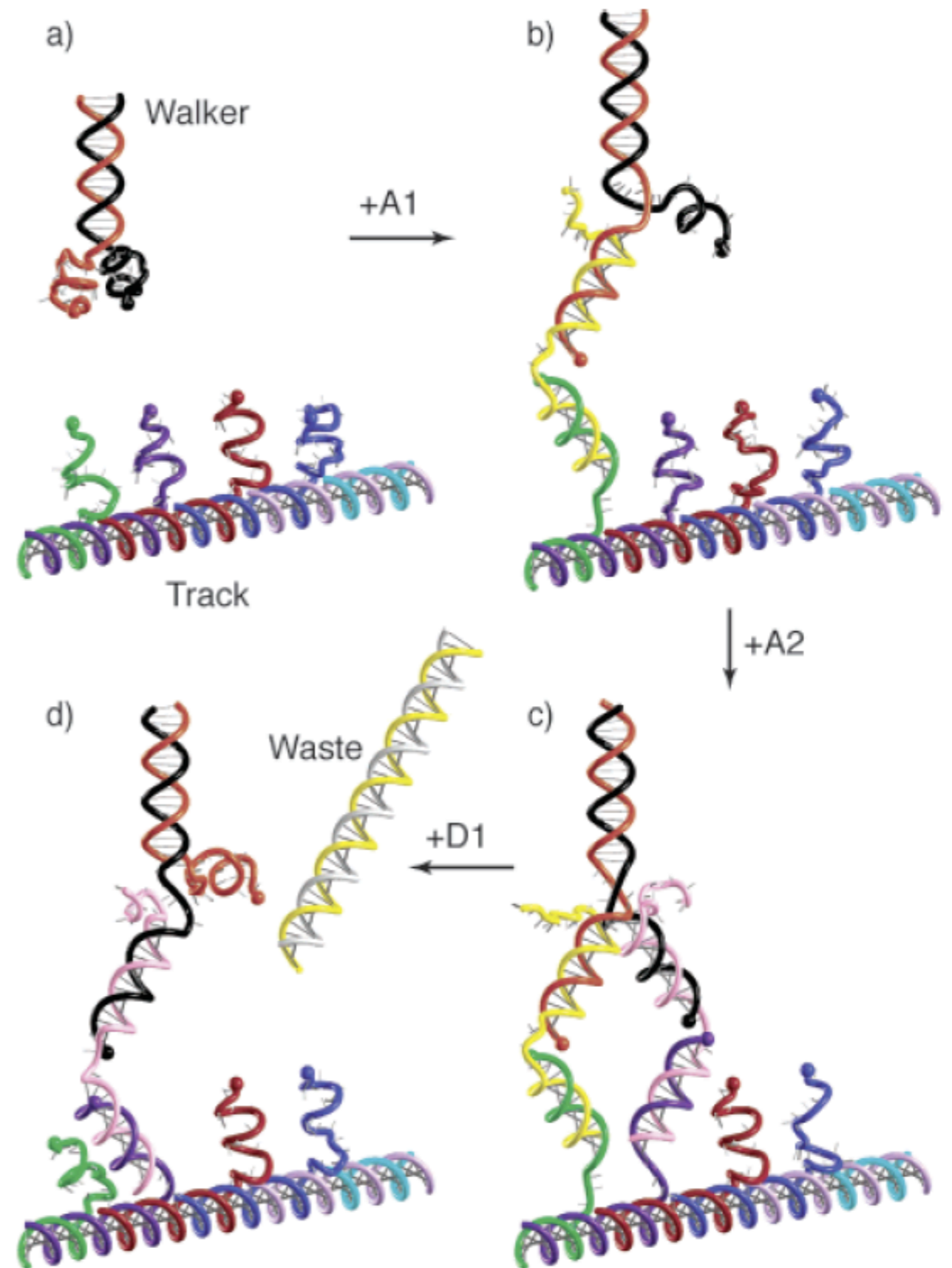
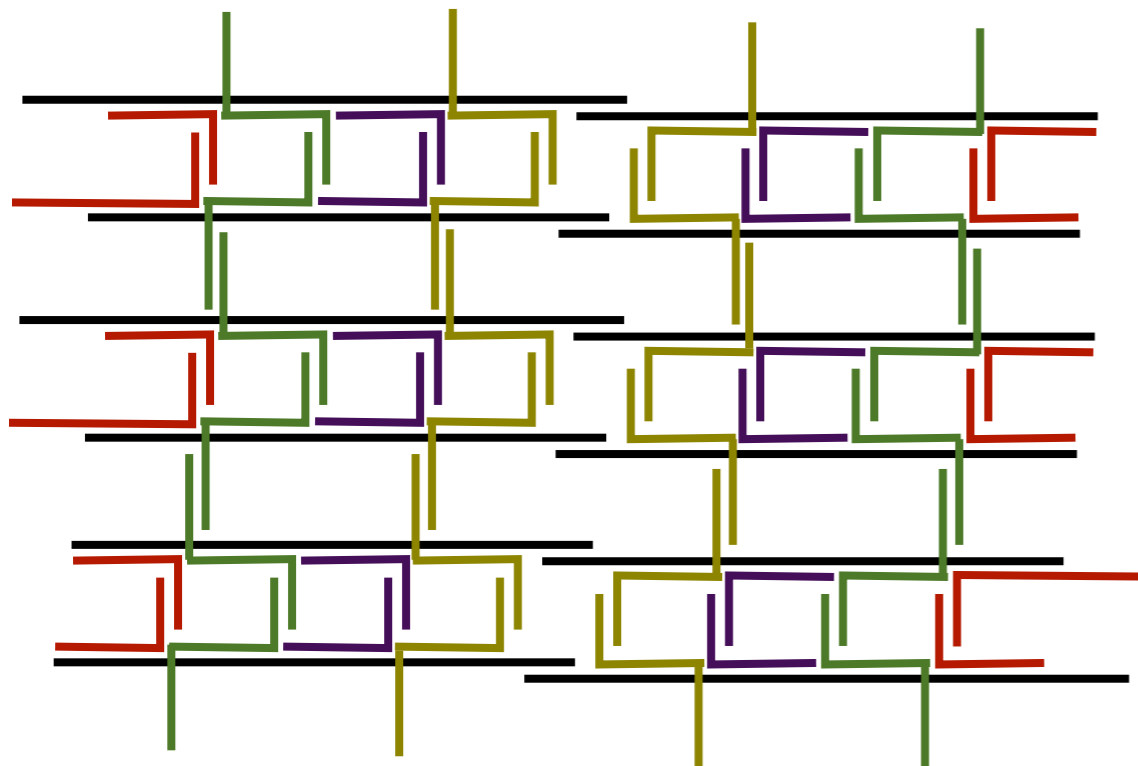
Kershner, R. J. et al. Placement and orientation of individual DNA shapes on lithographically patterned surfaces. *Nature Nanotechnol* 4, 557-561 (2009).



# Programmed Assembly

## “DNA Walkers”

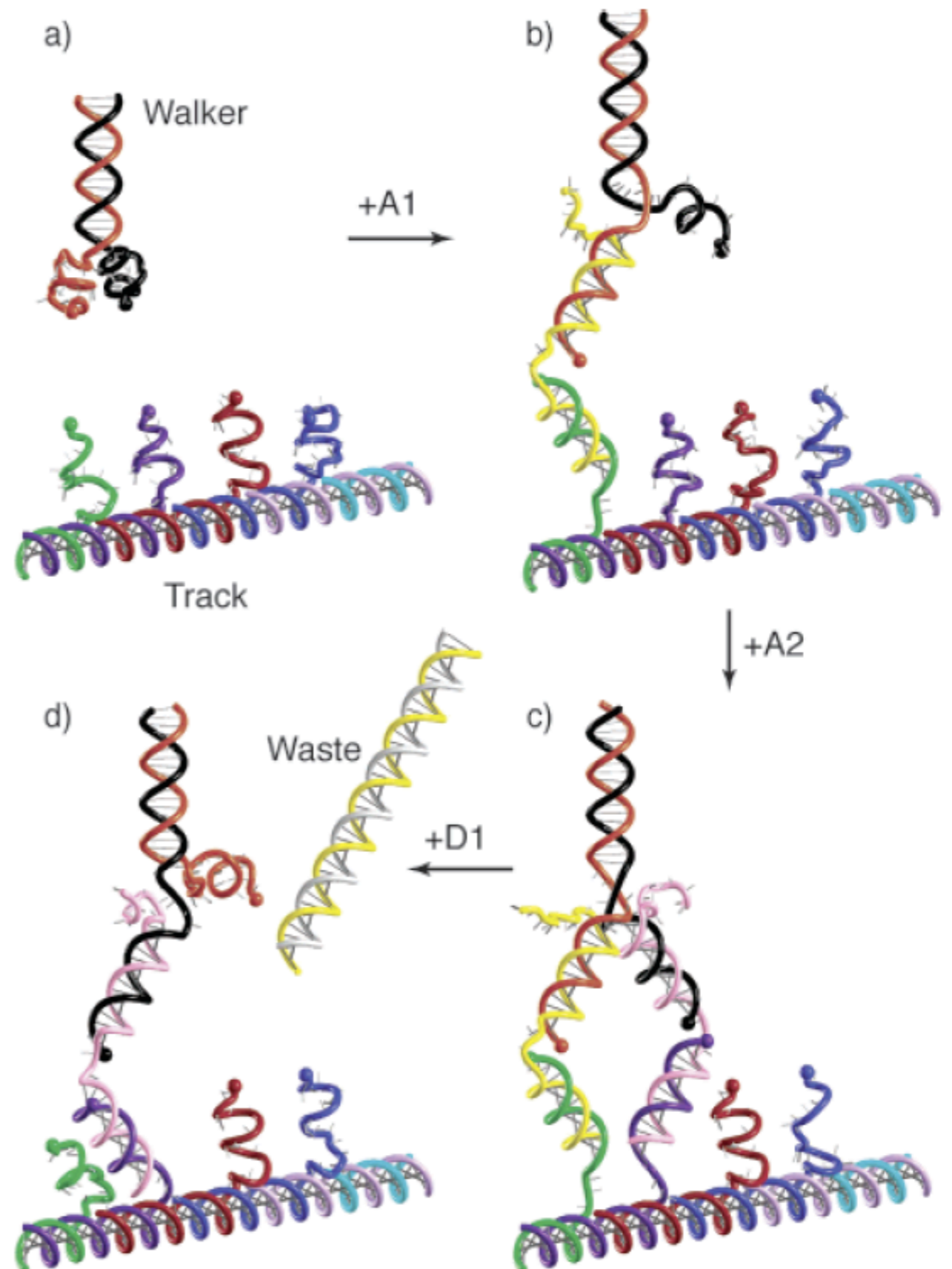
Shin, J. S. & Pierce, N. A. A synthetic DNA walker for molecular transport.  
J Am Chem Soc 126, 10834-10835 (2004)



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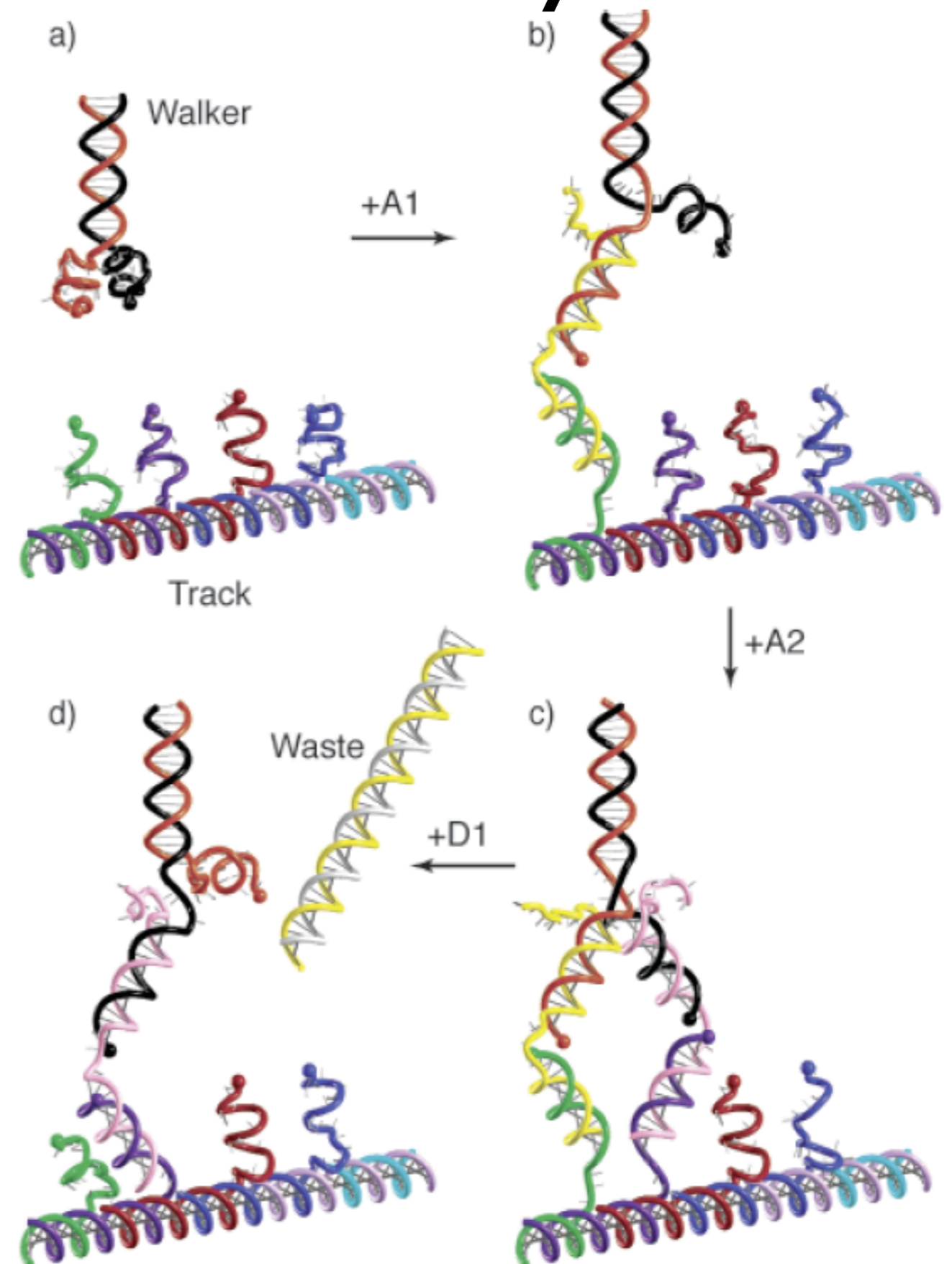
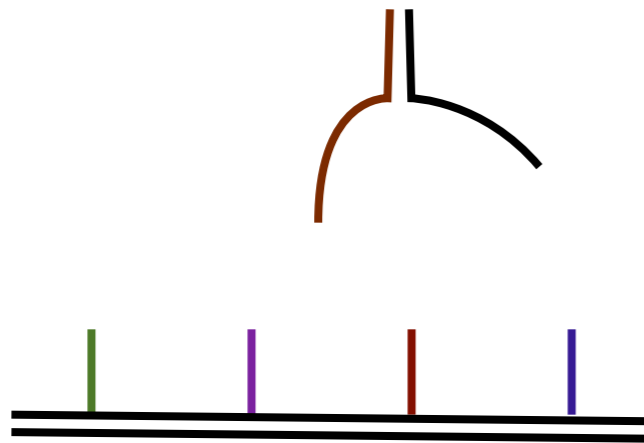
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Shin, J. S. & Pierce, N. A. A synthetic DNA walker for molecular transport. J Am Chem Soc 126, 10834-10835 (2004)



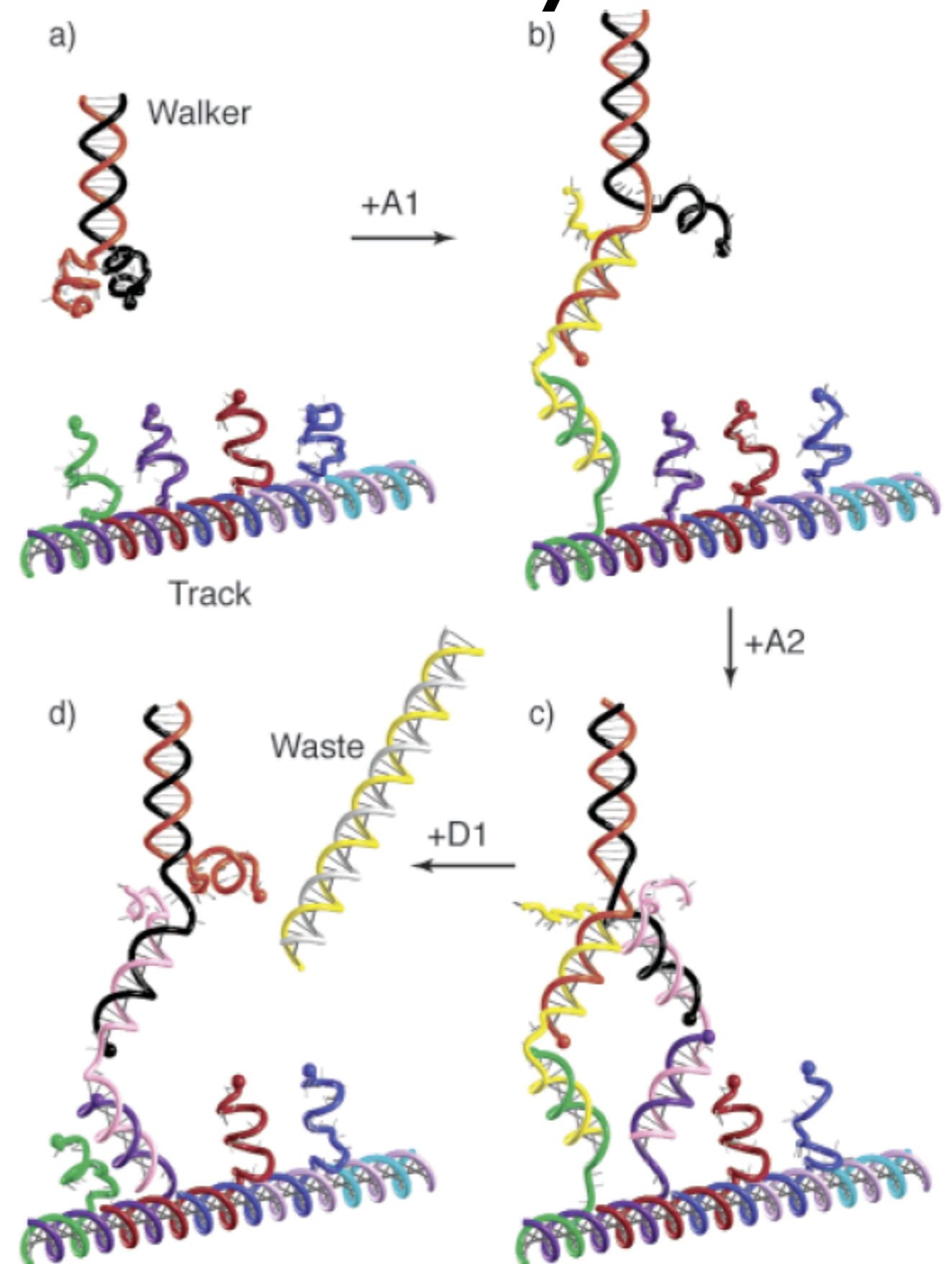
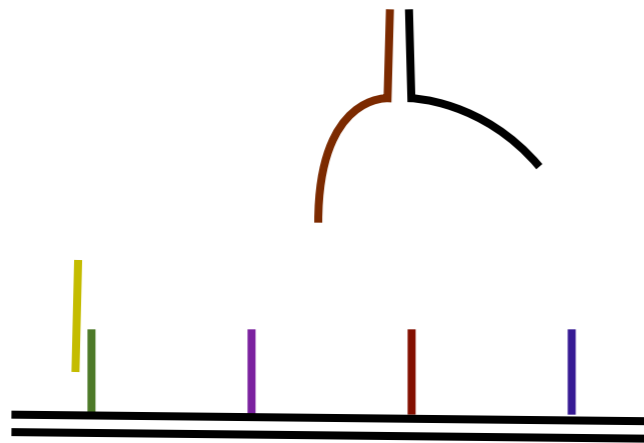
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“DNA Walkers”



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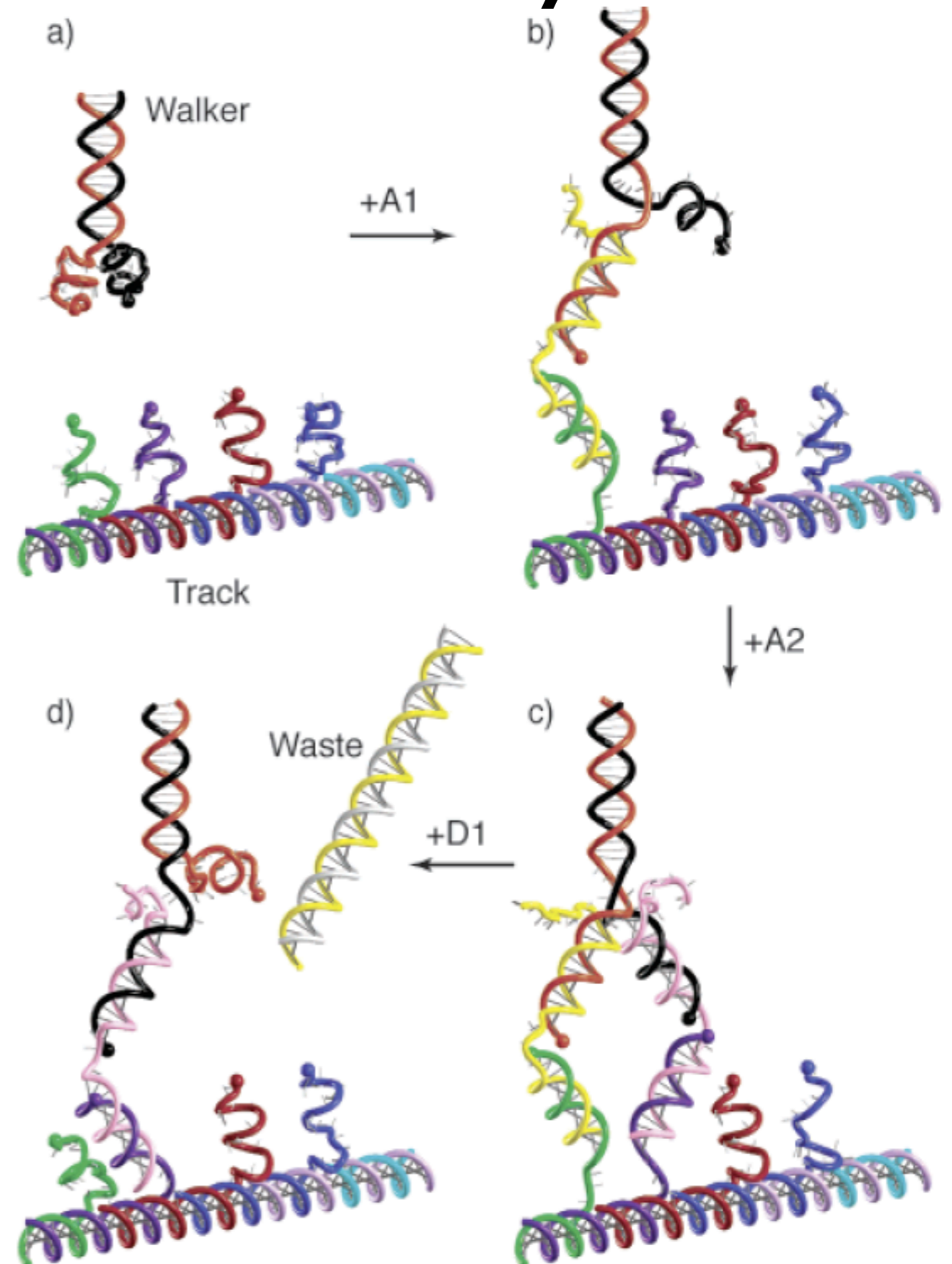
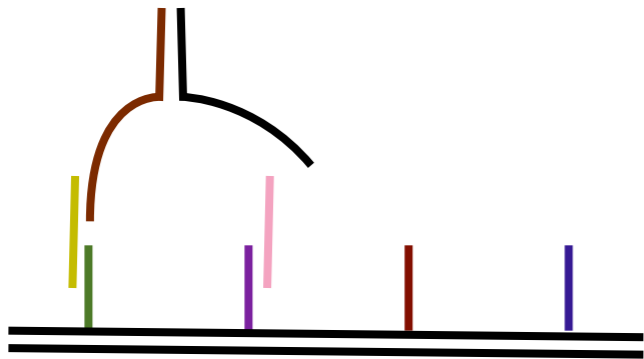
“DNA Walkers”





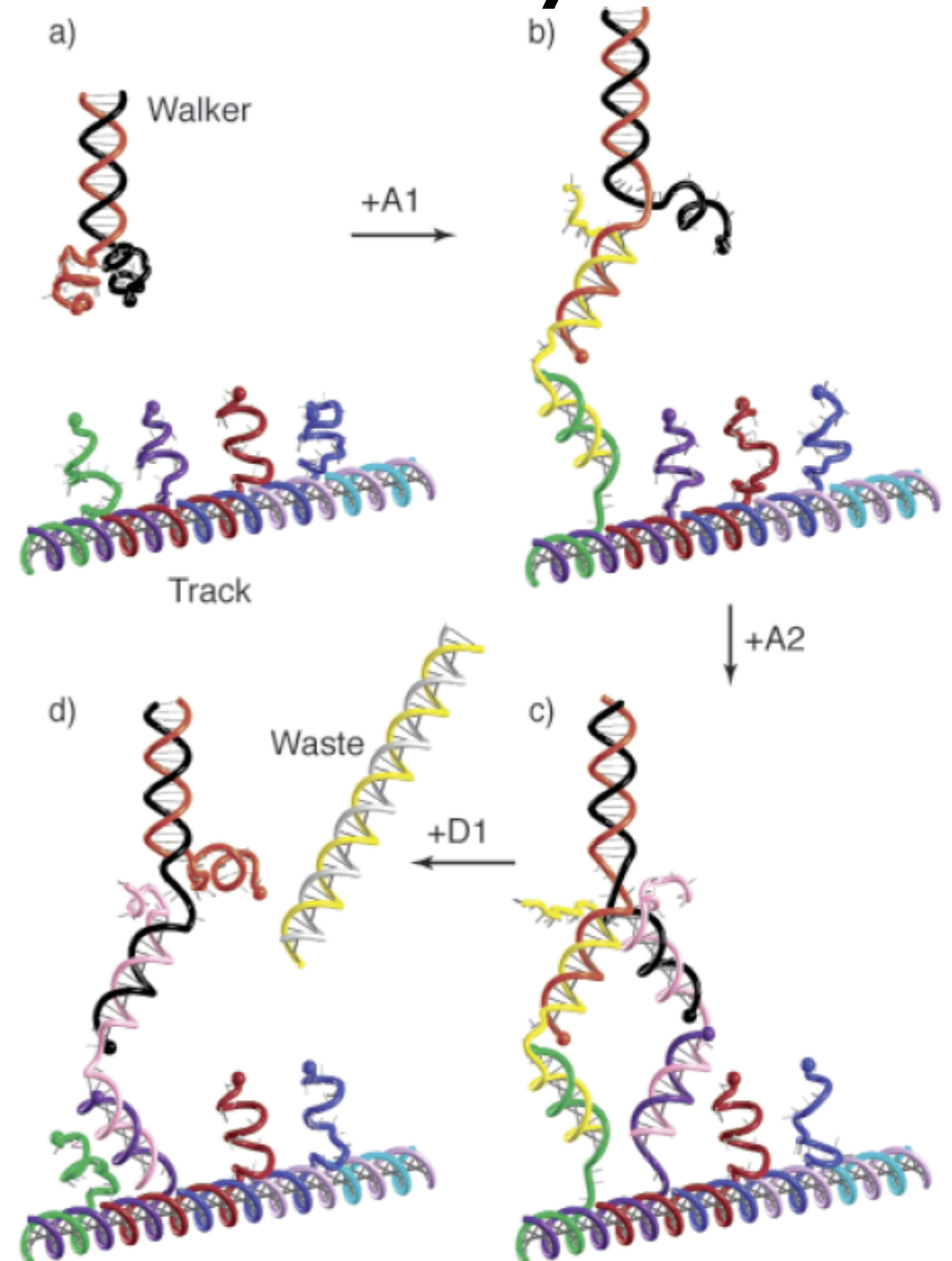
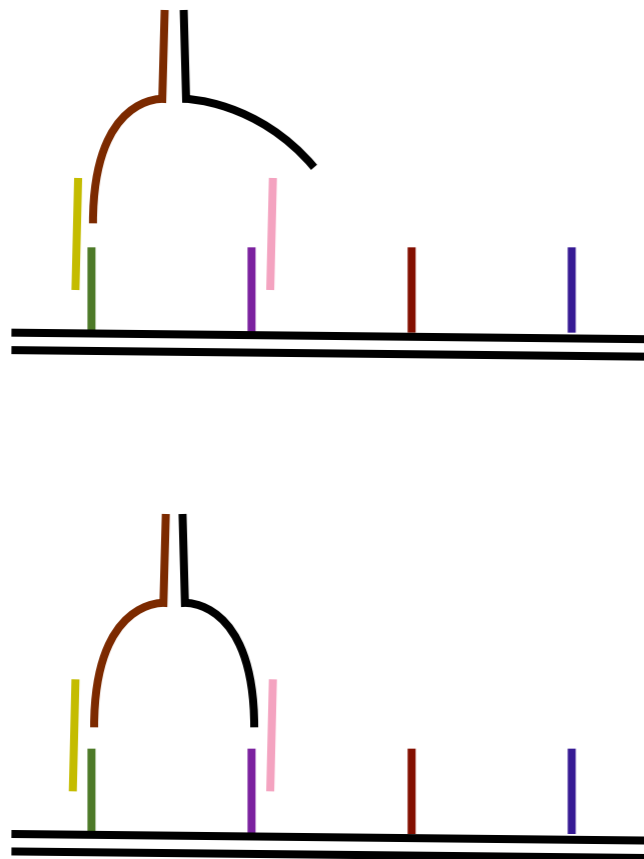
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“DNA Walkers”



