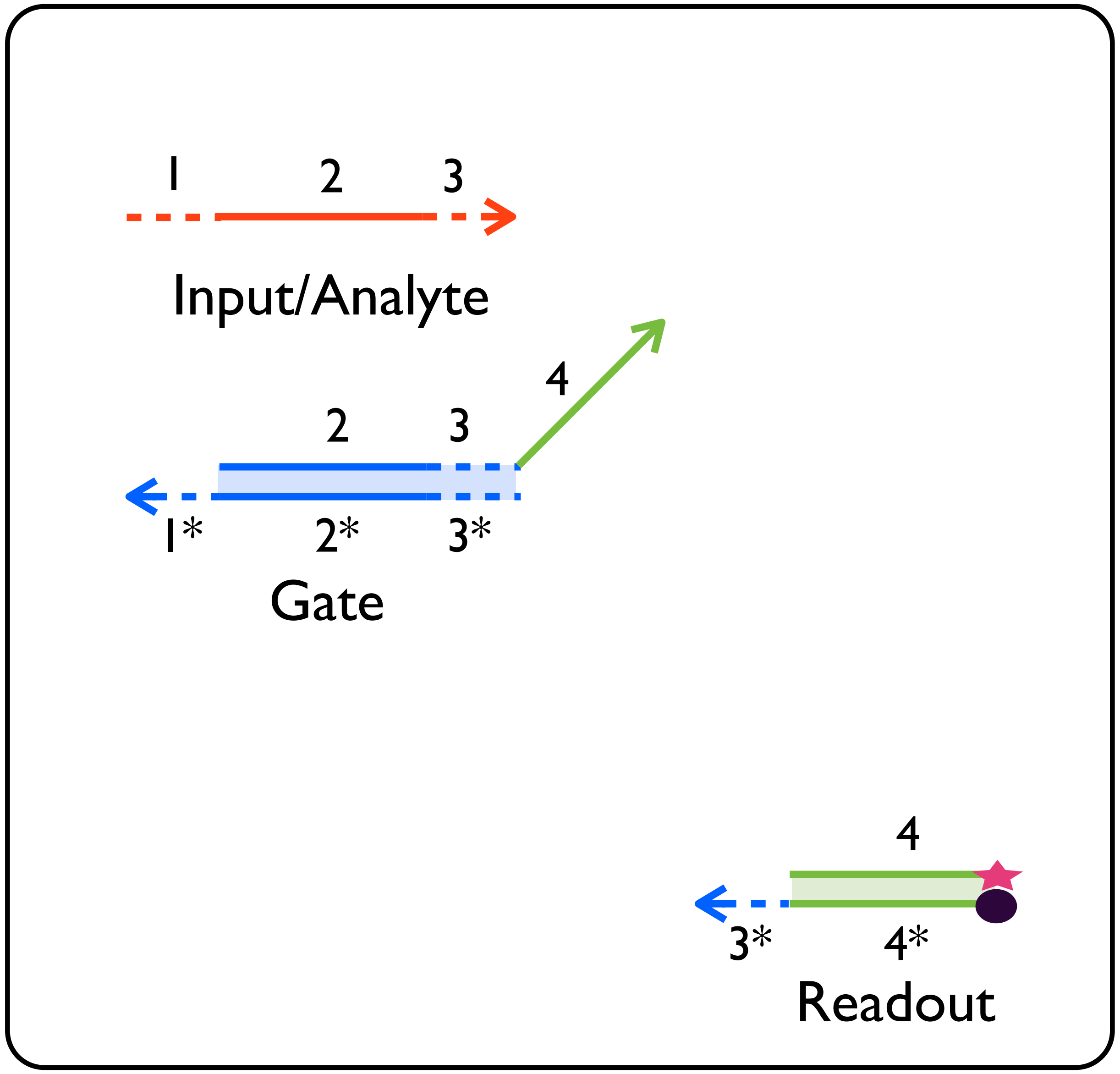
Module 6: Logic circuits with DNA strand displacement (part 2)

CSE590: Molecular programming and neural computation.

Fluorescent reporters can be used to follow reaction kinetics



The sequences of inputs and outputs can be completely independent.

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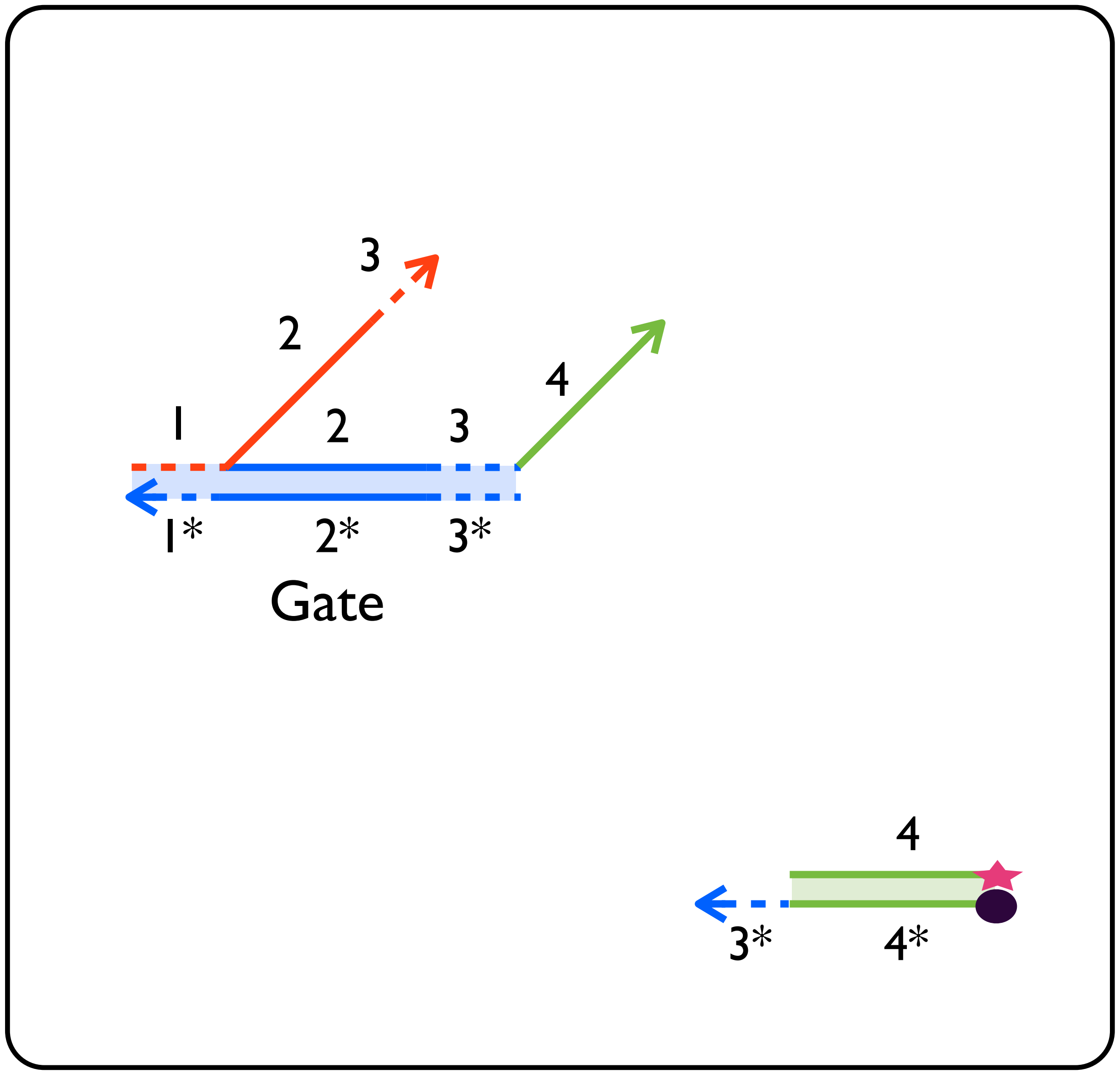

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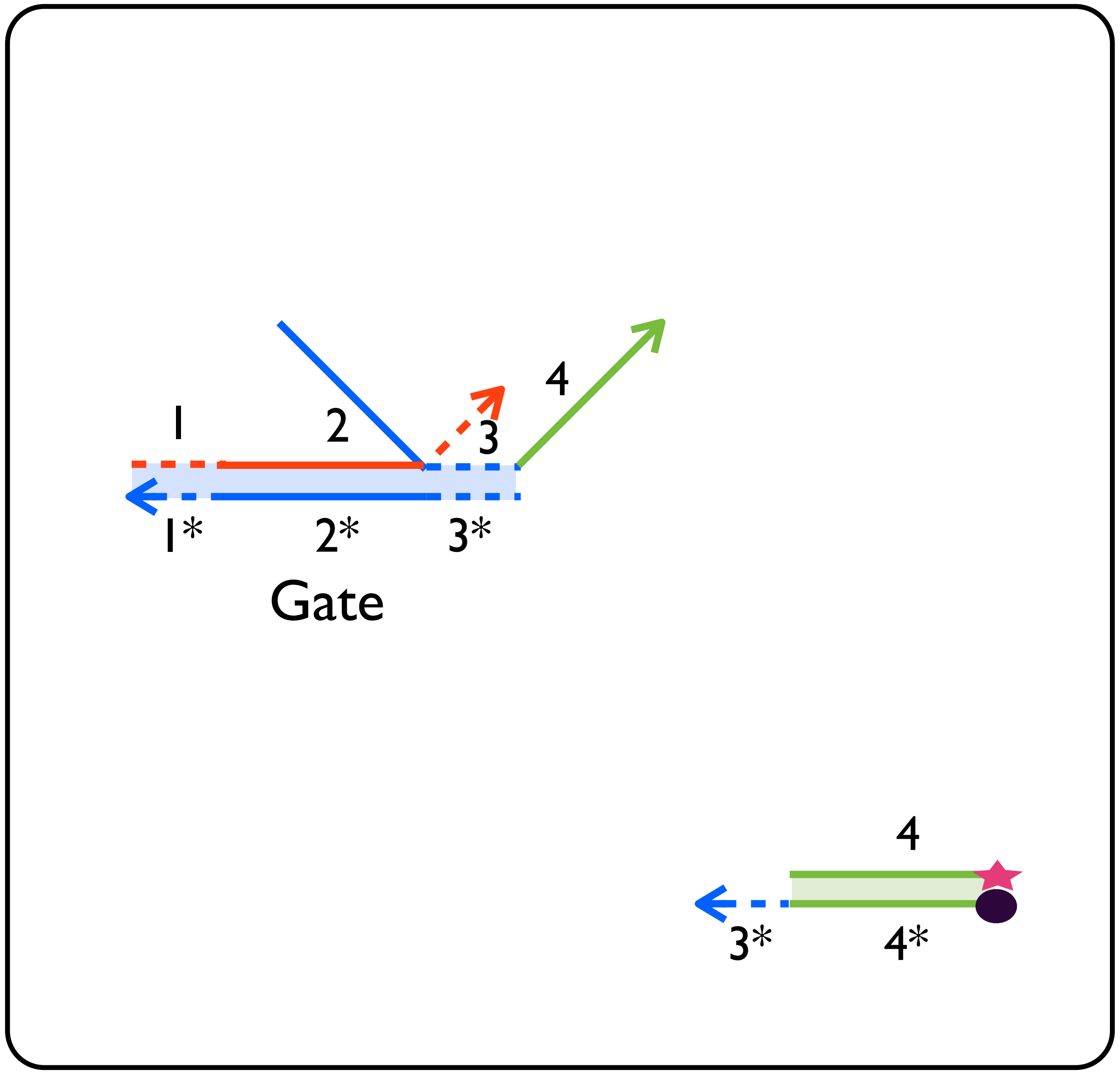

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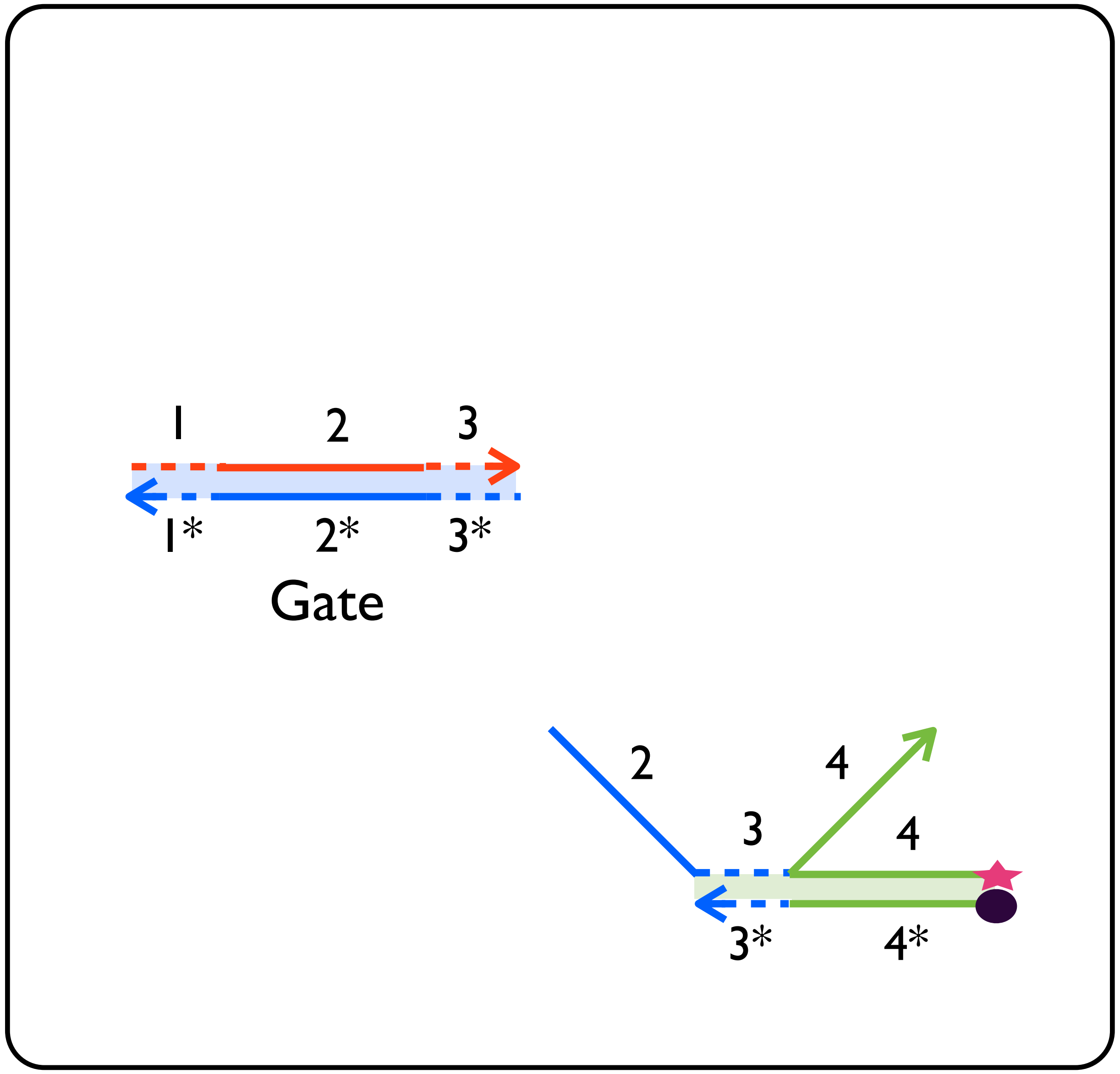

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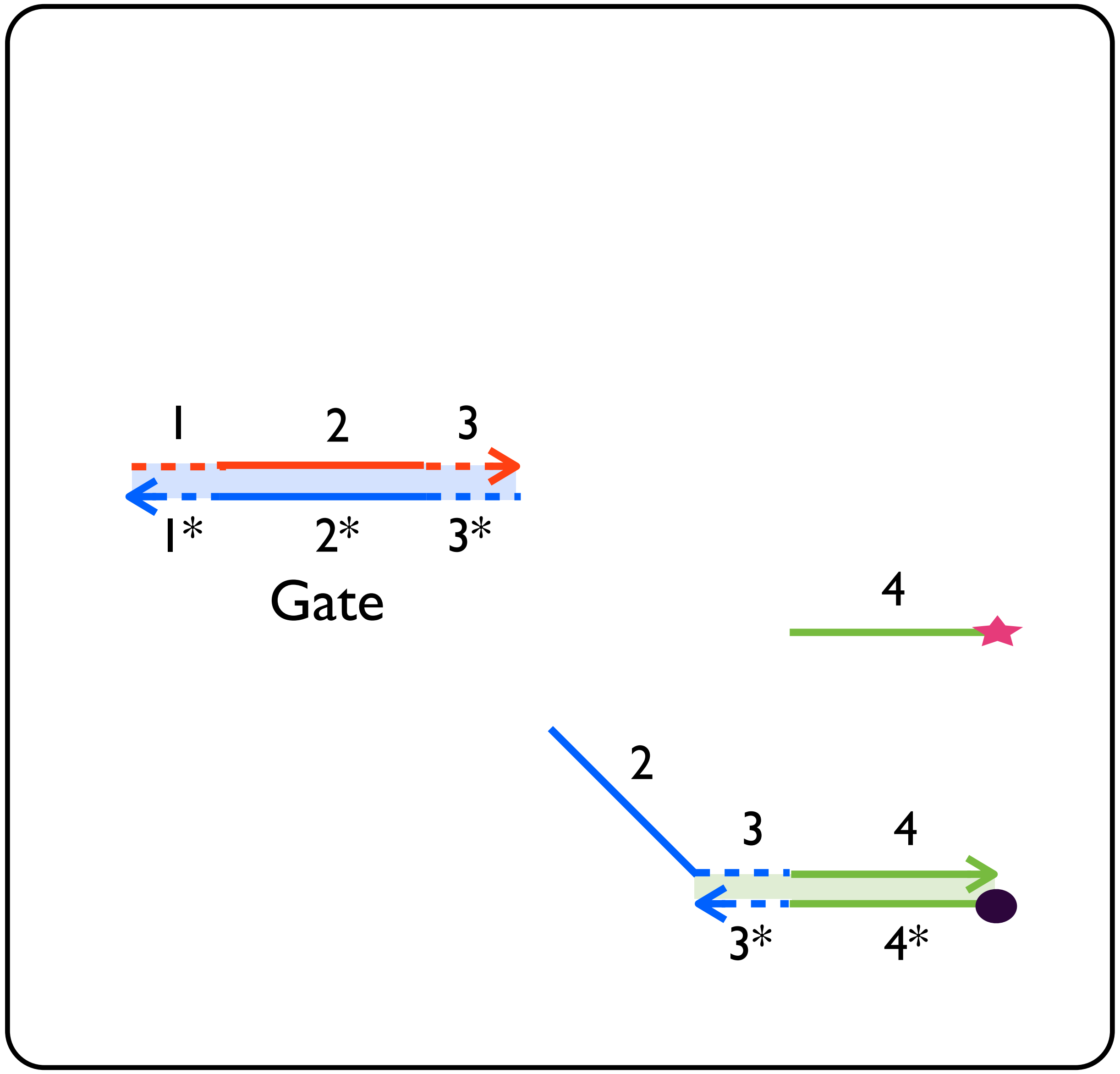

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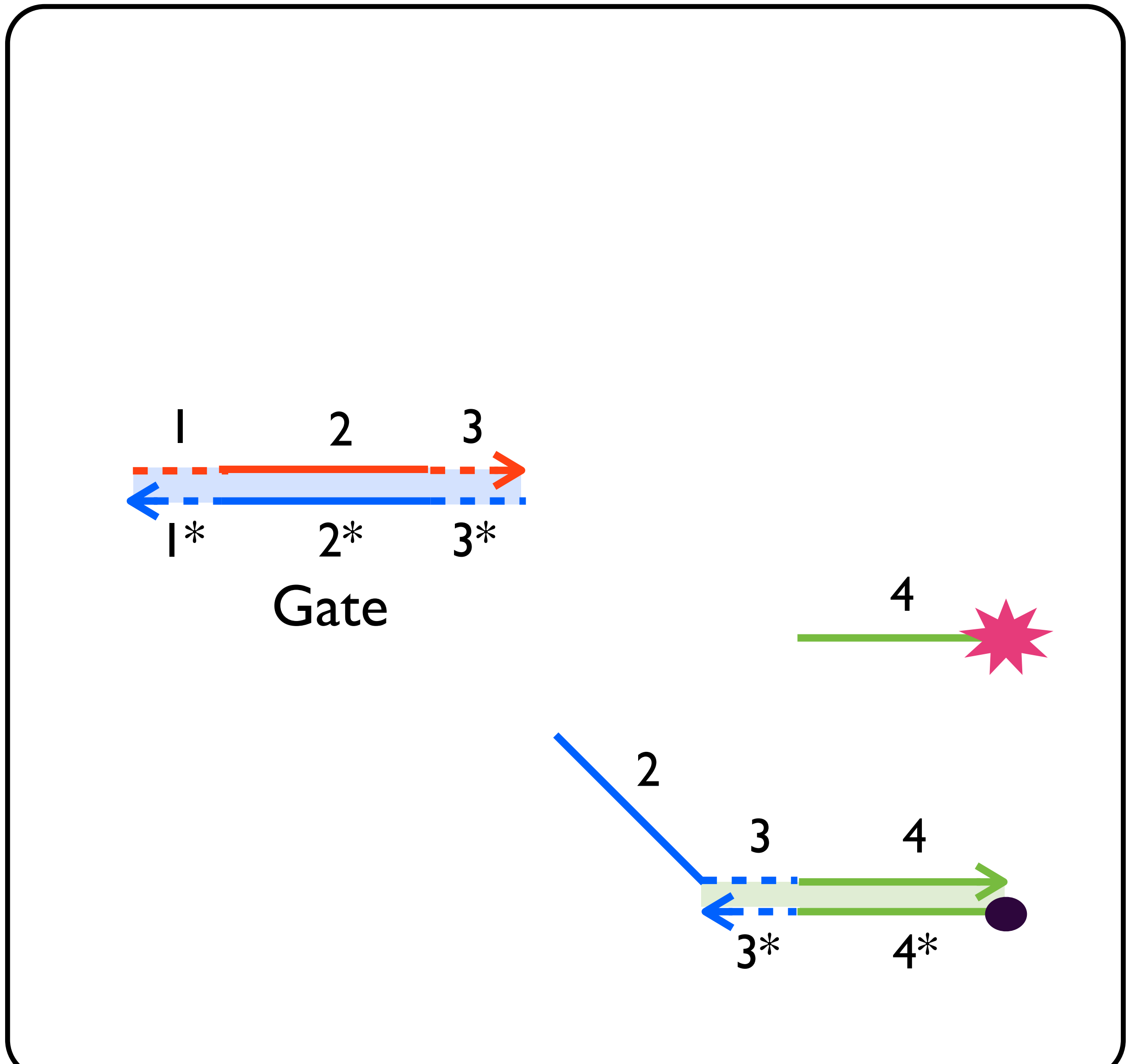

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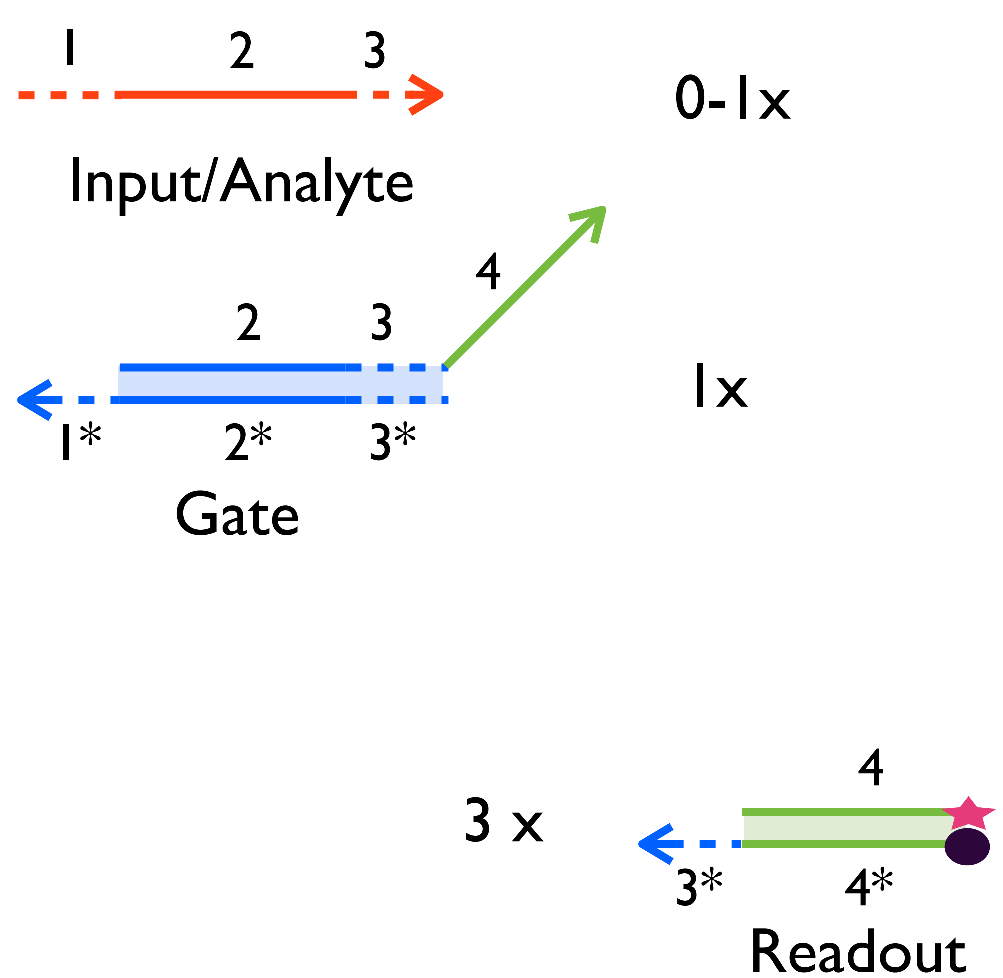
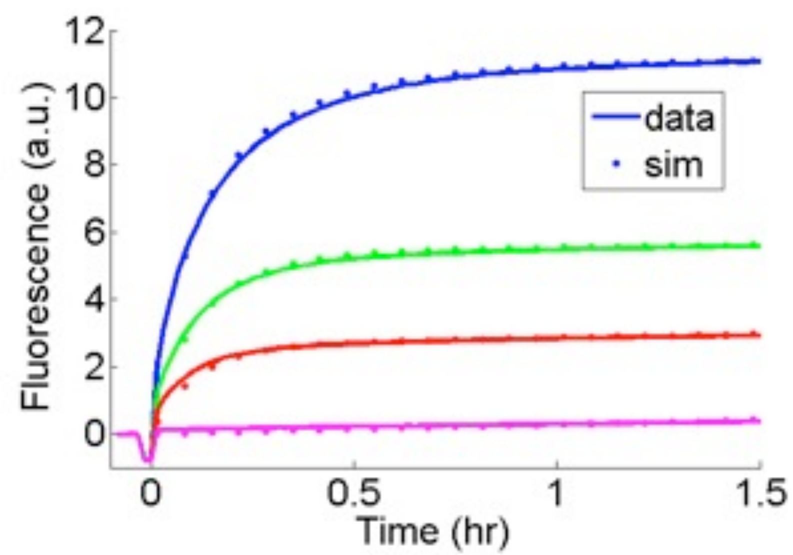
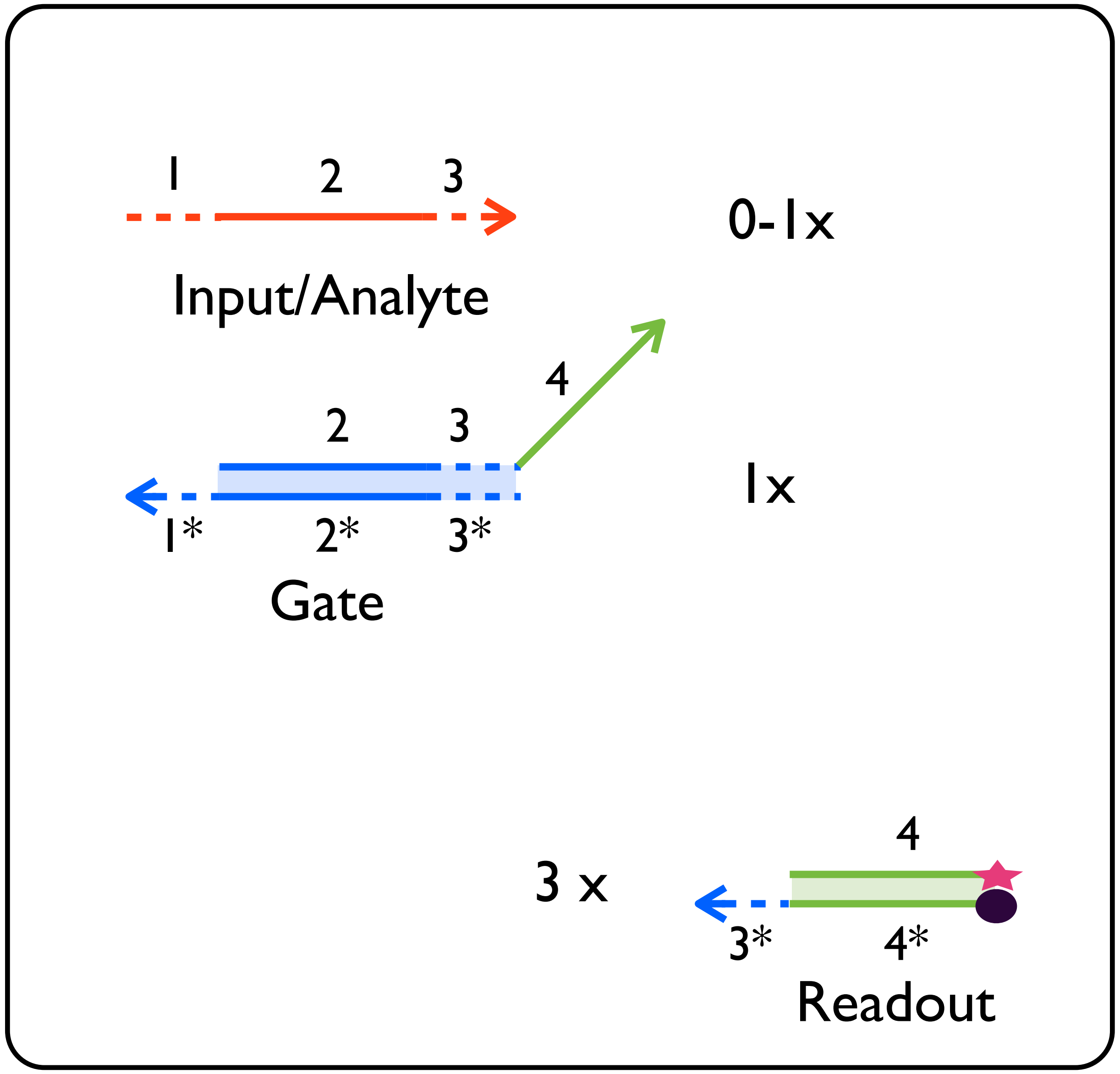