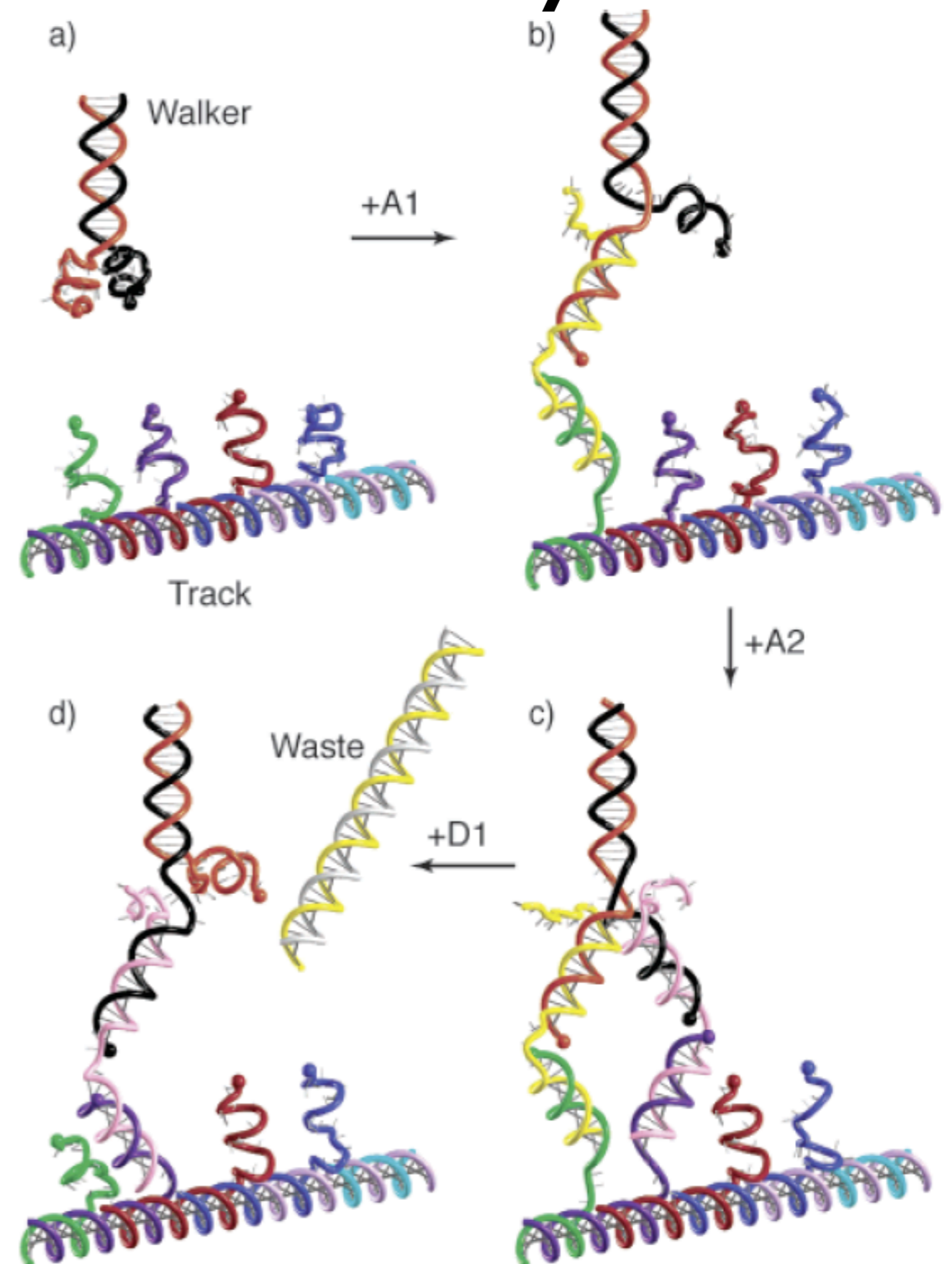
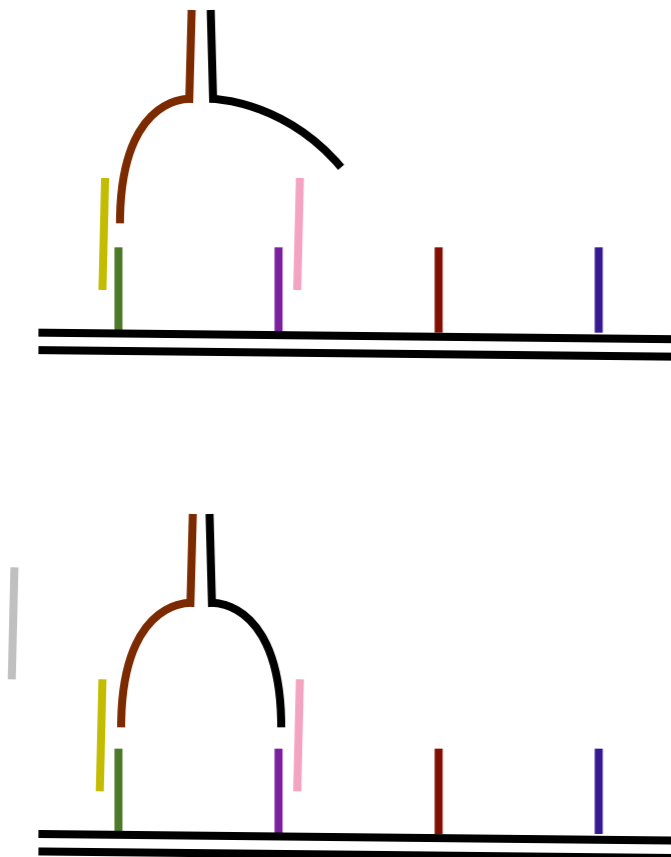
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“DNA Walkers”



# Programmed Assembly

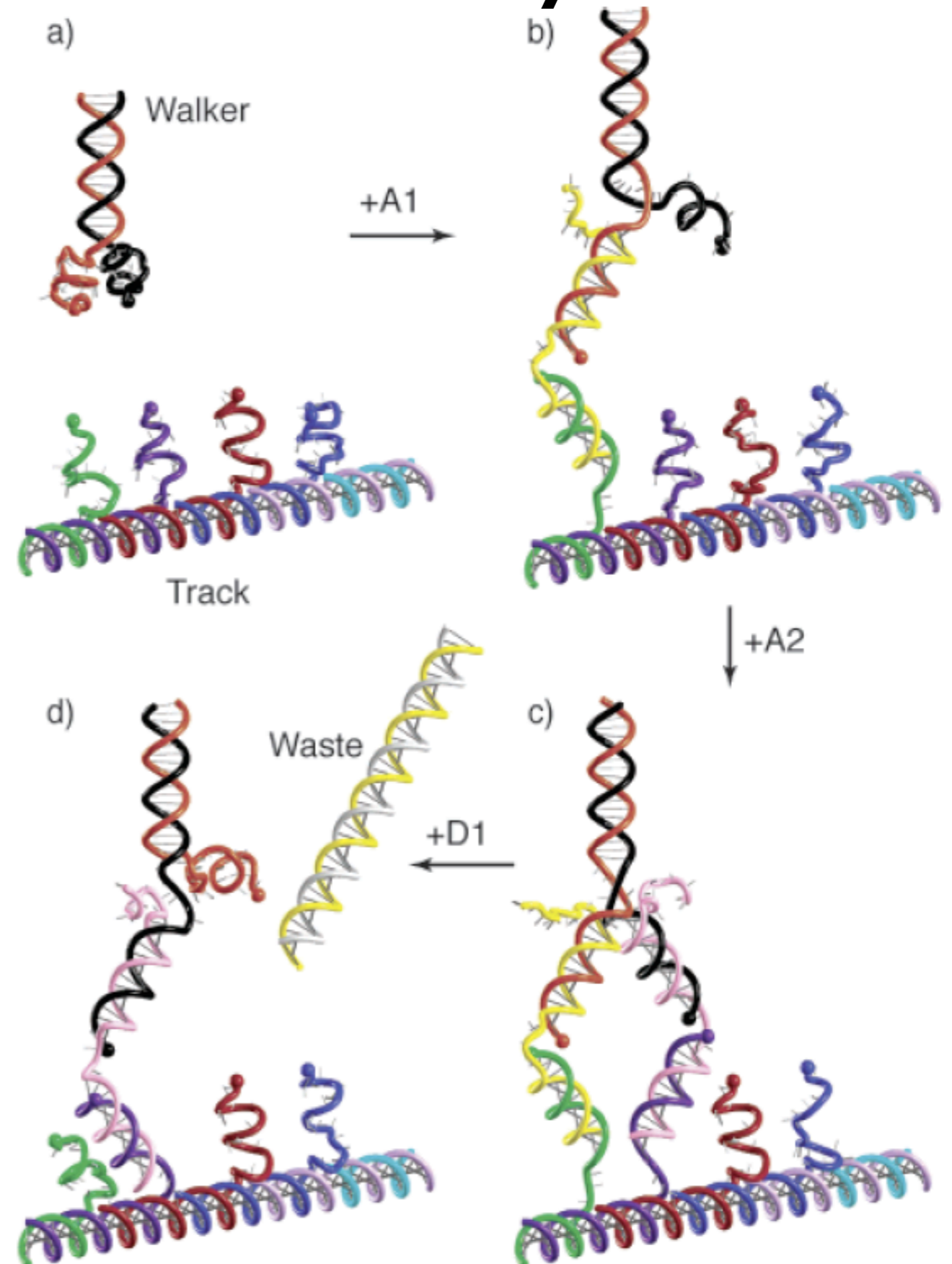
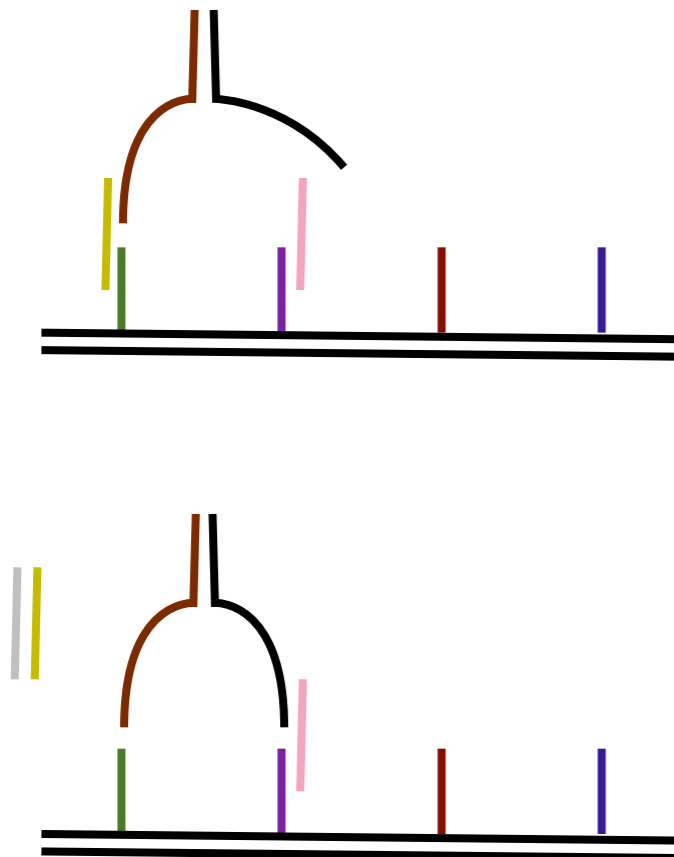
“DNA Walkers”





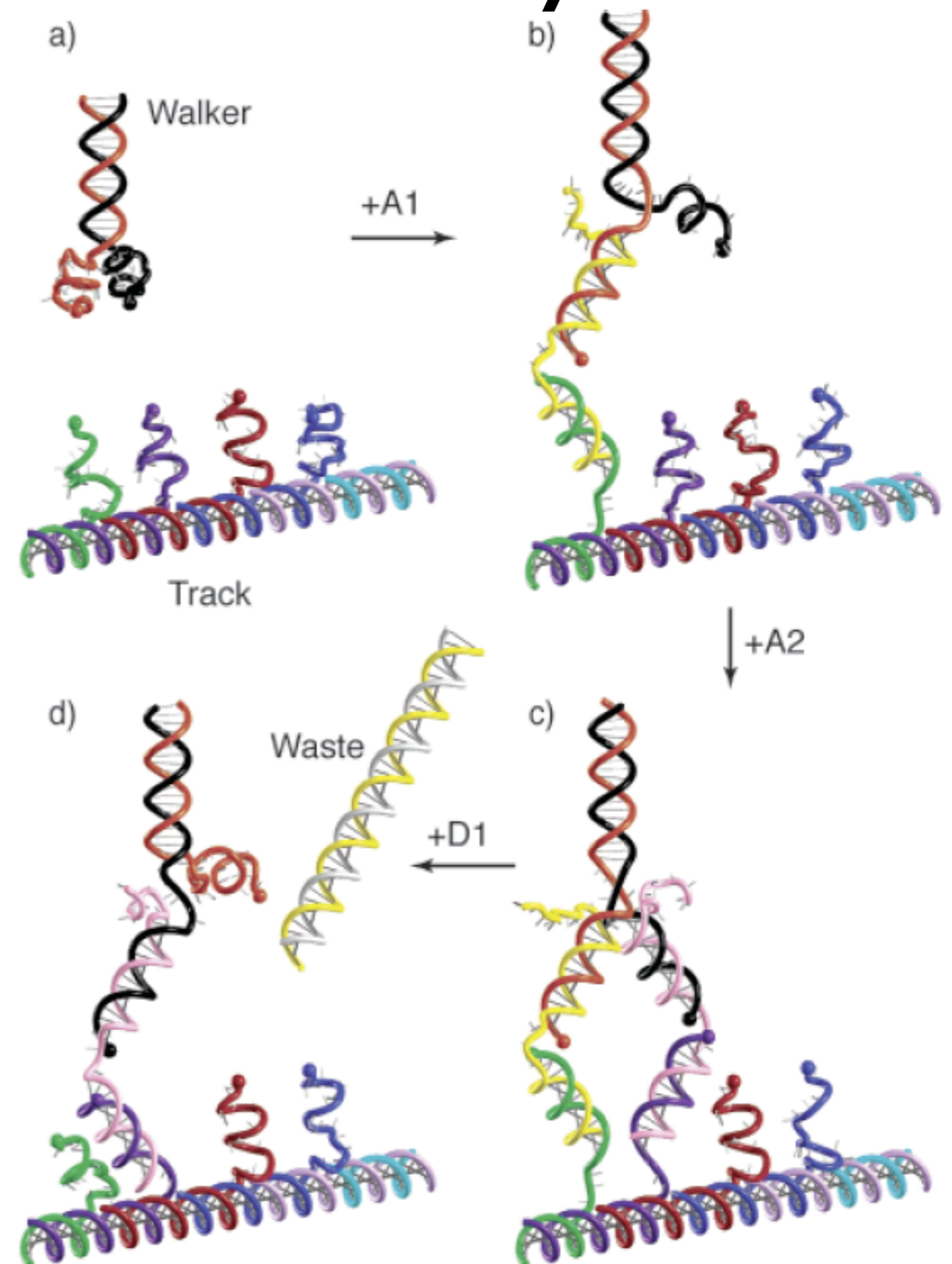
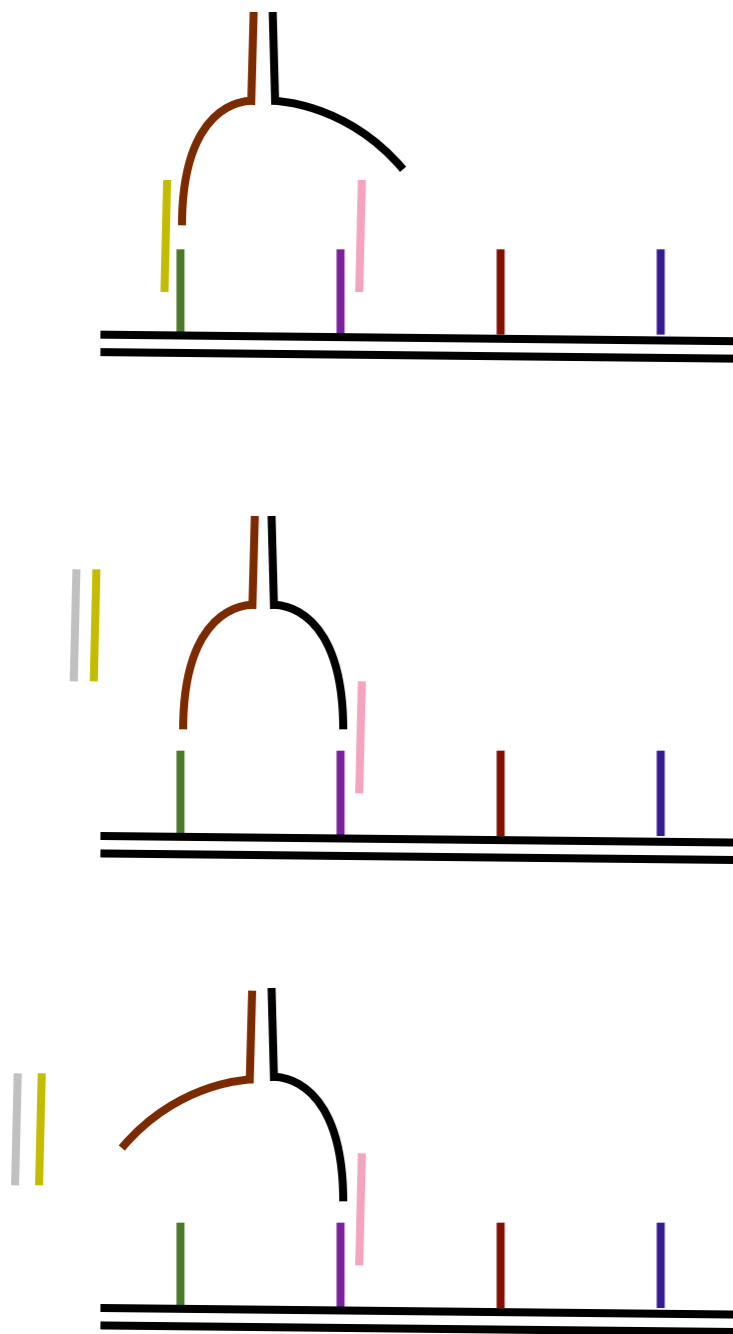
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“DNA Walkers”



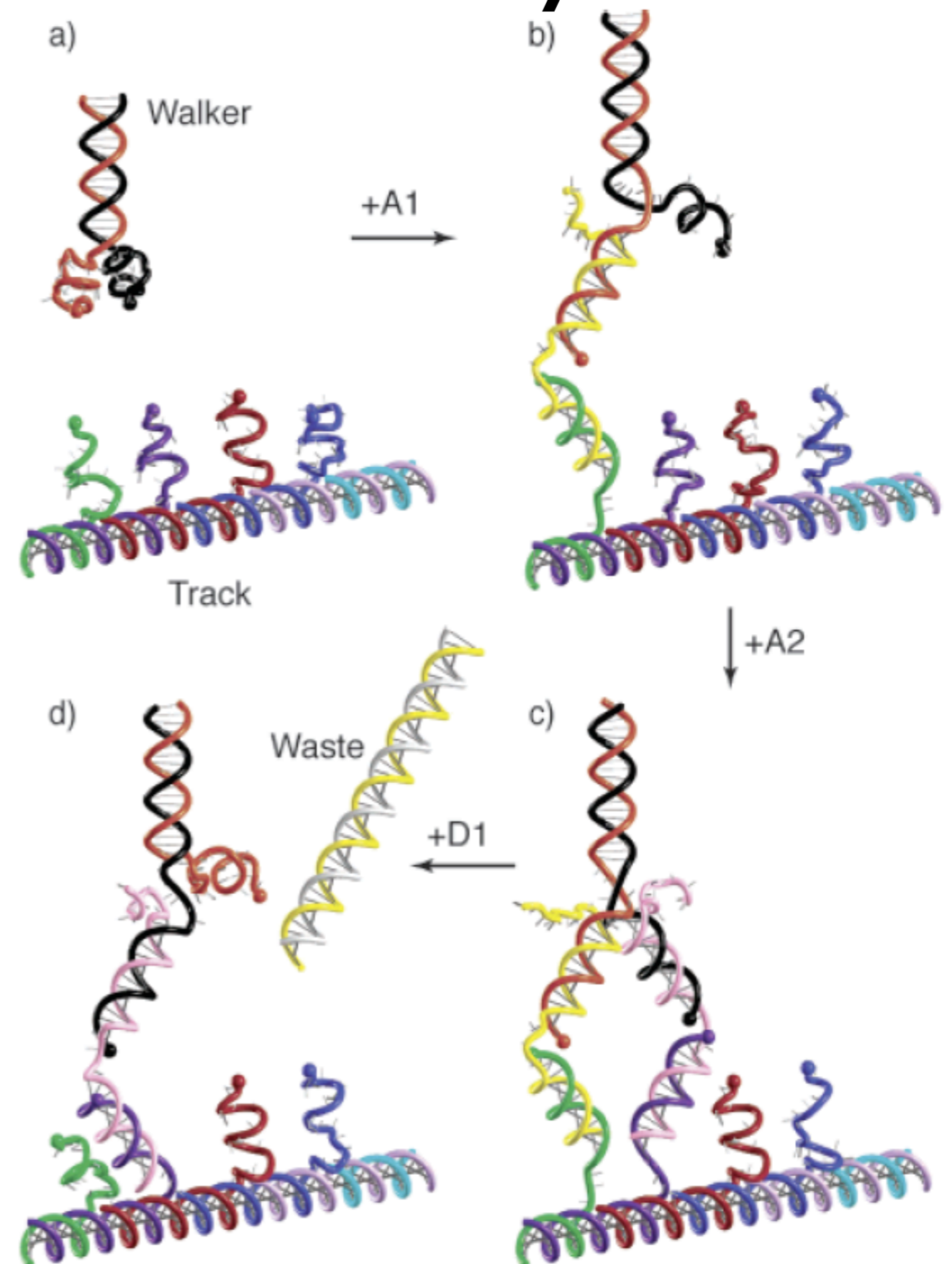
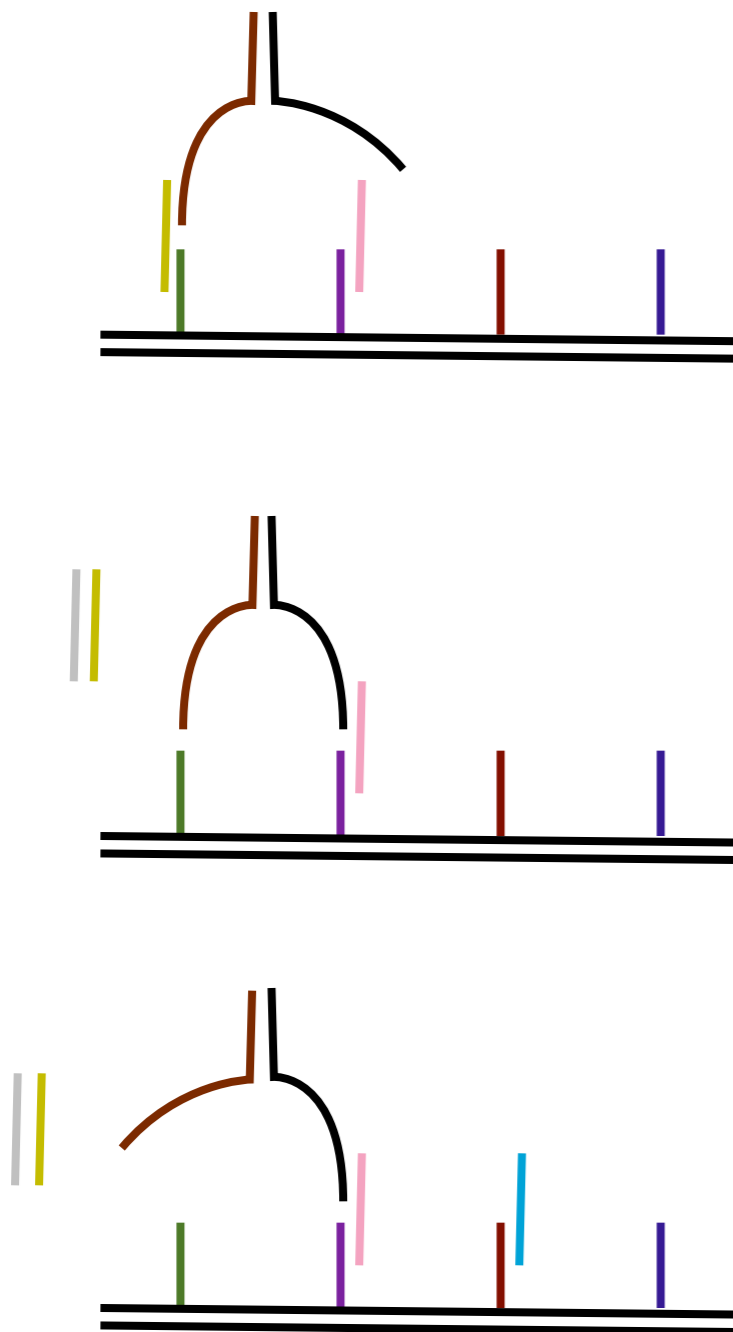
# Programmed Assembly

“DNA Walkers”



# Programmed Assembly

“DNA Walkers”



# Polymers

-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-

DNA

# Polymers

-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-

DNA

-S-M-T-G-T-W-R-Q-E-Q-D-N-P-F-H-I-L-V-A-C-K-Y-S-T-

Protein

# Polymers

-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-

DNA

Why is DNA a *unique* polymer?

-S-M-T-G-T-W-R-Q-E-Q-D-N-P-F-H-I-L-V-A-C-K-Y-S-T-

Protein

# Polymers

-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-

DNA

Why is DNA a *unique* polymer?

DNA is *self encoding*

-S-M-T-G-T-W-R-Q-E-Q-D-N-P-F-H-I-L-V-A-C-K-Y-S-T-

Protein

# Polymerase

5'-G-T-A-G-T

3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'

A key component of all of biology

A key tool for chemists



# Polymerase

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'

A key component of all of biology

A key tool for chemists

# Polymerase

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'

A key component of all of biology

A key tool for chemists

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T

# Polymerase

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'

A key component of all of biology

A key tool for chemists

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
G-C-A-G-T-T-5'

# Polymerase

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'

A key component of all of biology

A key tool for chemists

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-5'

# Polymerase

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'

A key component of all of biology

A key tool for chemists

5'-G-T-A-G-T-C-G-A-T-A-C-T-C-G-T-C-A-A-C-T  
C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-5'

# Polymerase

3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'

C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-5'

# Polymerase

3'-G-A-C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-G-A-5'  
C-A-T-C-A-G-C-T-A-T-G-A-G-C-A-G-T-T-5'

# Polymerase Chain Reaction (PCR)





# Polymerase Chain Reaction (PCR)

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**Heat**

# Polymerase Chain Reaction (PCR)



**Heat**

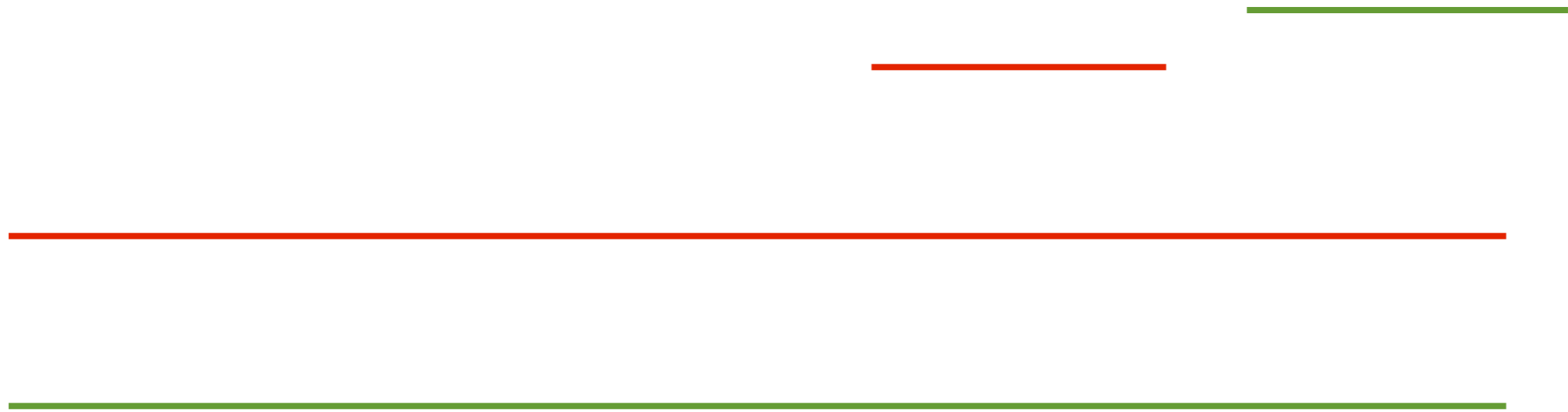
# Polymerase Chain Reaction (PCR)

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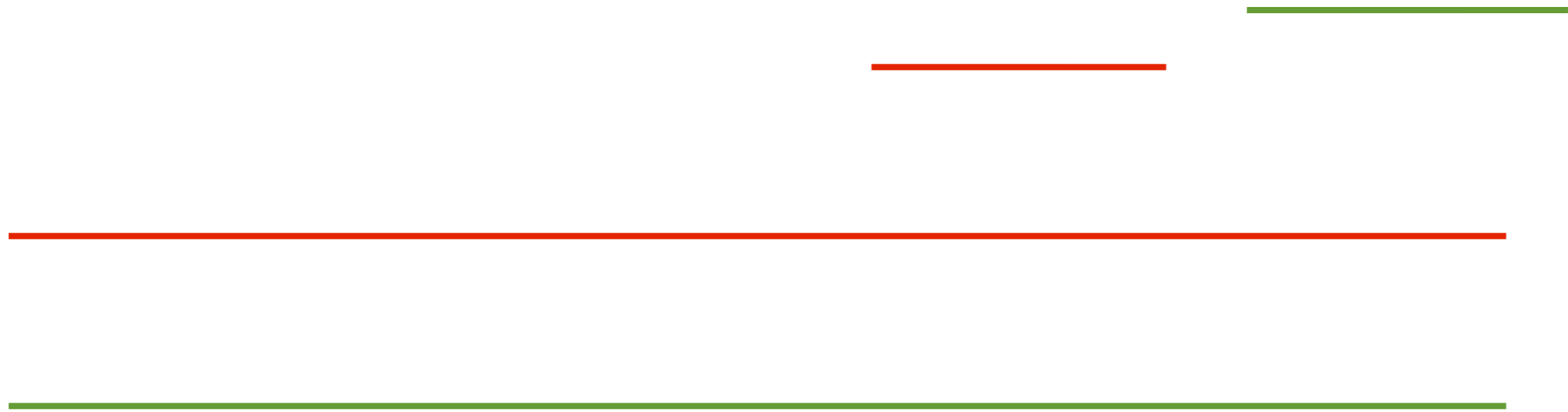
**Heat**

# Polymerase Chain Reaction (PCR)



**Heat**

# Polymerase Chain Reaction (PCR)



# Polymerase Chain Reaction (PCR)



# Polymerase Chain Reaction (PCR)



DNA polymerase

**Cool**

# Polymerase Chain Reaction (PCR)



DNA polymerase

**Cool**



# Polymerase Chain Reaction (PCR)



**Heat**

# Polymerase Chain Reaction (PCR)

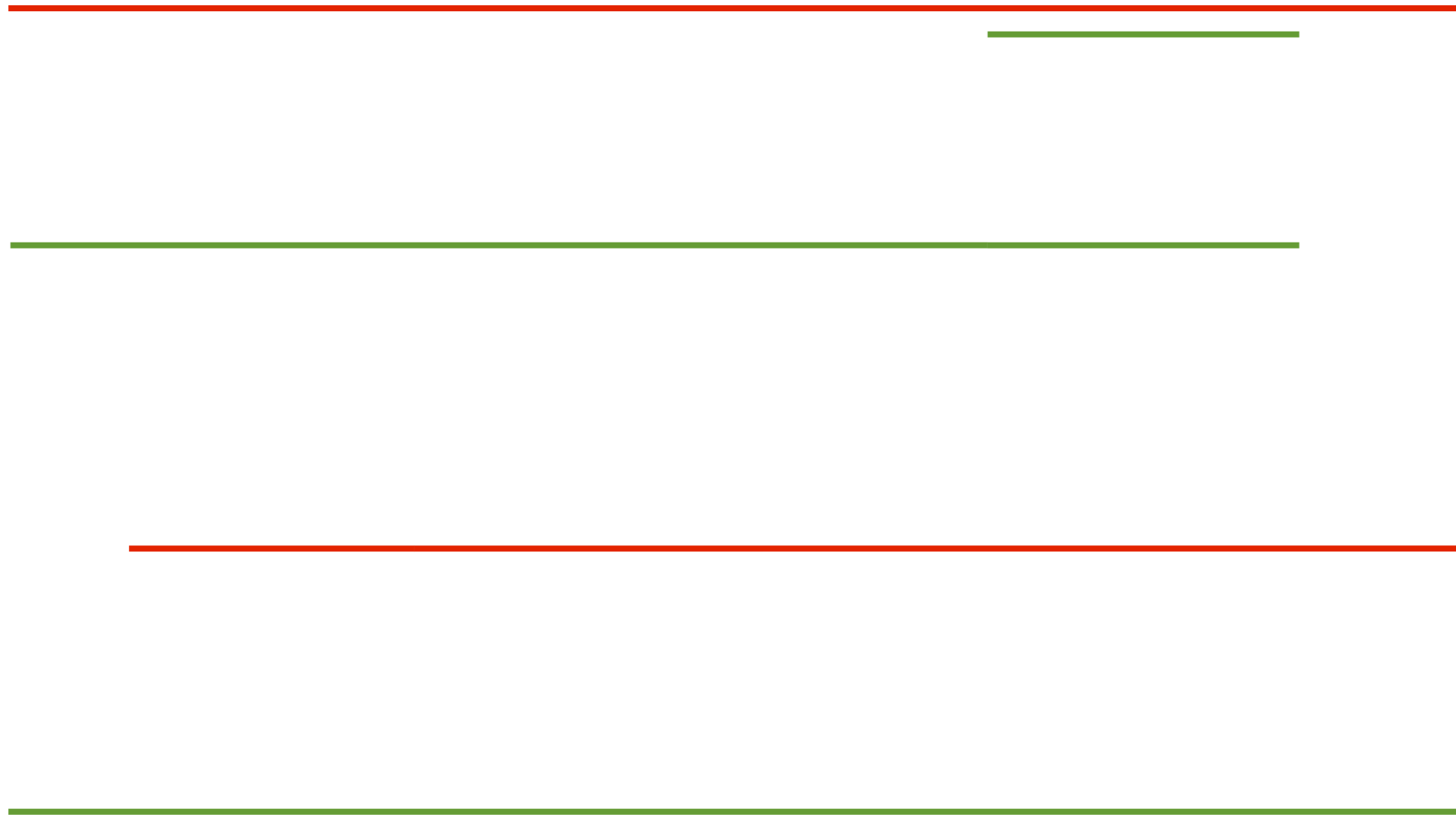
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# Polymerase Chain Reaction (PCR)



# Polymerase Chain Reaction (PCR)

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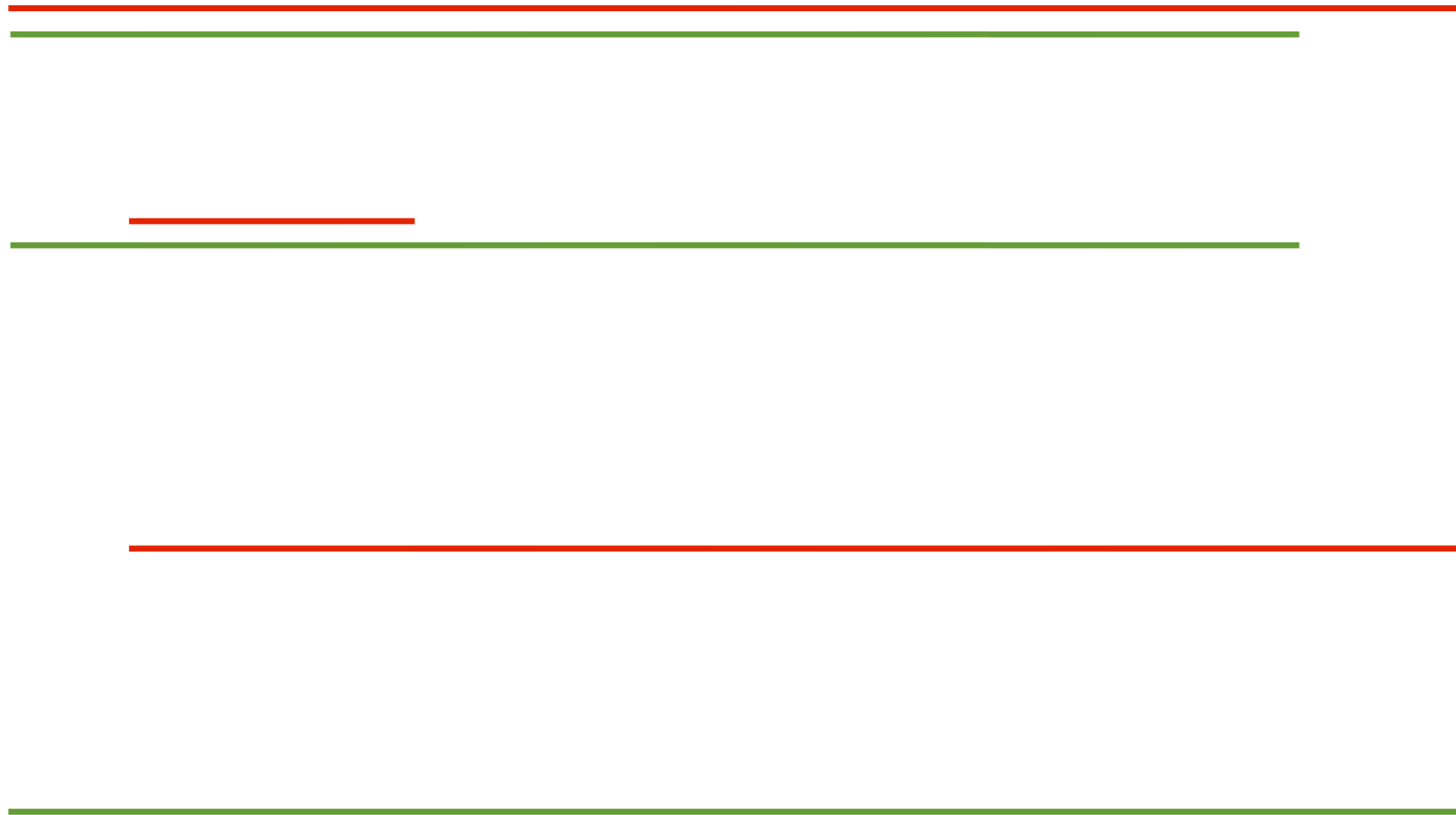
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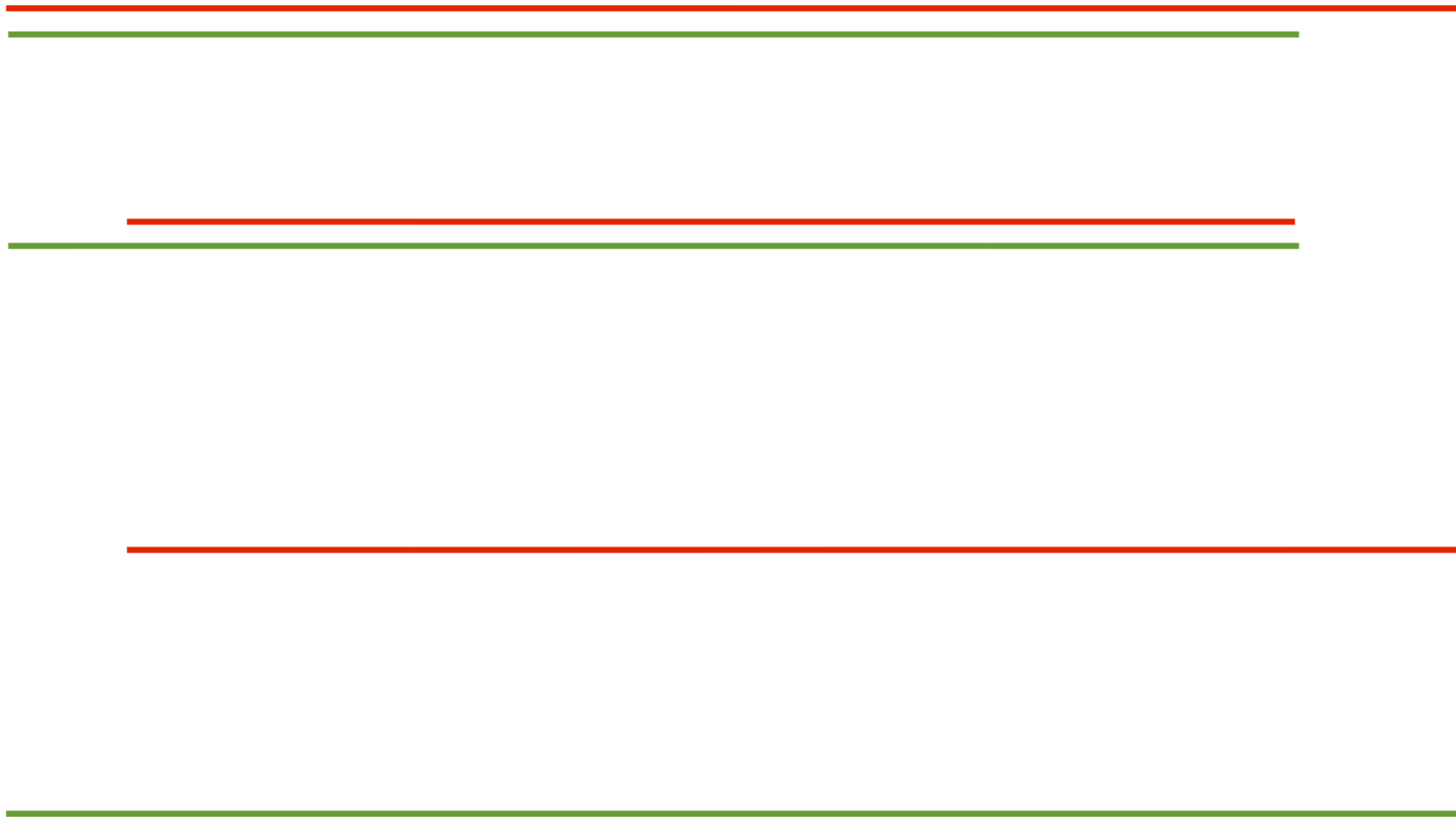
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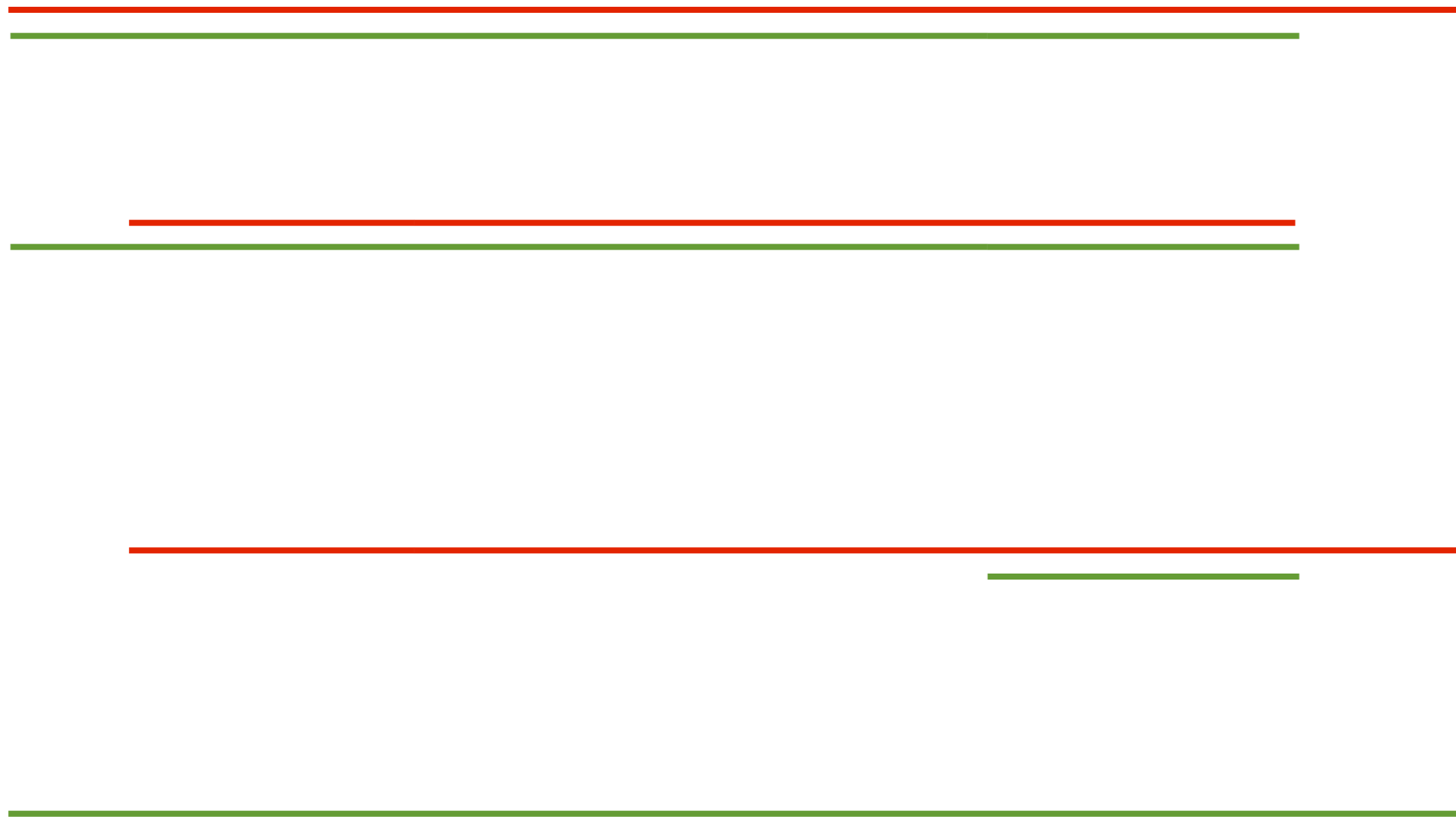
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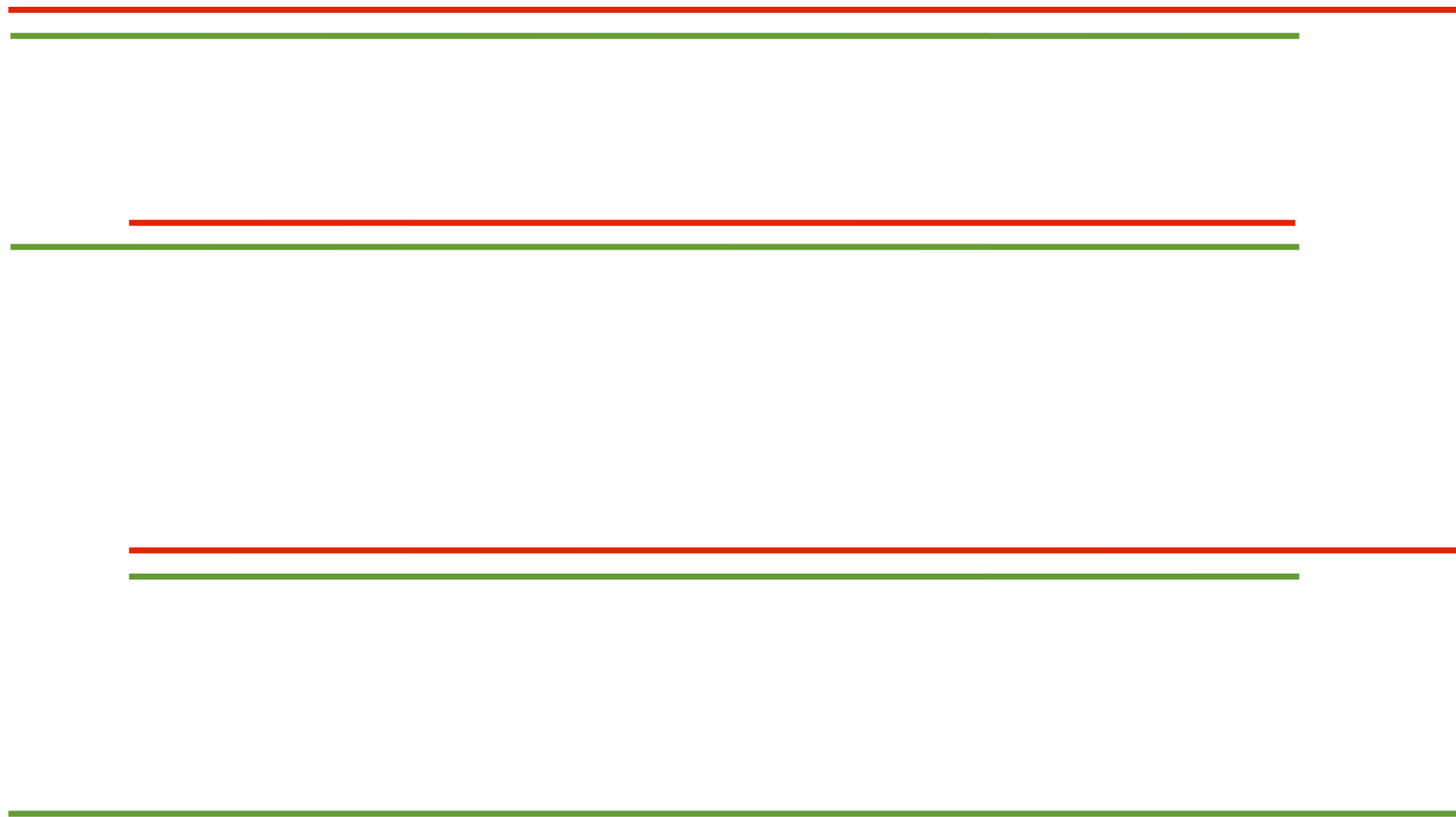
# Polymerase Chain Reaction (PCR)



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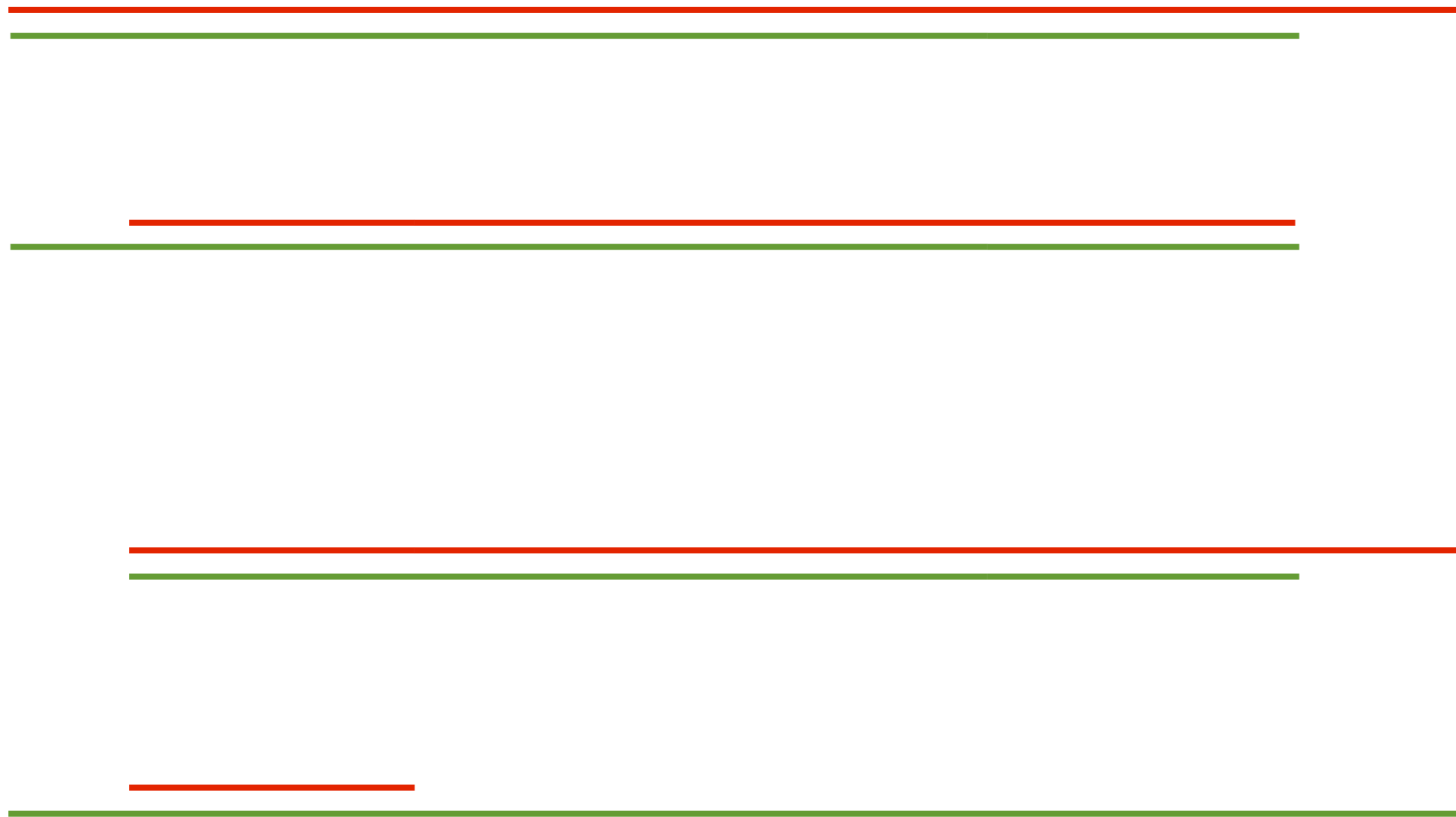


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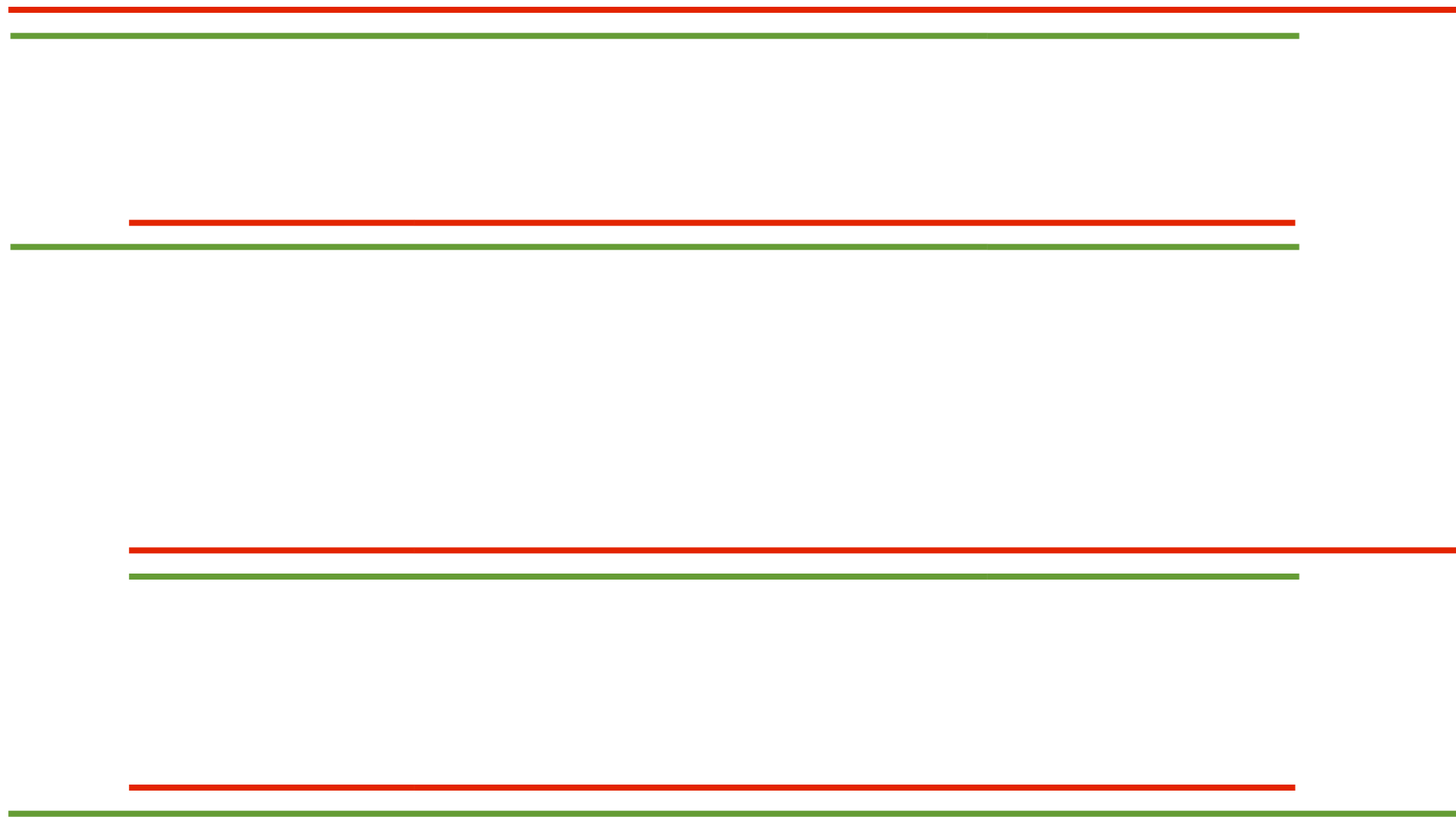