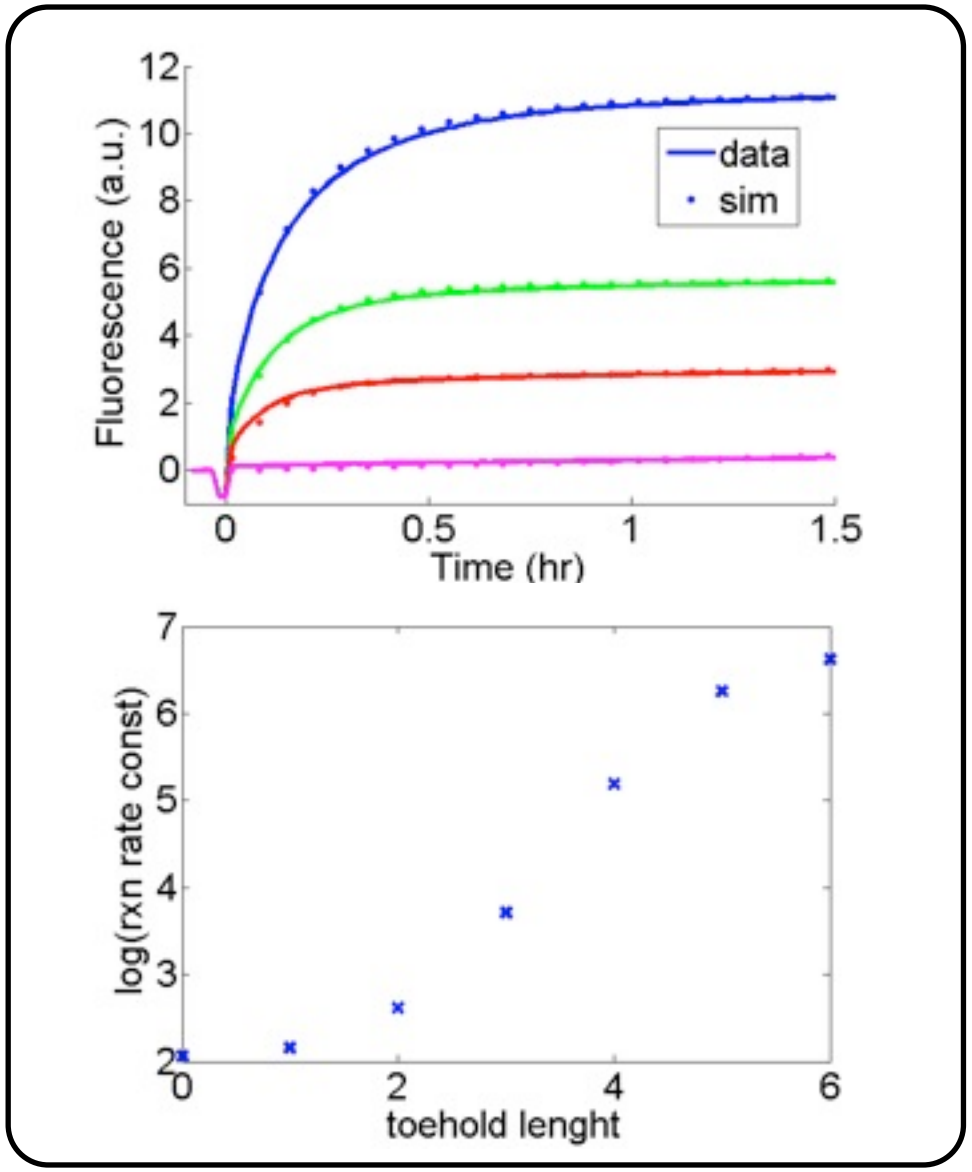


$$\text{In} + \text{Gate} \xrightarrow{k} \text{Out} + \text{Waste}$$

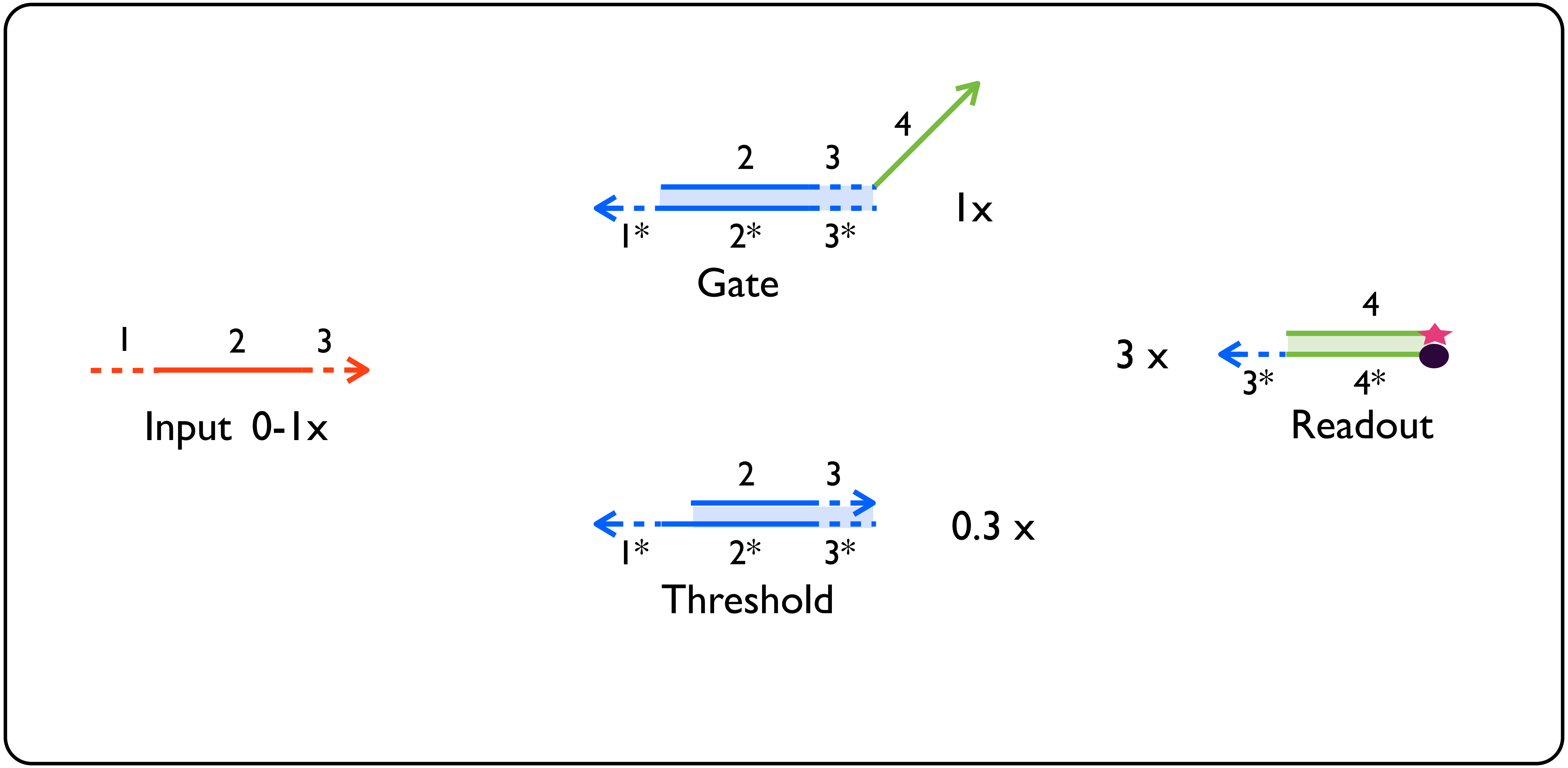
(10 nM gates, 30nM readout, TAE 12.5 mM Mg^{++})

Toehold strength determines reaction rate





Competition and thresholding



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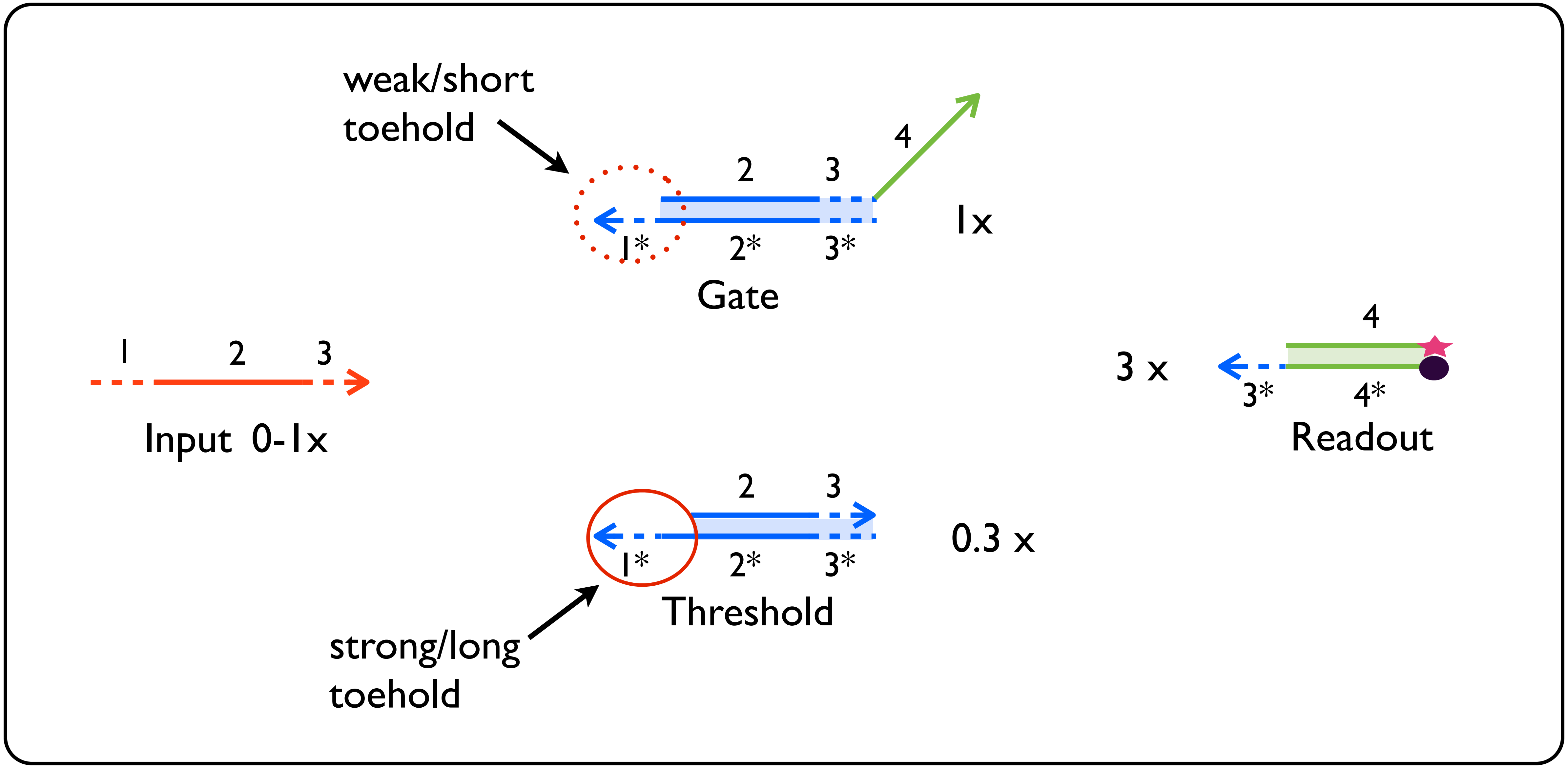

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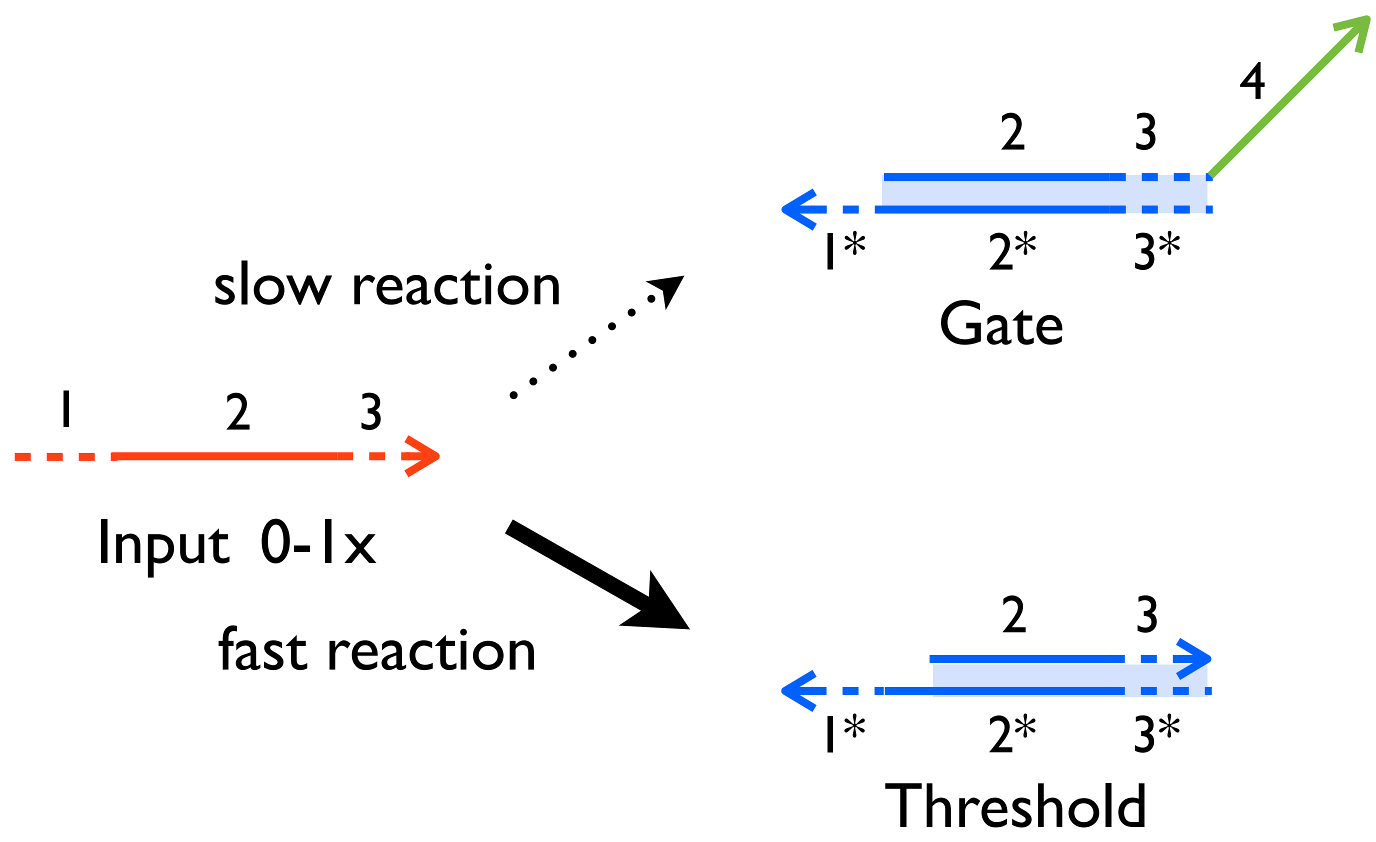
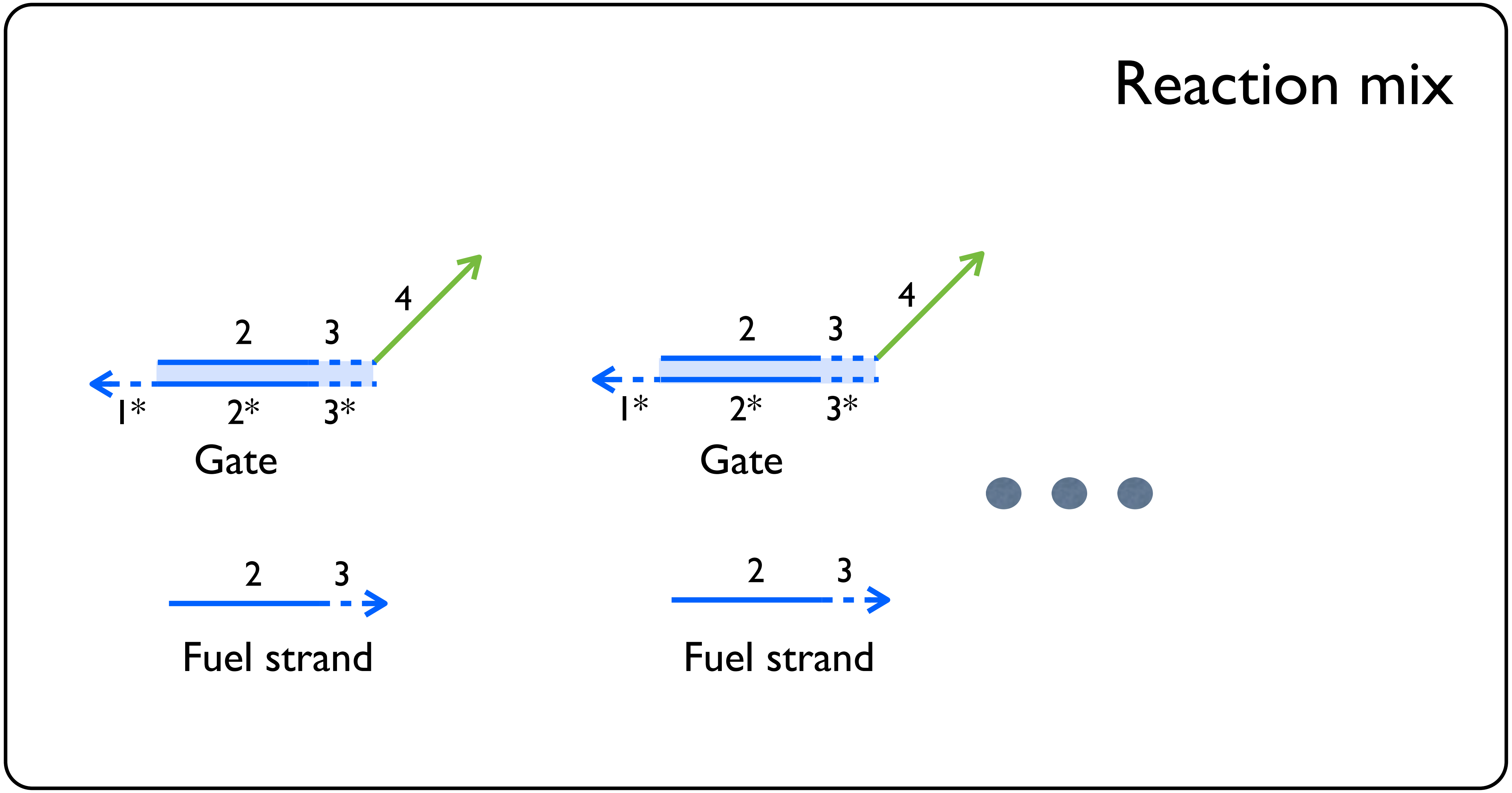


$$\Gamma = k_s \, [In] \, [G]$$

$$\Gamma = k_f \, [In] \, [T]$$

Amplification: An input can act catalytically and release multiple outputs



Qian and Winfree, Science (2011)
(see also Zhang et al. Science (2007), Seelig et al. JACS (2006), Turberfield et al. PRL (2004))

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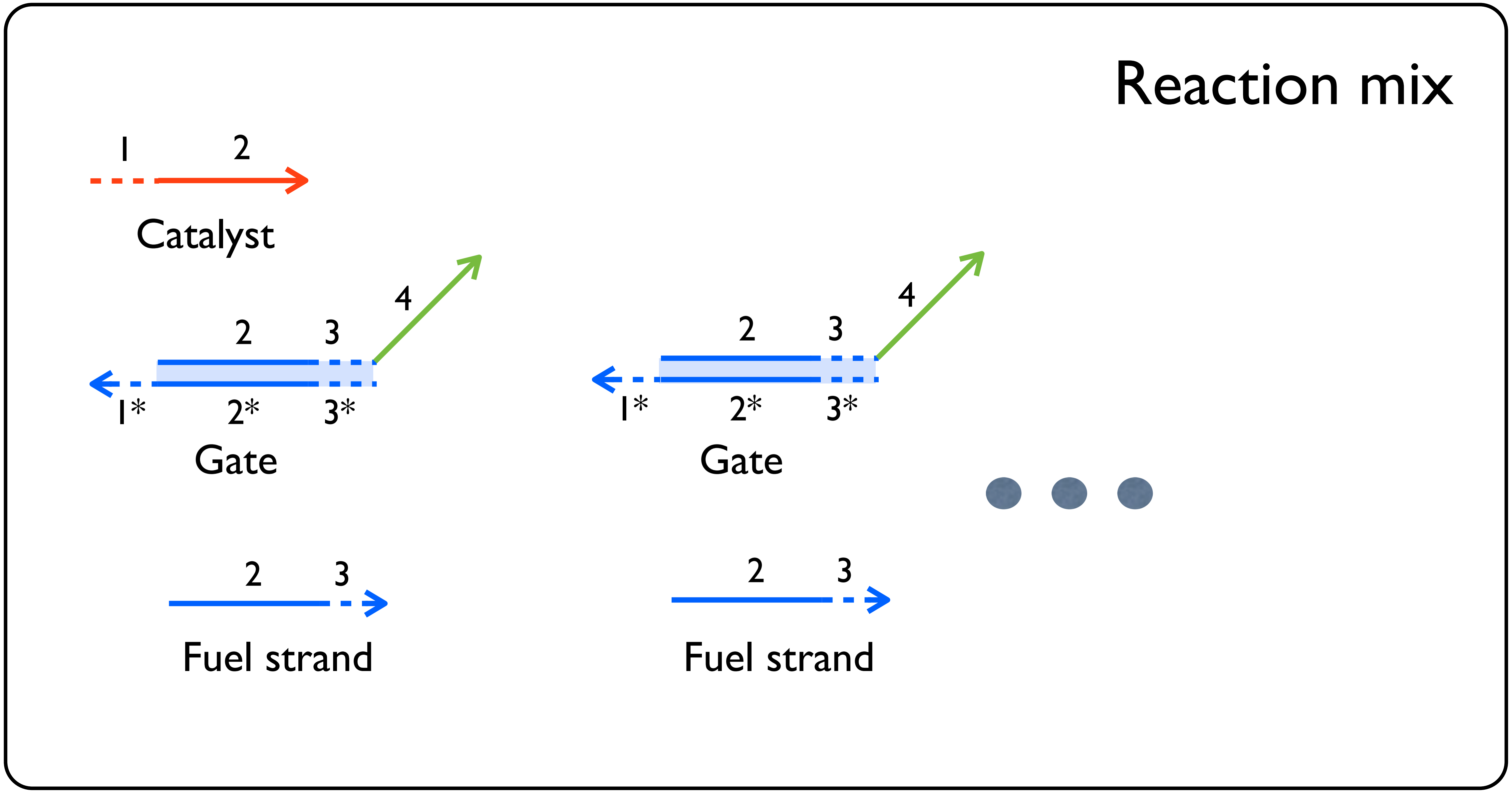

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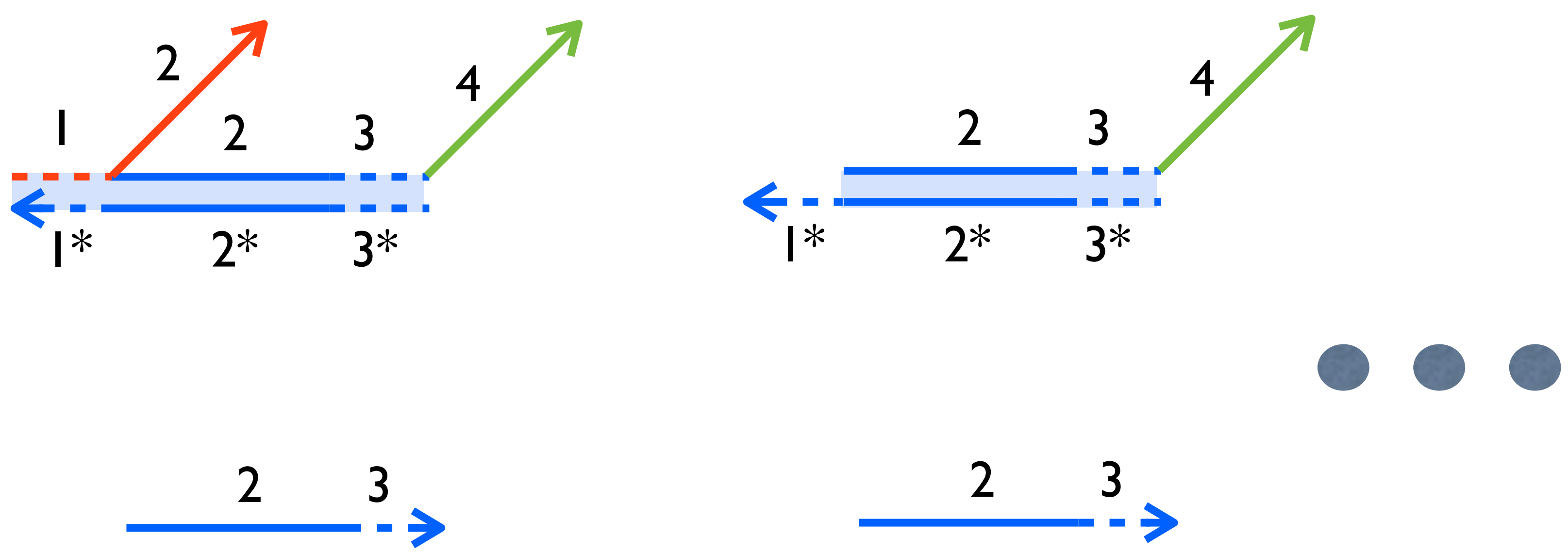

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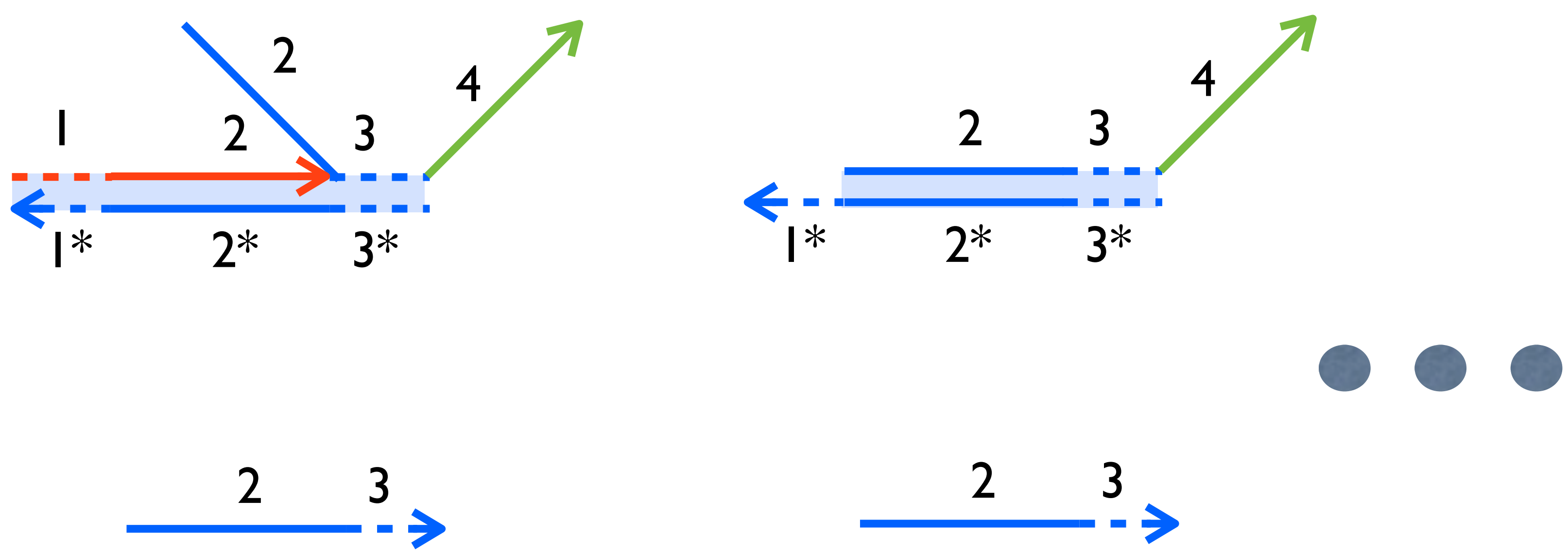

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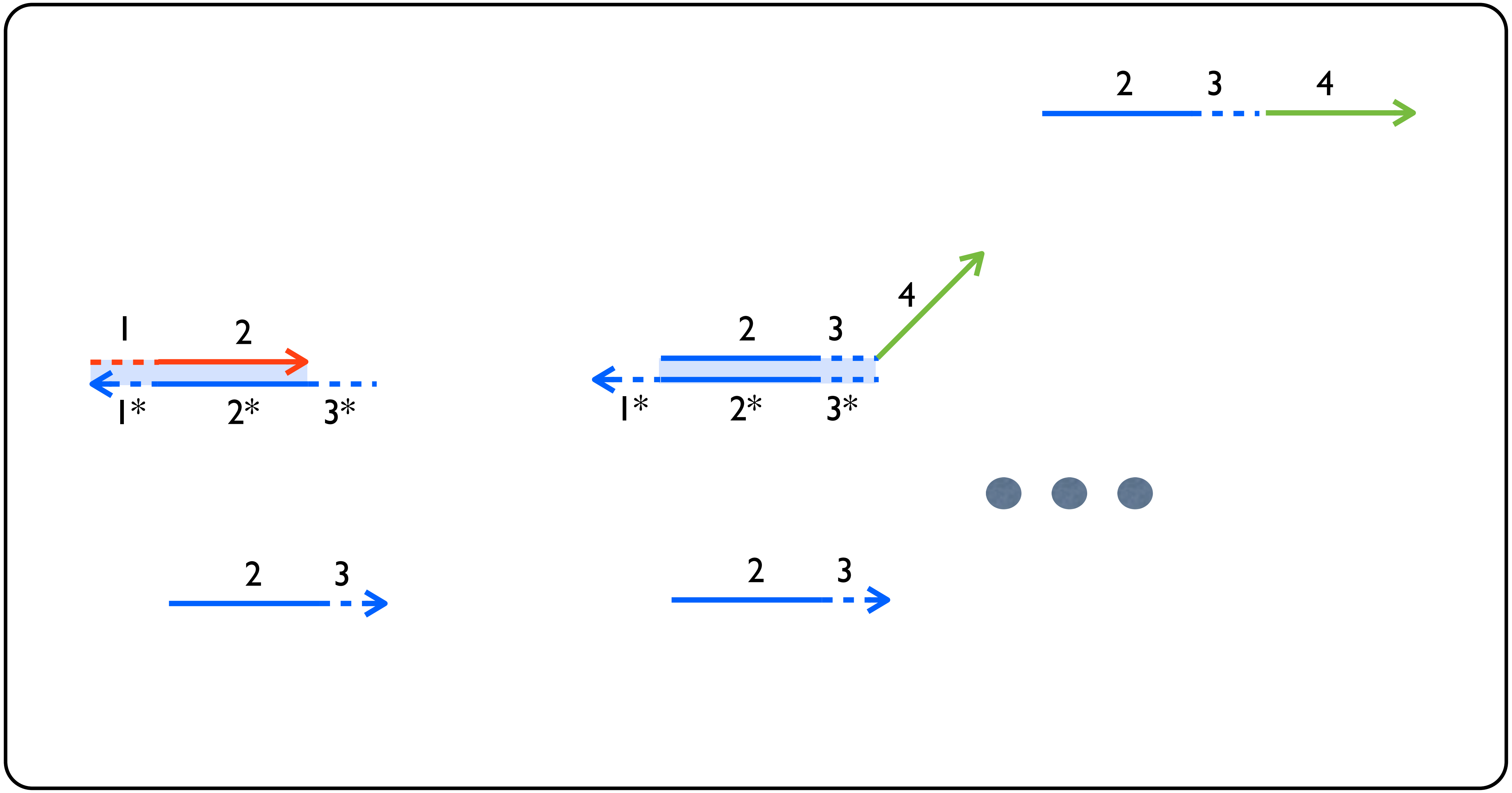