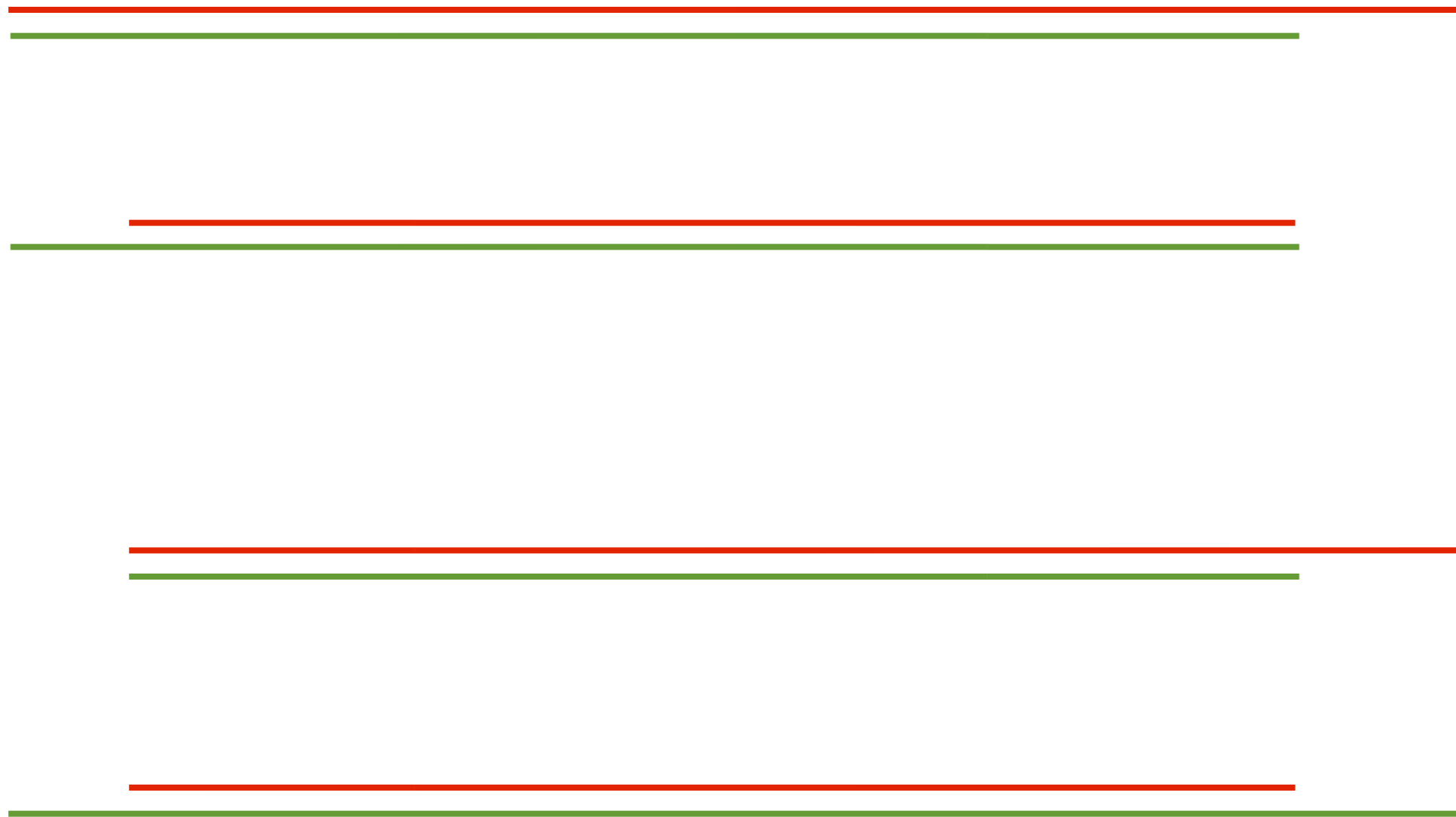
# Polymerase Chain Reaction (PCR)



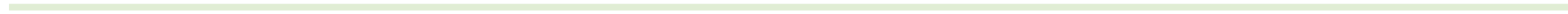
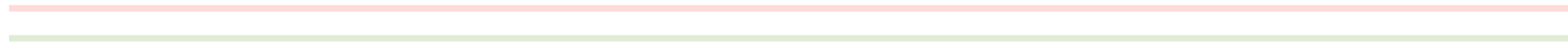
# Polymerase Chain Reaction (PCR)



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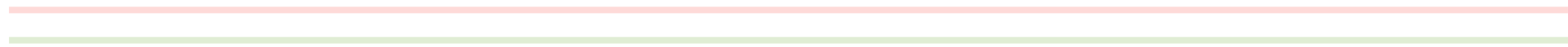


# Polymerase Chain Reaction (PCR)



# Polymerase Chain Reaction (PCR)

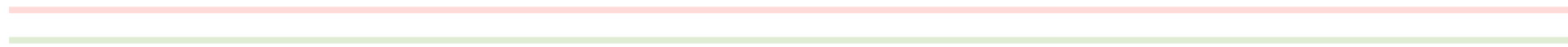
1 round = 2X



# Polymerase Chain Reaction (PCR)

1 round = 2X

2 rounds = 4X

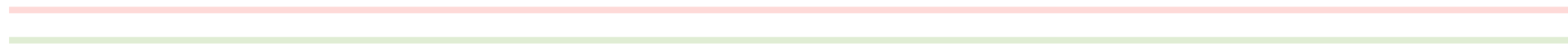


# Polymerase Chain Reaction (PCR)

1 round = 2X

2 rounds = 4X

3 rounds = 8X



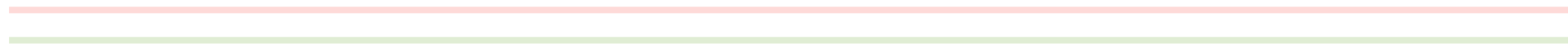
# Polymerase Chain Reaction (PCR)

1 round = 2X

2 rounds = 4X

3 rounds = 8X

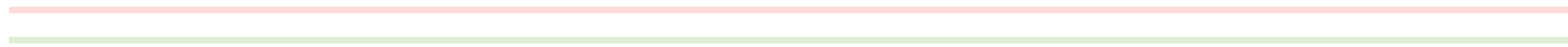
20 rounds = 1,048,576X





# Polymerase Chain Reaction (PCR)

Amplifies selectively the region between the primers



1 round = 2X

2 rounds = 4X

3 rounds = 8X

20 rounds = 1,048,576X



**So far...**

# So far...

Very careful and precise *design*

# So far...

Very careful and precise *design*

# Combinatorial Chemistry

# So far...

Very careful and precise *design*

# Combinatorial Chemistry

Facile synthesis of a large variety of molecules

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## Combinatorial Chemistry

Facile synthesis of a large variety of molecules

Then find which one has your desired properties

# So far...

Very careful and precise *design*

## Combinatorial Chemistry

Facile synthesis of a large variety of molecules

Then find which one has your desired properties

Screen  $\approx$ 100 member library - tedious

# Polymerase Chain Reaction (PCR)

GACTCAGACNNNNNNNNNCTGACGAATCCA

---

N = mixture of 1/4 G and 1/4 C and 1/4 T and 1/4 A



# Polymerase Chain Reaction (PCR)

GACTCAGACNNNNNNNNNCTGACGAATCCA

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N = mixture of 1/4 G and 1/4 C and 1/4 T and 1/4 A

# Polymerase Chain Reaction (PCR)

GACTCAGACNNNNNNNNNCTGACGAATCCA

CTGAGTCTGNNNNNNNNNGACTGCTTAGGT

N = mixture of 1/4 G and 1/4 C and 1/4 T and 1/4 A

# Polymerase Chain Reaction (PCR)

GACTCAGACNNNNNNNNNNCTGACGAATCCA

CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT

20 rounds = 1,048,576 total molecules

N = mixture of 1/4 G and 1/4 C and 1/4 T and 1/4 A

# Polymerase Chain Reaction (PCR)

GACTCAGACNNNNNNNNNNCTGACGAATCCA

CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT

20 rounds = 1,048,576 total molecules

4 things taken 9 ways  $4^9 = 262,144$  different molecules

N = mixture of 1/4 G and 1/4 C and 1/4 T and 1/4 A

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But who wants to purify the mixture and screen 262,144 molecules!?

N = mixture of 1/4 G and 1/4 C and 1/4 T and 1/4 A

# Polymerase Chain Reaction (PCR)

GACTCAGACNNNNNNNNNNCTGACGAATCCA

CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT

20 rounds = 1,048,576 total molecules

4 things taken 9 ways  $4^9 = 262,144$  different molecules

But who wants to purify the mixture and screen 262,144 molecules!?

Don't!

N = mixture of 1/4 G and 1/4 C and 1/4 T and 1/4 A



# SELEX

**S**ystematic **E**volution of **L**igands by **E**xponential Enrichment

GACTCAGACNNNNNNNNNCTGACGAATCCA  
CTGAGTCTGNNNNNNNNNGACTGCTTAGGT

# SELEX

Systematic **E**volution of **L**igands by **E**xponential Enrichment

GACTCAGACNNNNNNNNNCTGACGAATCCA  
CTGAGTCTGNNNNNNNNNGACTGCTTAGGT



# SELEX

Systematic Evolution of Ligands by Exponential Enrichment

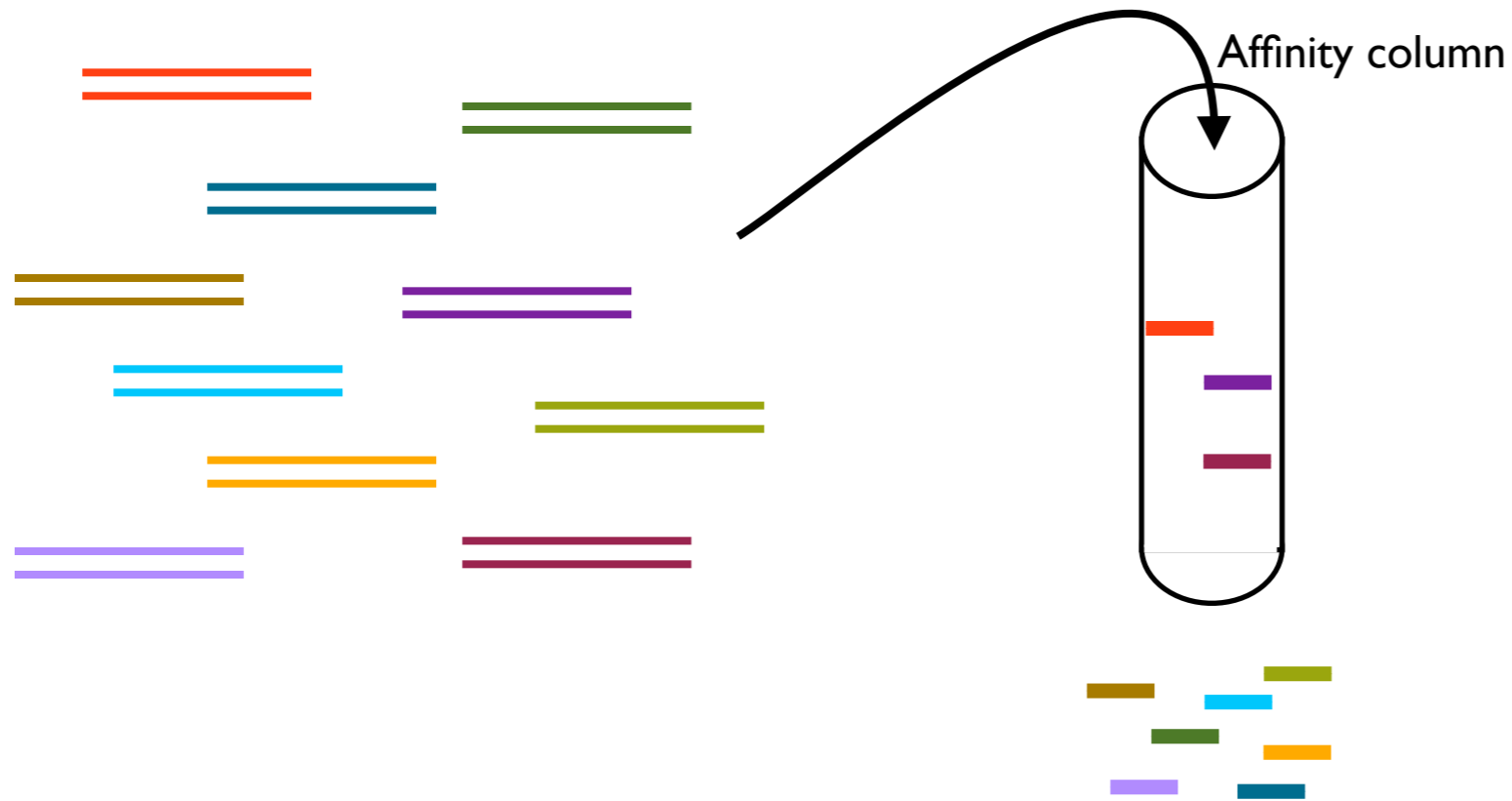
GACTCAGACNNNNNNNNNNCTGACGAATCCA  
CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT



# SELEX

Systematic Evolution of Ligands by Exponential Enrichment

GACTCAGACNNNNNNNNNNCTGACGAATCCA  
CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT



# SELEX

Systematic Evolution of Ligands by Exponential Enrichment

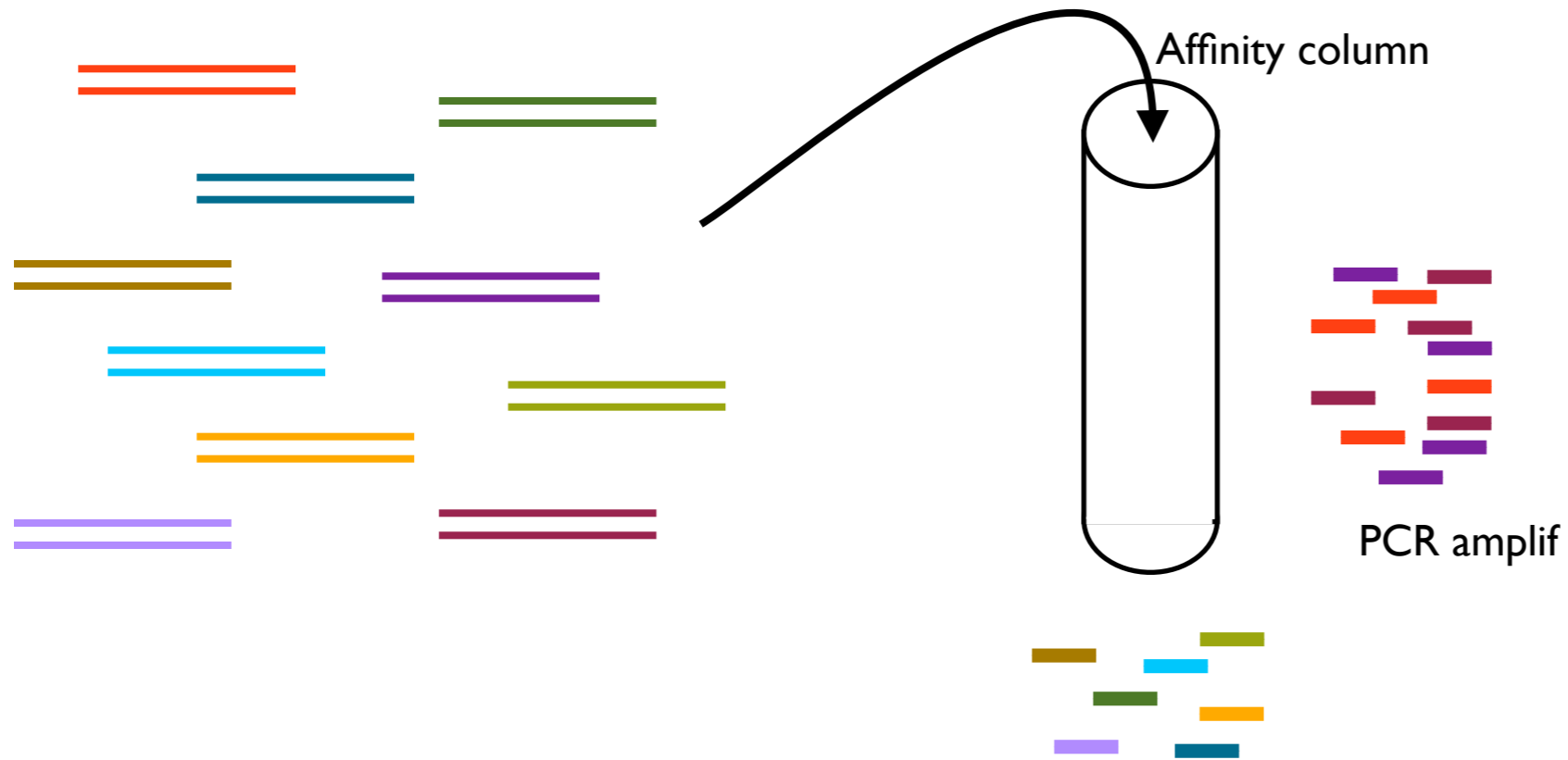
GACTCAGACNNNNNNNNNCTGACGAATCCA  
CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT



# SELEX

Systematic Evolution of Ligands by Exponential Enrichment

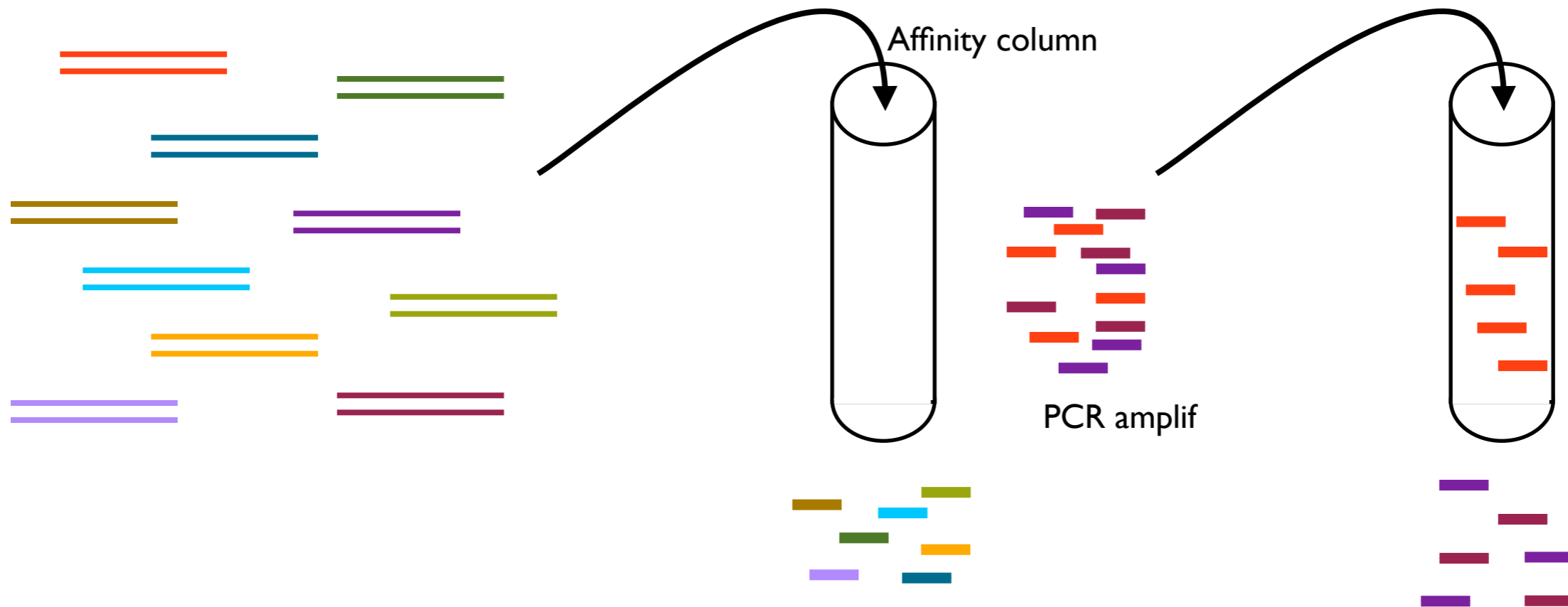
GACTCAGACNNNNNNNNNNCTGACGAATCCA  
CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT



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Systematic Evolution of Ligands by Exponential Enrichment

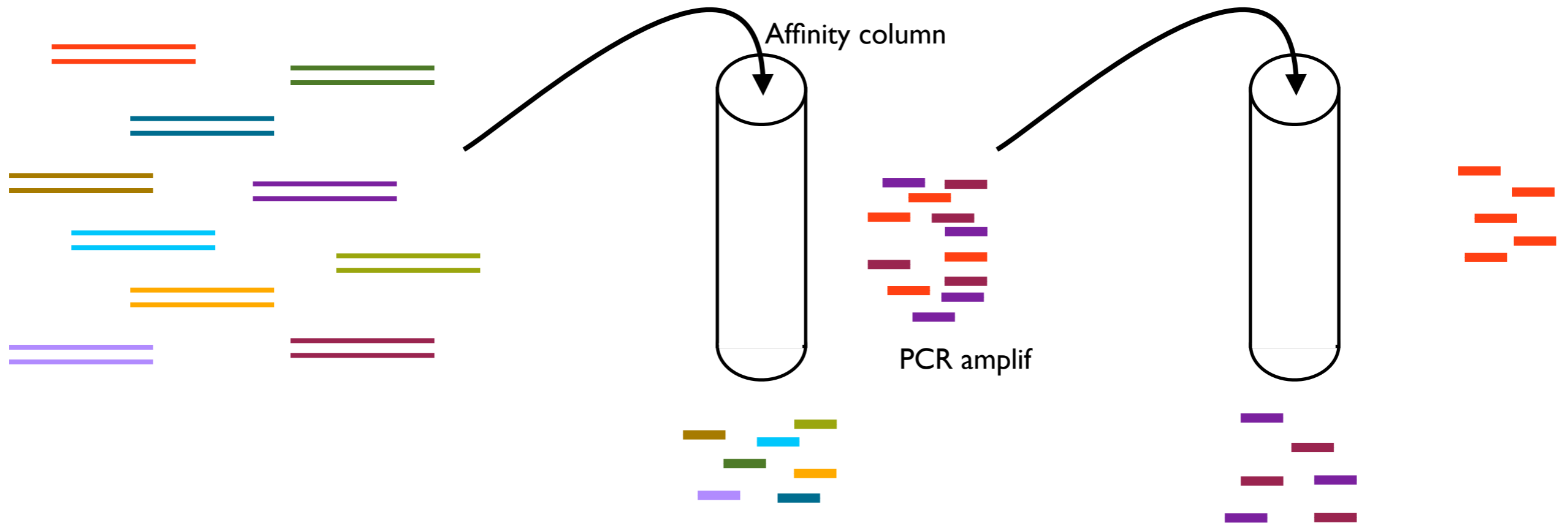
GACTCAGACNNNNNNNNNNCTGACGAATCCA  
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GACTCAGACNNNNNNNNNNCTGACGAATCCA  
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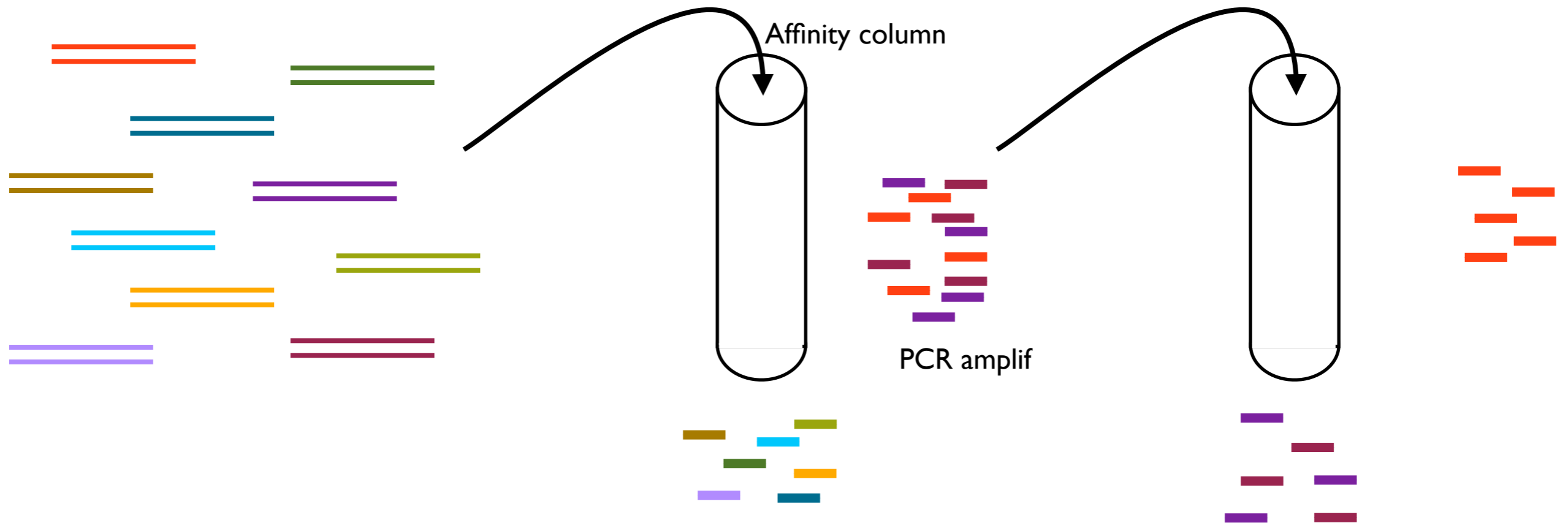