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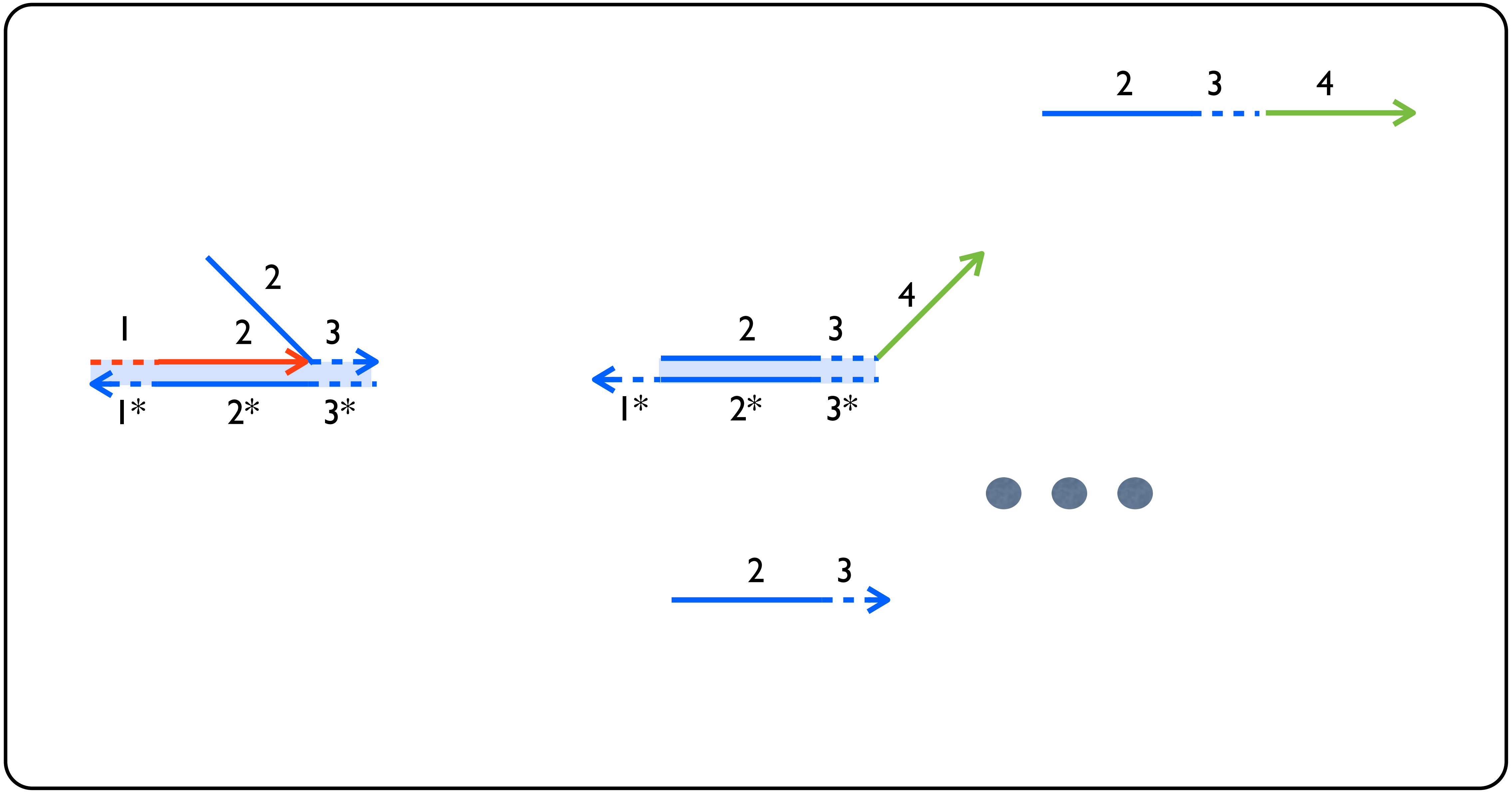

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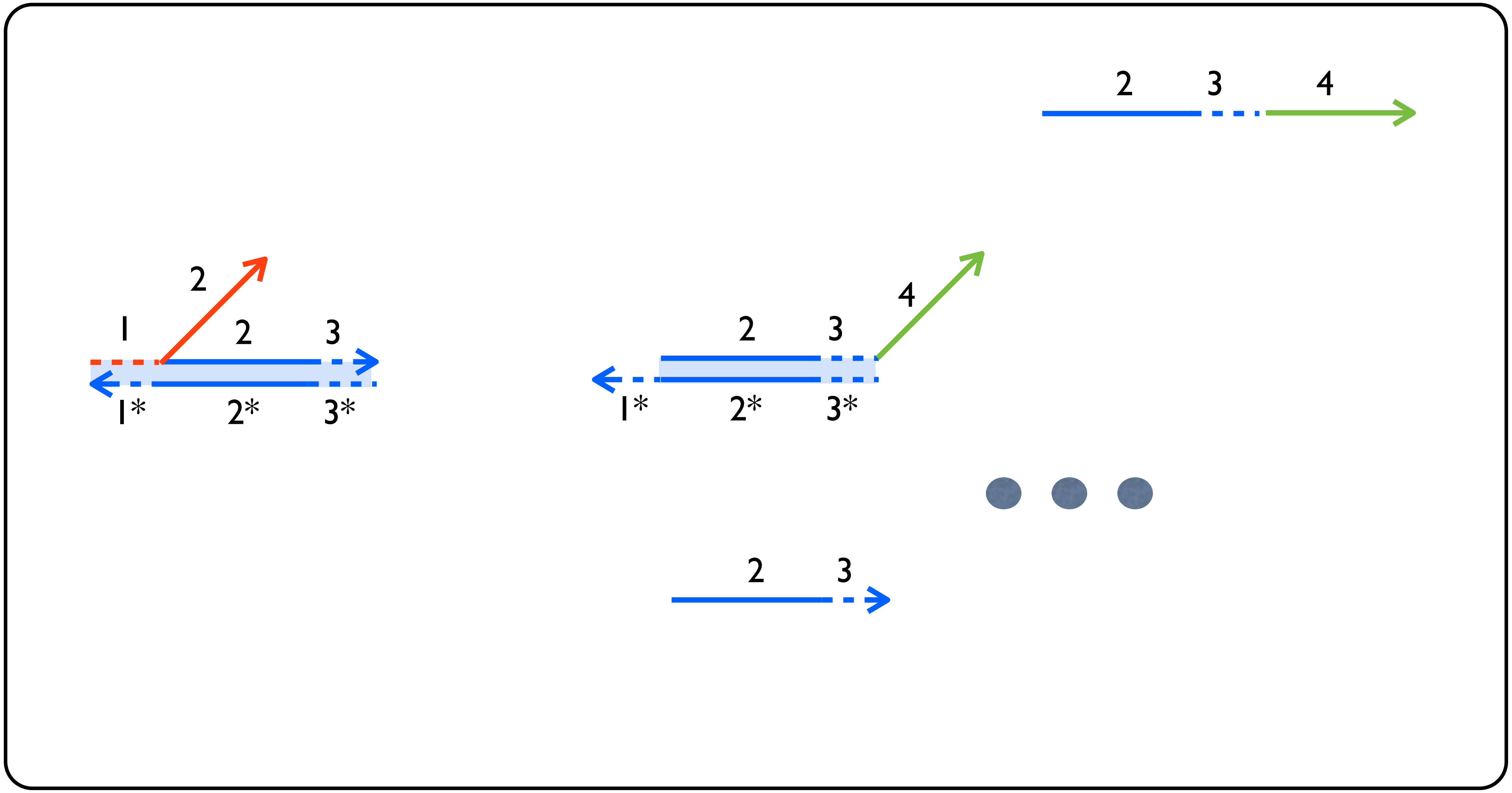

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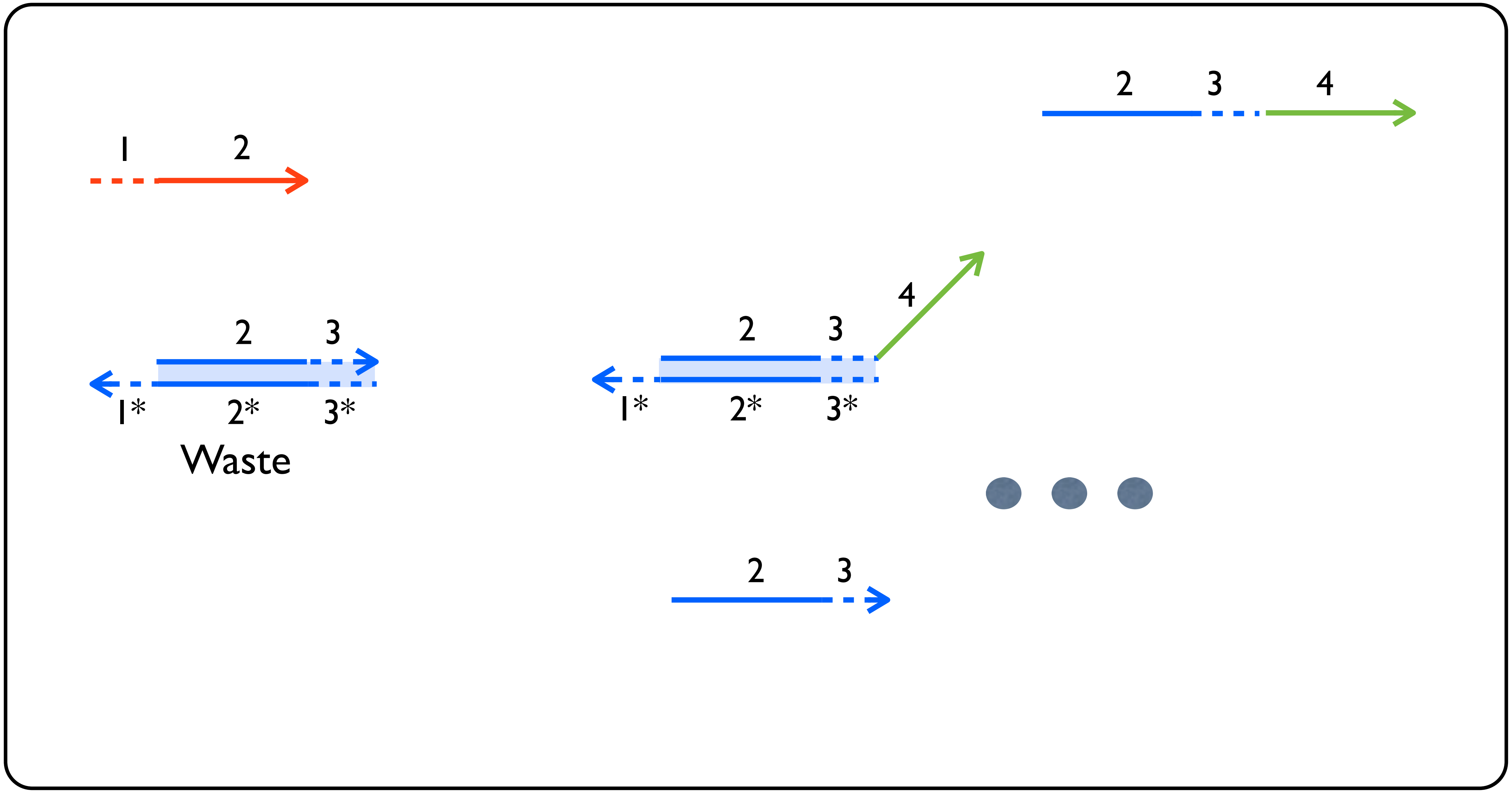

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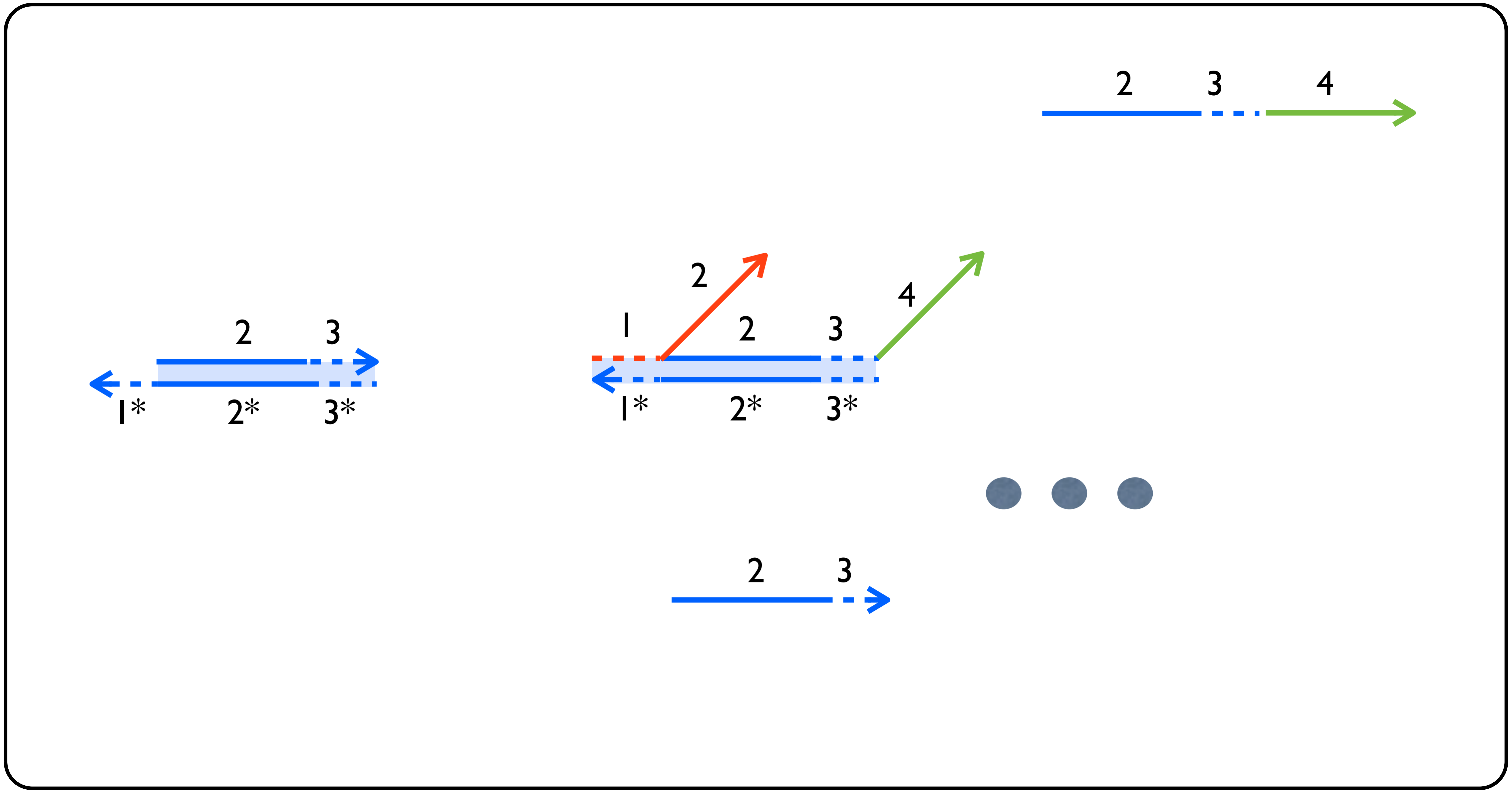

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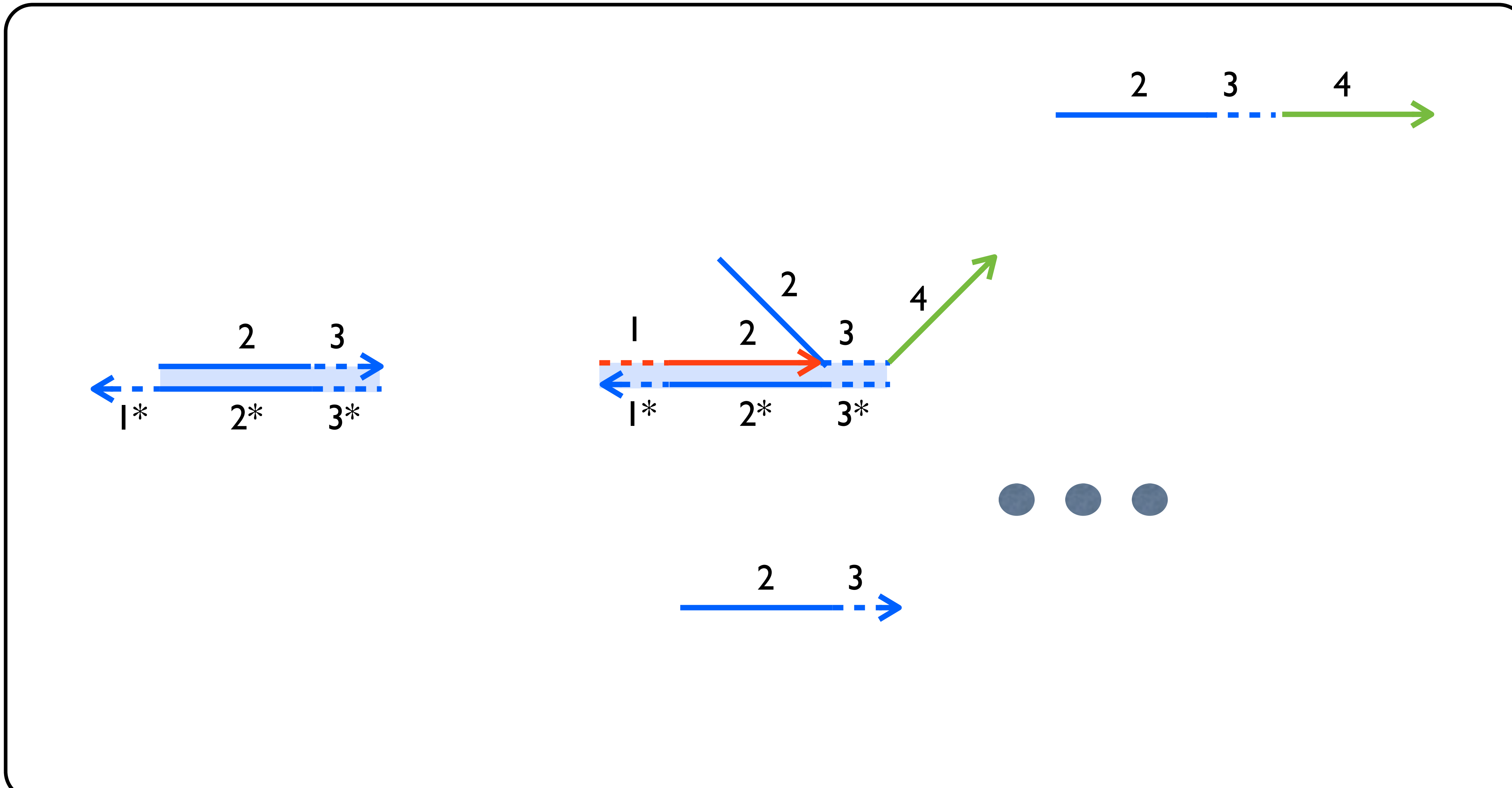

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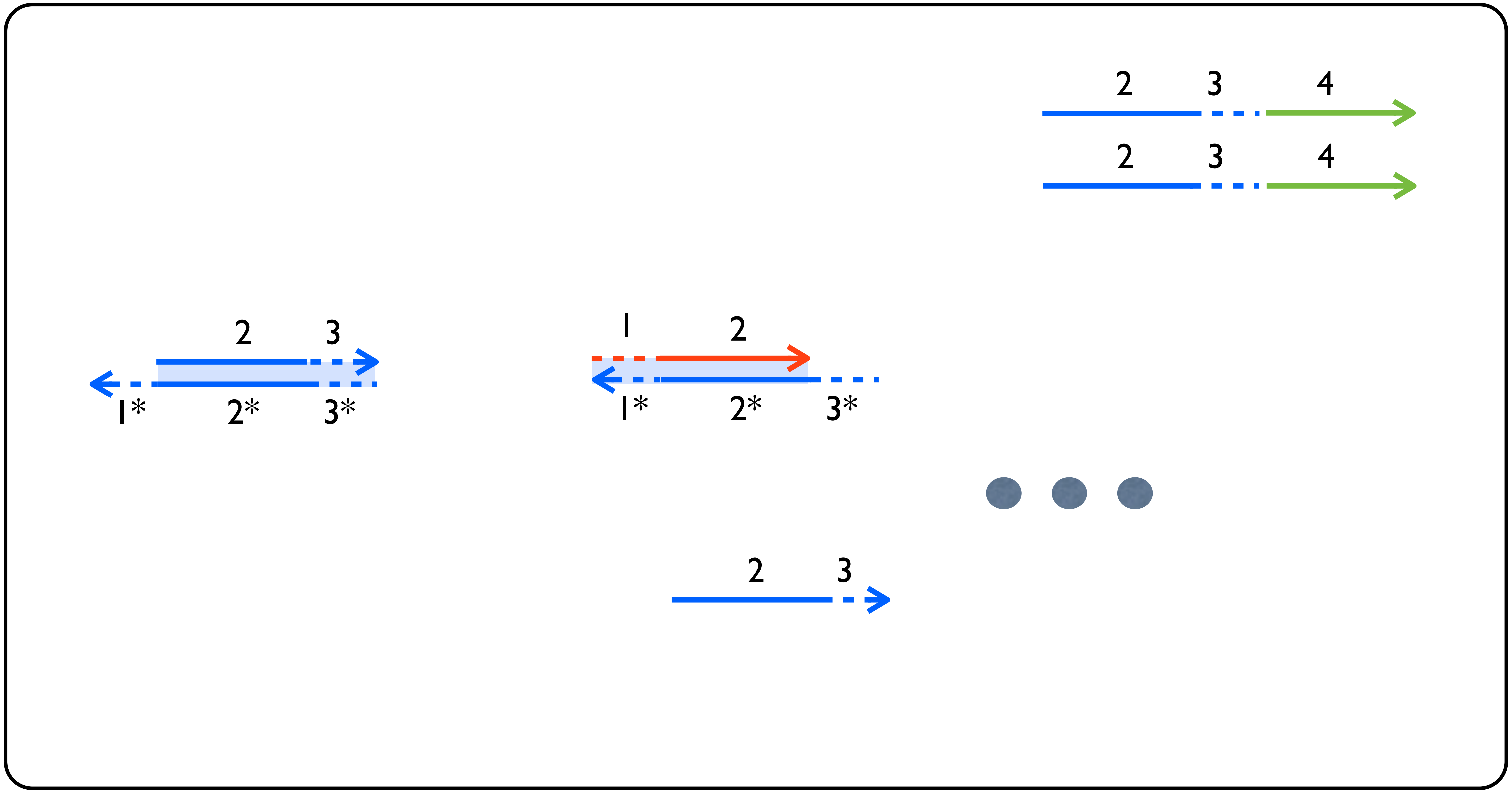

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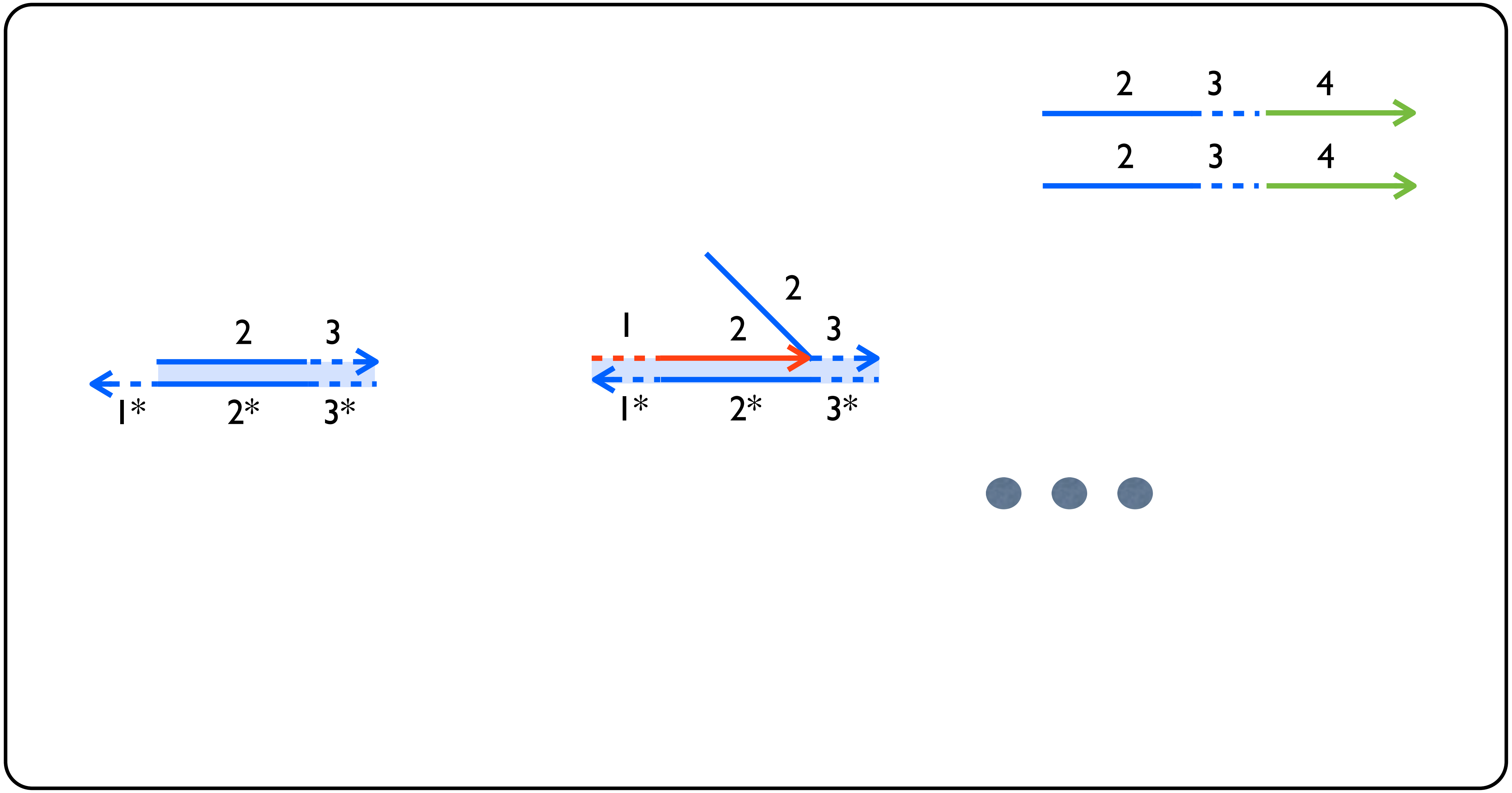

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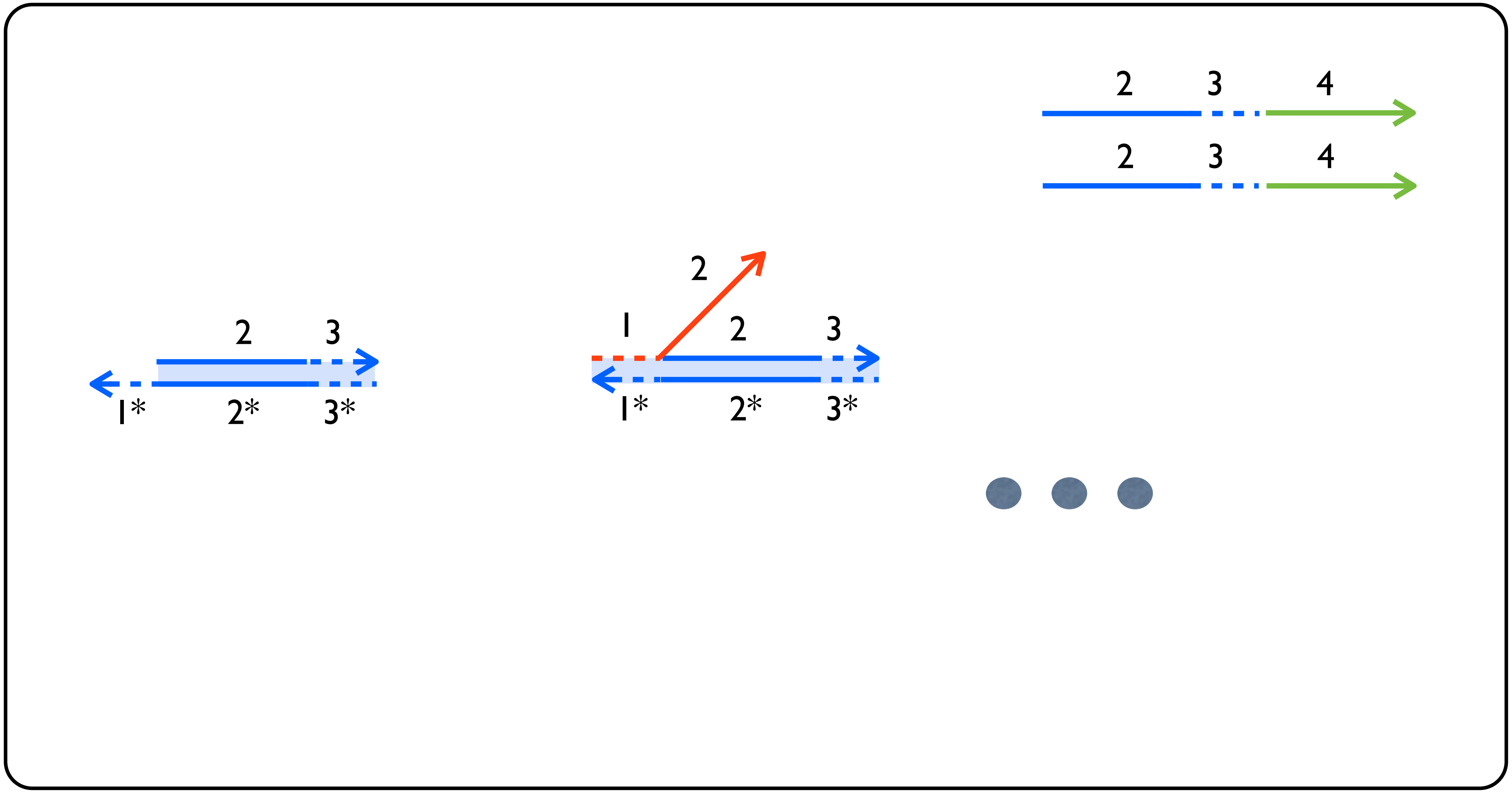

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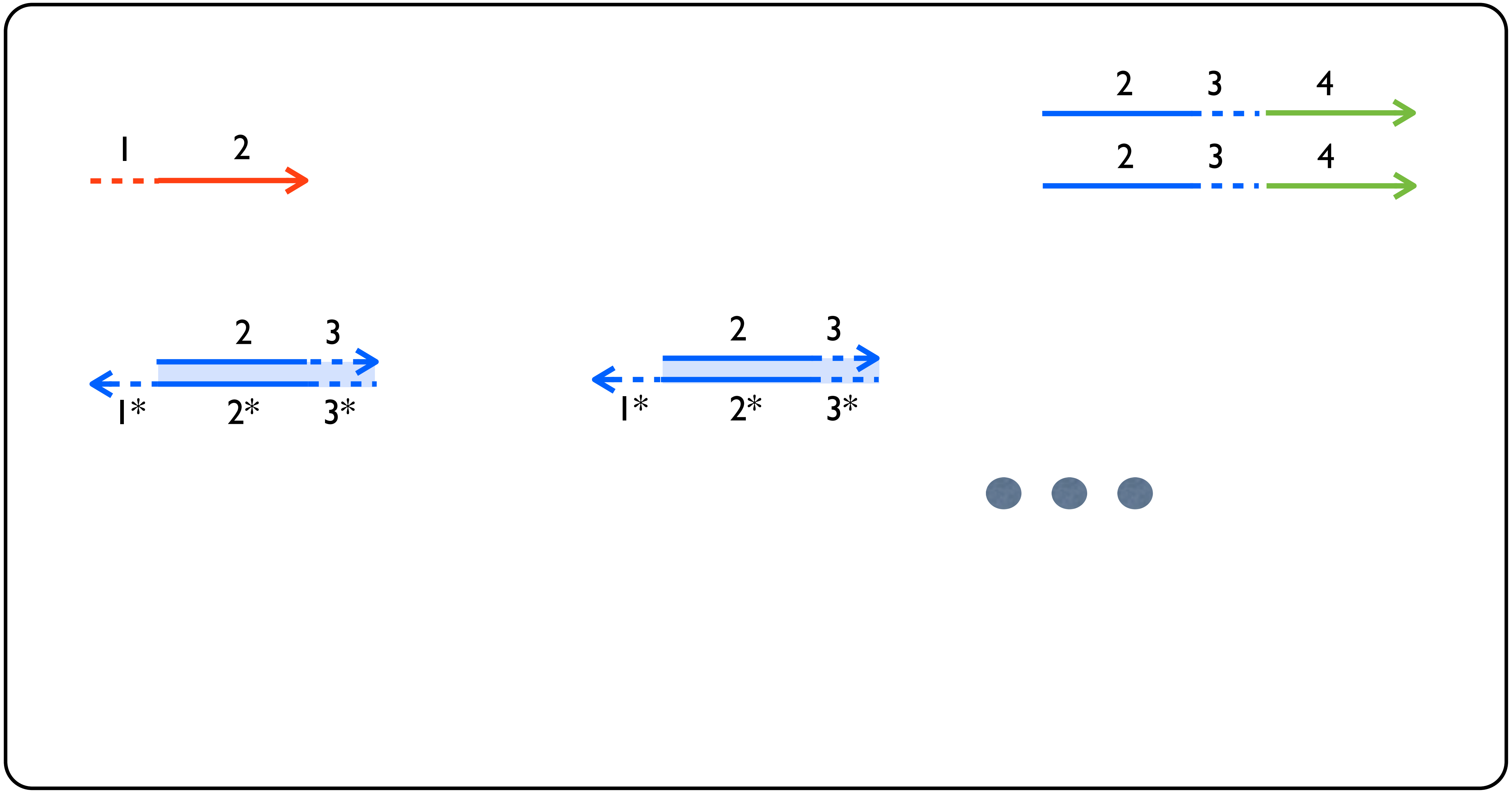

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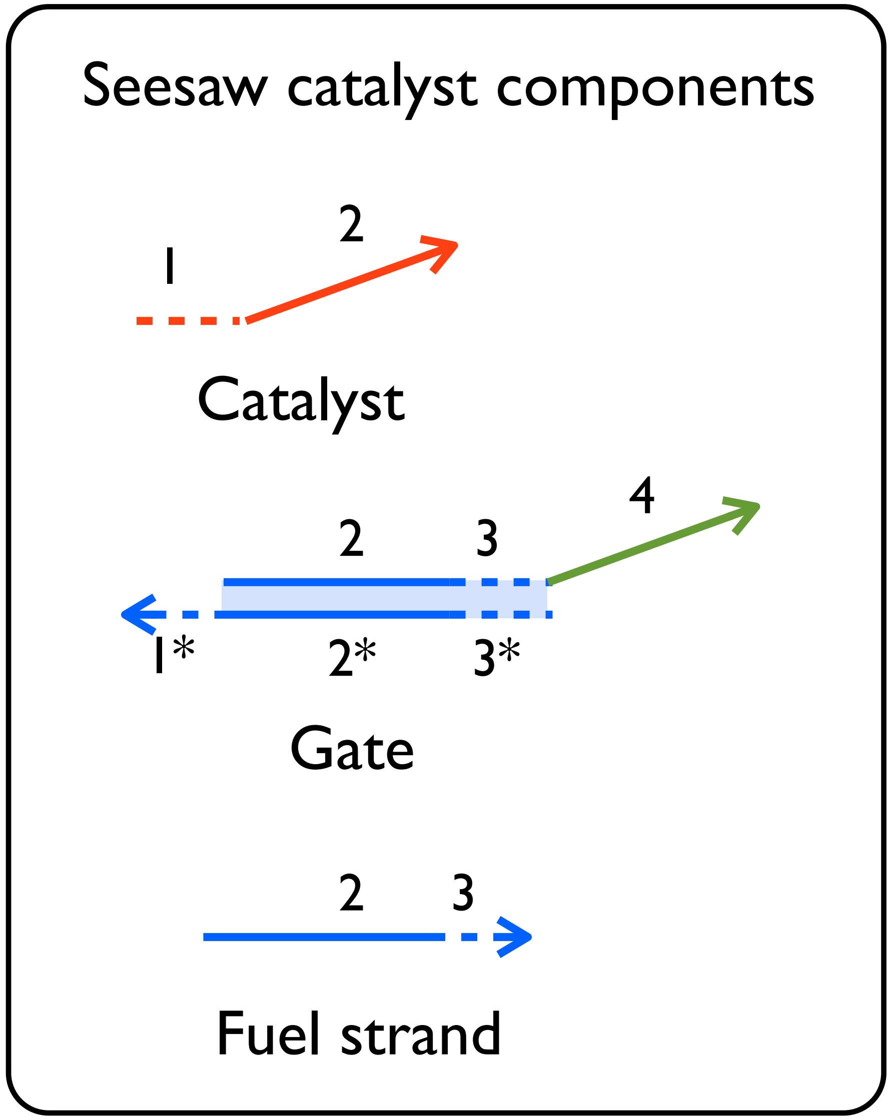

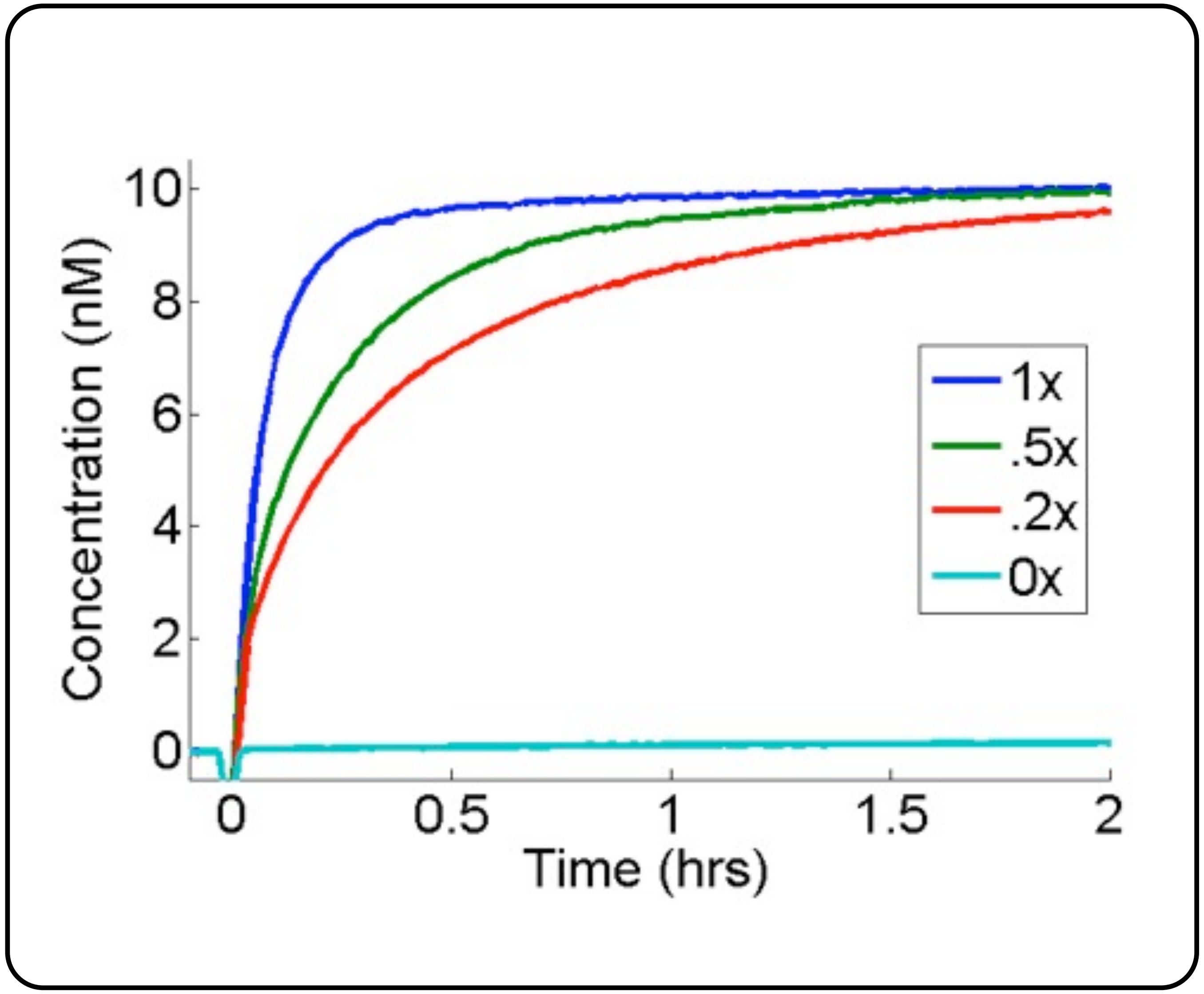

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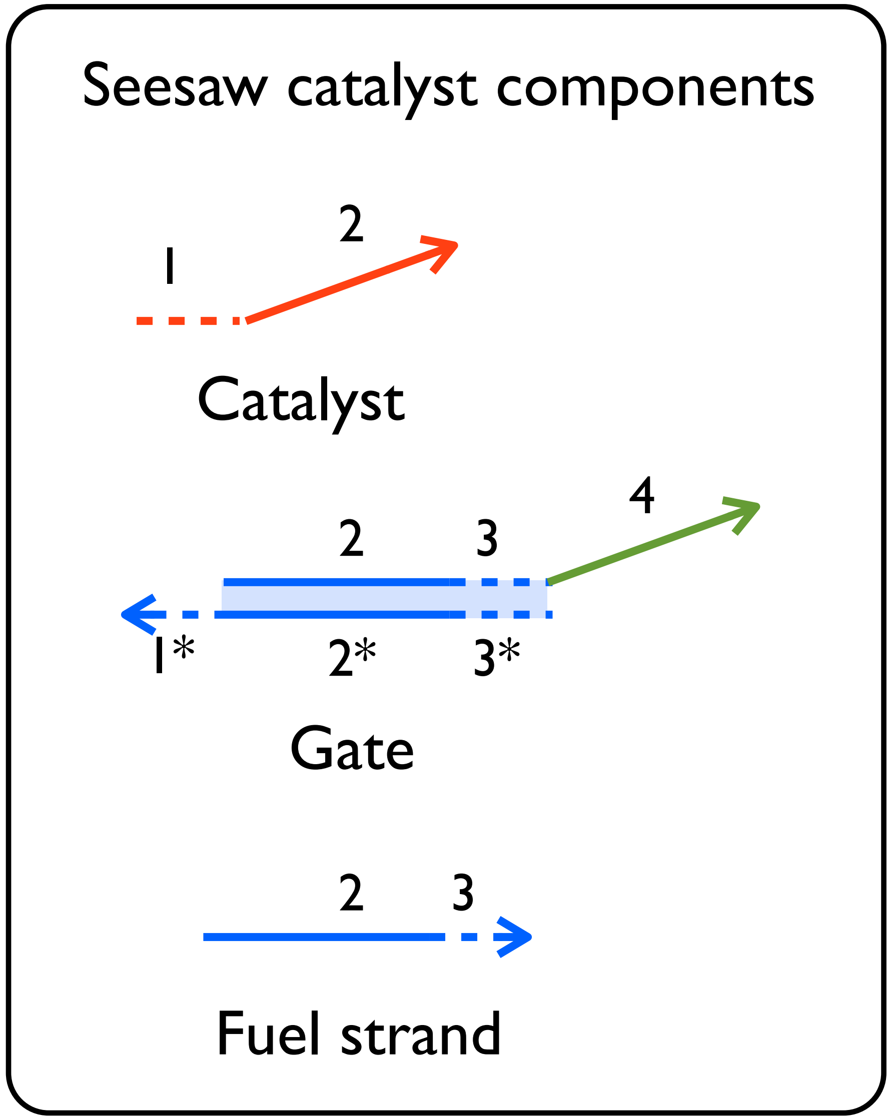
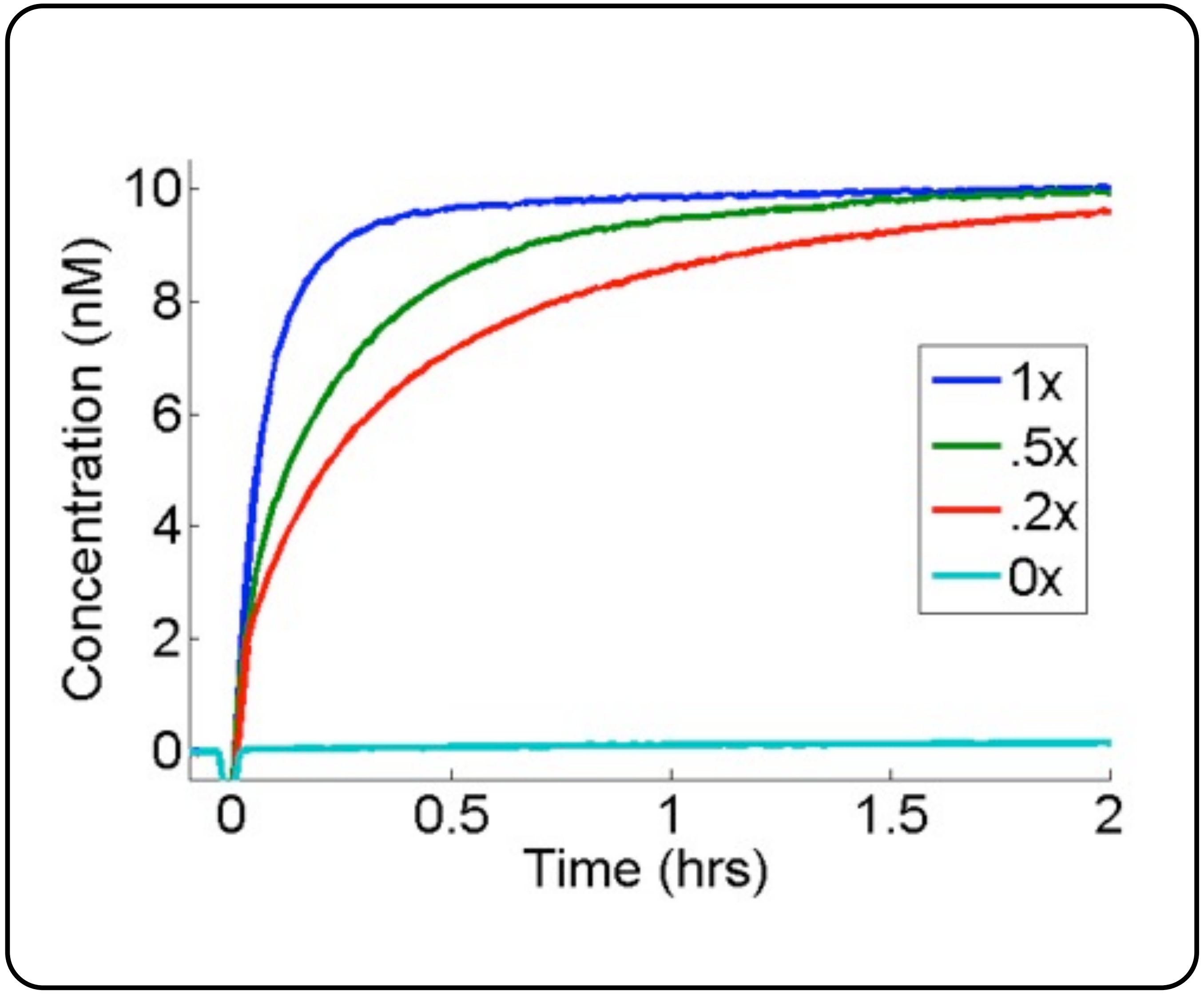
Combining amplification and thresholding





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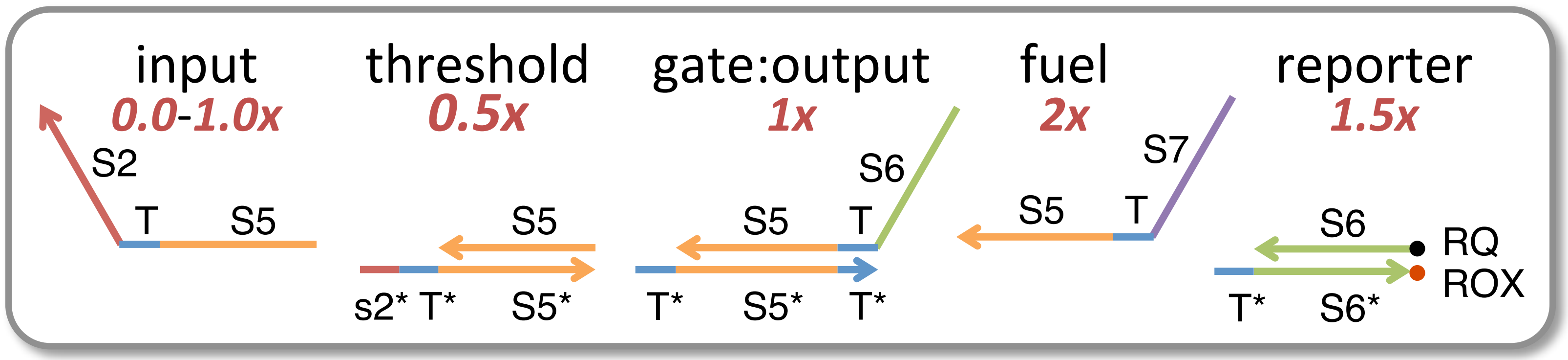
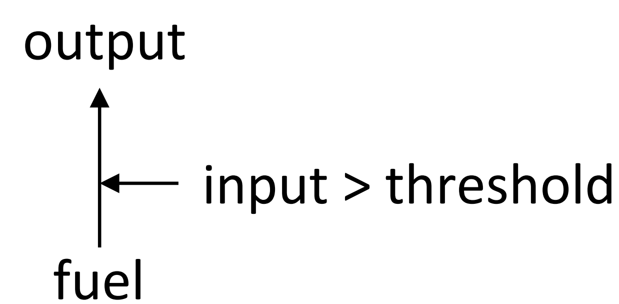
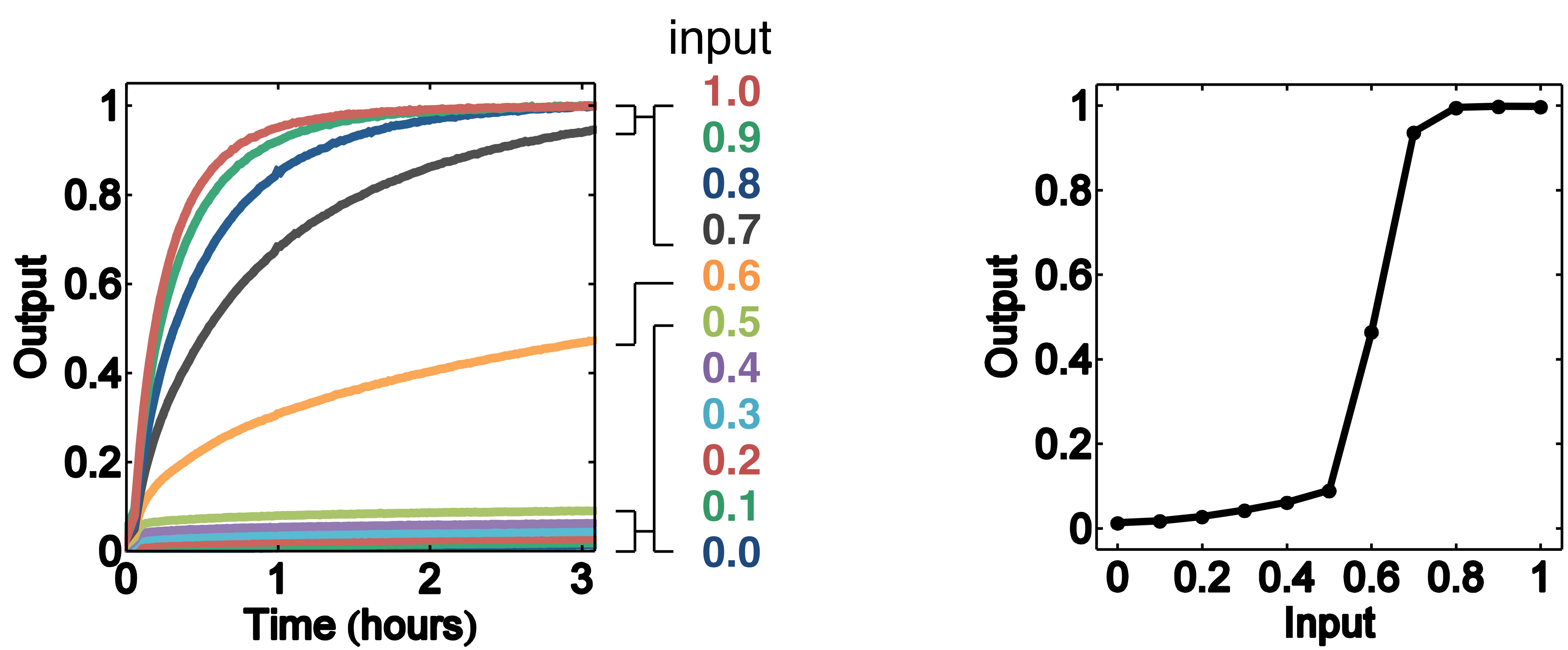


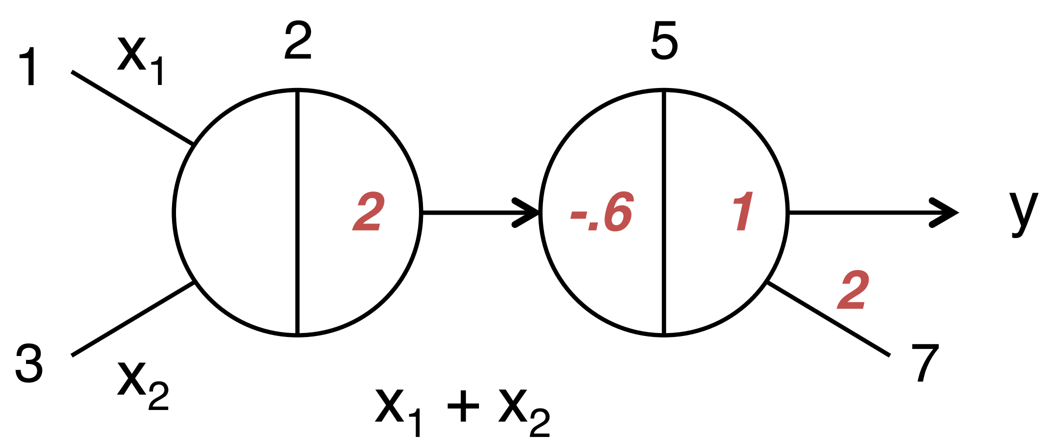


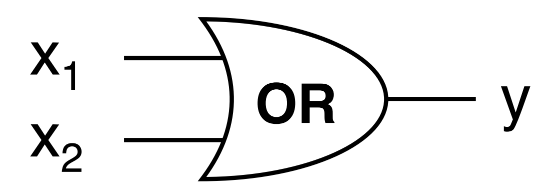
1x = 100nM



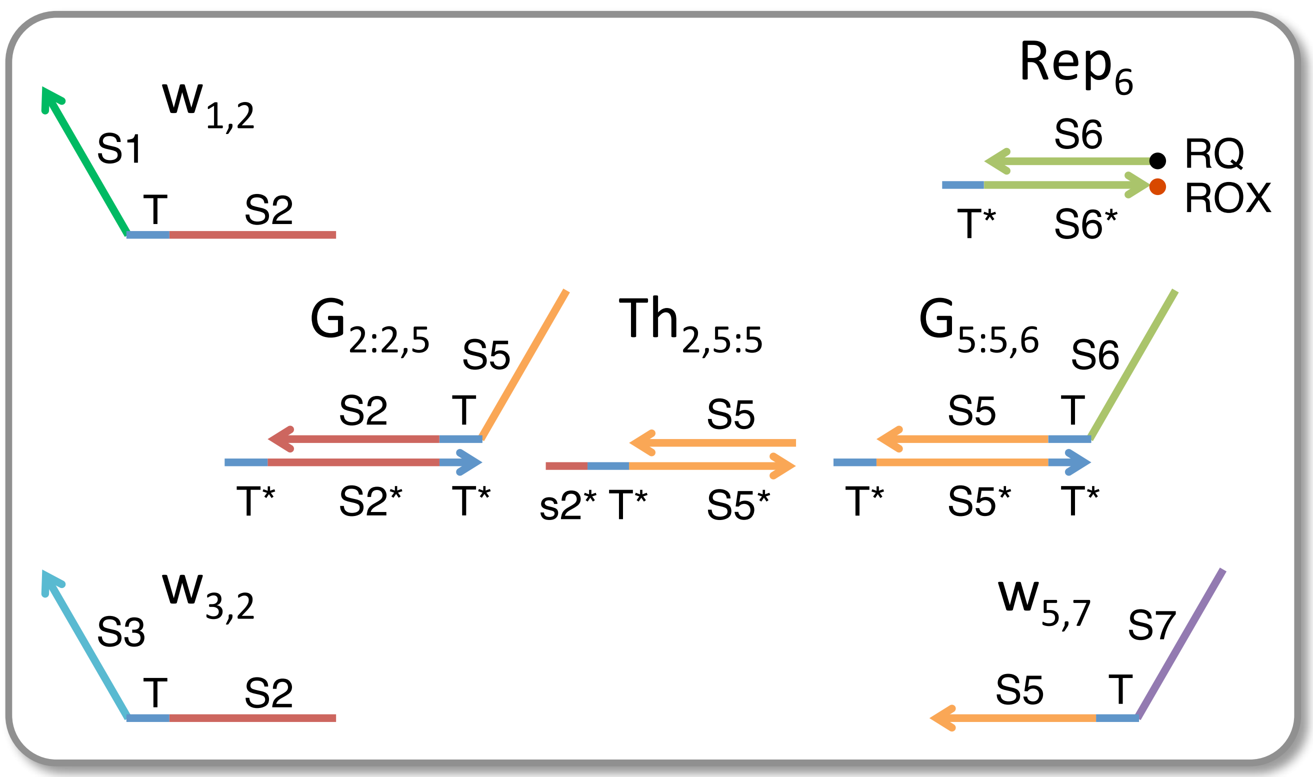
Slide credit: Lulu Qian

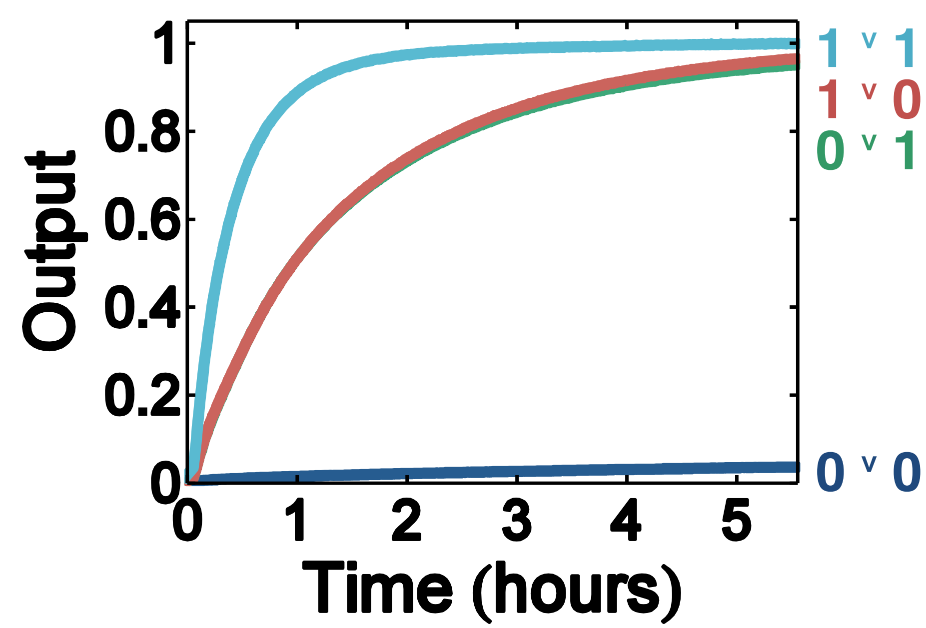
Seesaw OR logic





OFF: 0 ~ 0.2
ON: 0.8 ~ 1

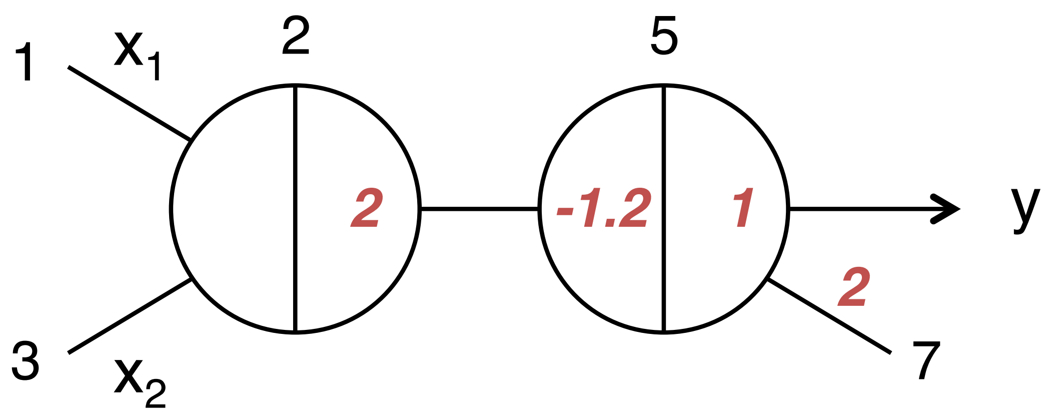




0=0.1x 1=0.9x 1x = 100 nM

Slide credit: Lulu Qian

Seesaw AND logic



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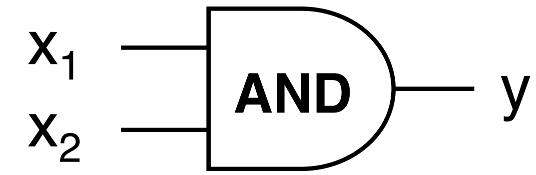
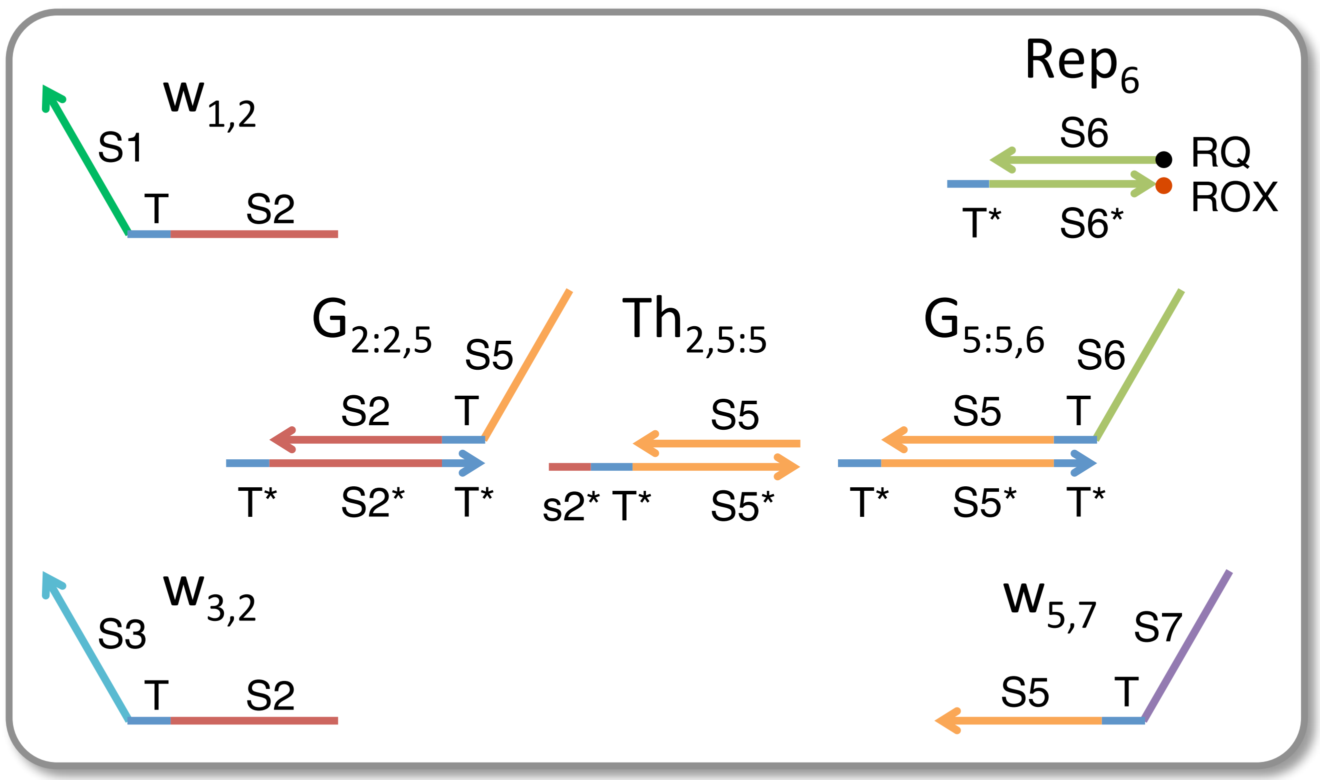
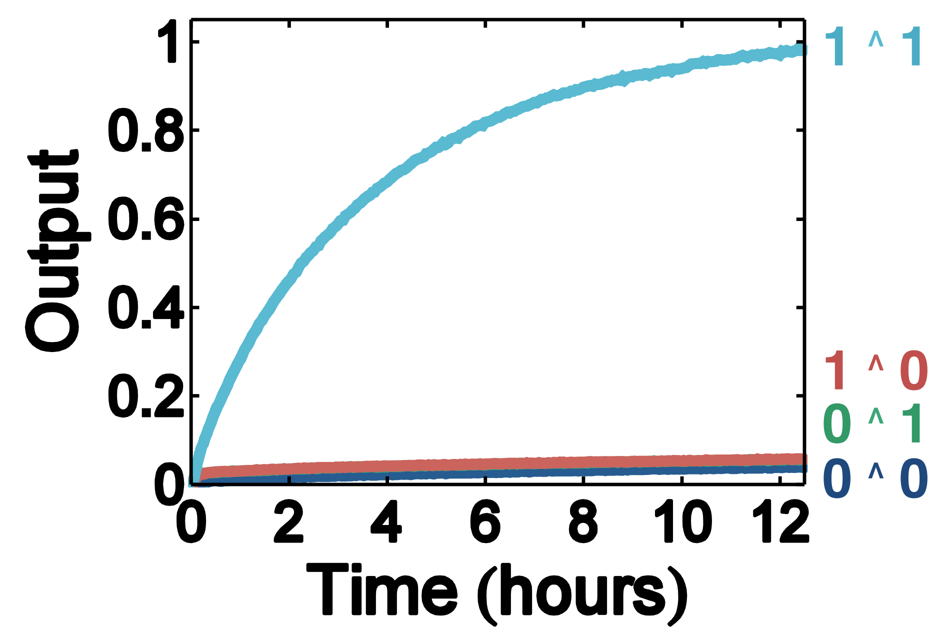