# SELEX

Systematic Evolution of Ligands by Exponential Enrichment

GACTCAGACNNNNNNNNNNCTGACGAATCCA  
CTGAGTCTGNNNNNNNNNNGACTGCTTAGGT



Can PCR-prepare dsDNA, ssDNA, or ssRNA

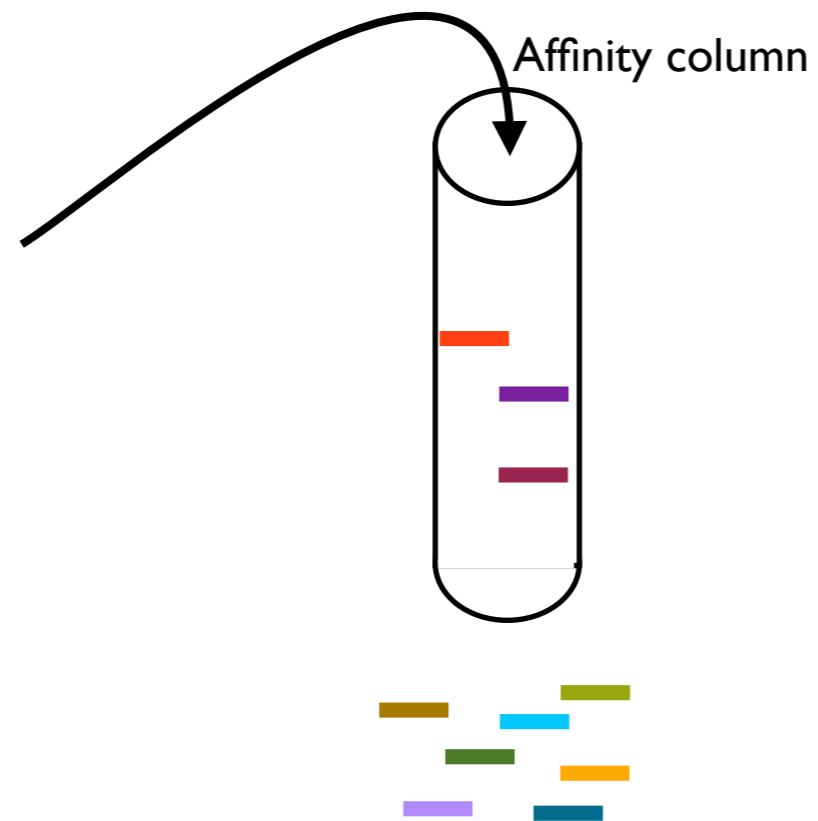
**Goal: a ssDNA that binds flavin**

# Goal: a ssDNA that binds flavin

Use an affinity column with covalently tethered flavin

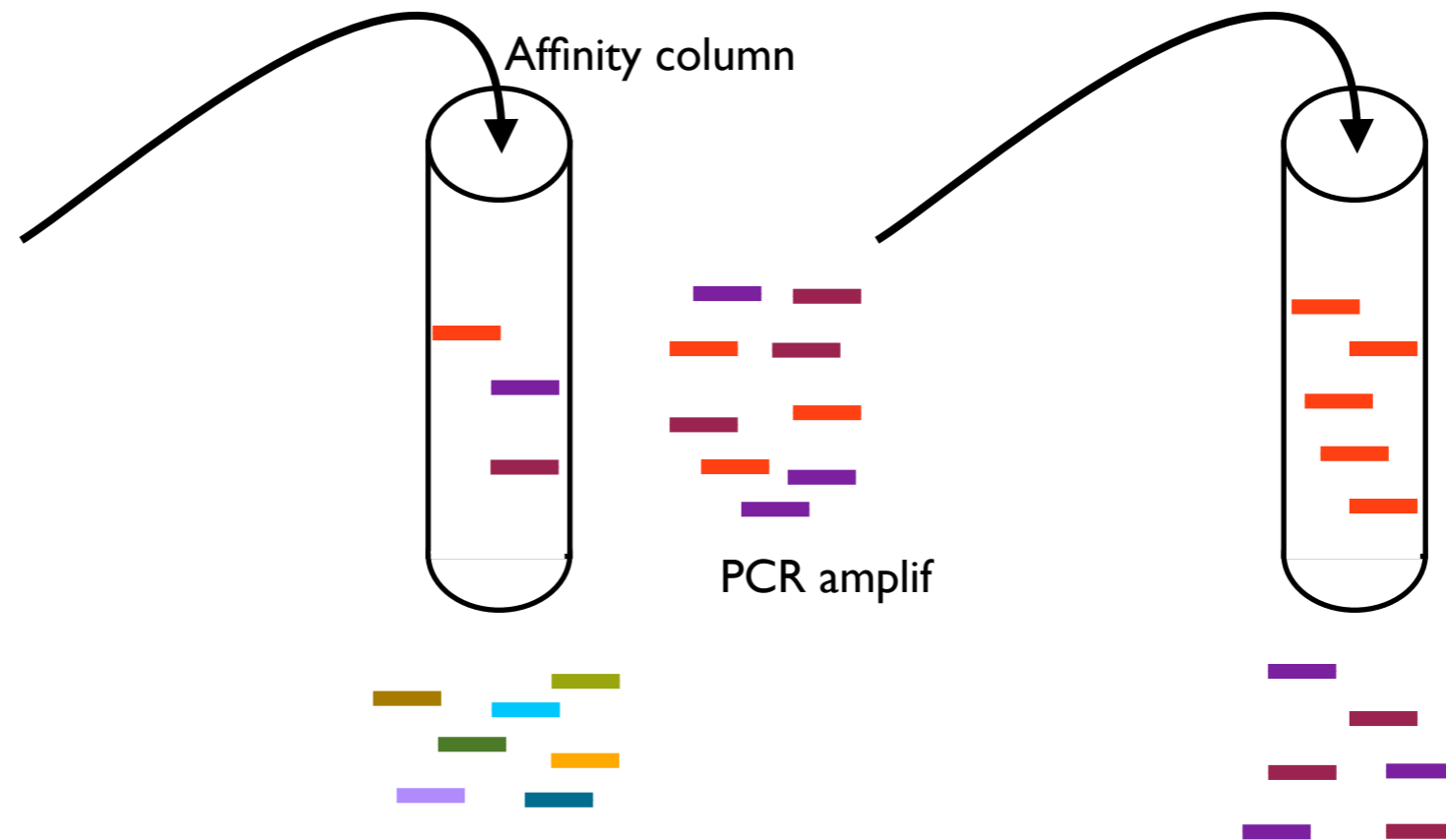
# Goal: a ssDNA that binds flavin

Use an affinity column with covalently tethered flavin



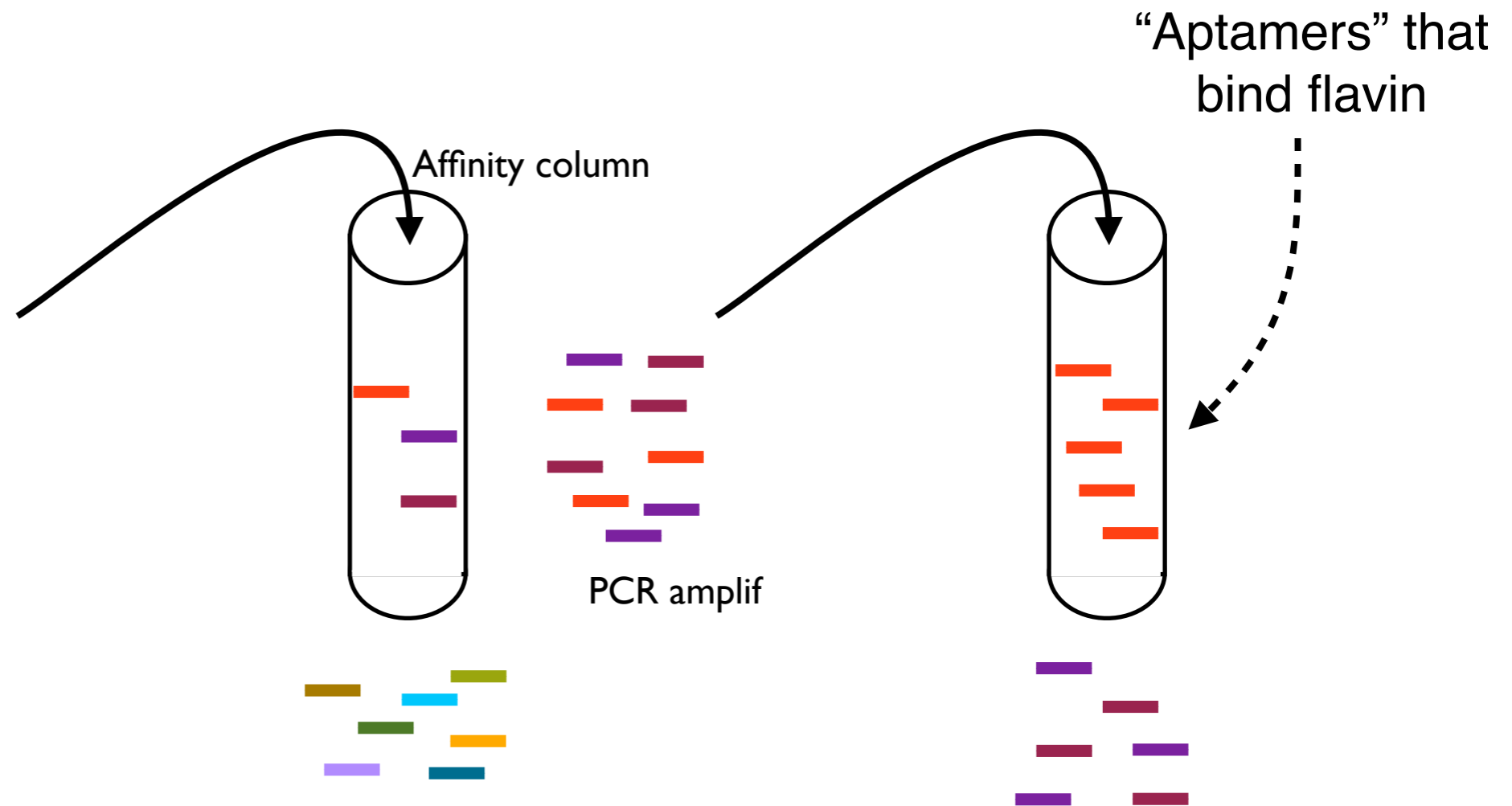
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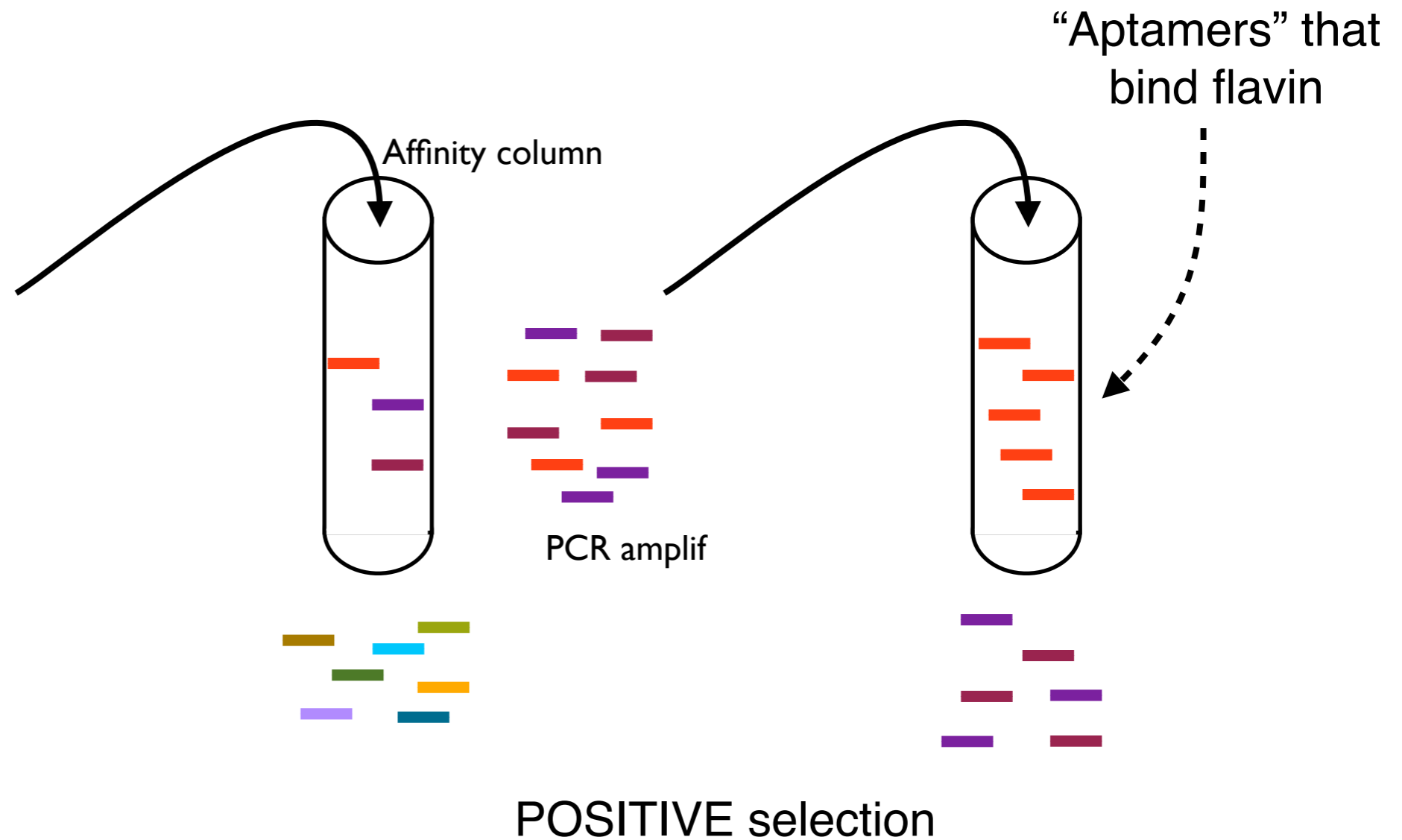
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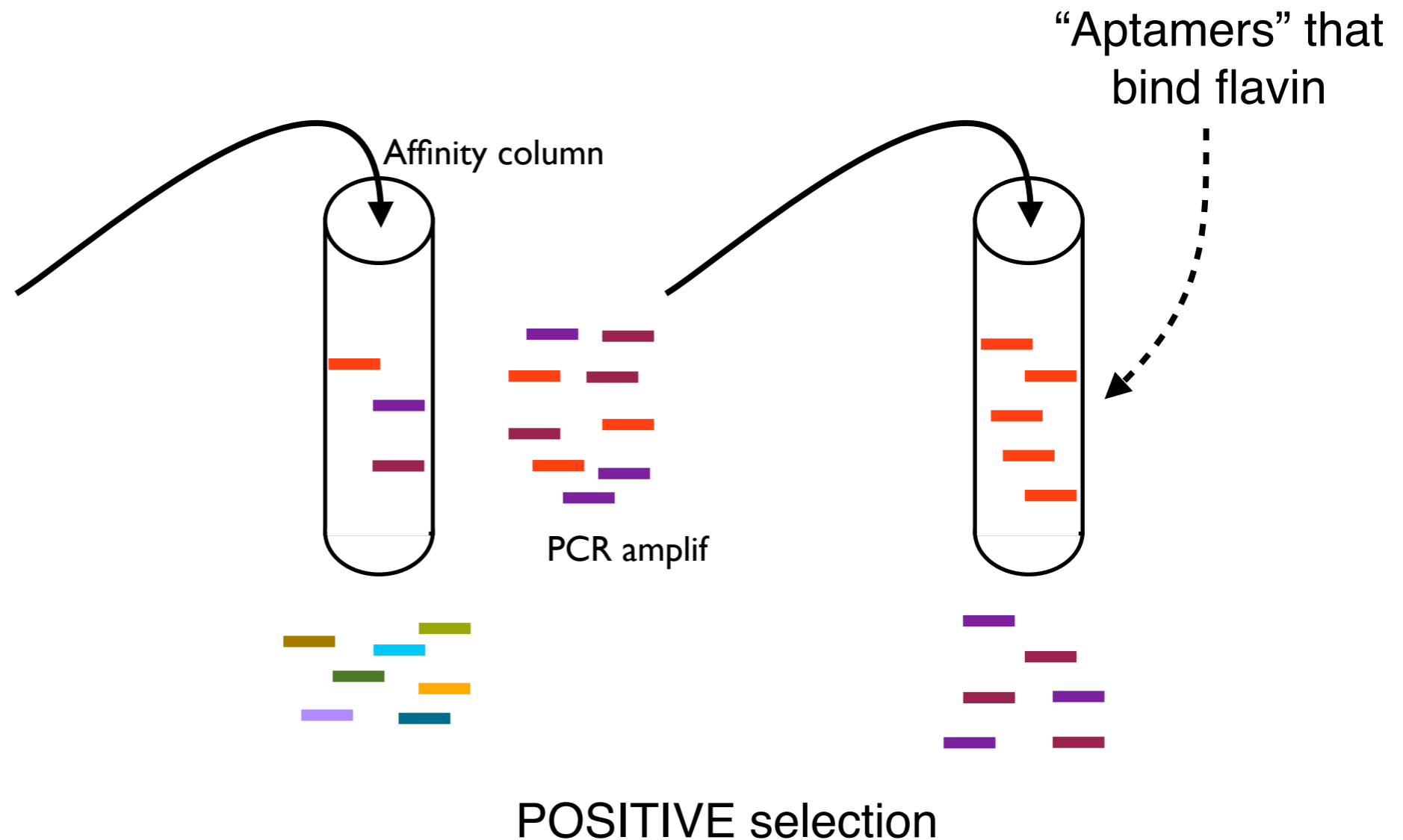
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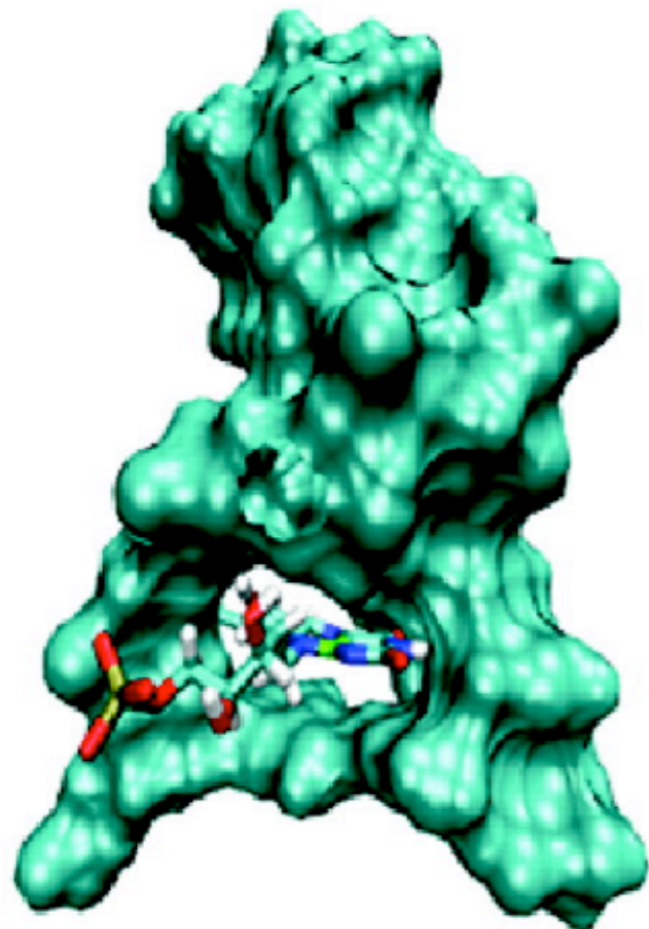
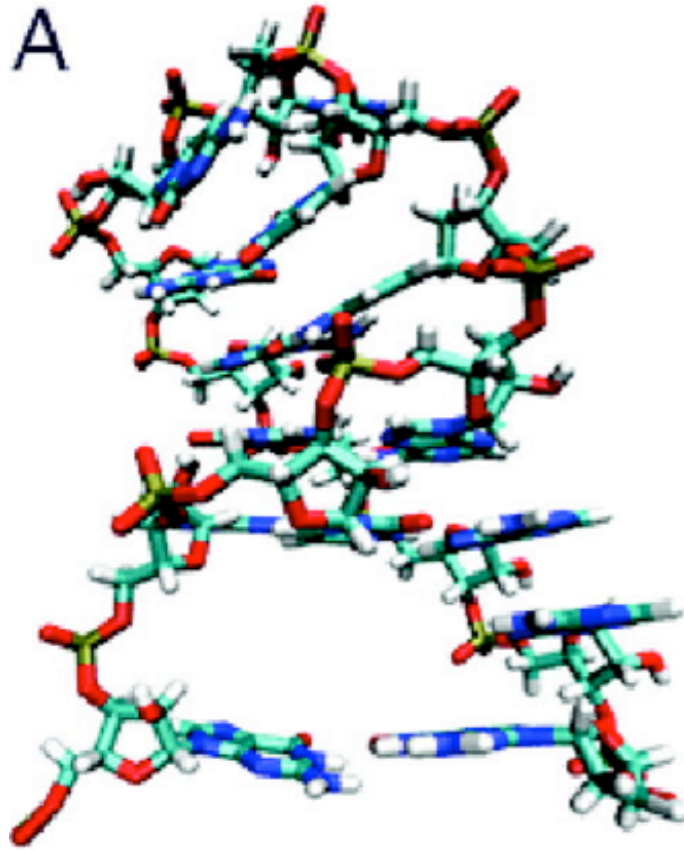
Use an affinity column with covalently tethered flavin



For increased selectivity:  
also include a *negative* selection step

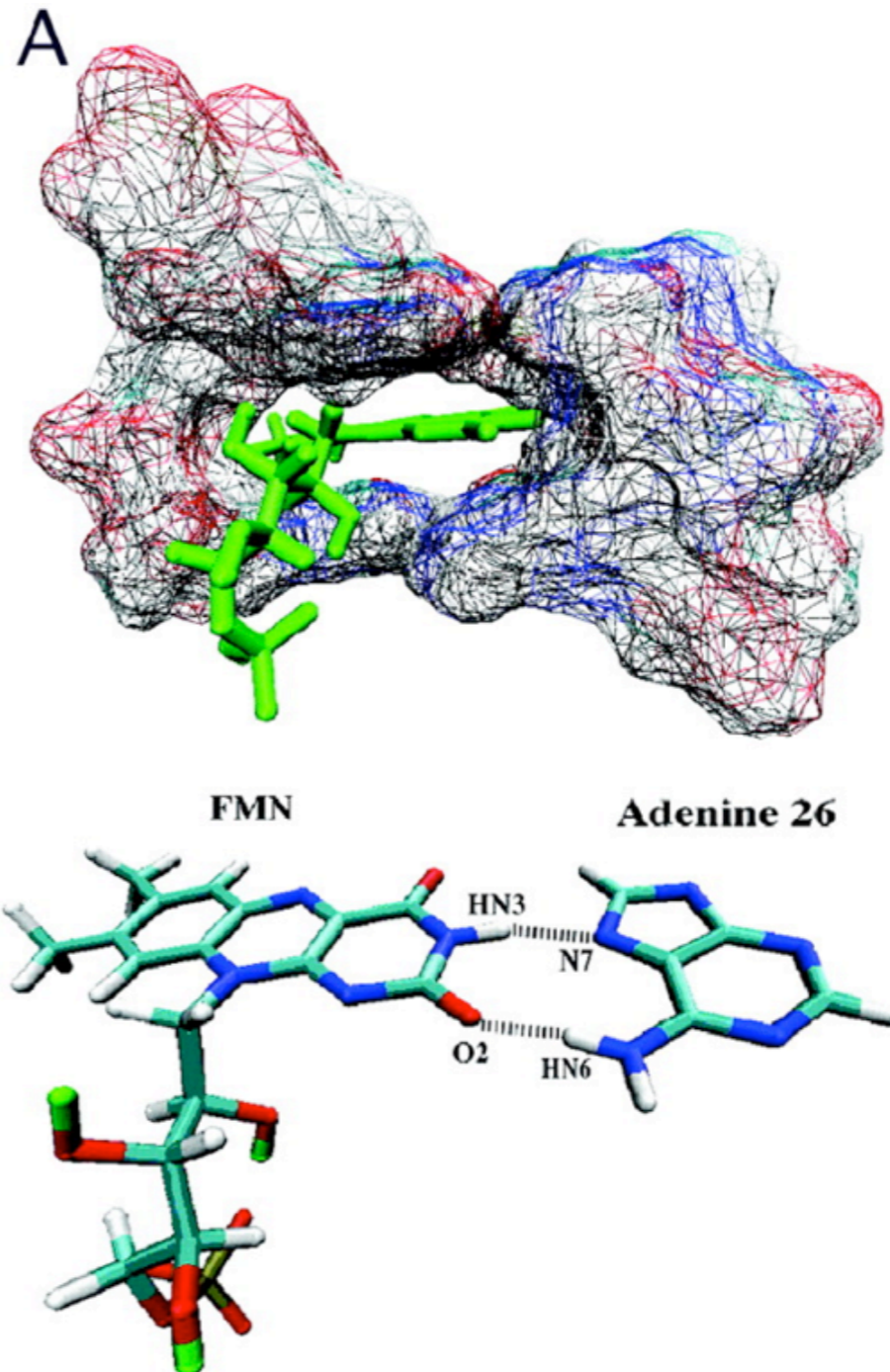
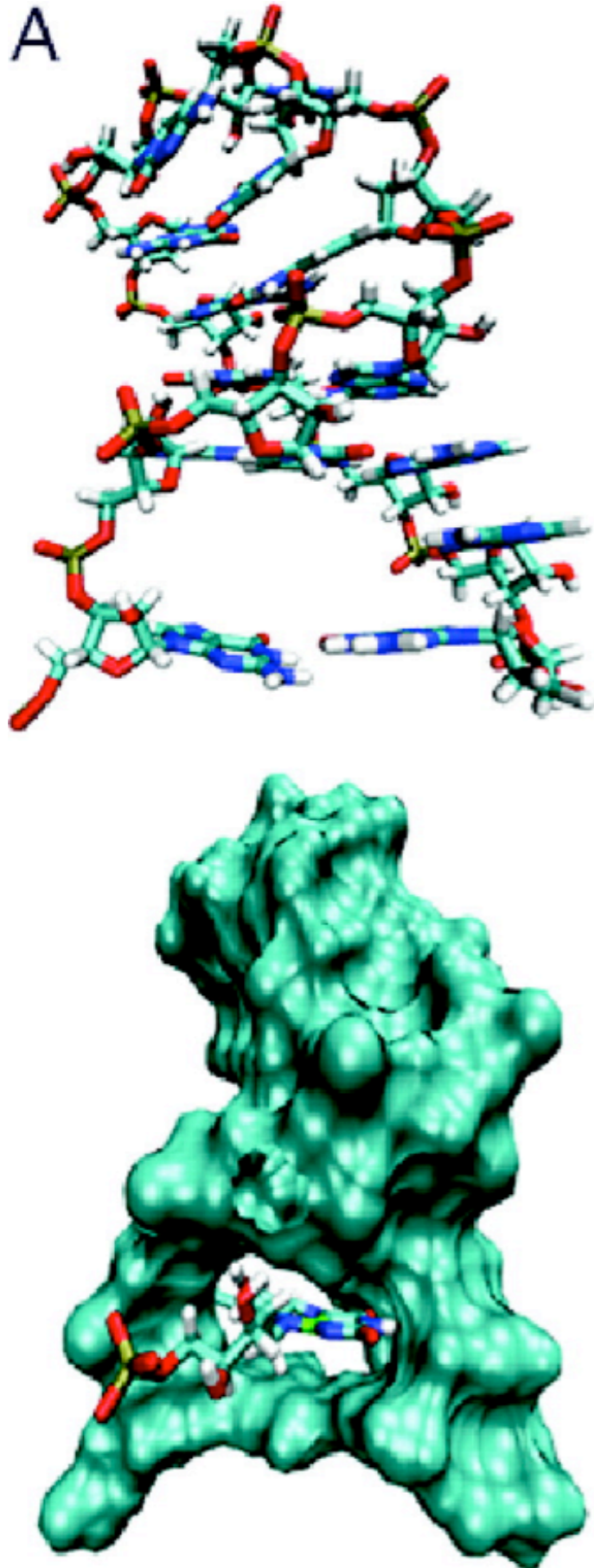


# Flavin aptamer



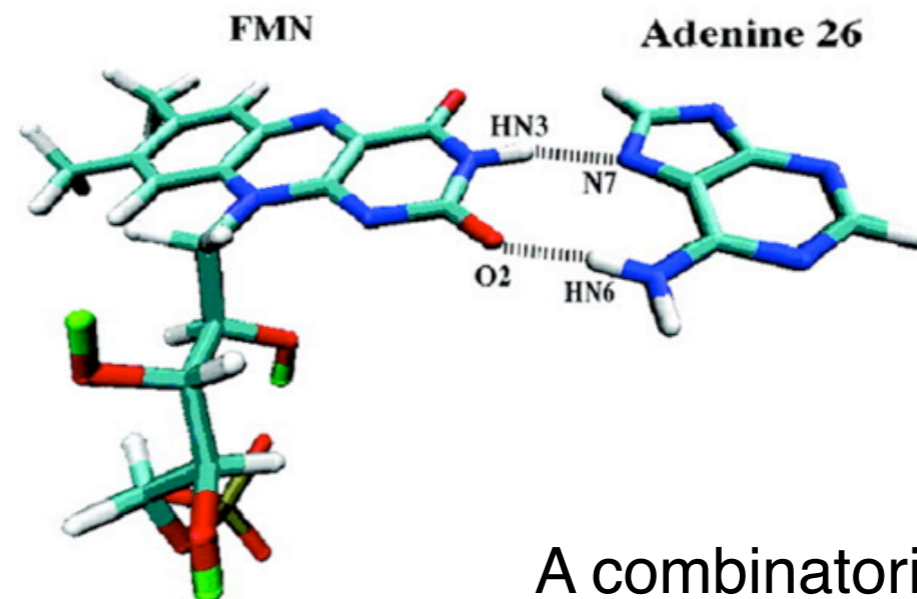
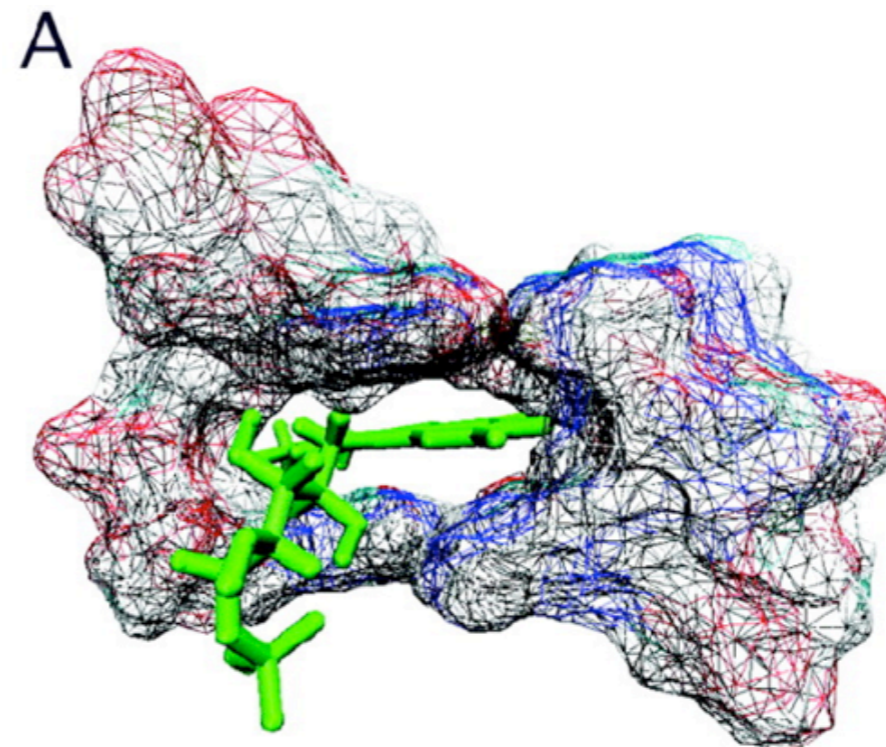
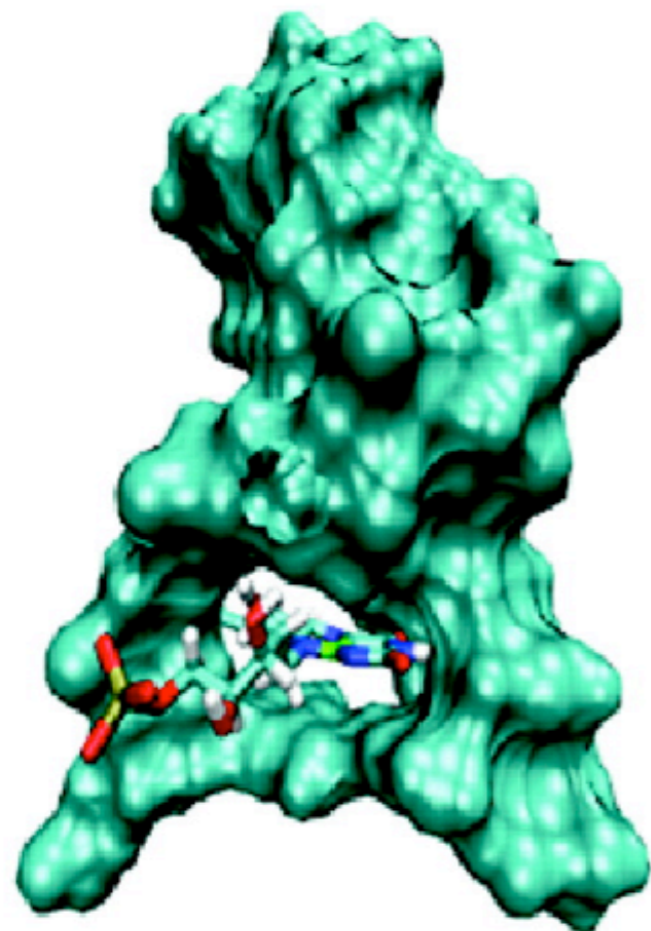
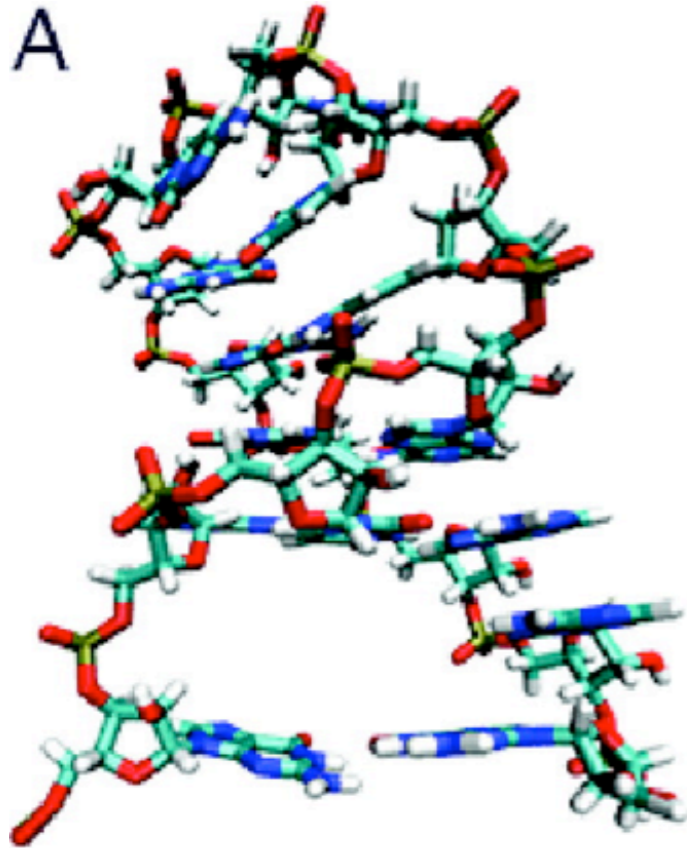
Anderson, P. C. & Mecozi, S. Identification of a 14mer RNA that recognizes and binds flavin mononucleotide with high affinity. *Nucleic Acids Res* 33, 6992-6999 (2005)