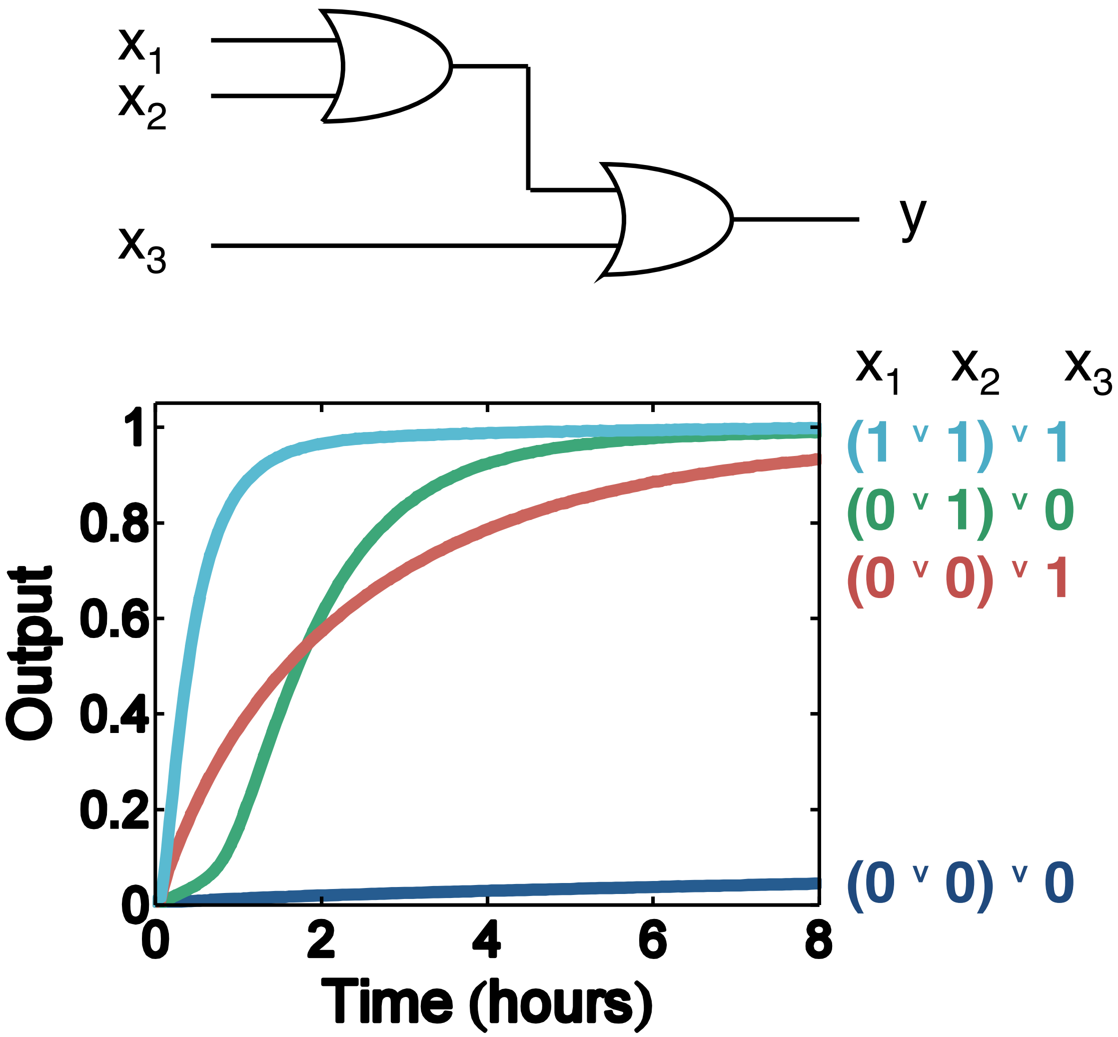


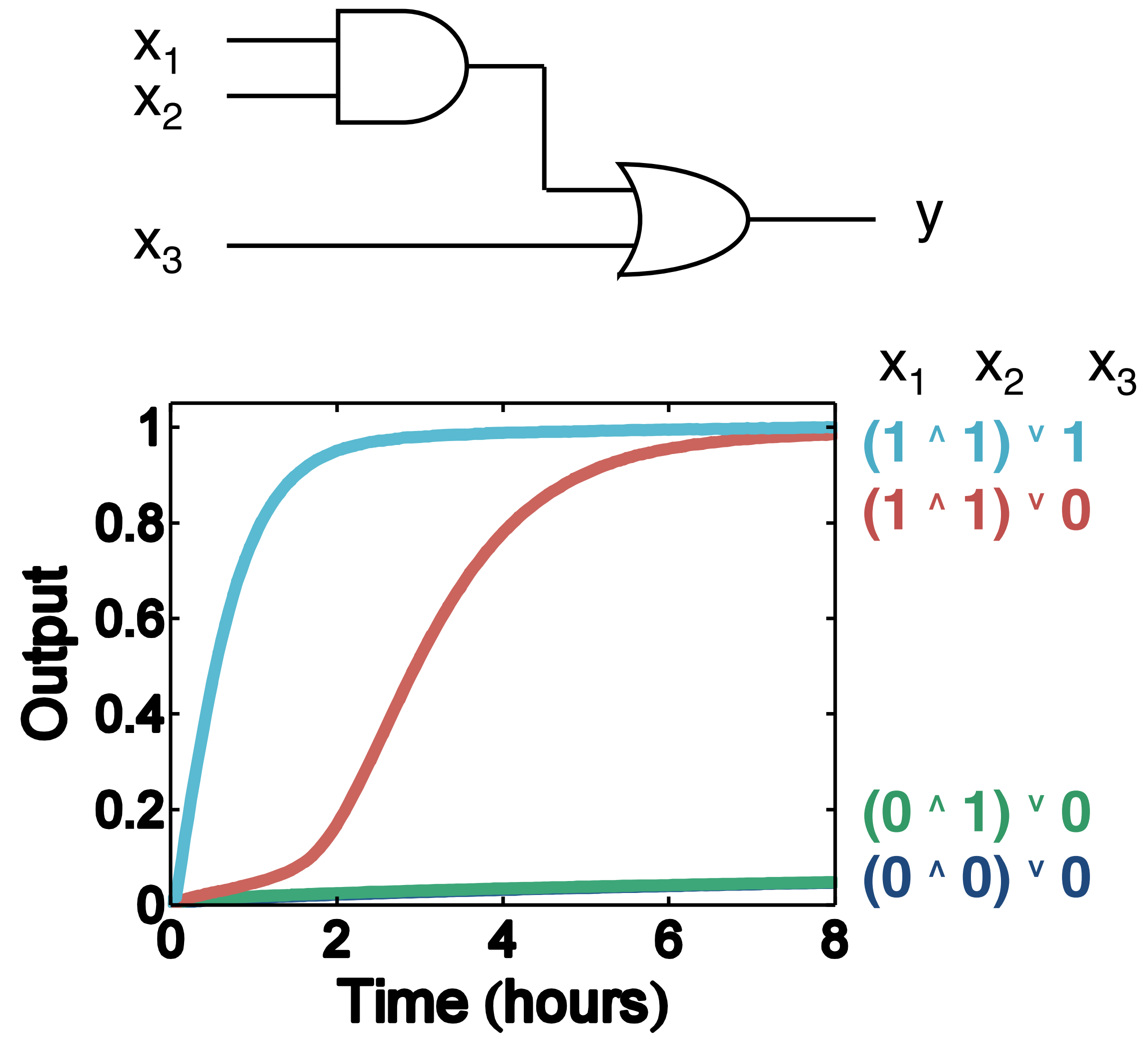


0=0.1x 1=0.9x 1x = 100 nM

Slide credit: Lulu Qian

Logic gate cascades

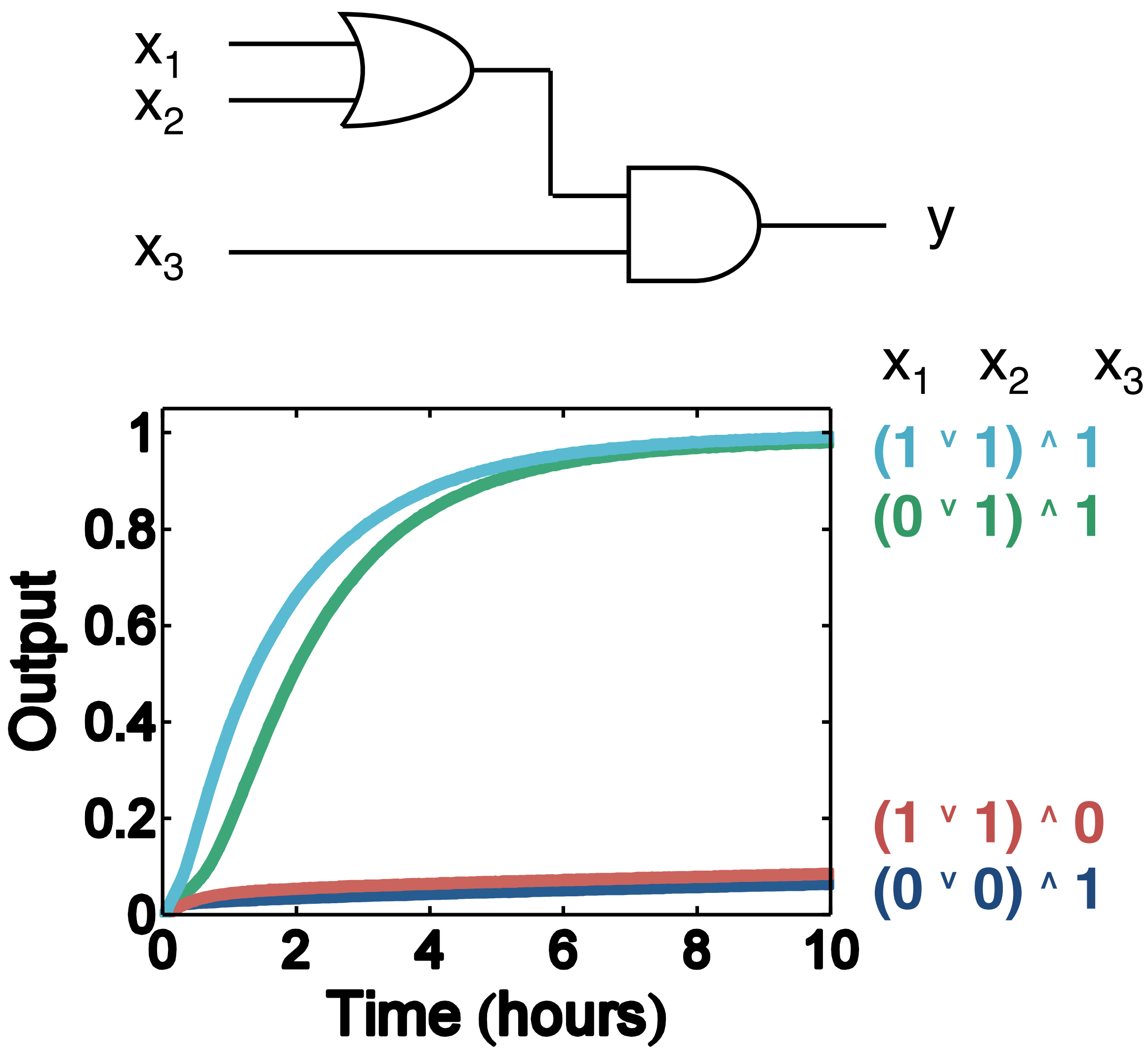


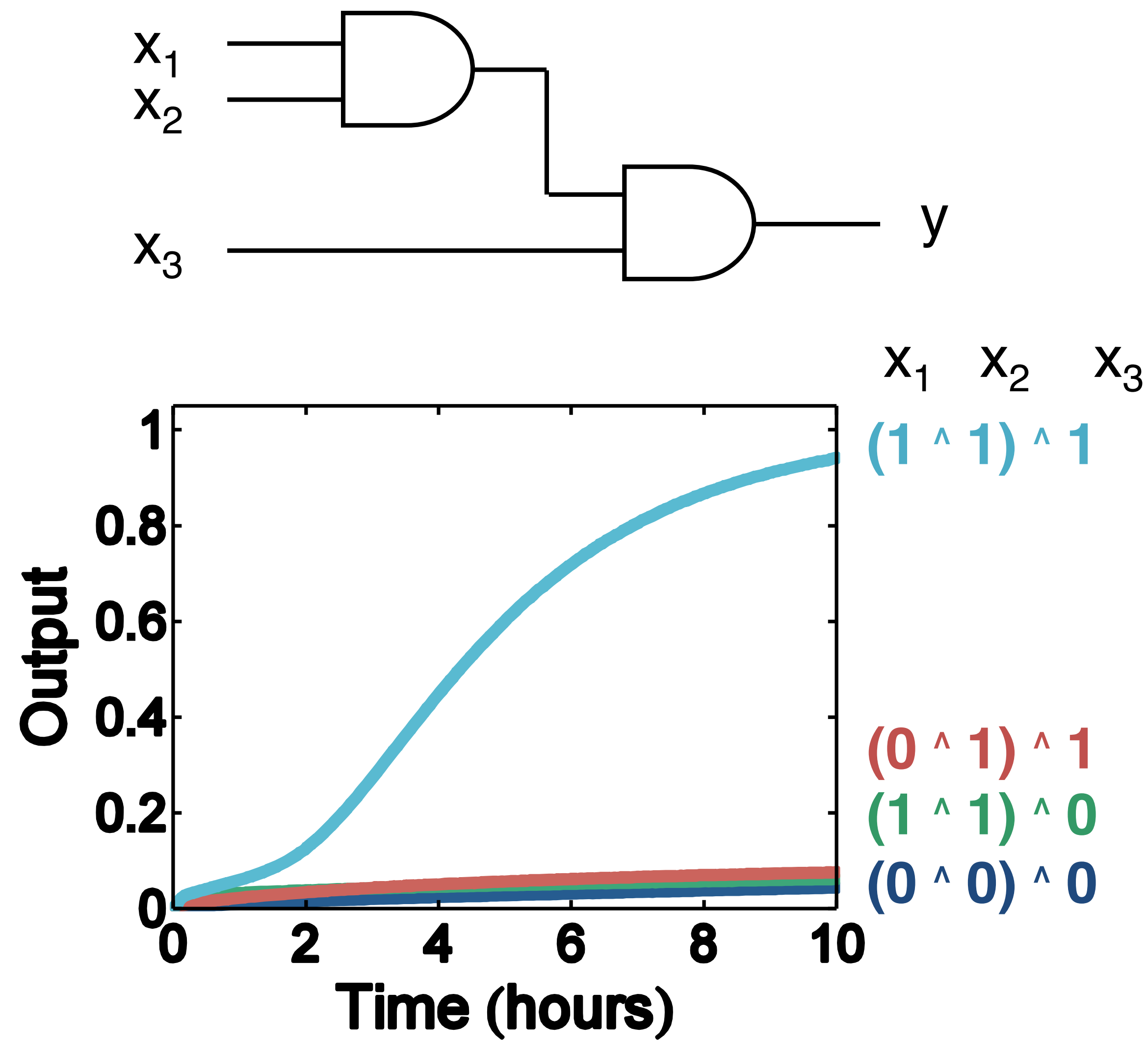


0=0.1x 1=0.9x 1x = 100 nM

Slide credit: Lulu Qian

Logic gate cascades

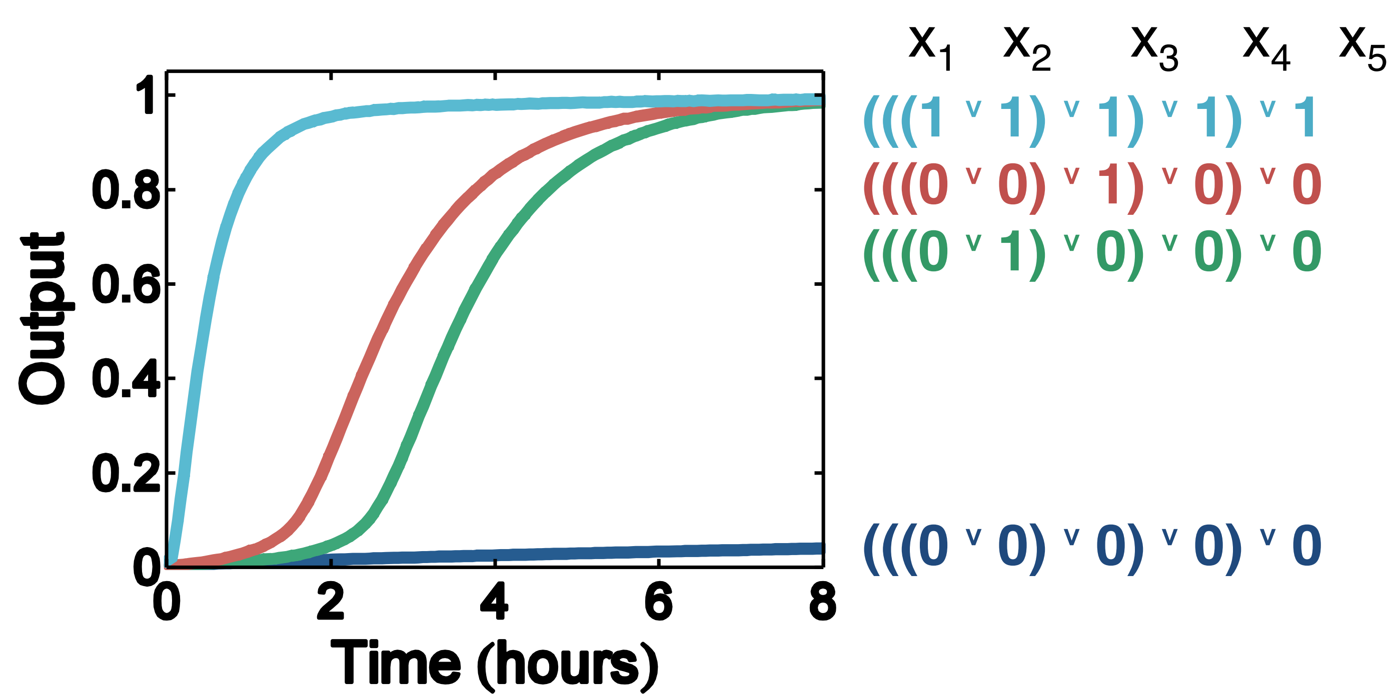


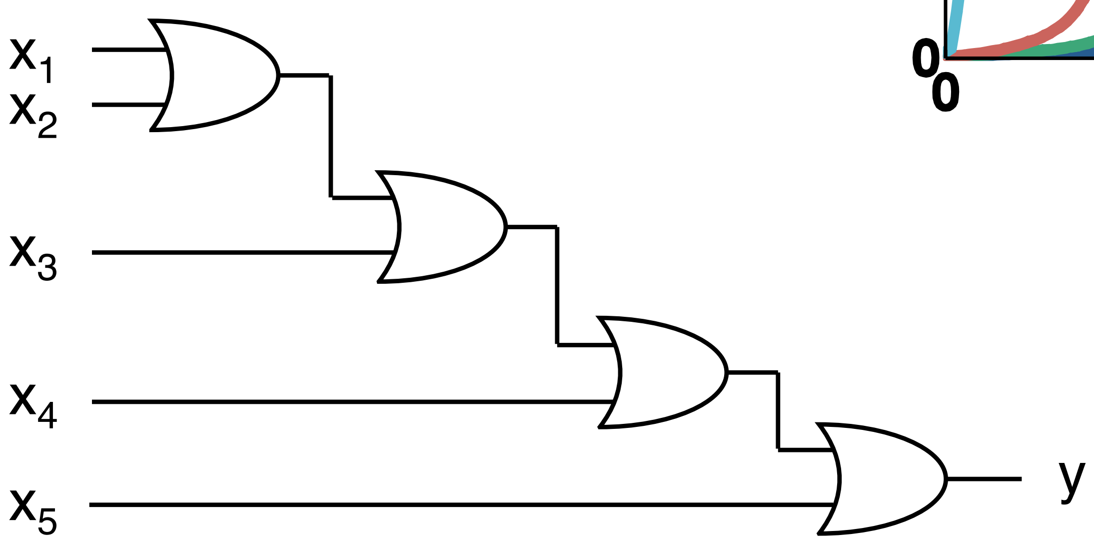


0=0.1x 1=0.9x 1x = 100 nM

Slide credit: Lulu Qian

Logic gate cascades

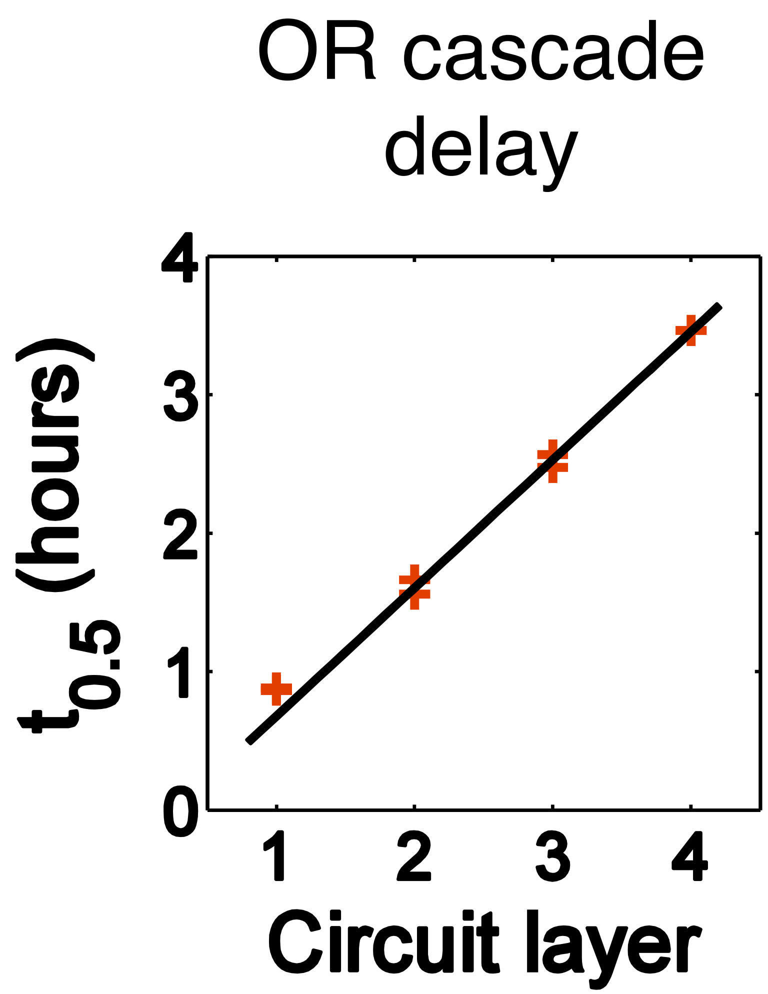


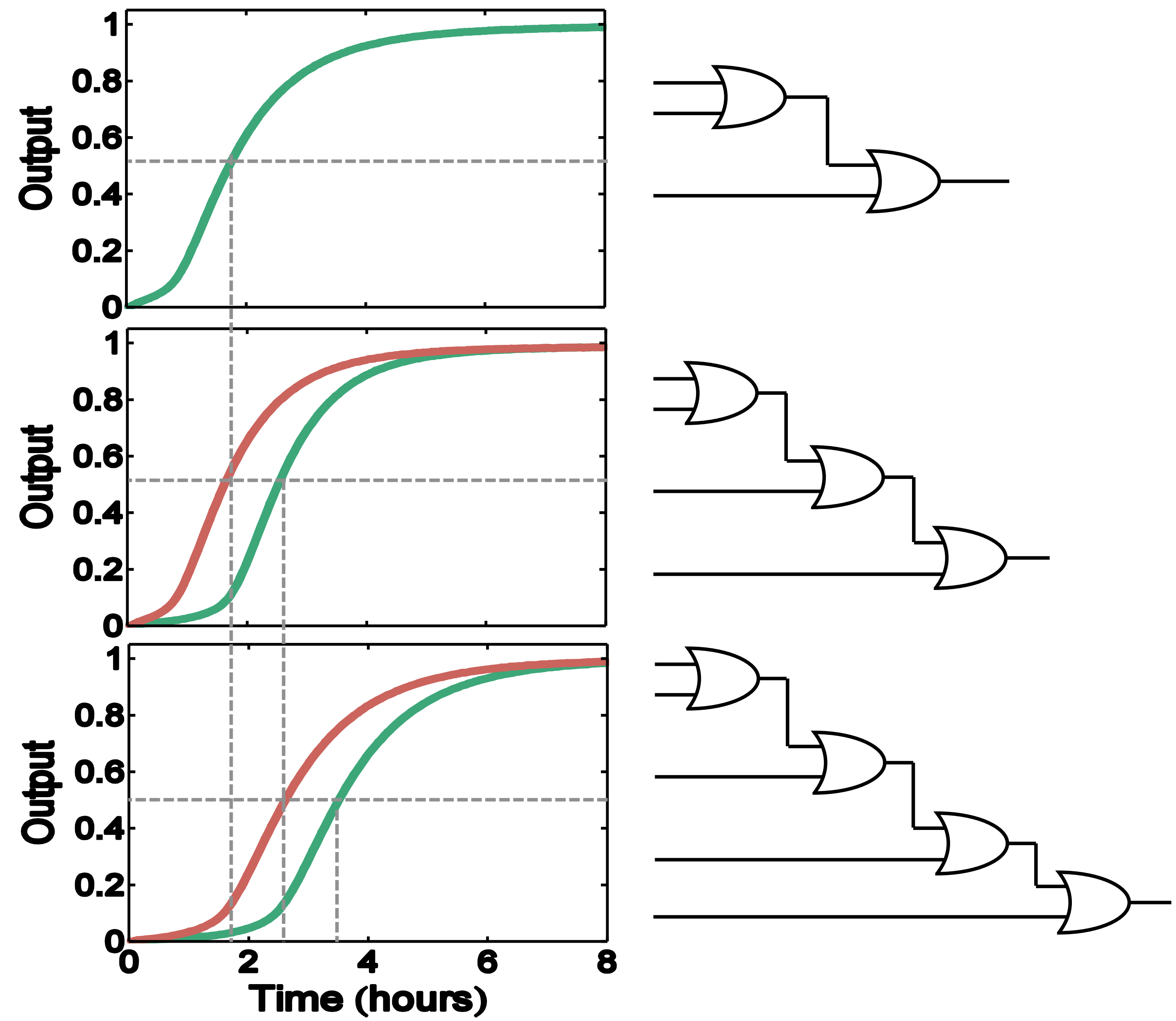


0=0.1x 1=0.9x 1x = 100 nM

Slide credit: Lulu Qian

Logic gate cascades





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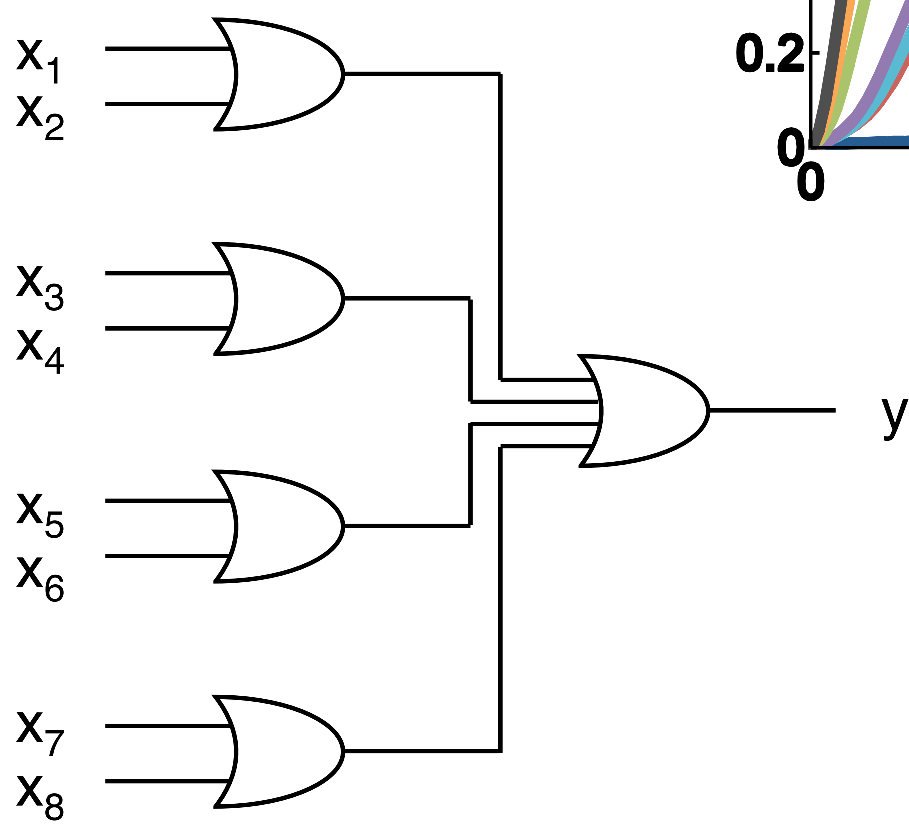
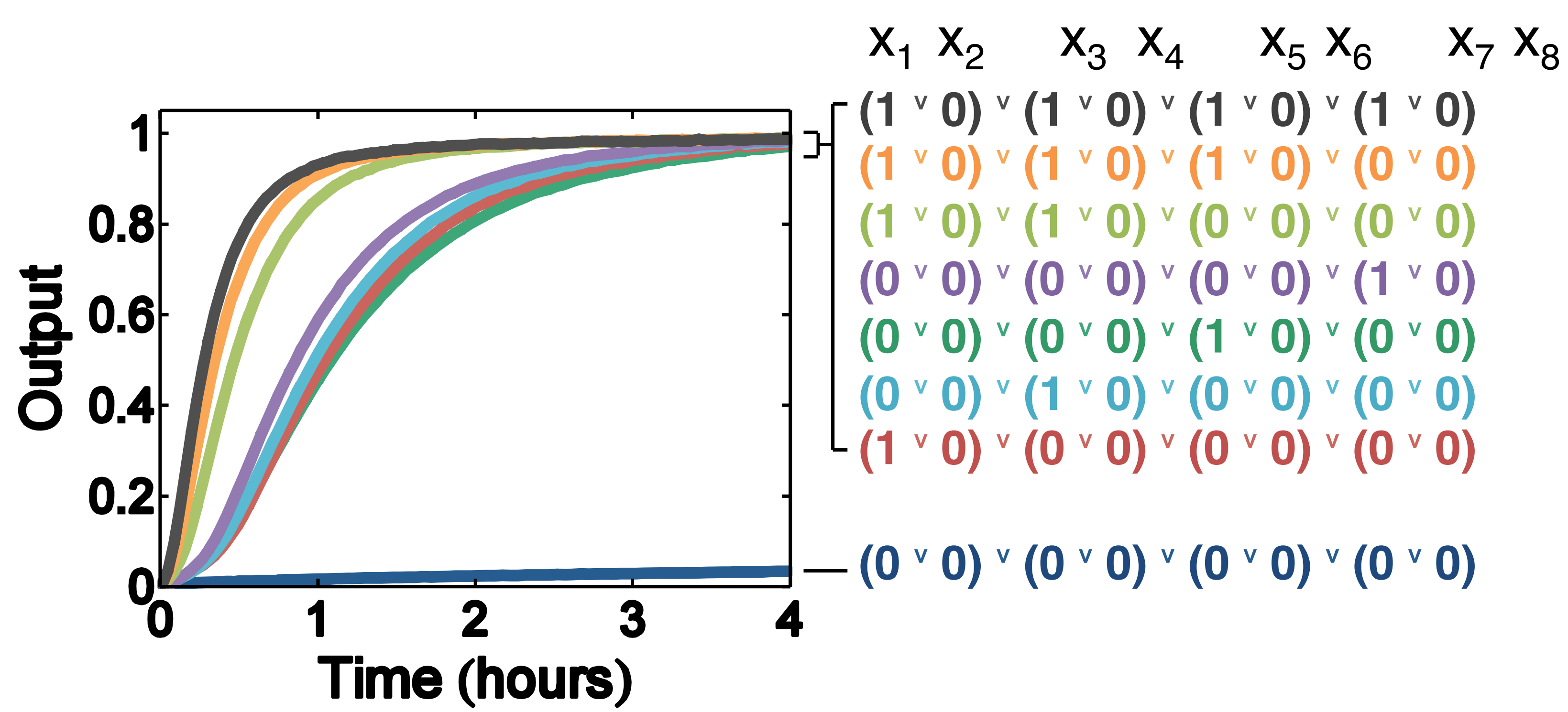
Multi input logic gates