# Flavin aptamer



Anderson, P. C. & Mecozi, S. Identification of a 14mer RNA that recognizes and binds flavin mononucleotide with high affinity. *Nucleic Acids Res* 33, 6992-6999 (2005)

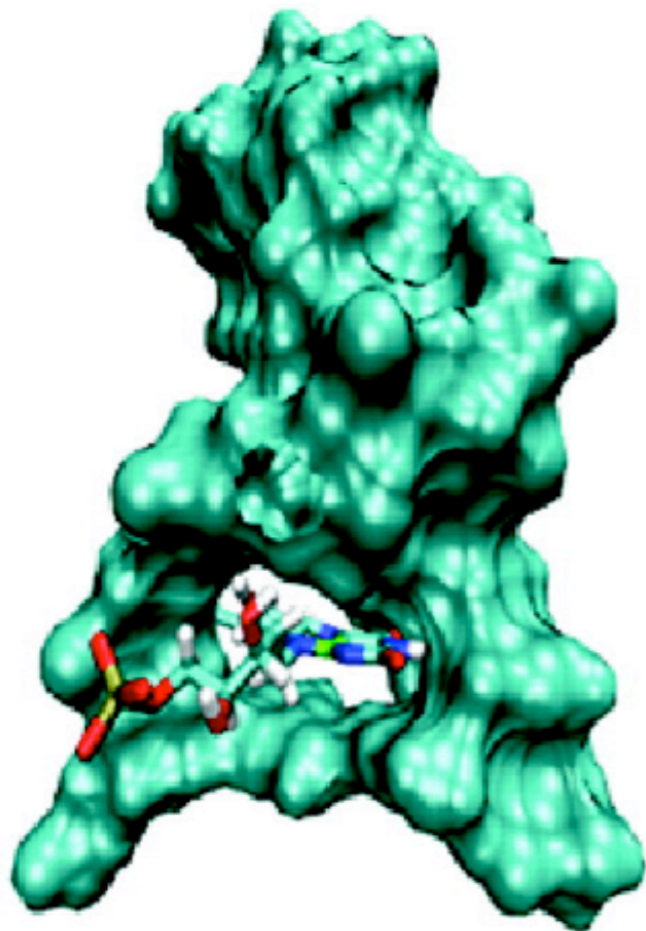
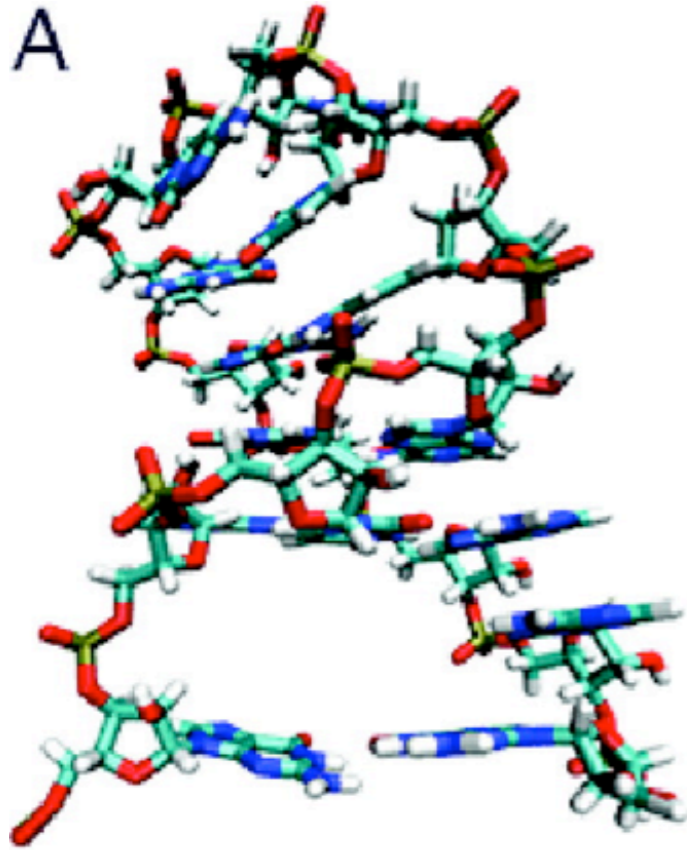
# Flavin aptamer



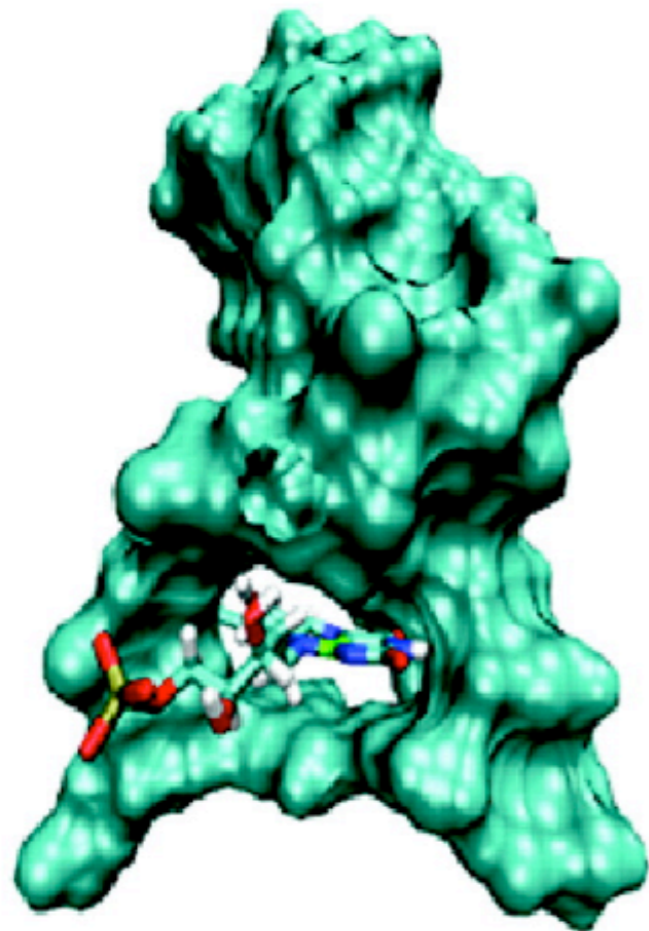
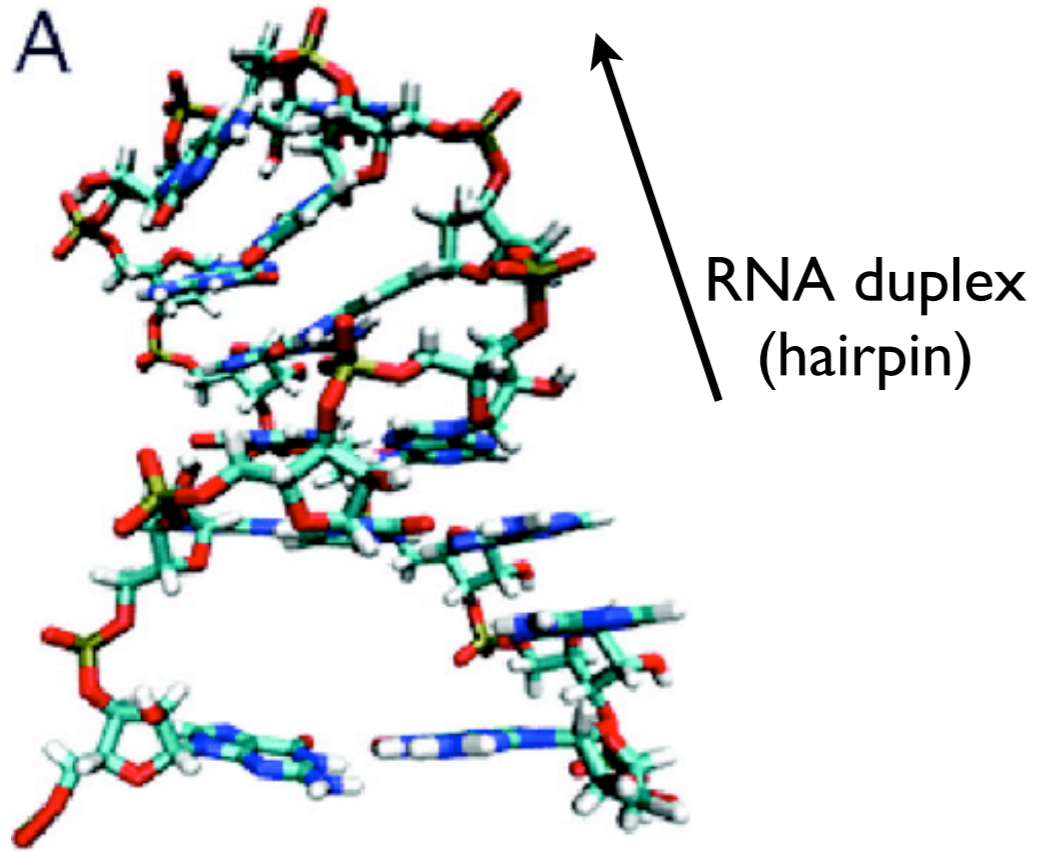
A combinatorial success!

Anderson, P. C. & Mecozi, S. Identification of a 14mer RNA that recognizes and binds flavin mononucleotide with high affinity. *Nucleic Acids Res* 33, 6992-6999 (2005)

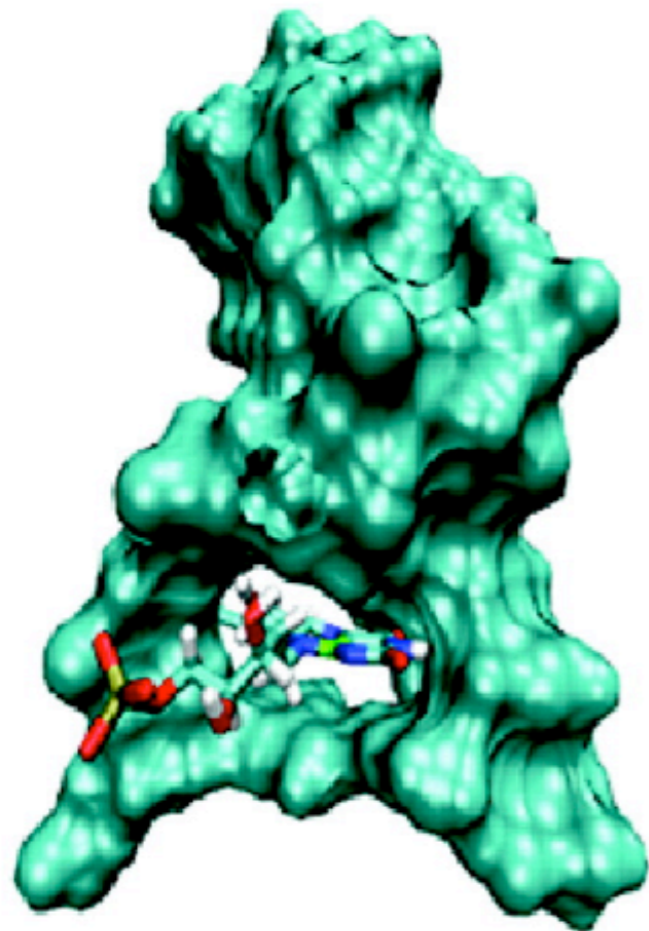
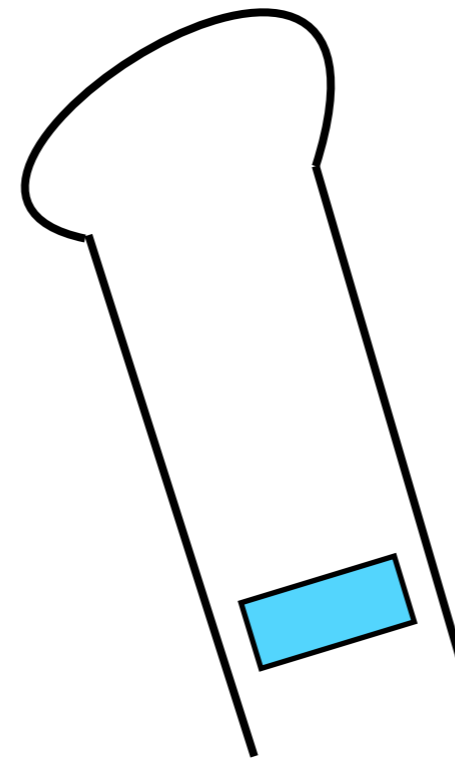
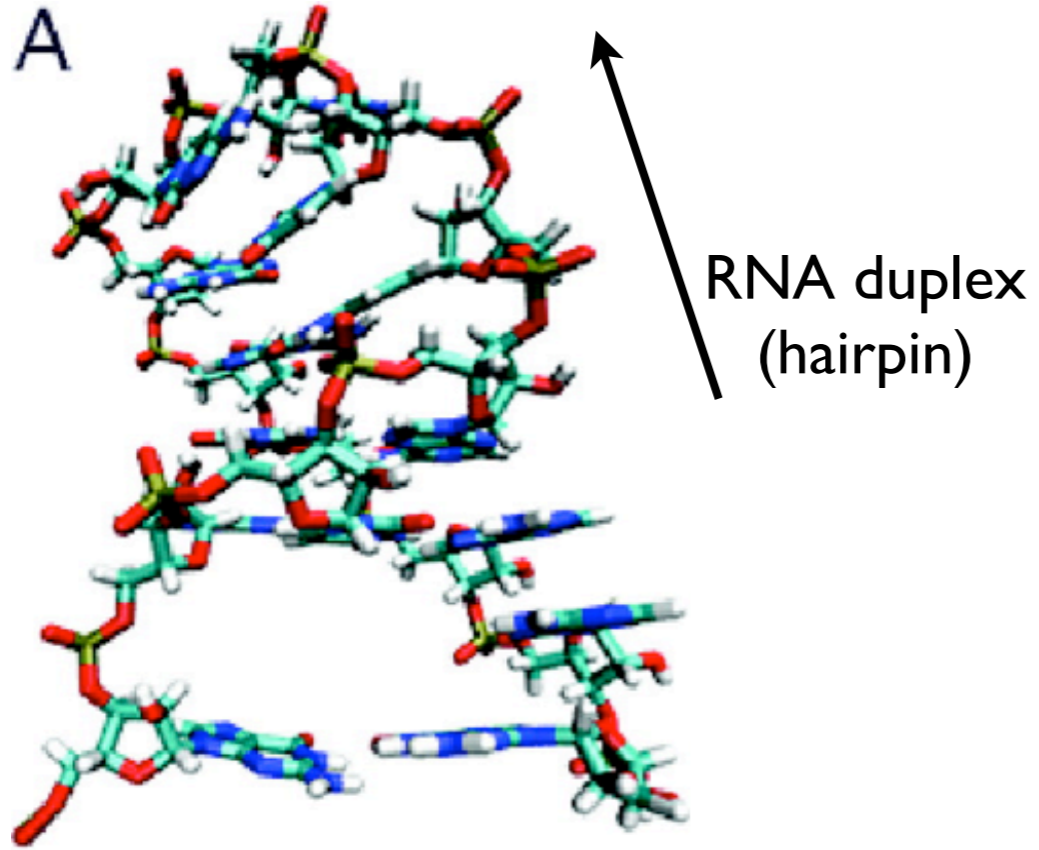
# Flavin biosensor



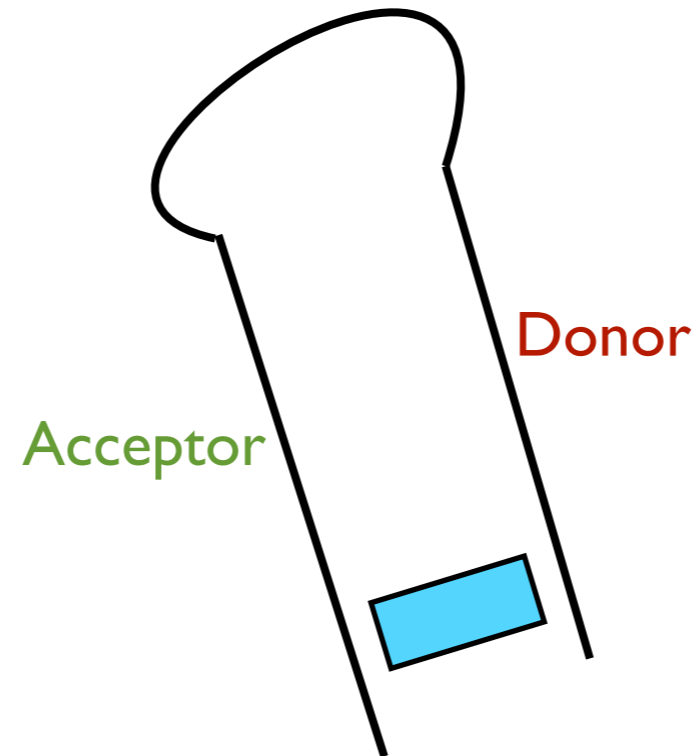
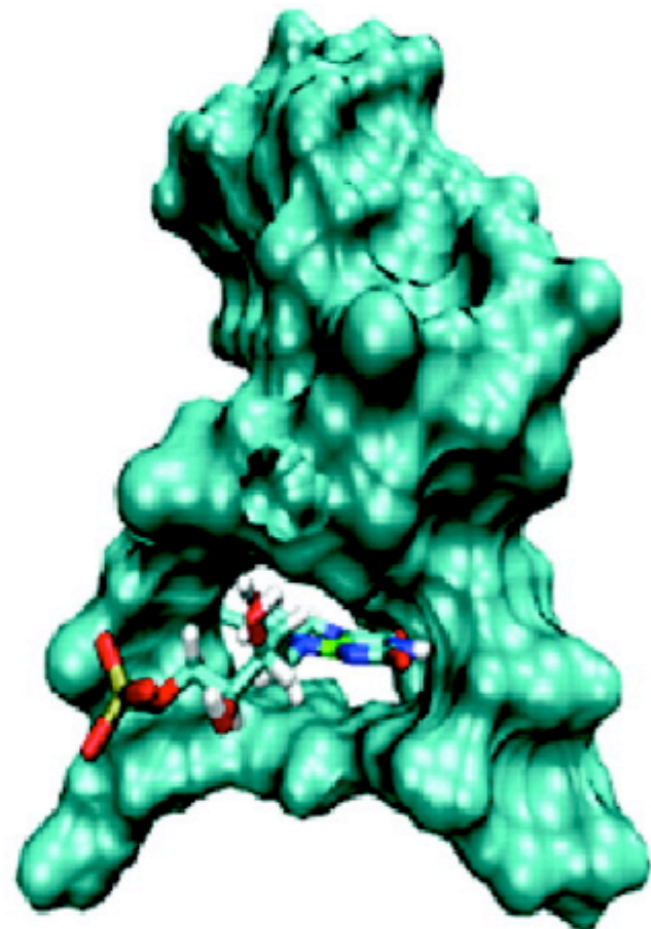
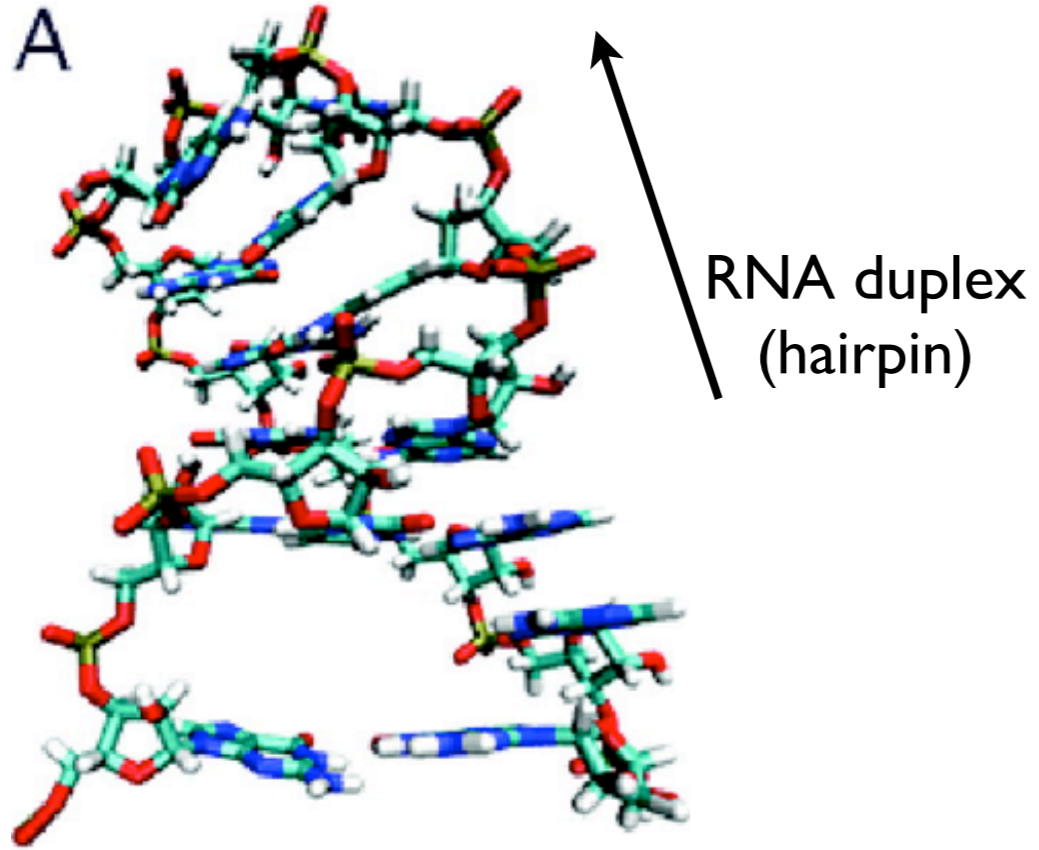
# Flavin biosensor



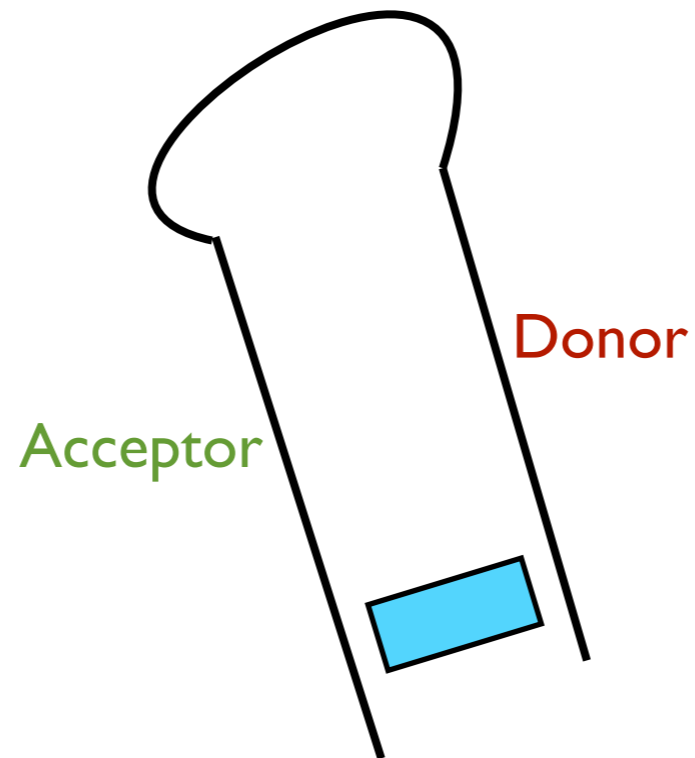
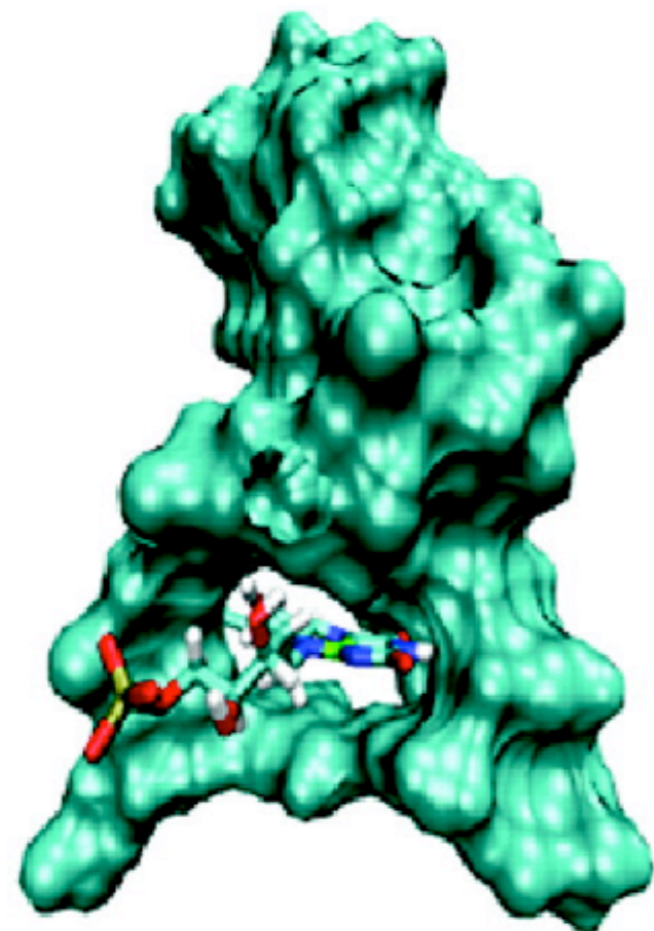
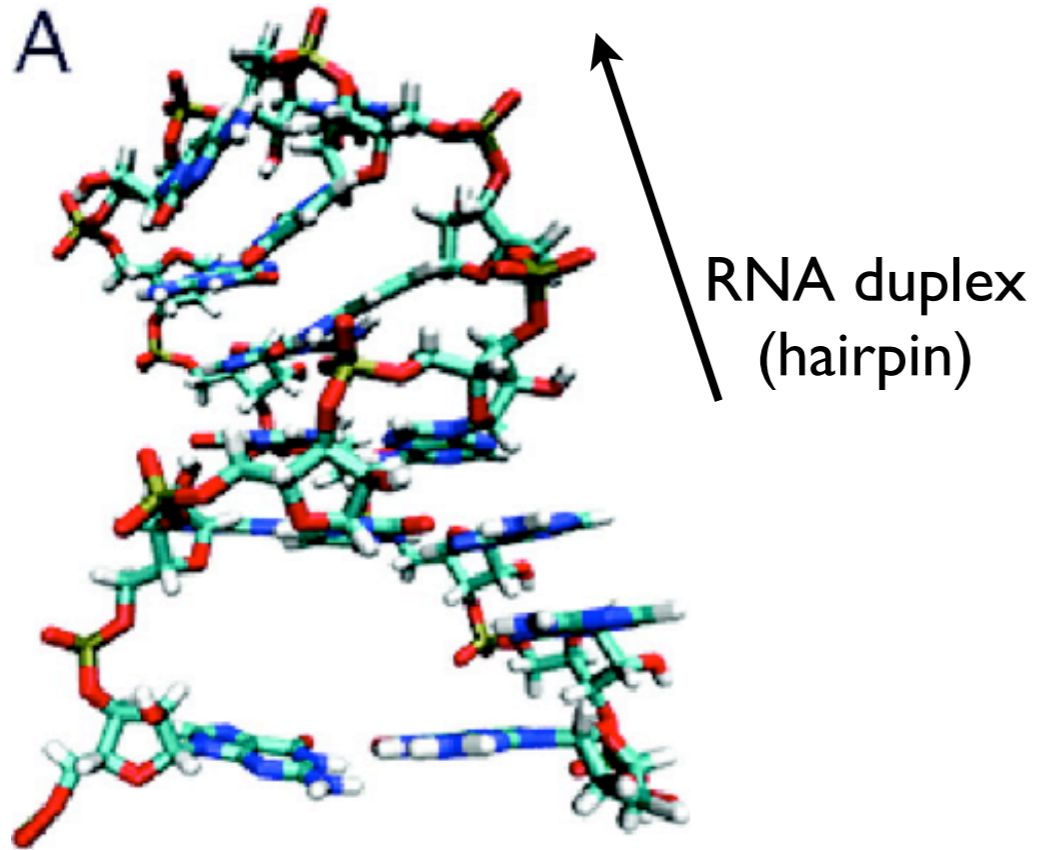
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# Flavin biosensor