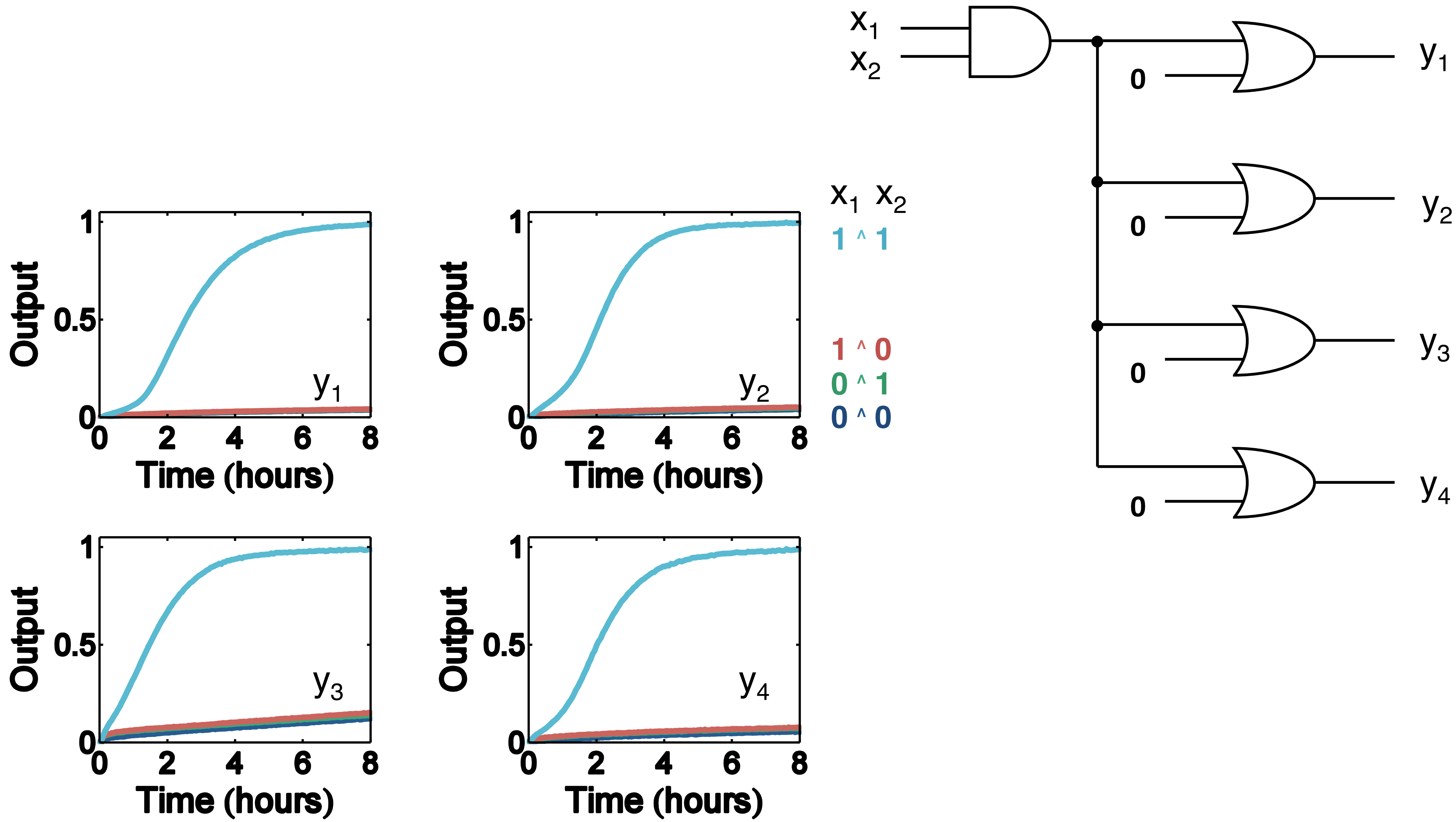




0=0.1x 1=0.9x 1x = 100 nM

Slide credit: Lulu Qian

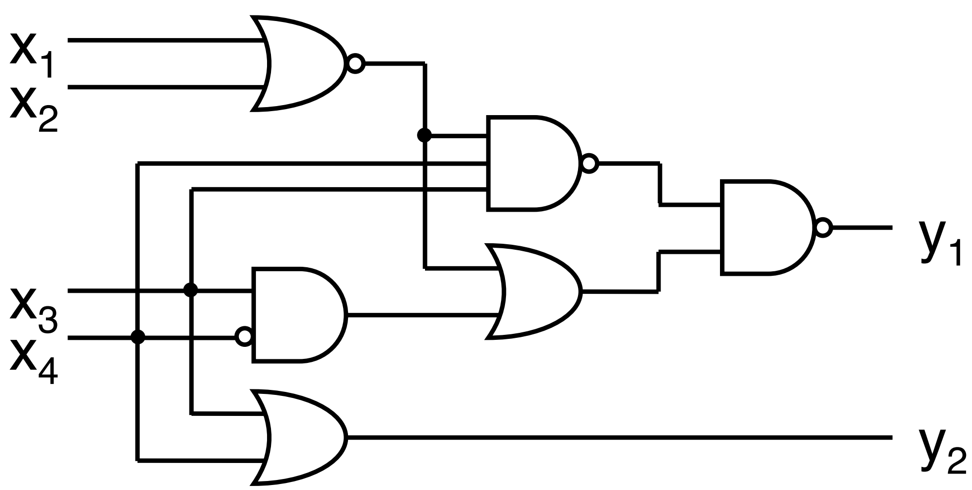
Multi output logic gates

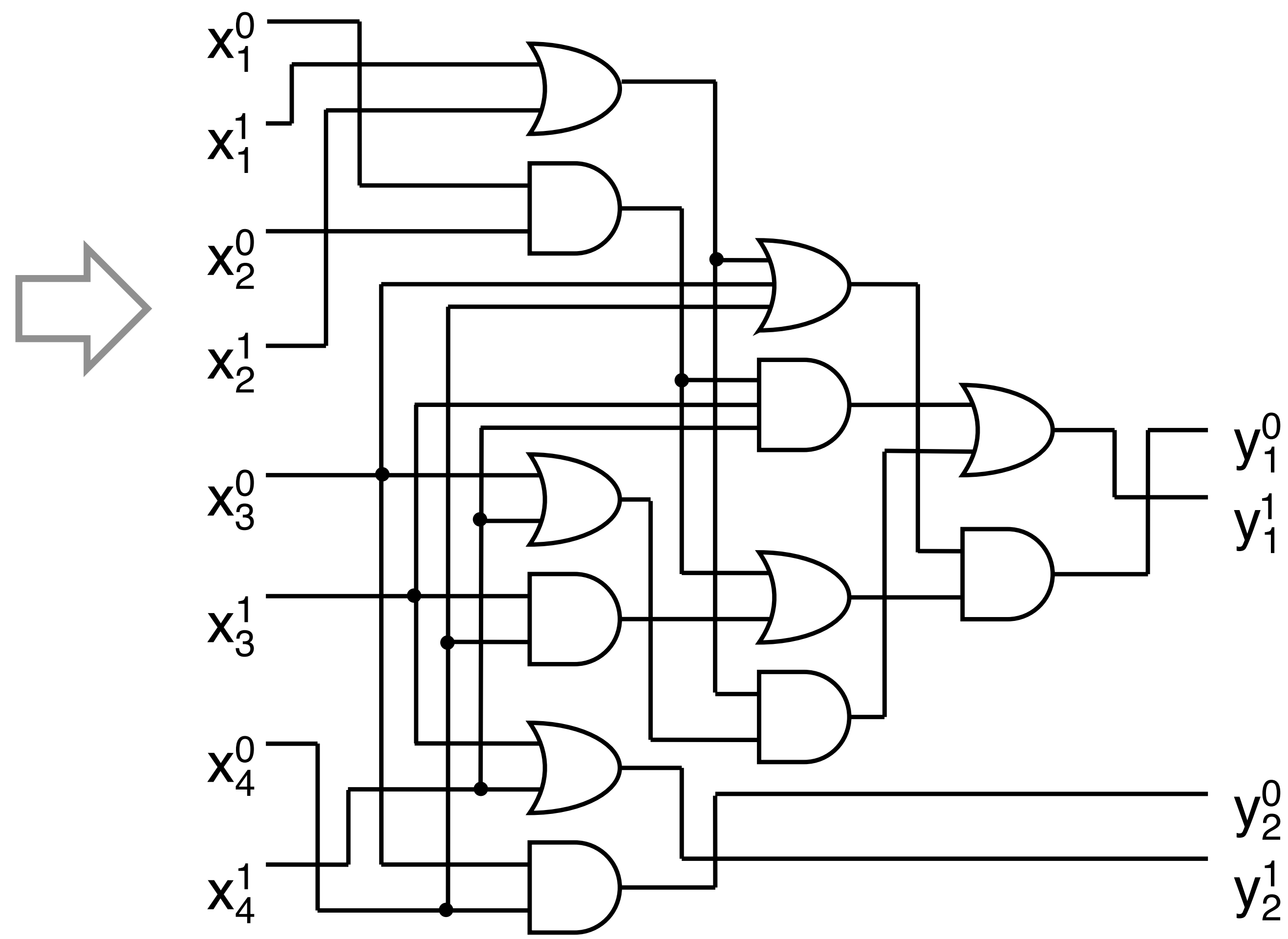


0=0.1x 1=0.9x 1x = 100 nM

Slide credit: Lulu Qian

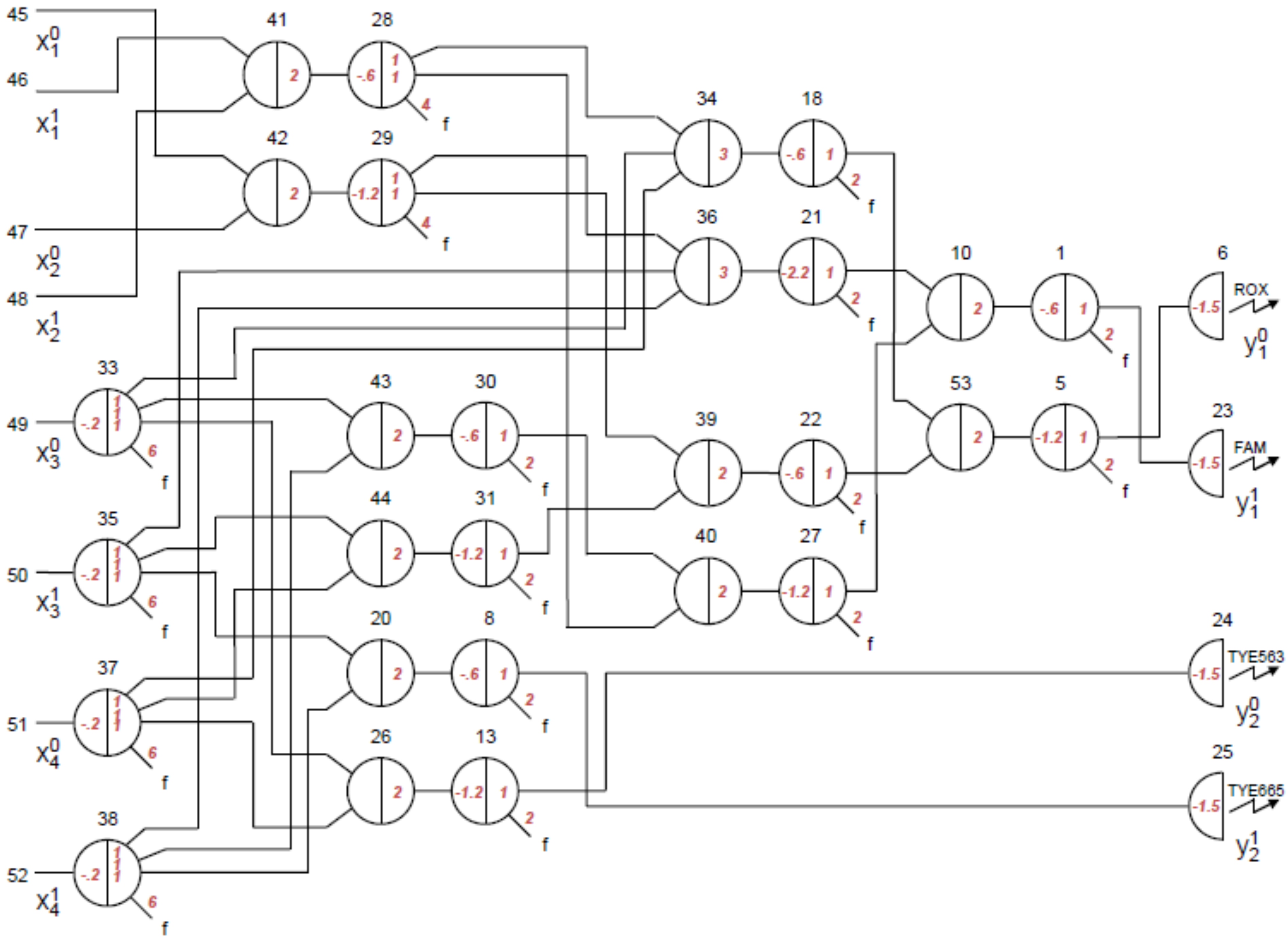
A four-bit square root circuit





Slide credit: Lulu Qian

A four-bit square root circuit



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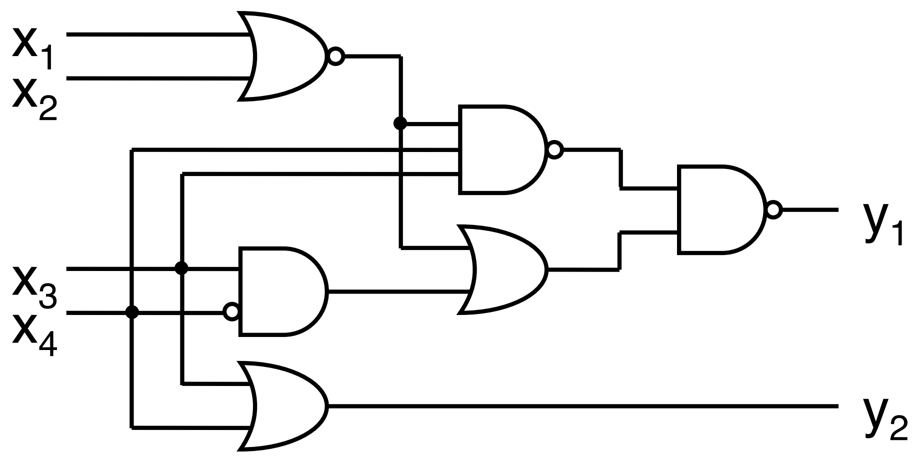
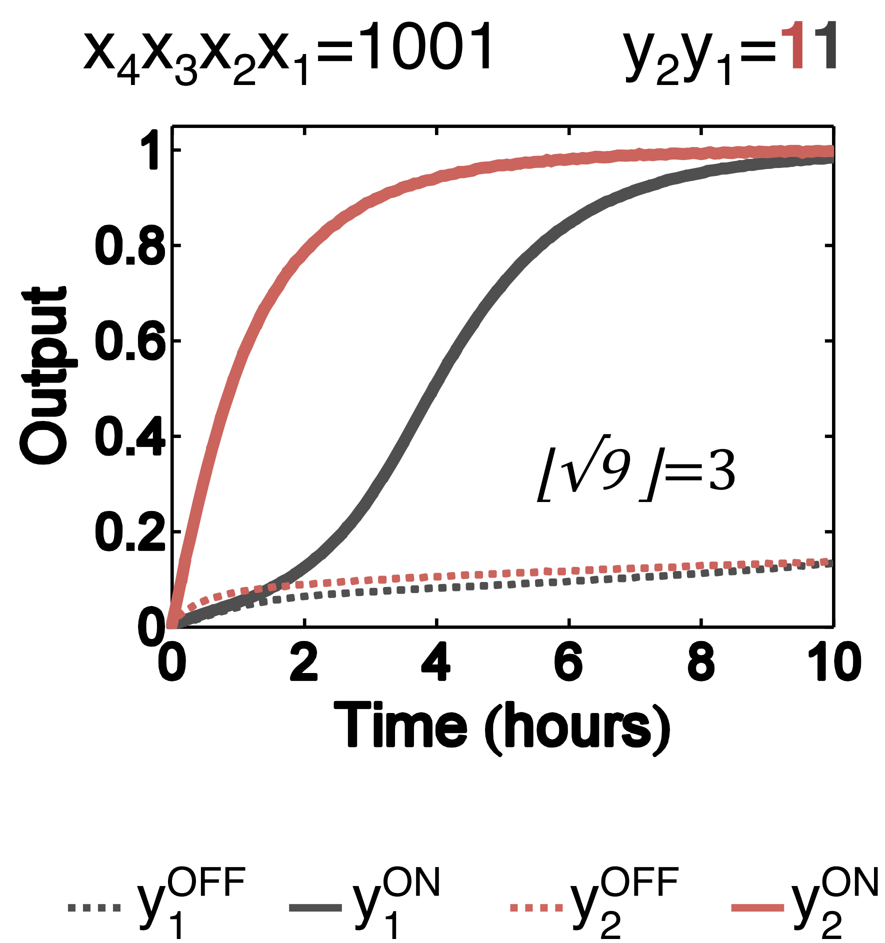
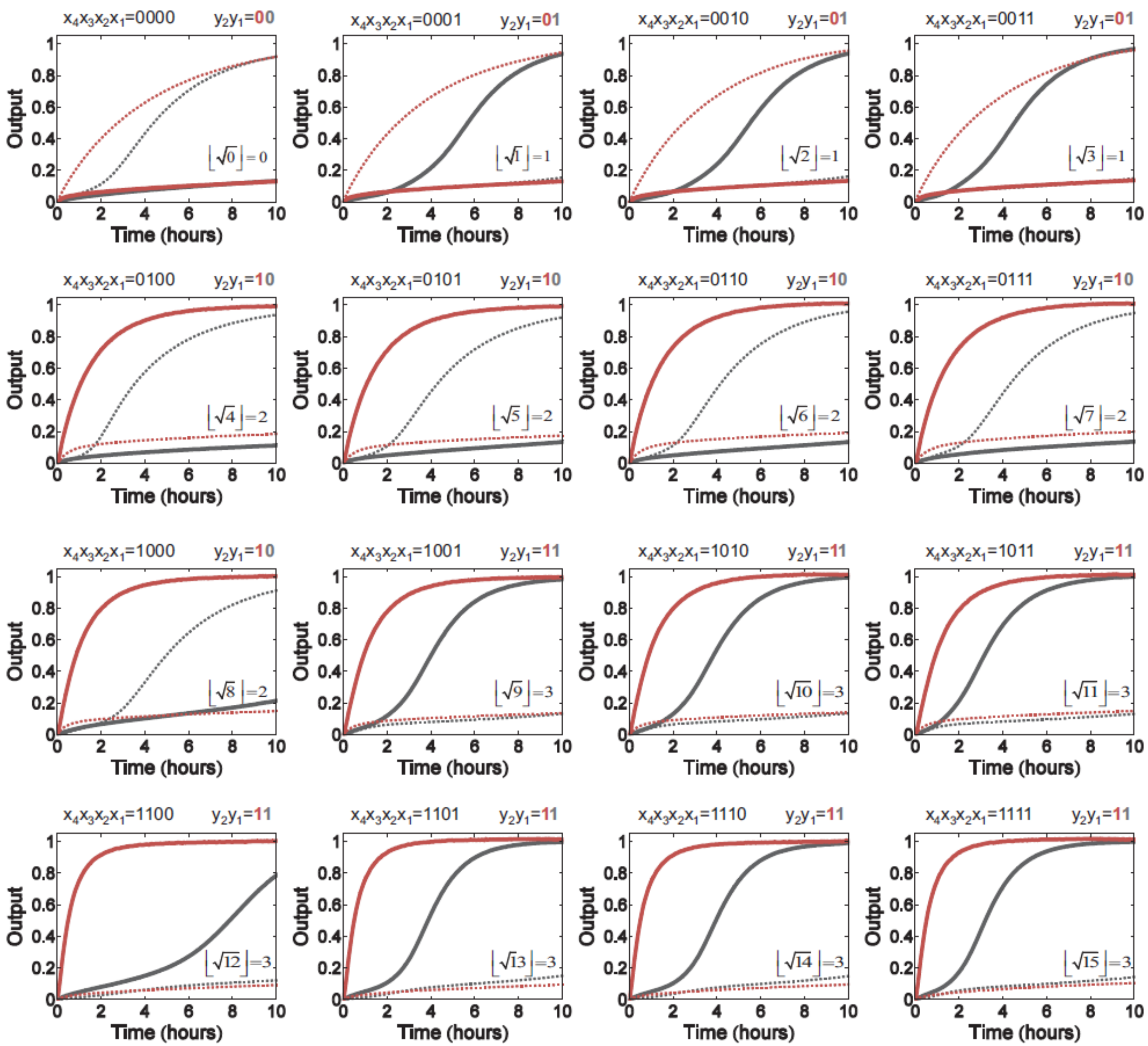




0=0.1x 1=0.9x 1x = 50 nM

Slide credit: Lulu Qian

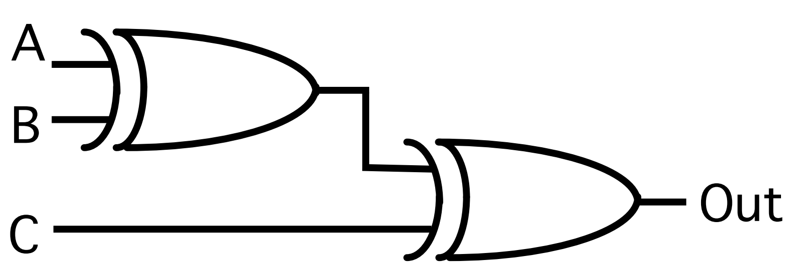
A four-bit square root circuit

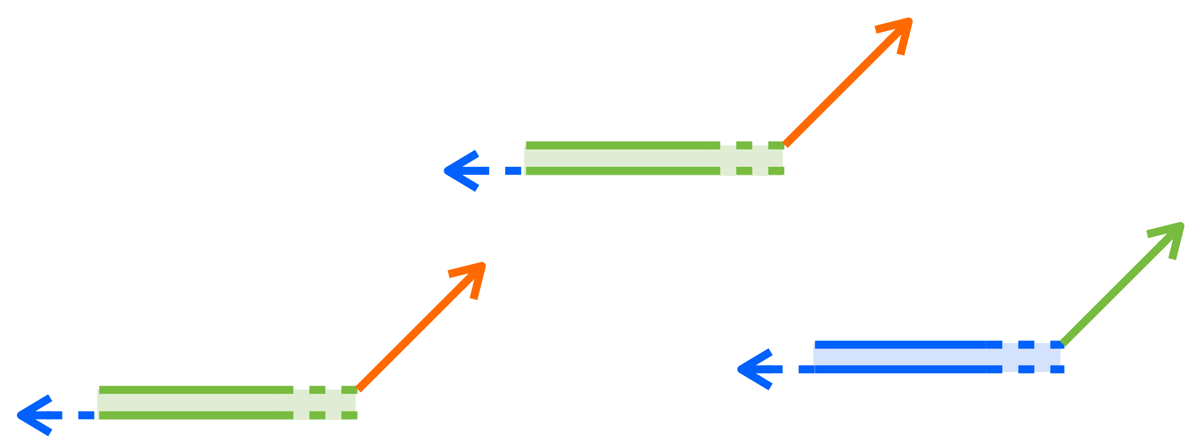


Slide credit: Lulu Qian

Take home message so far

We can build simple logic gates and circuits using DNA. DNA strand displacement circuits are the largest engineered molecular circuits built so far. But they are still really small compared to electronic ciruits or biological gene regulatory networks.





Differences and similarities between electronic and molecular circuits

1. **Lack of spatial isolation limits reusability and leads to crosstalk**

2. Computation energy and non-reusable gates: Both inputs and gates are consumed as the circuit is evaluated by cascade reactions, so they cannot be reused.

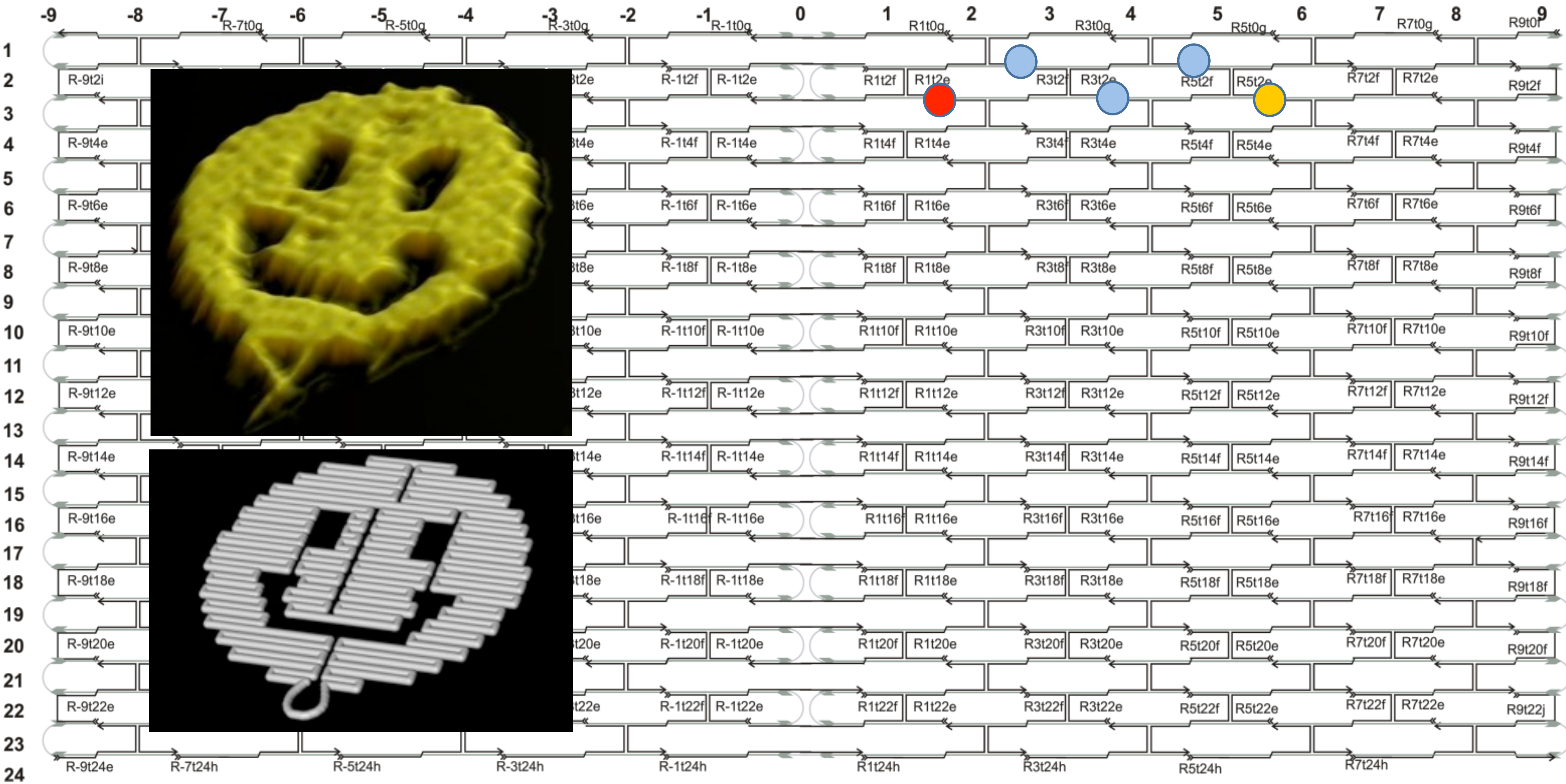
3. Data encoding: Information is encoded in the sequences and concentration of biomolecules.

4. Lack of clear hardware software separation: Gates and circuits come pre-programmed for the specific computation they are meant to carry out.