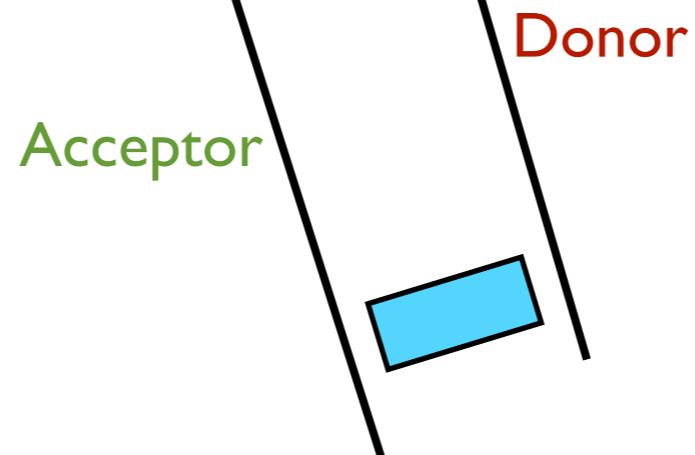
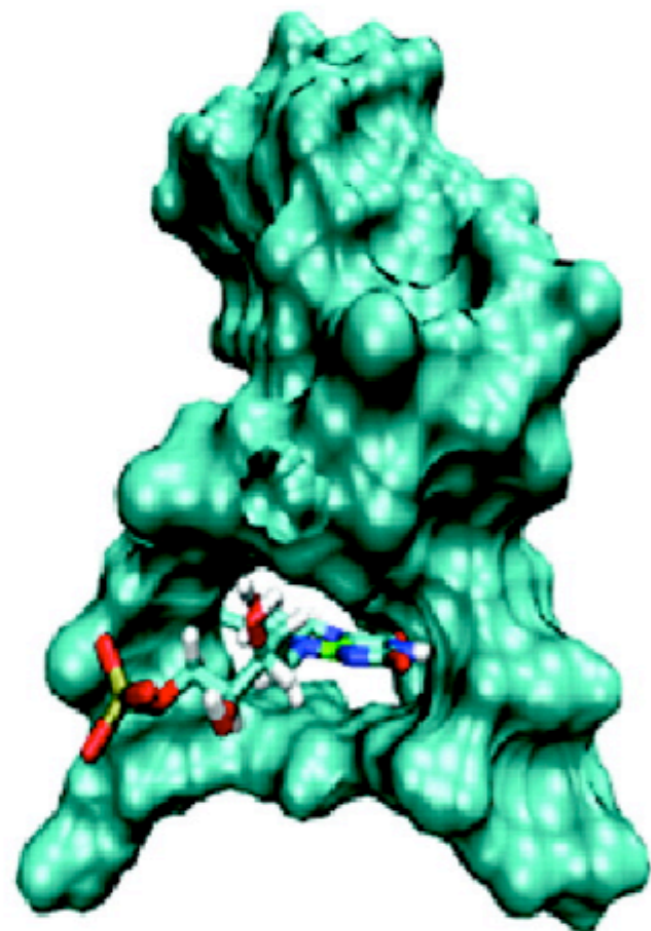
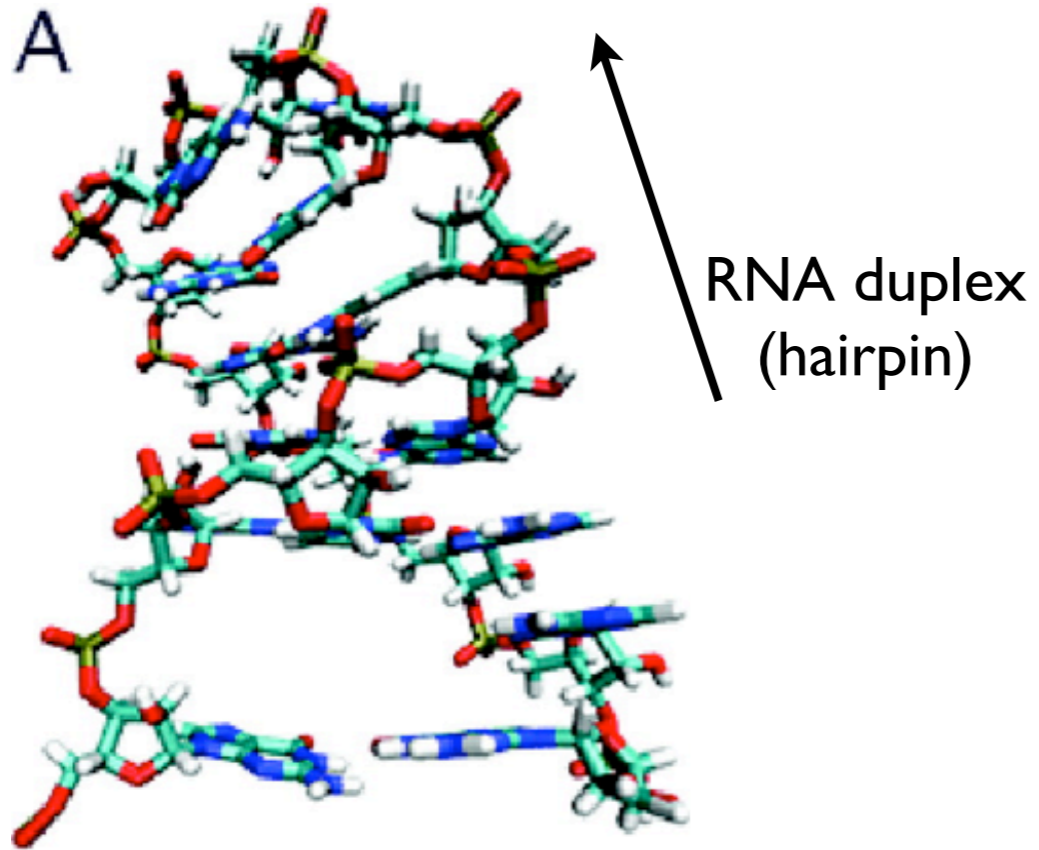
# Flavin biosensor



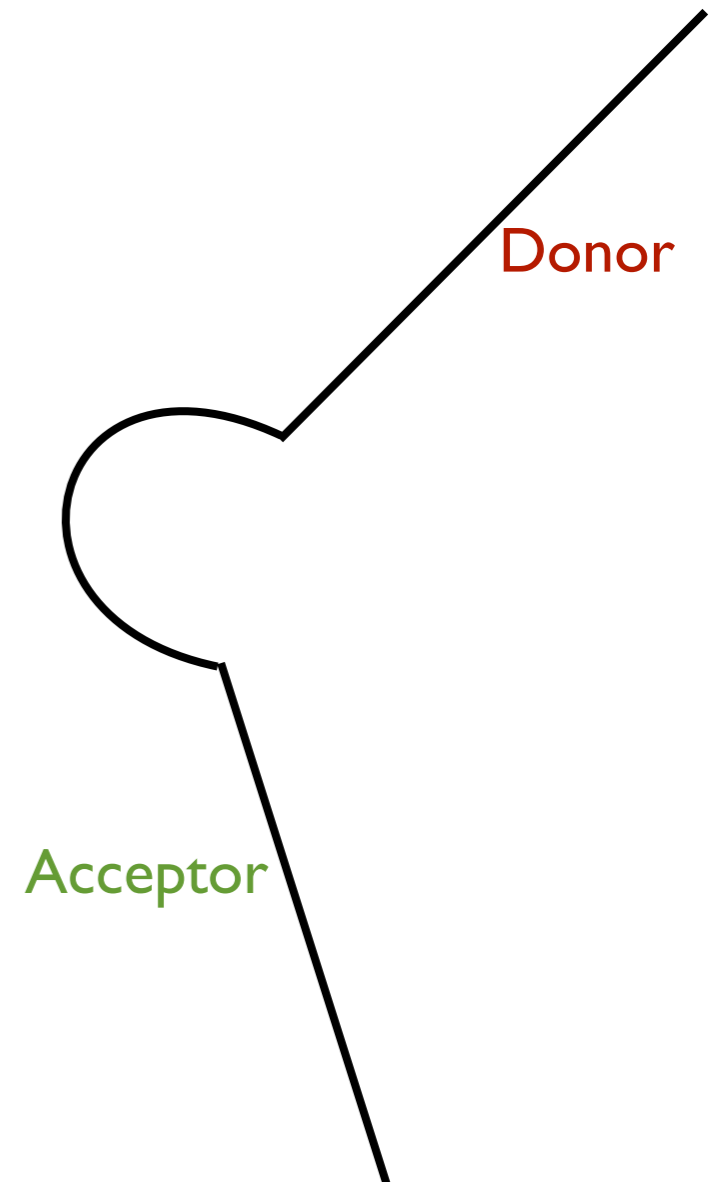
FRET "on"



# Flavin biosensor



FRET "on"



FRET "off"

# Aptamers

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Selectivity in binding

# Aptamers

Selectivity in binding  
naturally stereospecific

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Selectivity in binding  
naturally stereospecific

Easy to generate

# Aptamers

Selectivity in binding  
naturally stereospecific

Easy to generate  
it's all in the selection

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Can be combined modularly

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Easy to generate  
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Can be combined modularly

Can incorporate chemical modifications



# Aptamers

Selectivity in binding  
naturally stereospecific

Easy to generate  
it's all in the selection

Can be combined modularly

Can incorporate chemical modifications  
add unnatural chemical functionality

# Aptamers

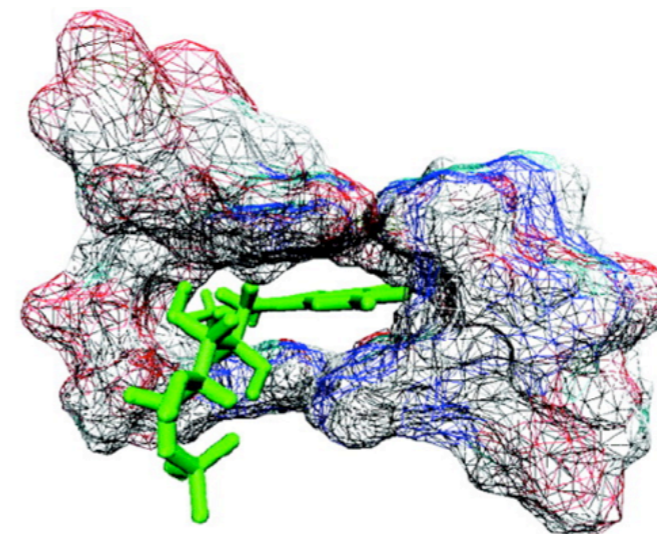
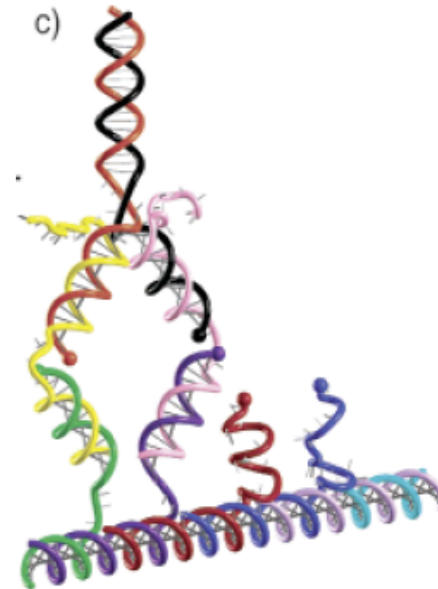
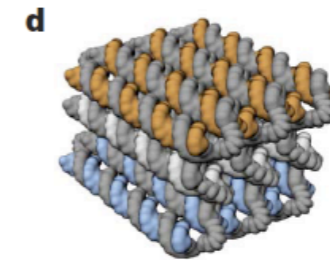
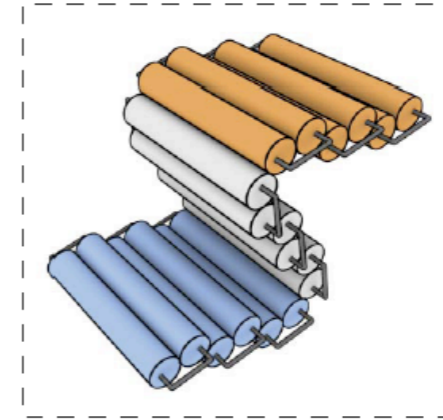
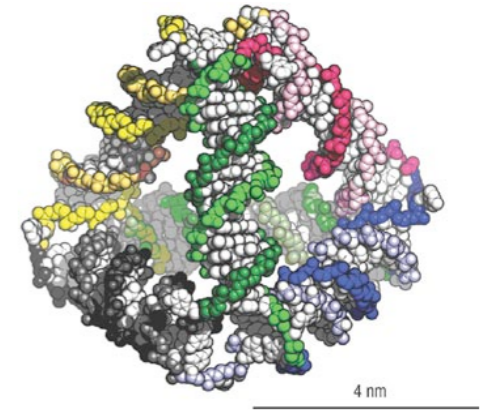
Selectivity in binding  
naturally stereospecific

Easy to generate  
it's all in the selection

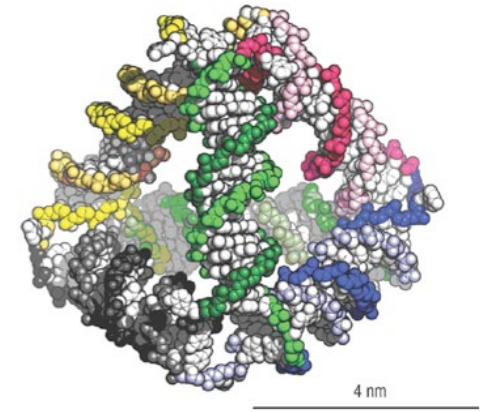
Can be combined modularly

Can incorporate chemical modifications  
add unnatural chemical functionality  
(eg, fluorophores)

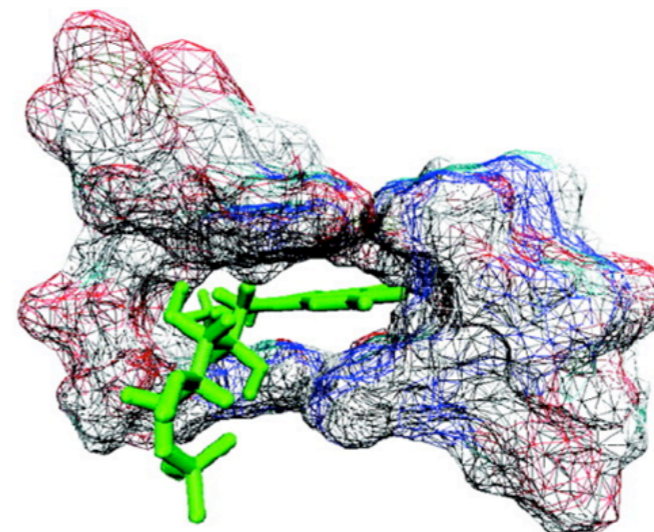
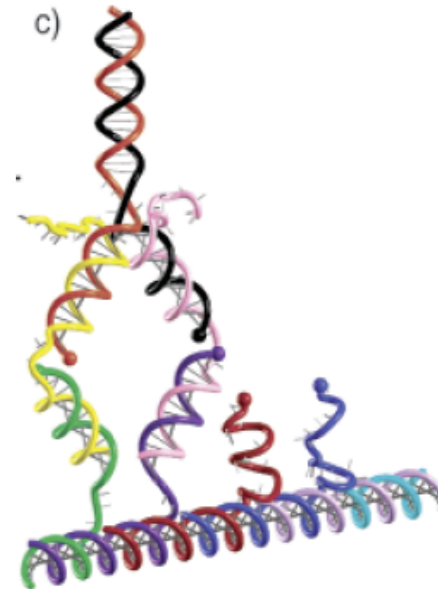
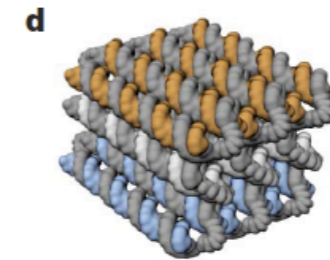
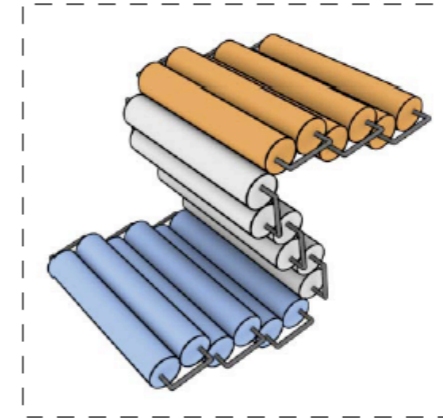
# Nucleic Acids



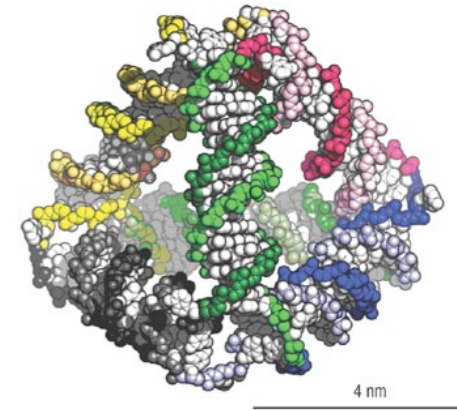
# Nucleic Acids



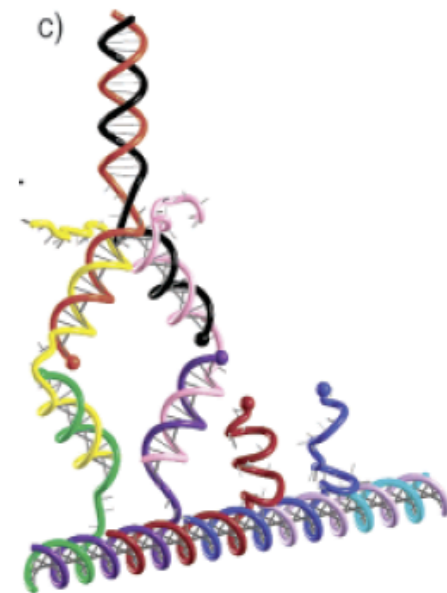
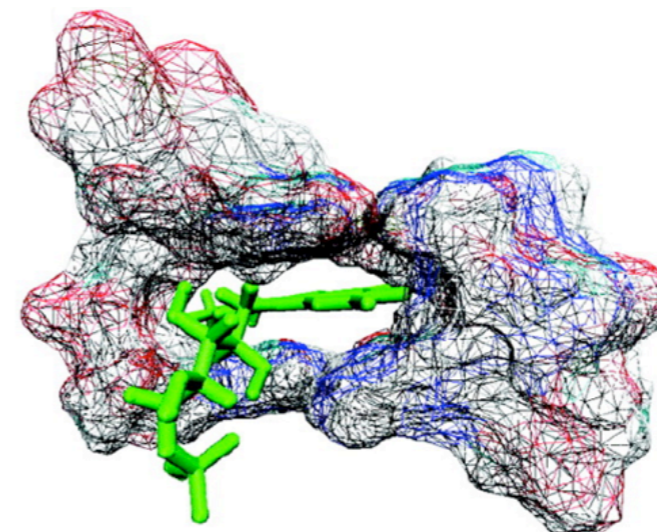
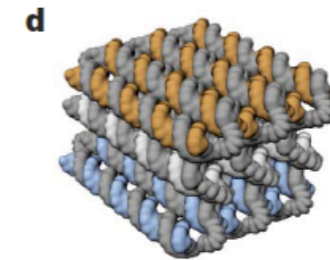
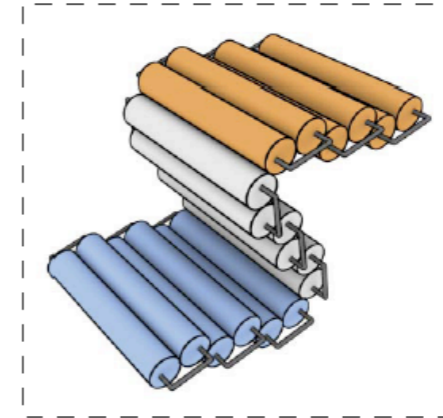
Excellent for rational design



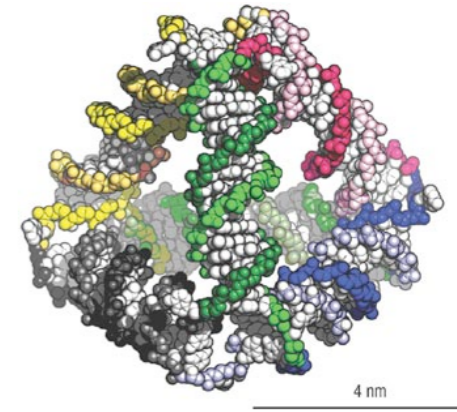
# Nucleic Acids



Excellent for rational design  
exquisitely addressable

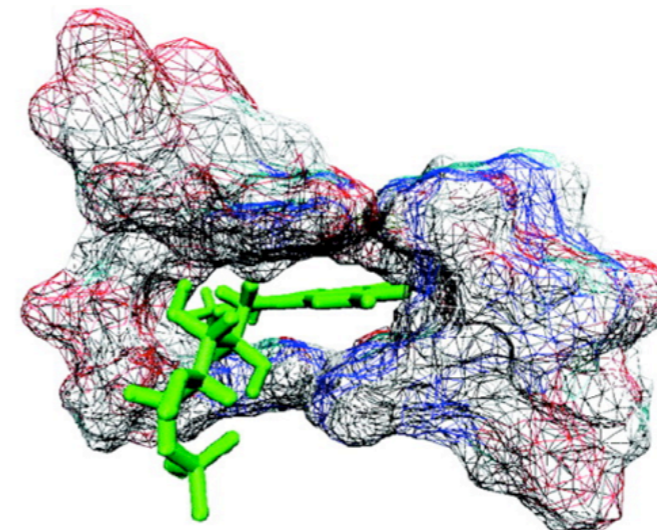
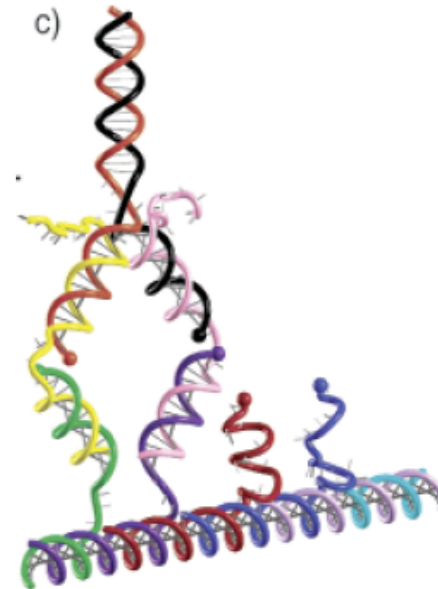
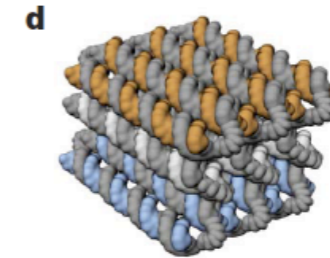
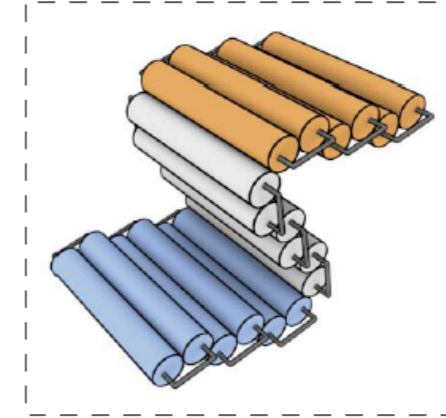


# Nucleic Acids

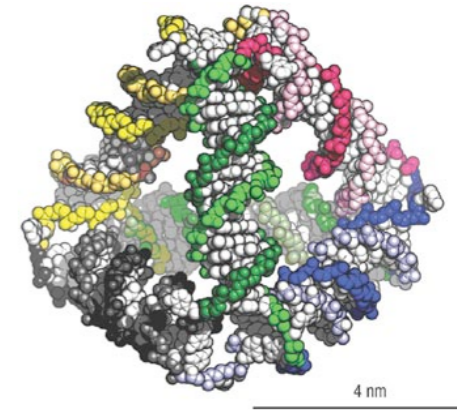


Excellent for rational design  
exquisitely addressable

Synthesize chemically or biosynthetically



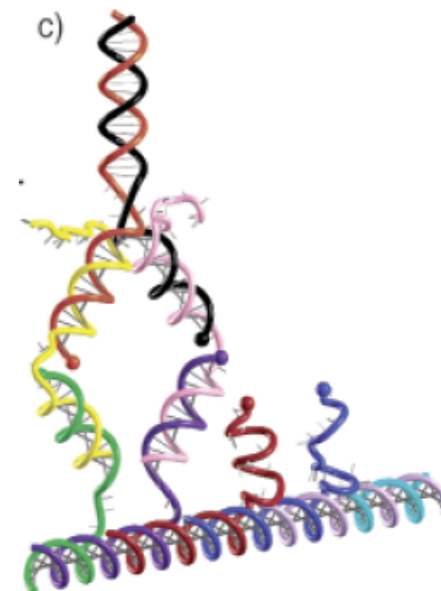
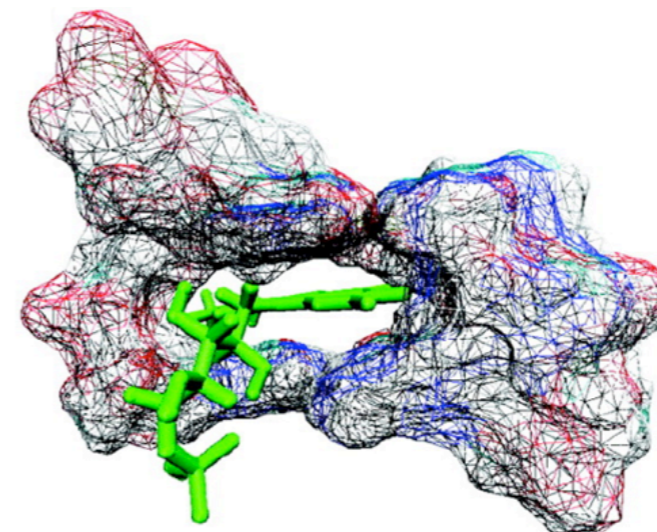
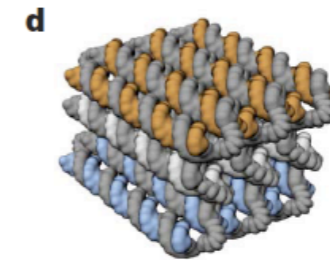
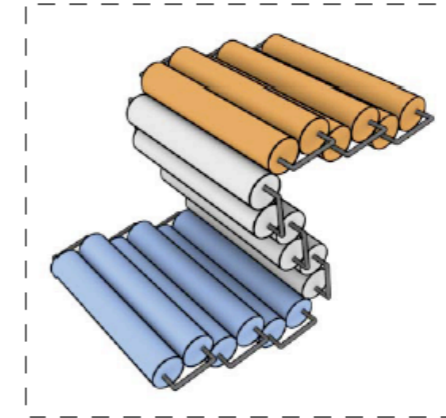
# Nucleic Acids



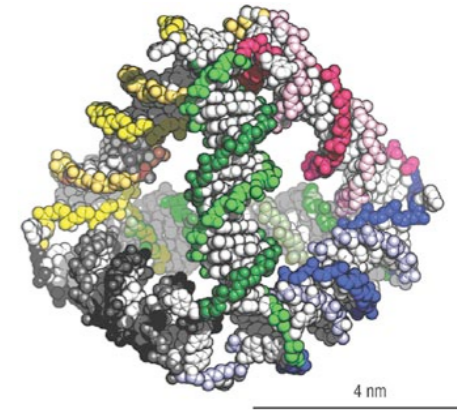
Excellent for rational design  
exquisitely addressable