5. Speed of computation: A circuits evaluation under typical reaction conditions takes minutes to hours.

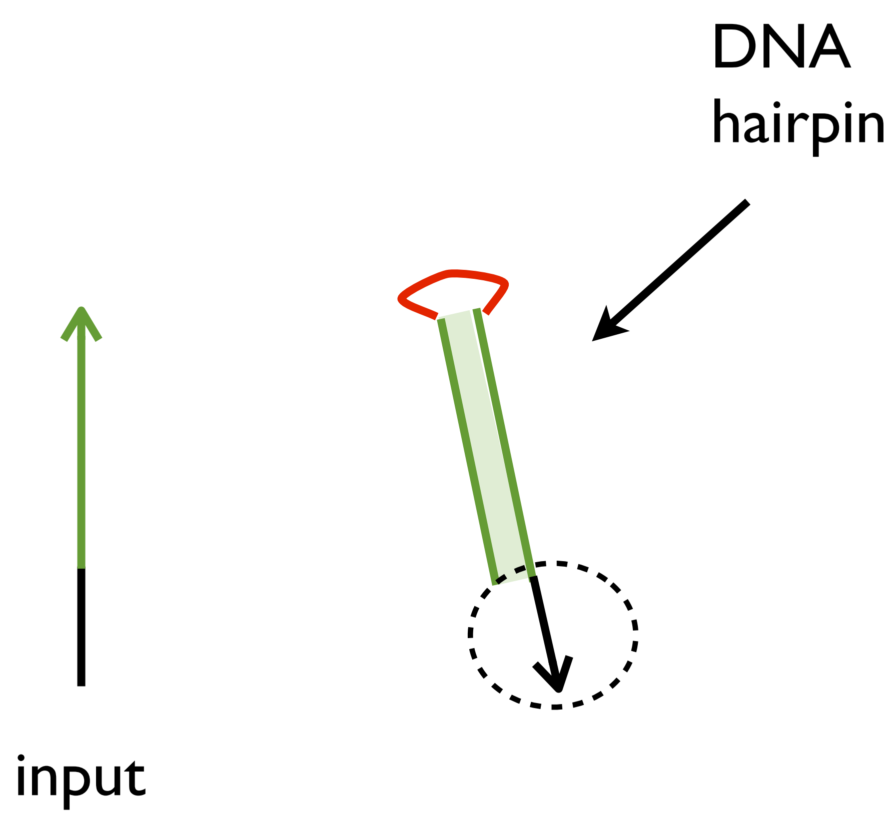
6. Need for dual-rail logic: NOT is difficult to implement

One way forward: spatially localized DNA circuits



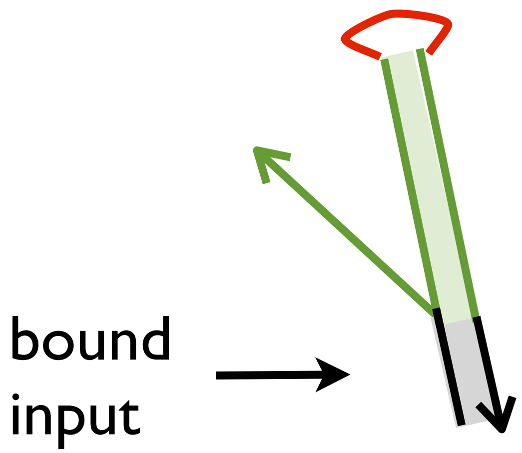
8 bp = 2.64 nm

Strand displacement with DNA hairpins

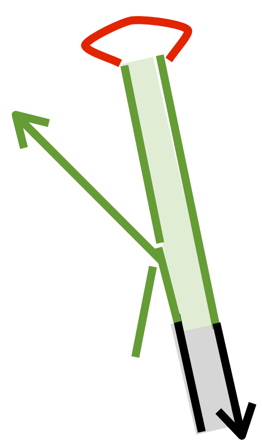


Single-stranded DNA can bind to itself

Strand displacement with DNA hairpins

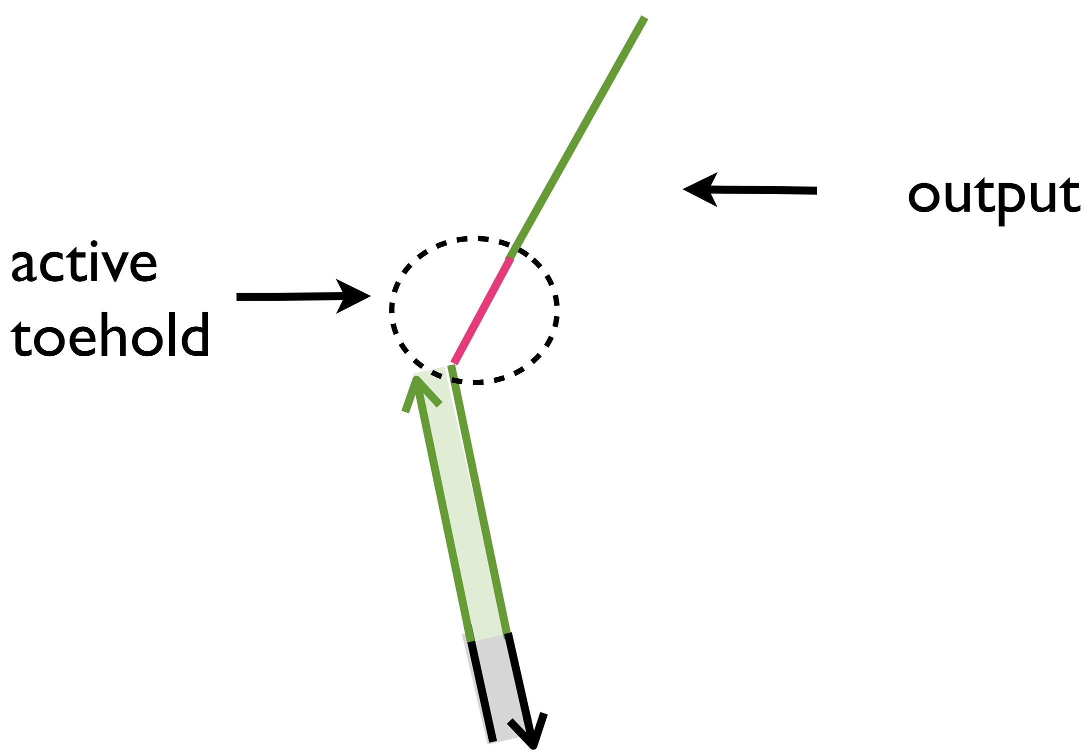


Strand displacement with DNA hairpins



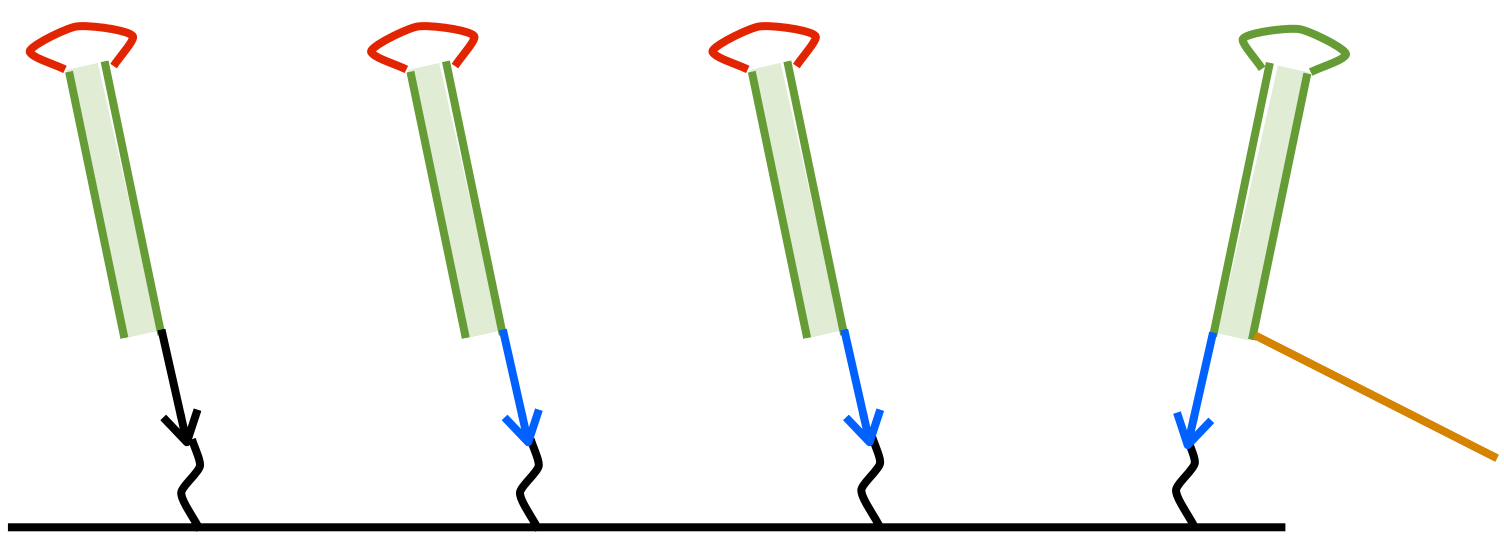
hairpin transmission line

Strand displacement with DNA hairpins



output remains attached
input and output have the same sequence

Rows of DNA hairpins act as wires



hairpin transmission line

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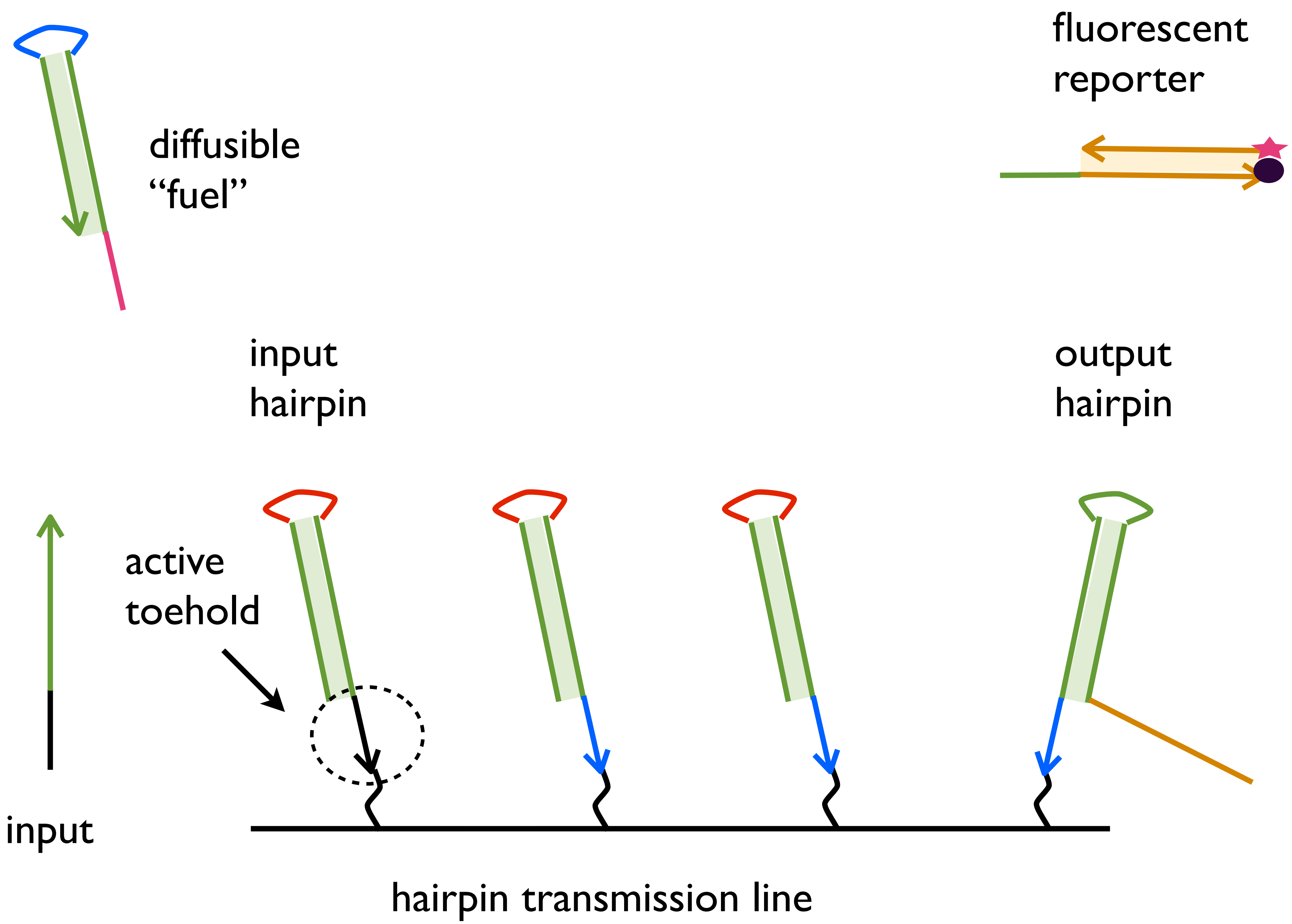

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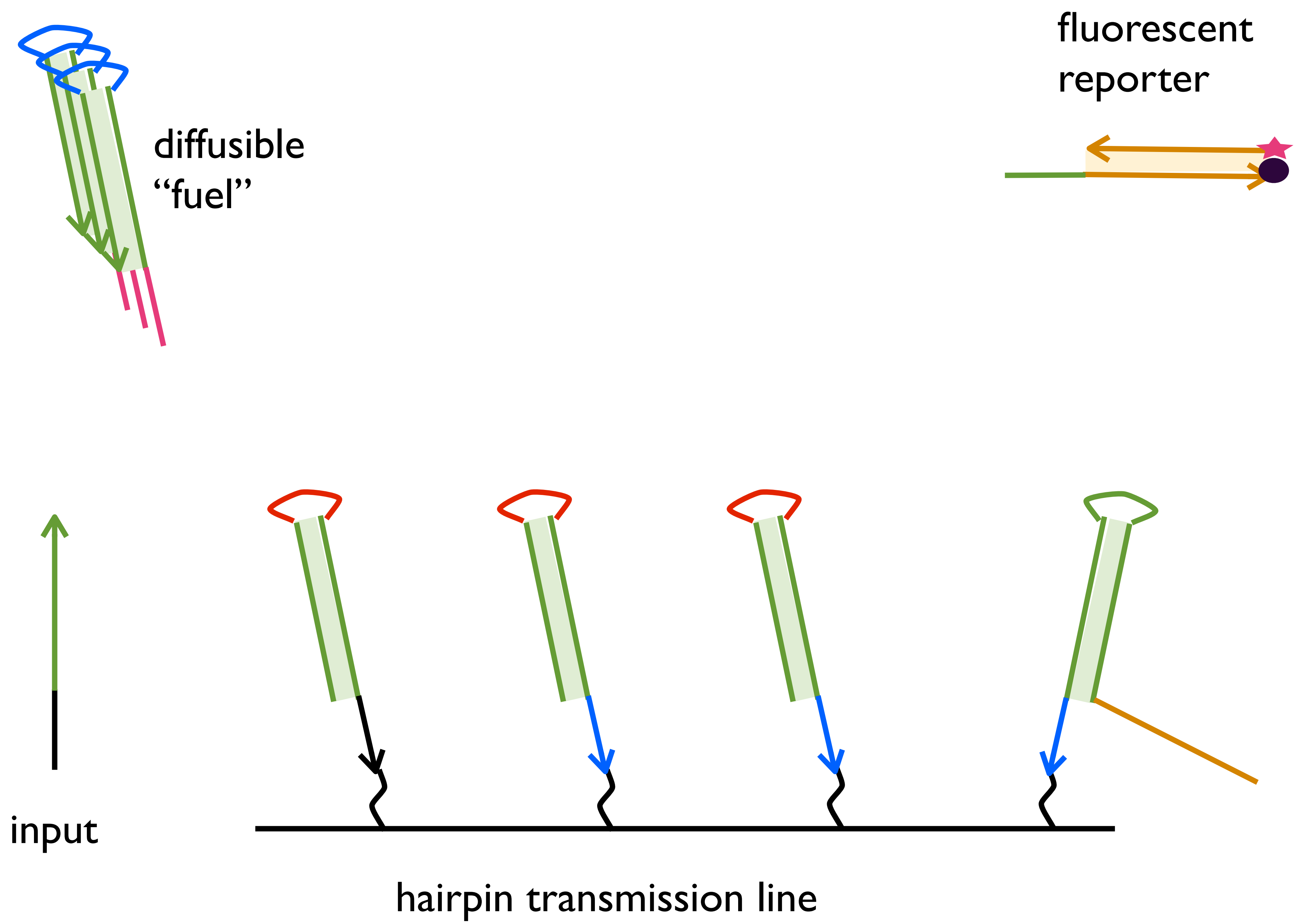

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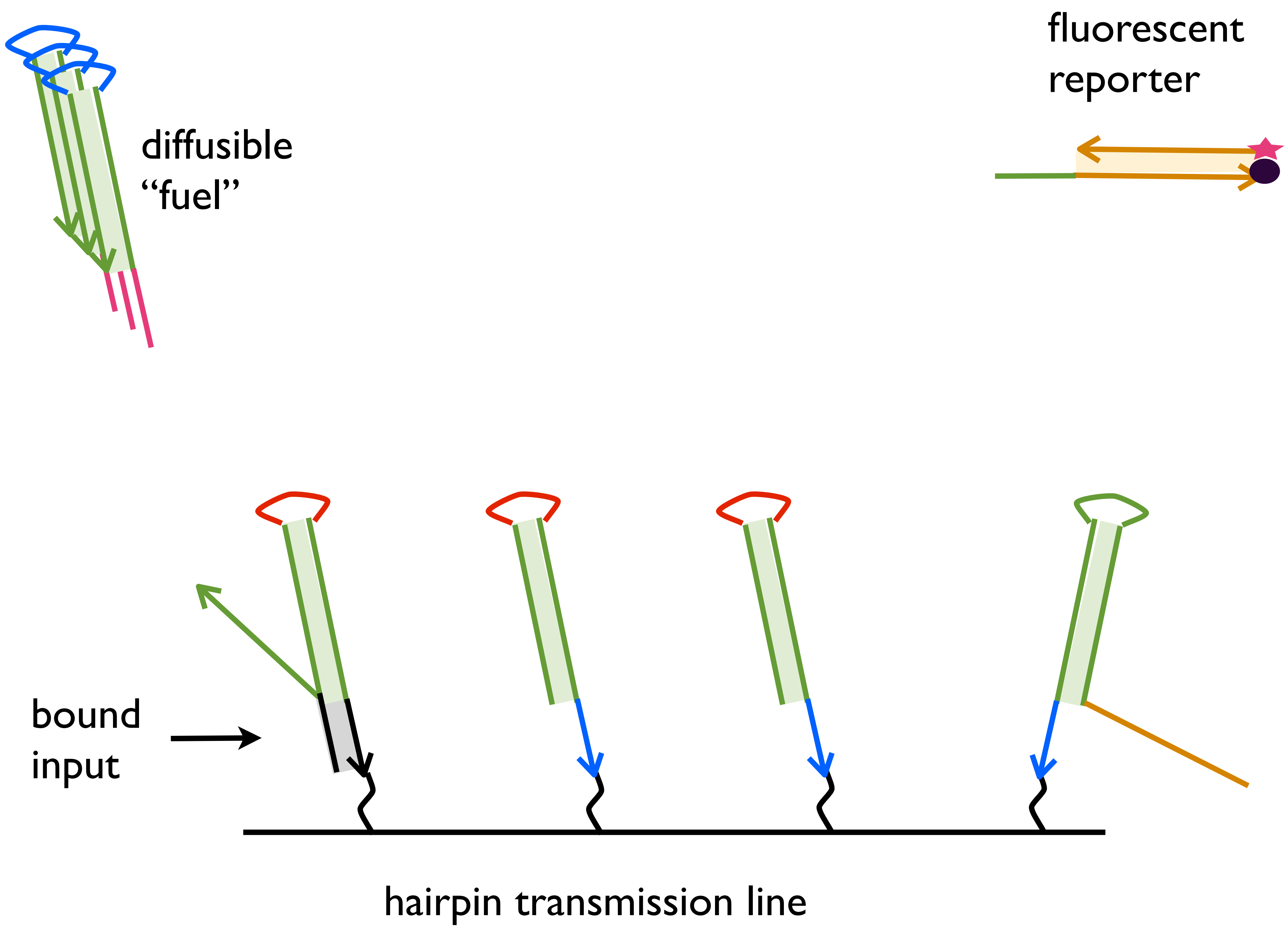

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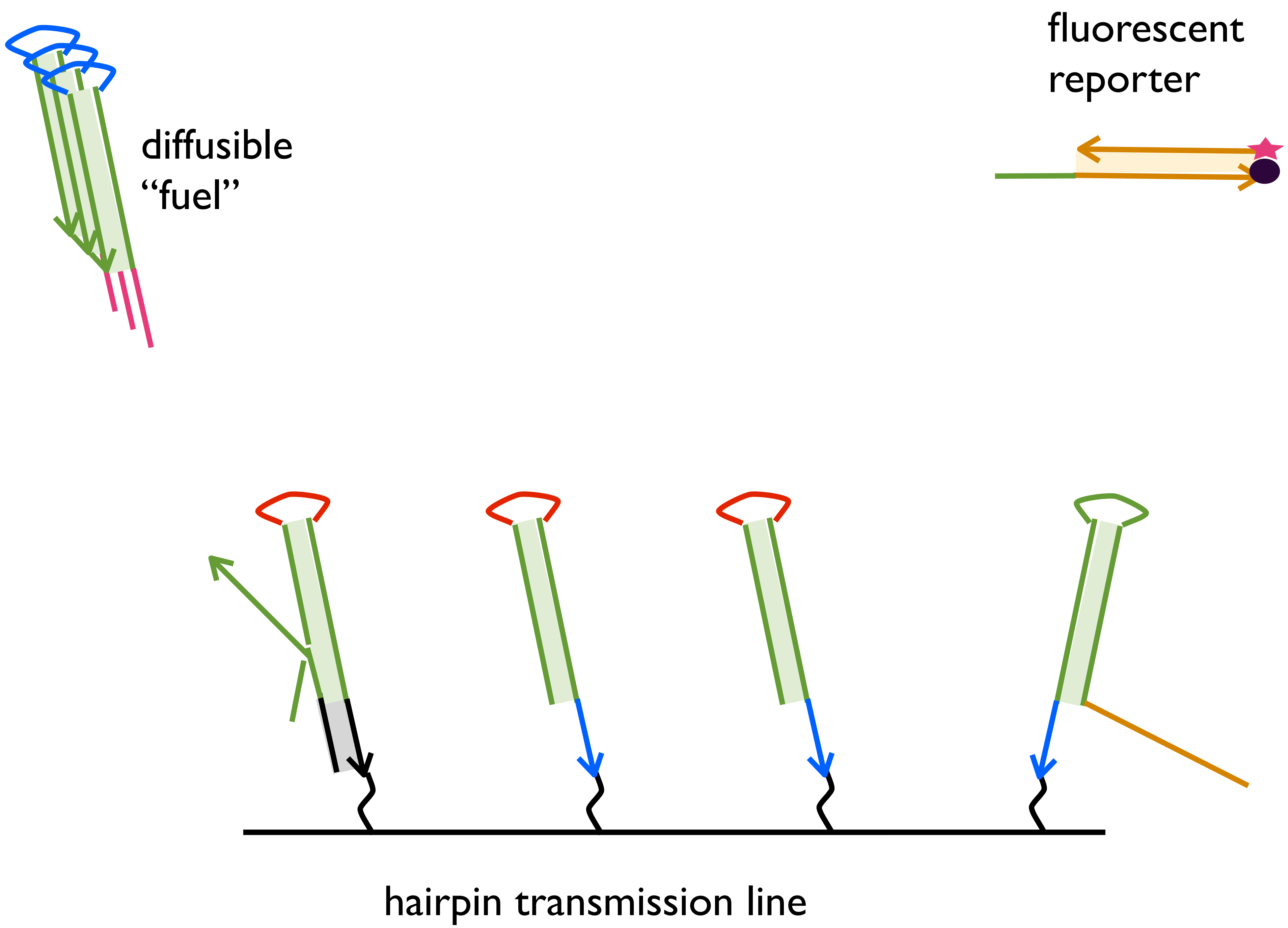

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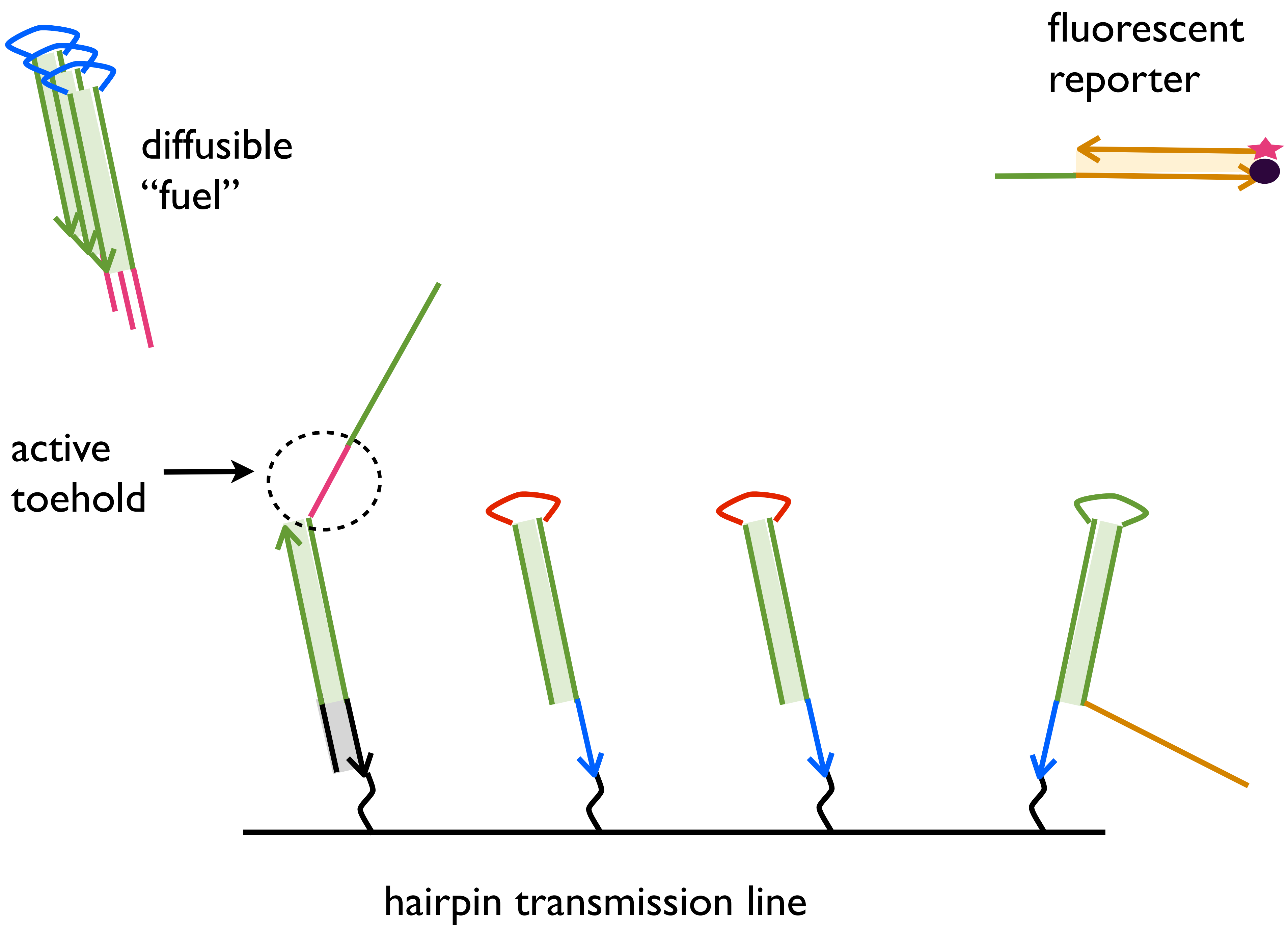

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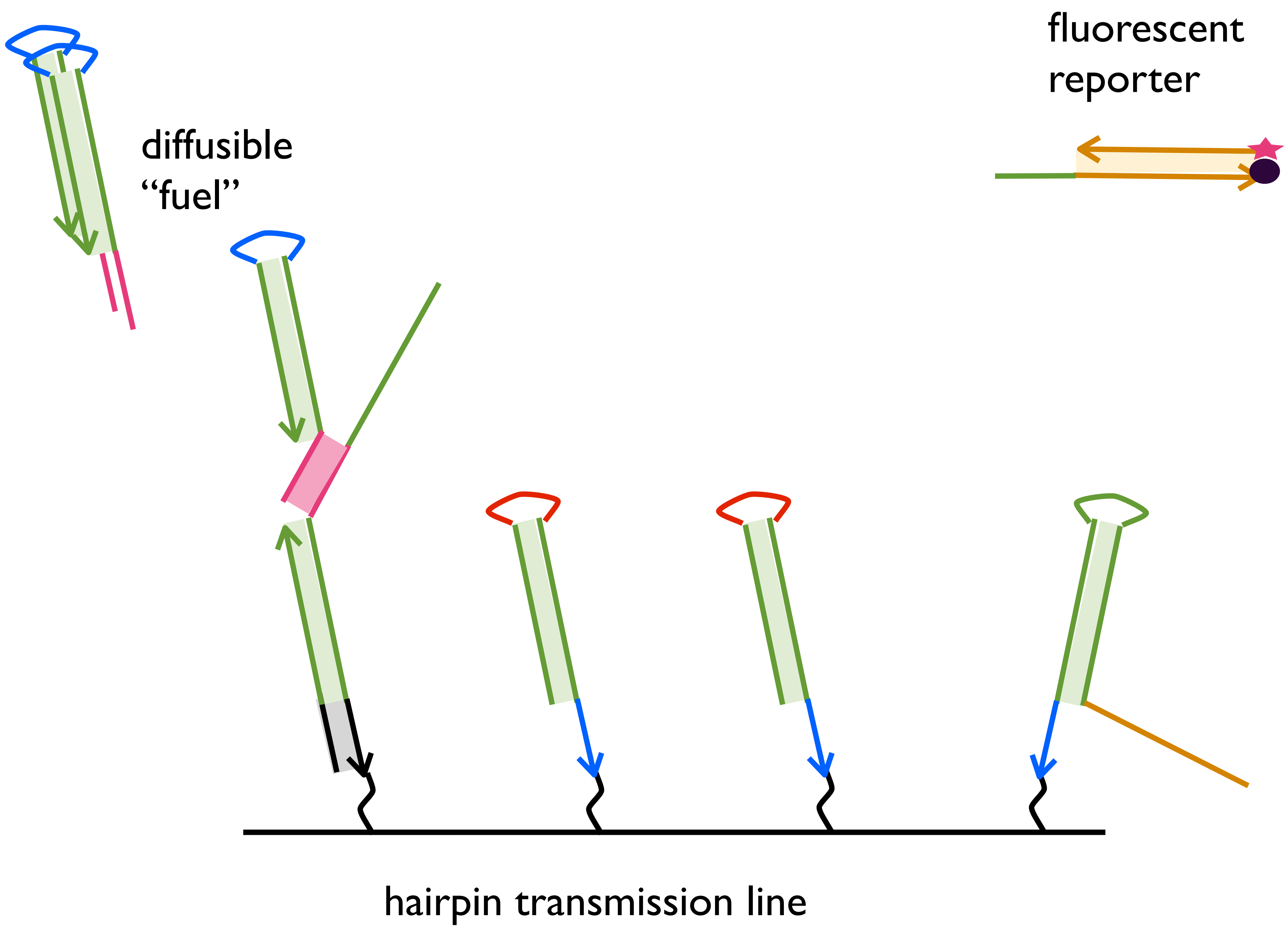