Synthesize chemically or biosynthetically

Combinatorial selection



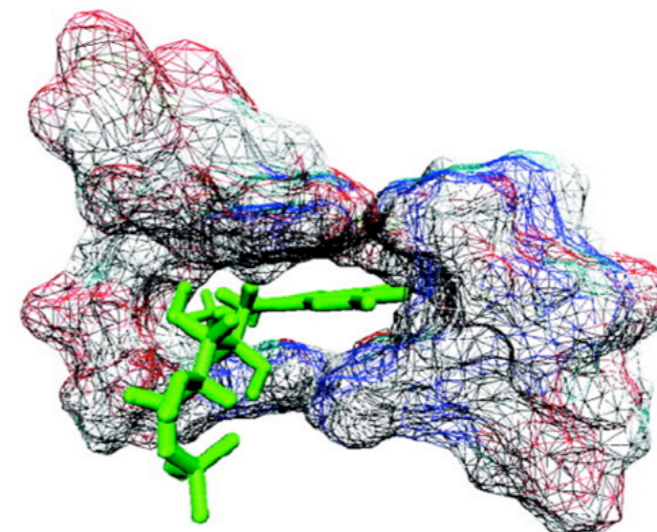
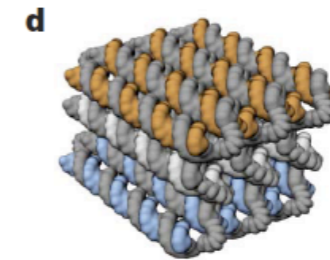
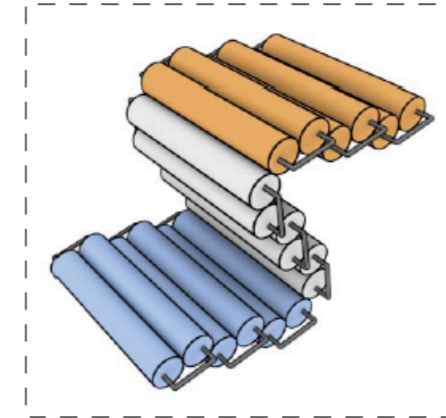
# Nucleic Acids



Excellent for rational design  
exquisitely addressable

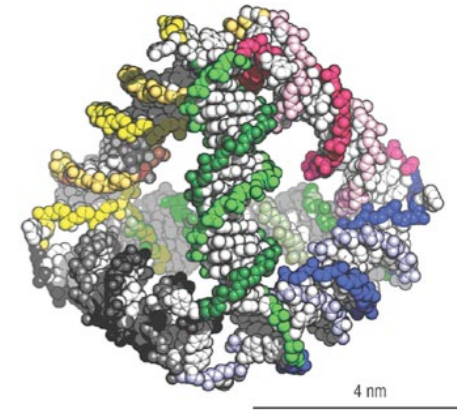
Synthesize chemically or biosynthetically

Combinatorial selection  
extremely powerful





# Nucleic Acids

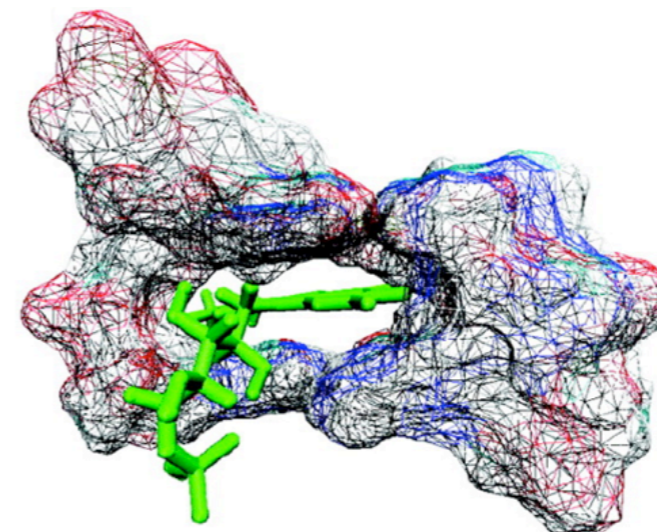
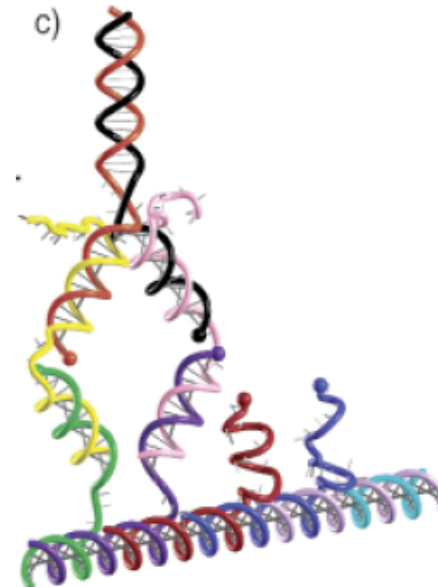
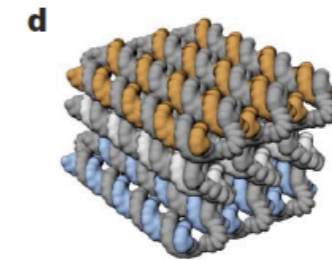
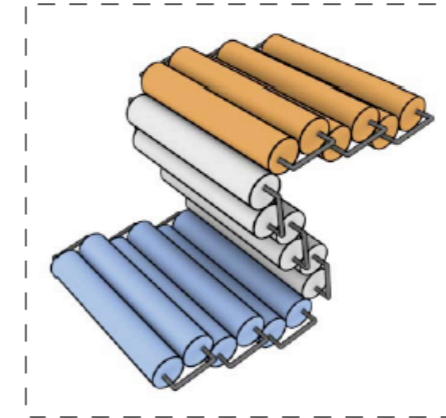


Excellent for rational design  
exquisitely addressable

Synthesize chemically or biosynthetically

Combinatorial selection  
extremely powerful

Readily re-designed after selection



**For next time...**

# For next time...

## Which is most stable?

5' -ACCGCCGACGT-3'  
3' -TGGCGGCTGCA-5'

5' -ACCGCCGACGT-3'  
3' -AGGCGGCTGCC-5'

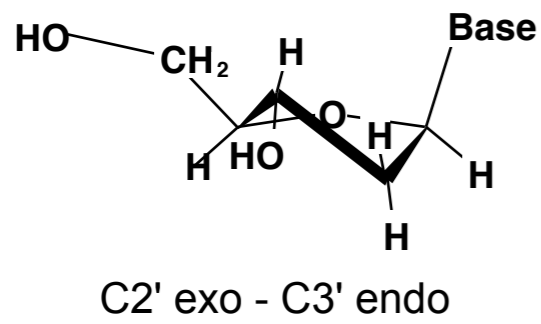
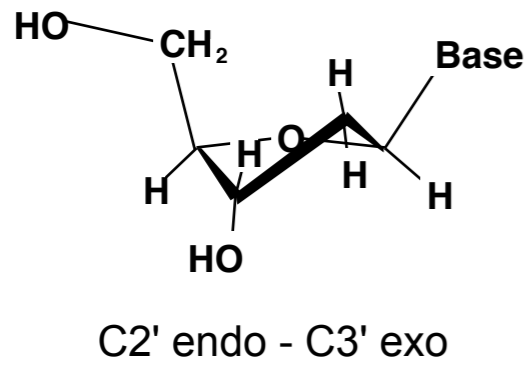
# For next time...

## Which is most stable?

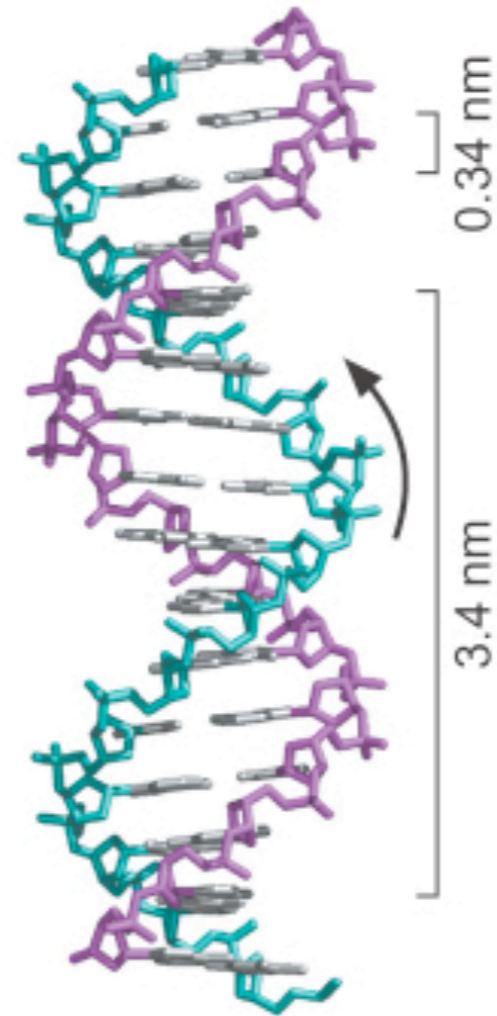
5' -ACCGCCGACGT-3'  
3' -TGGCGGCTGCA-5'

5' -ACCGCCGACGT-3'  
3' -AGGCGGCTGCC-5'

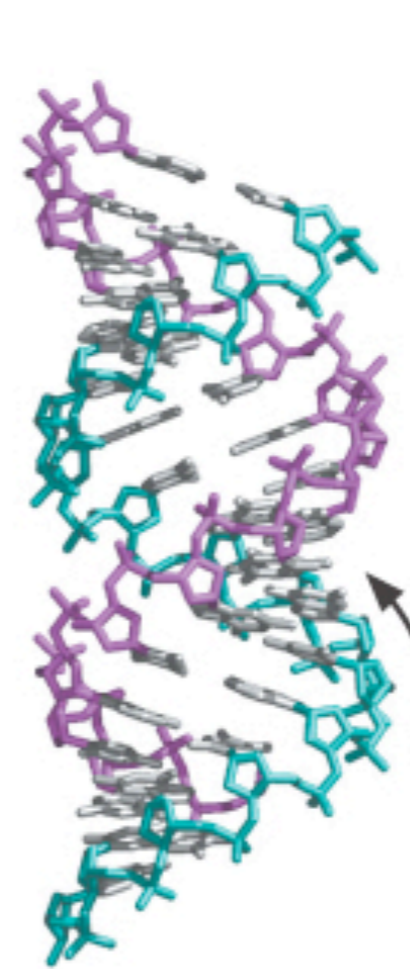




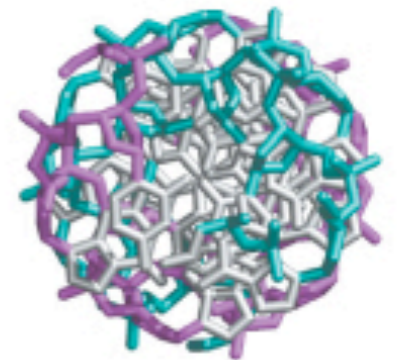
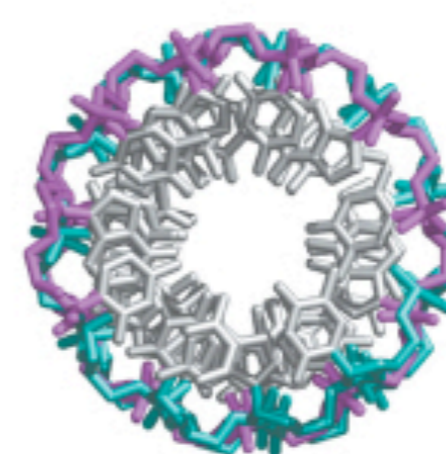
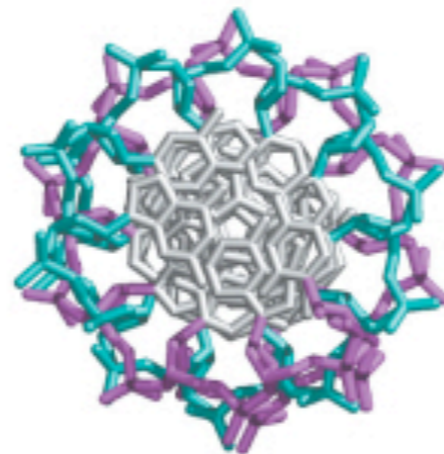
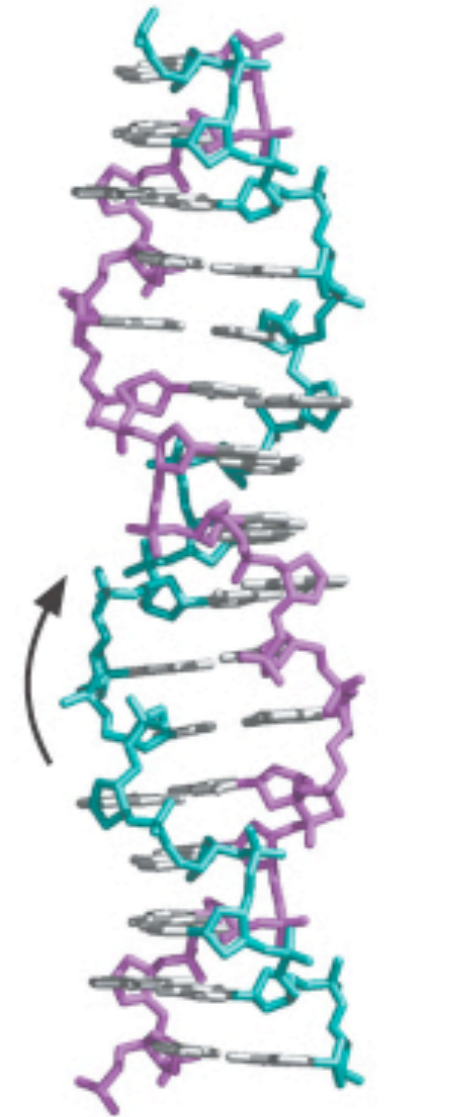
a B DNA



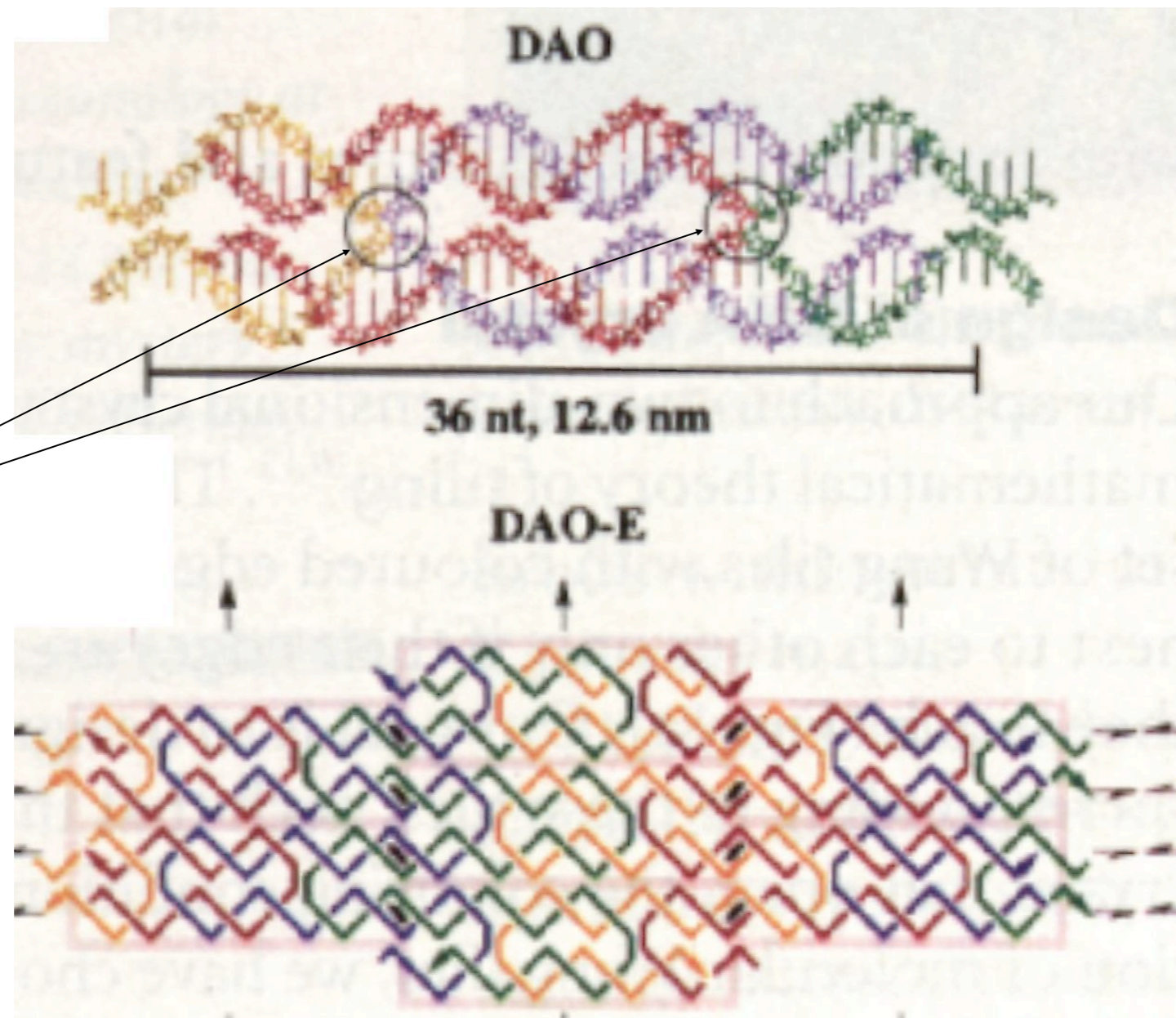
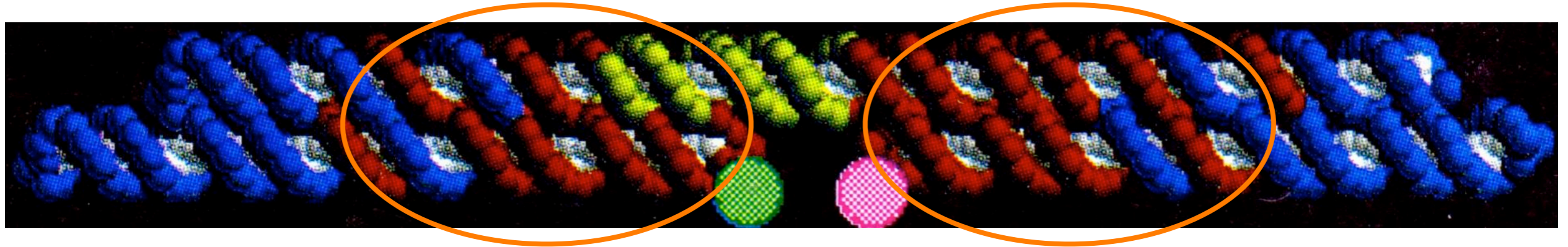
b A DNA



c Z DNA

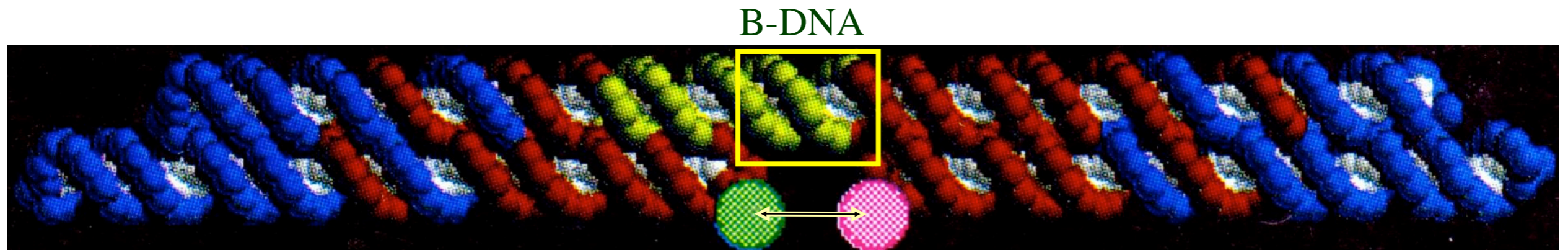


# Setup - Double crossover “wings”



Color schemes **not**  
the same

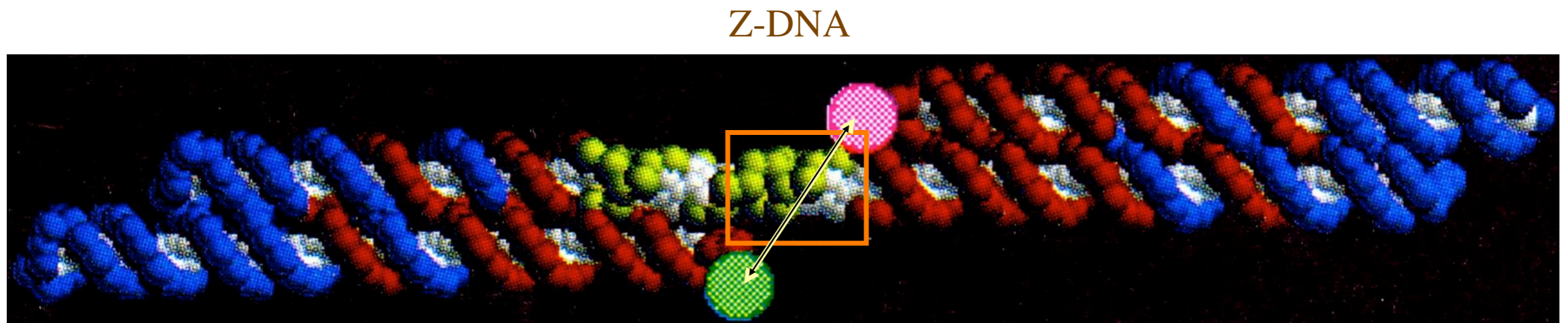
# B->Z leads to Rotation, leads to $\Delta d$



Rise per nucleotide =  $3.38 \text{ \AA}$

Rotation per nucleotide =  $36^\circ$

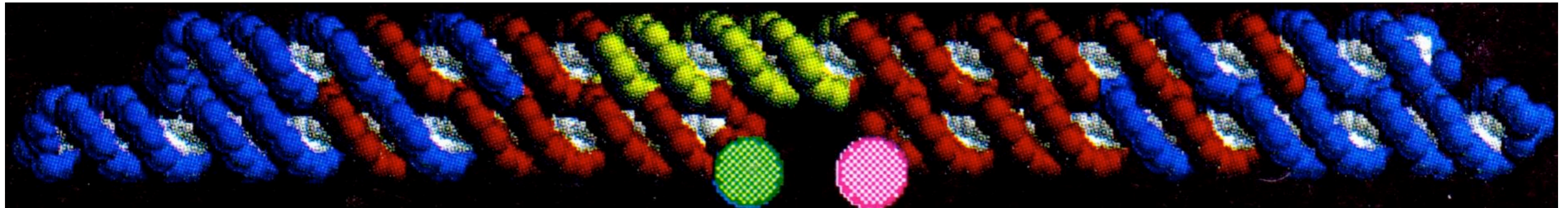
Difference =  $6^\circ$  per nucleotide



Ave. rise per nucleotide =  $3.71 \text{ \AA}$

Ave. rotation per nucleotide =  $30^\circ$

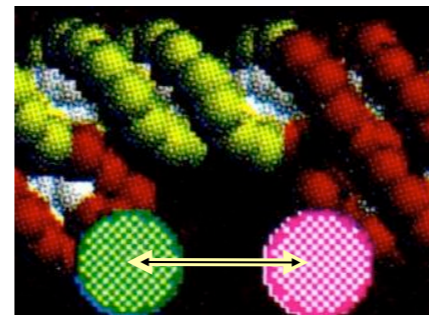
# Förster Energy Transfer - Setup



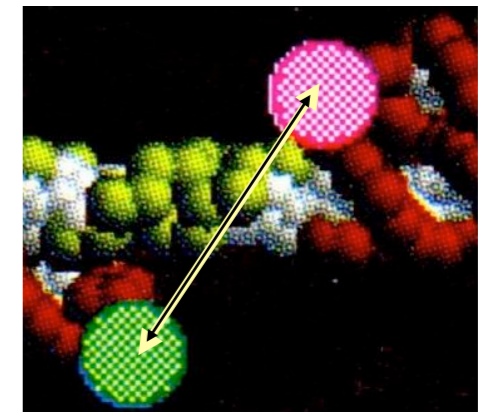
Donor: **Fluorescein**      Acceptor: **Cy3** (a sulfoindocarbocyanine)

Efficiency of transfer:

$$E = \frac{R_o^6}{R_o^6 + R^6}$$



51 Å  
B-form

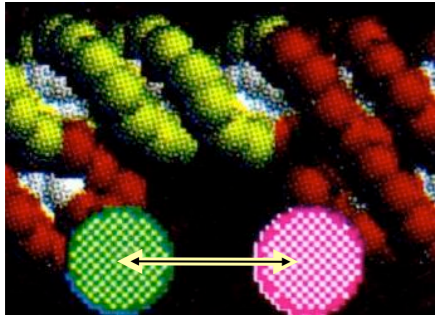


70 Å  
Z-form

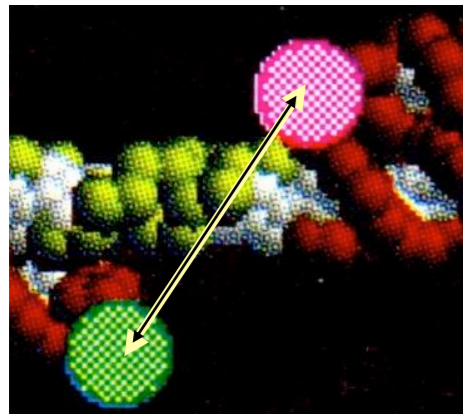
Distances from model building



# Förster Energy Transfer - Results

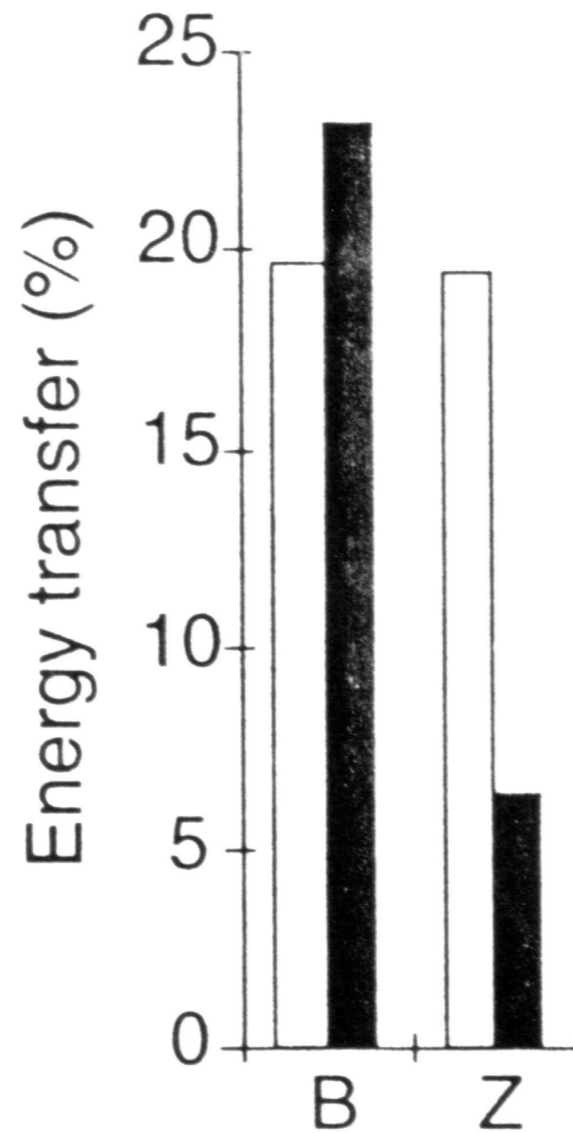


B-form

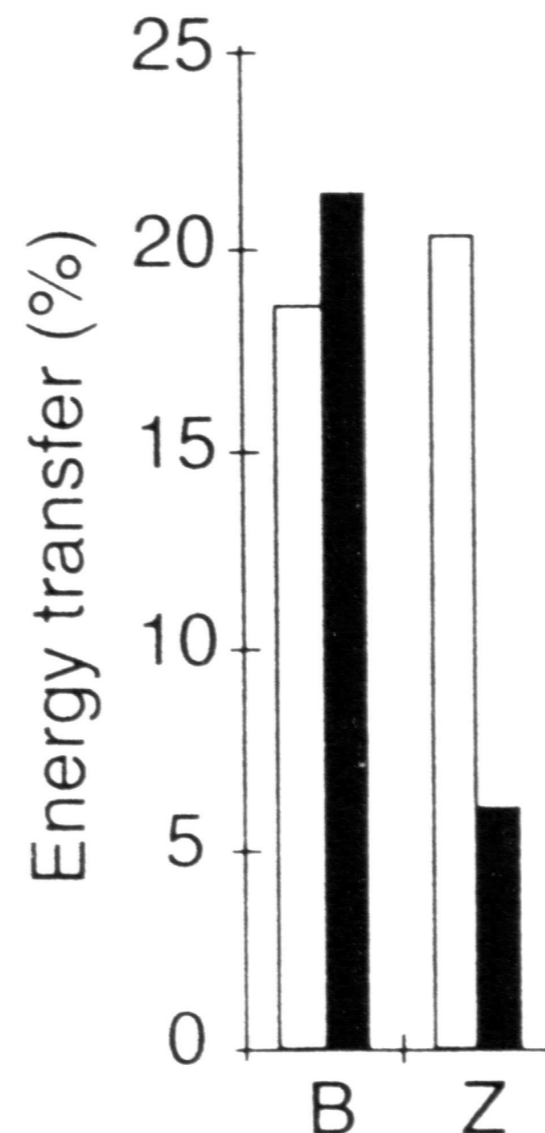


Z-form

From decrease in donor fluorescence



From increase in acceptor fluorescence



□ Control  
 ■ Proto-Z d(CG)<sub>10</sub>

**Conditions:**

10 mM cacodylate  
 pH 7.5  
 100 mM MgCl<sub>2</sub>  
 100 mM NaCl

plus

“B” 0.00 mM Co(NH<sub>3</sub>)<sub>6</sub>Cl<sub>3</sub>

“Z” 0.25 mM Co(NH<sub>3</sub>)<sub>6</sub>Cl<sub>3</sub>

$R_0$  for the pair (calculated) = 55.7 Å (B-DNA conditions)  
 = 56.1 Å (Z-DNA conditions)

# Ribosome

An RNA machine with protein cofactors