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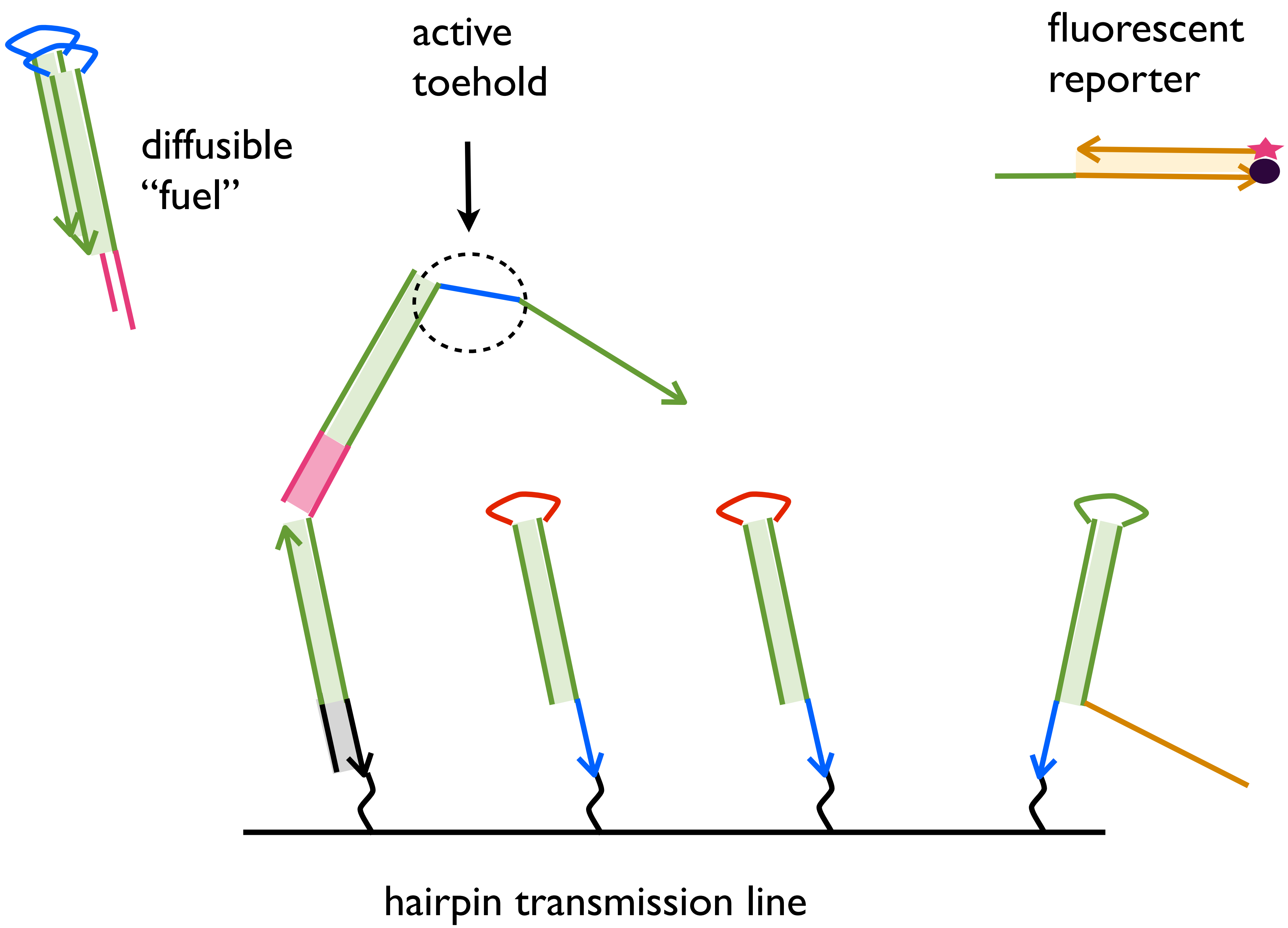

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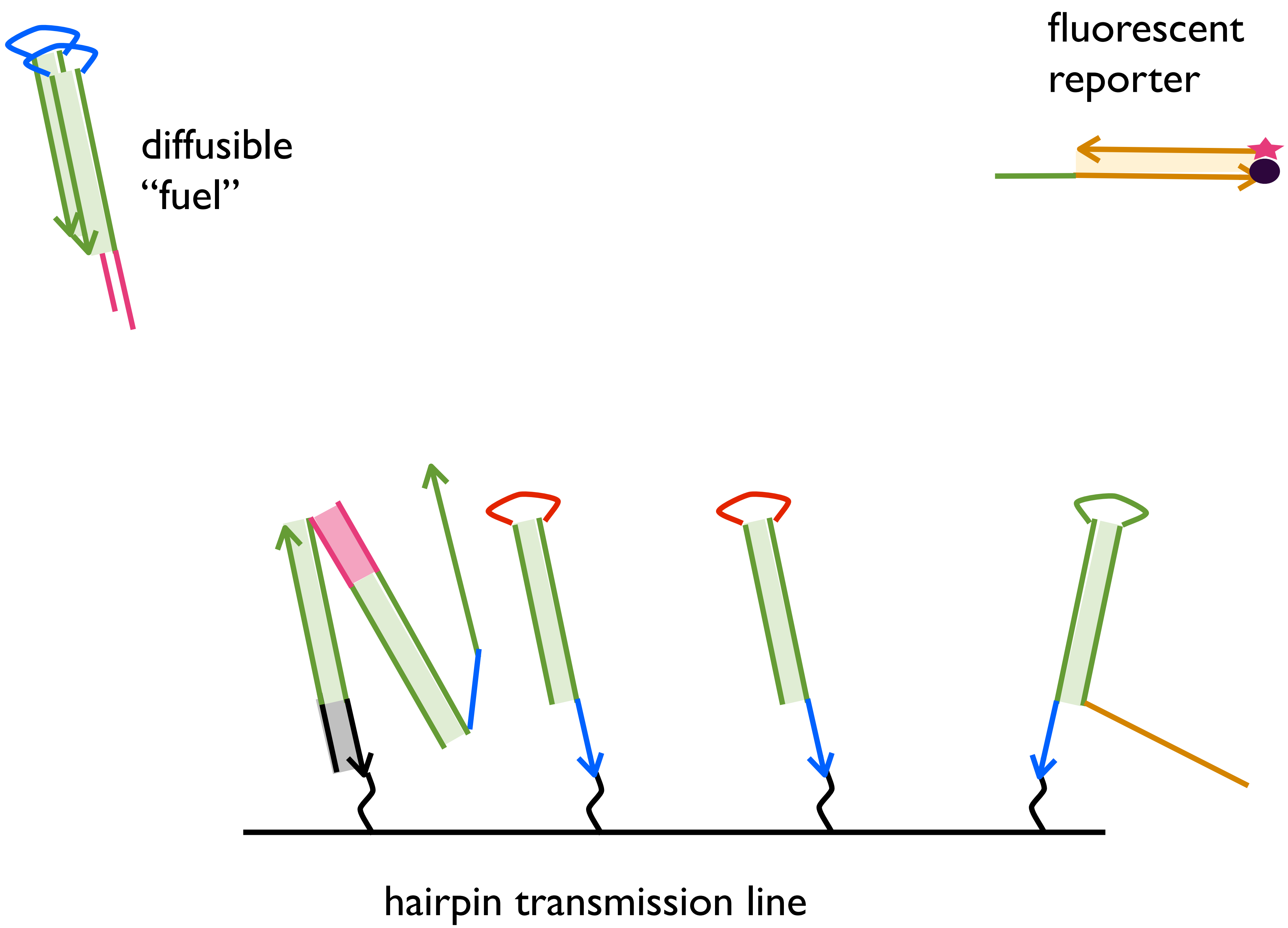

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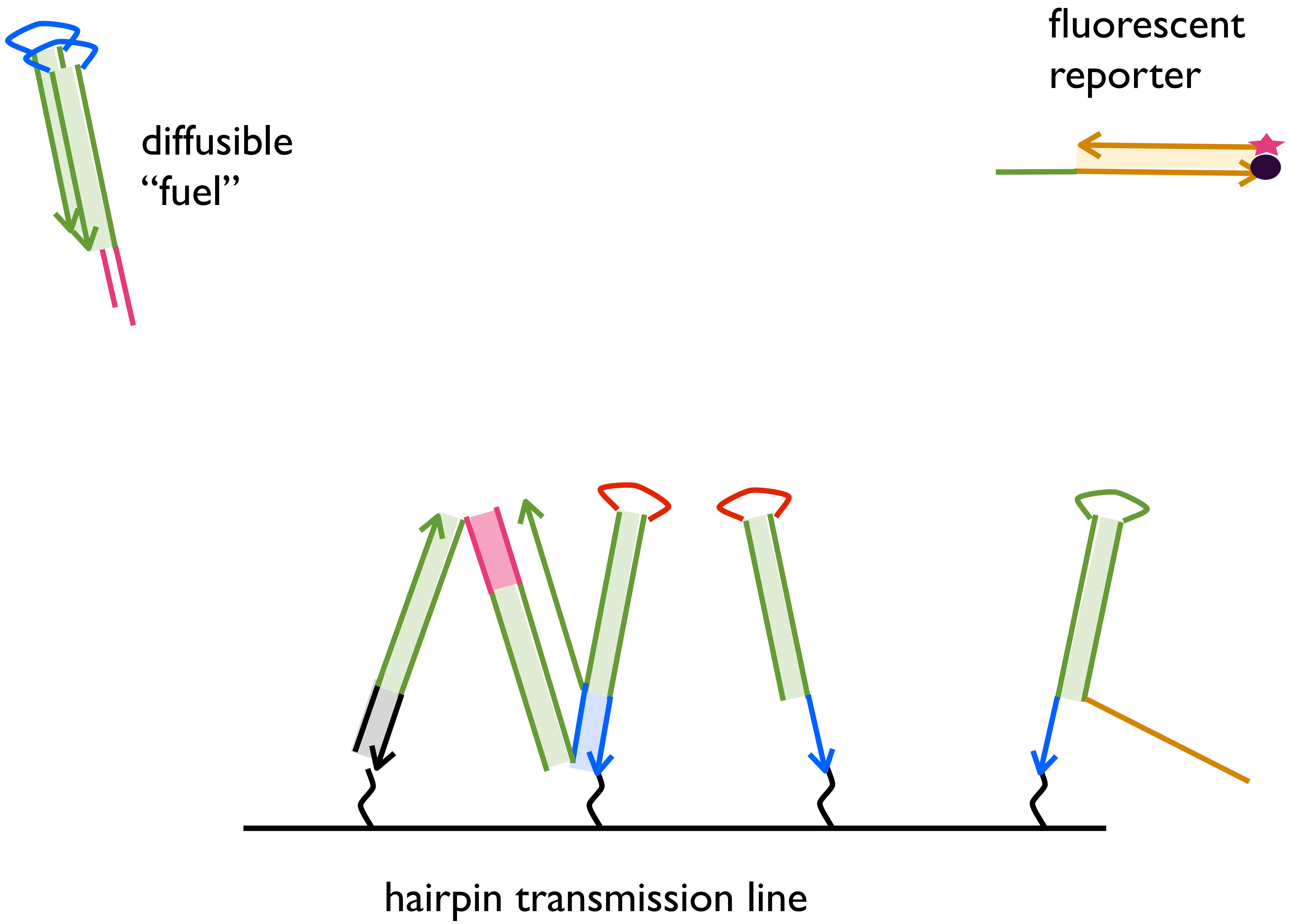

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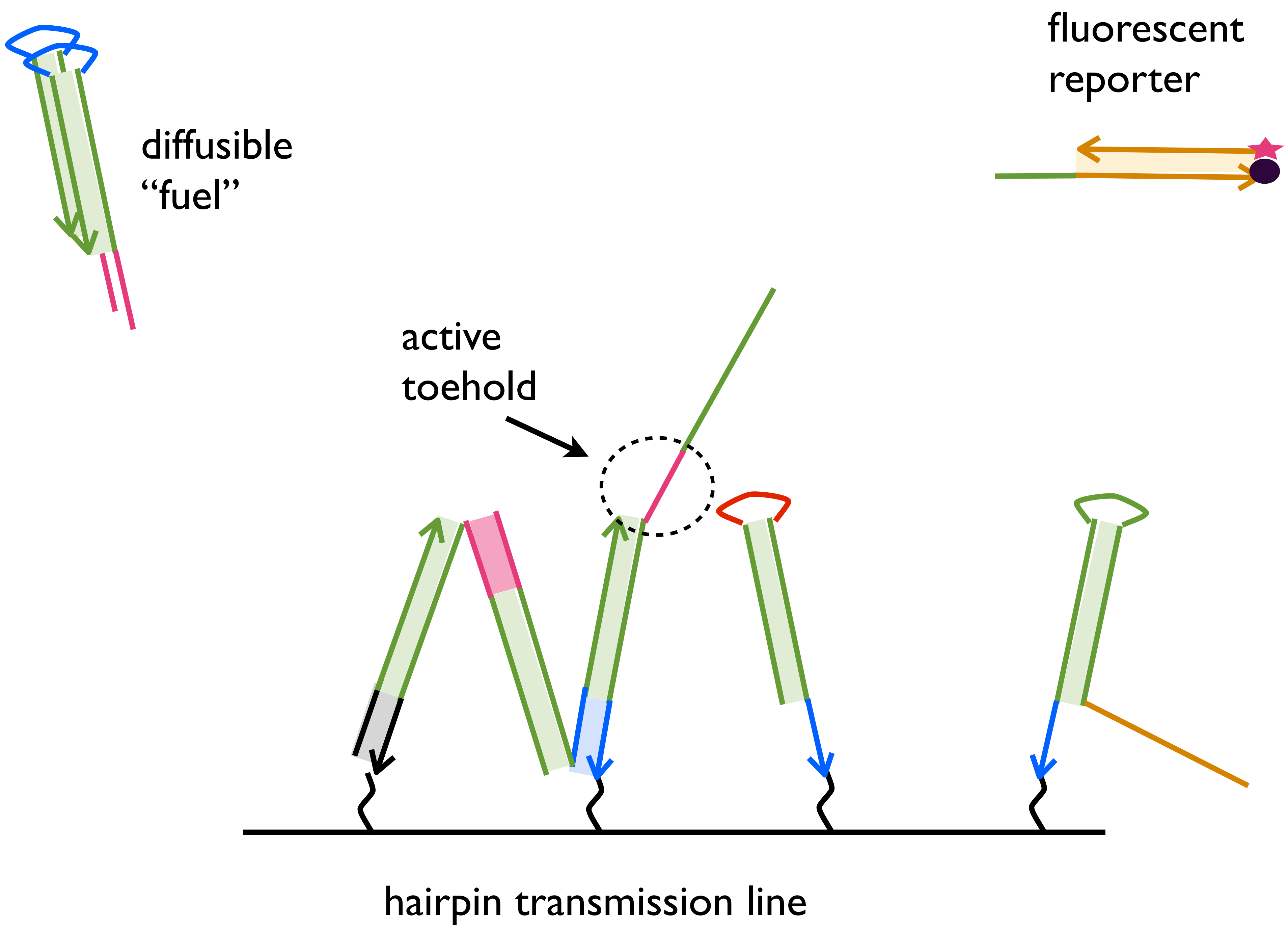

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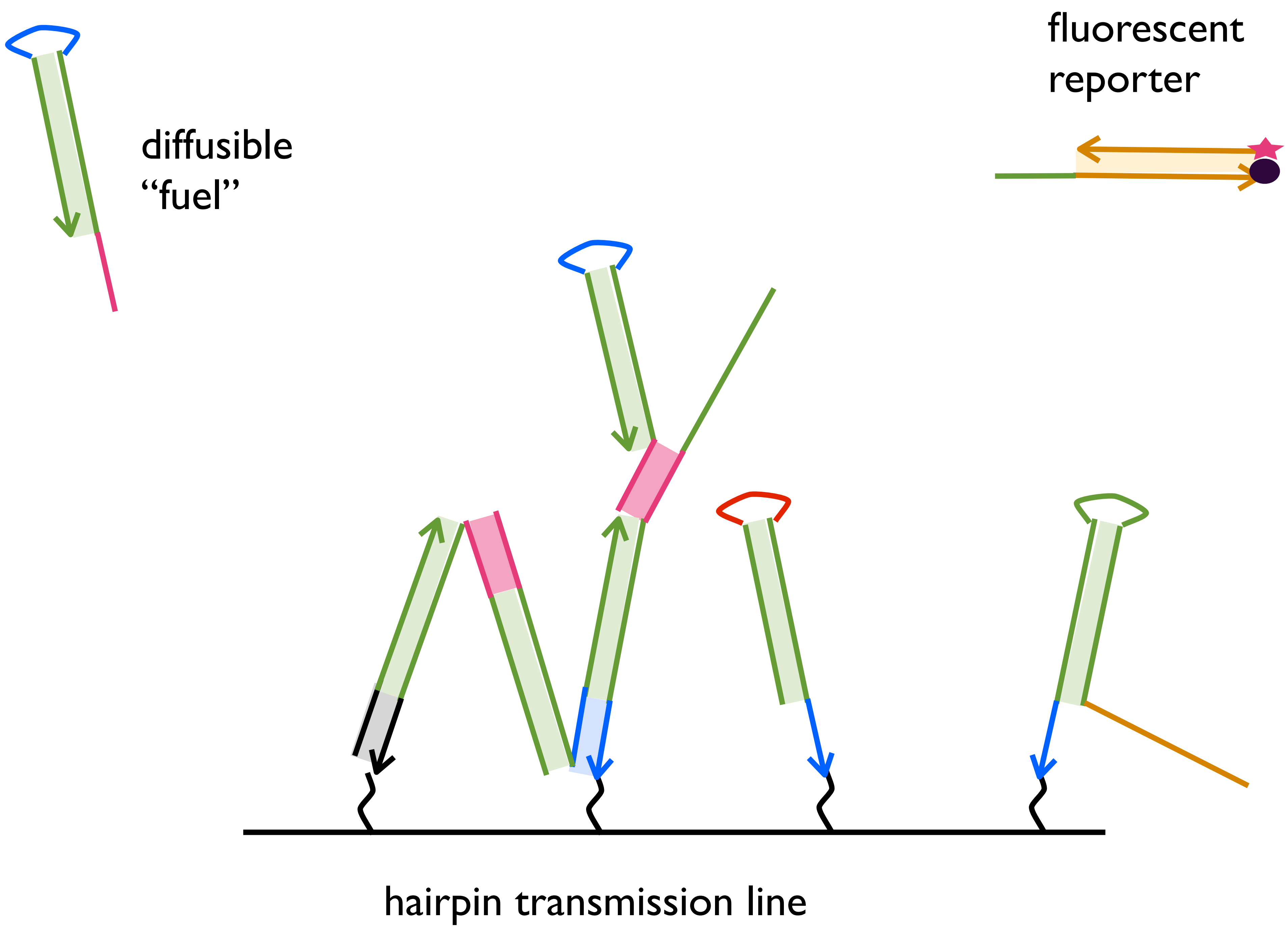

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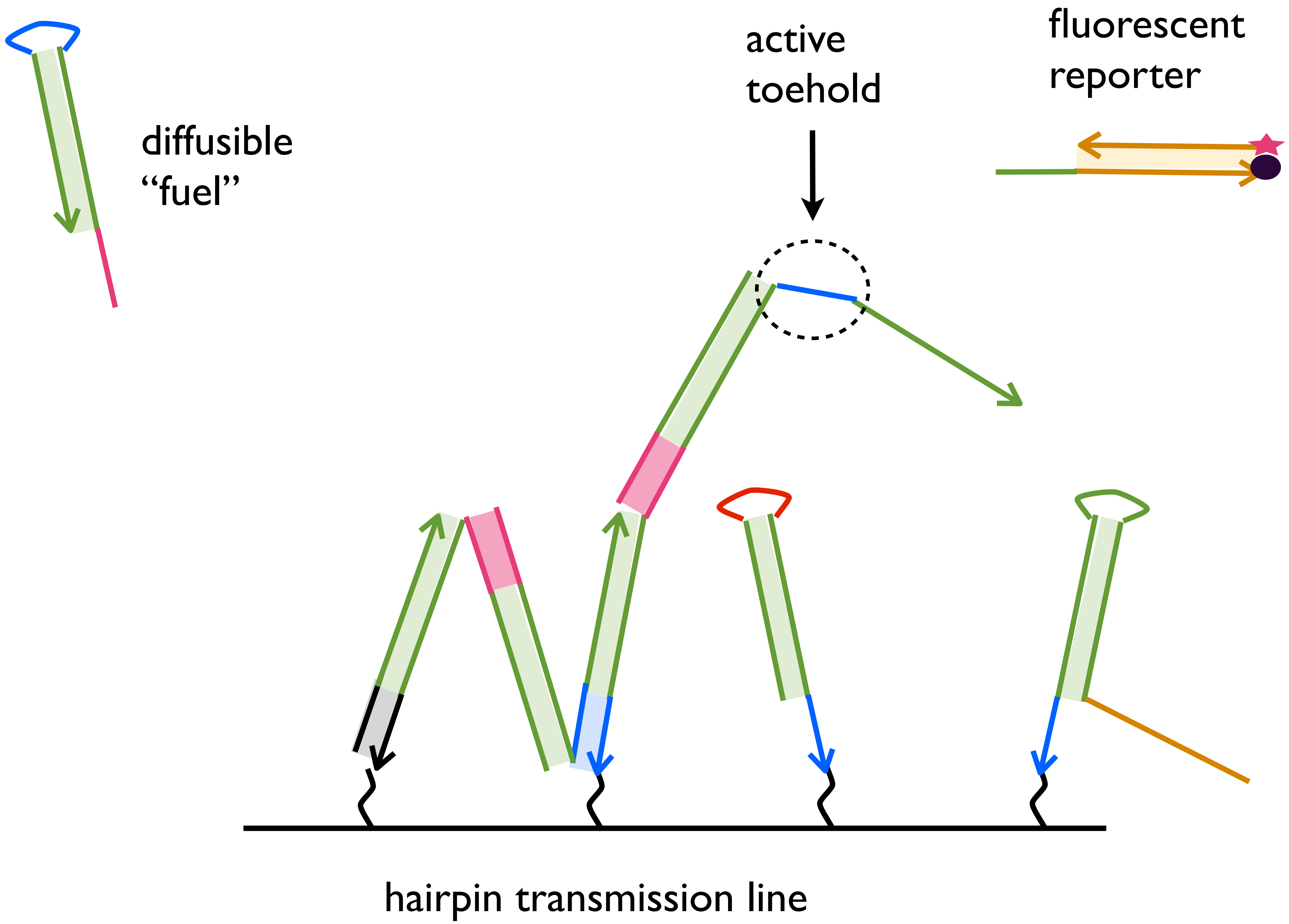

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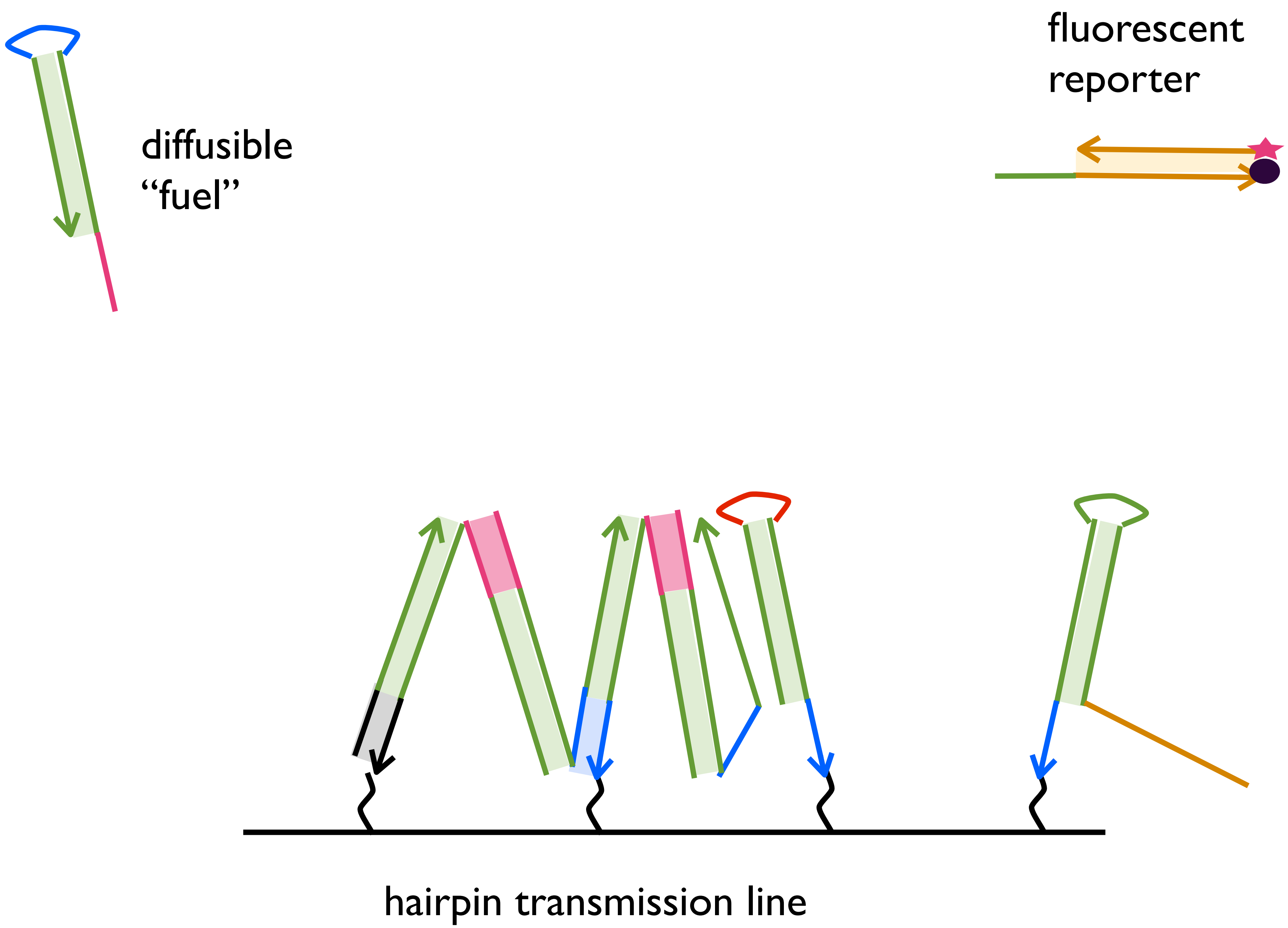

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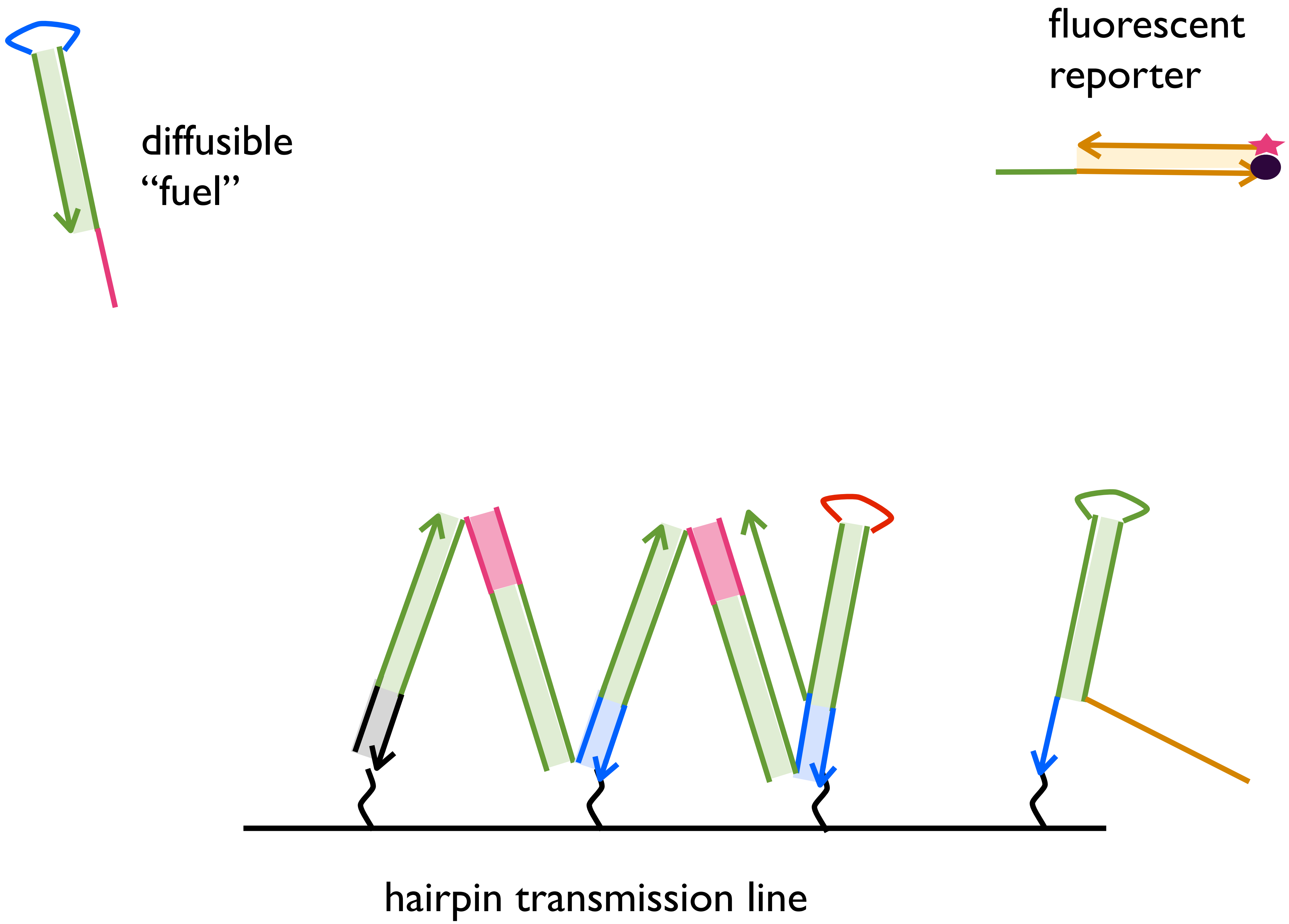

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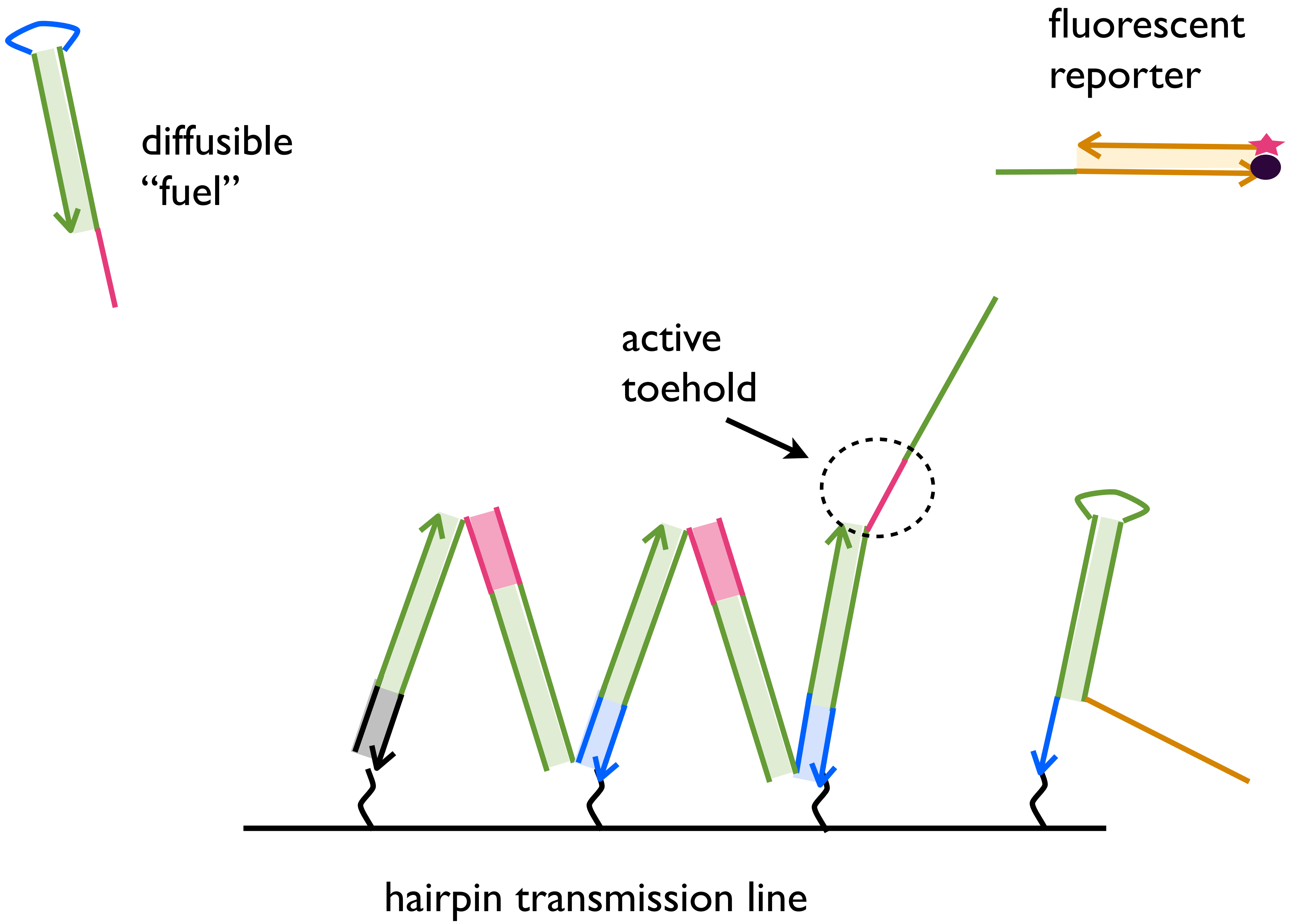

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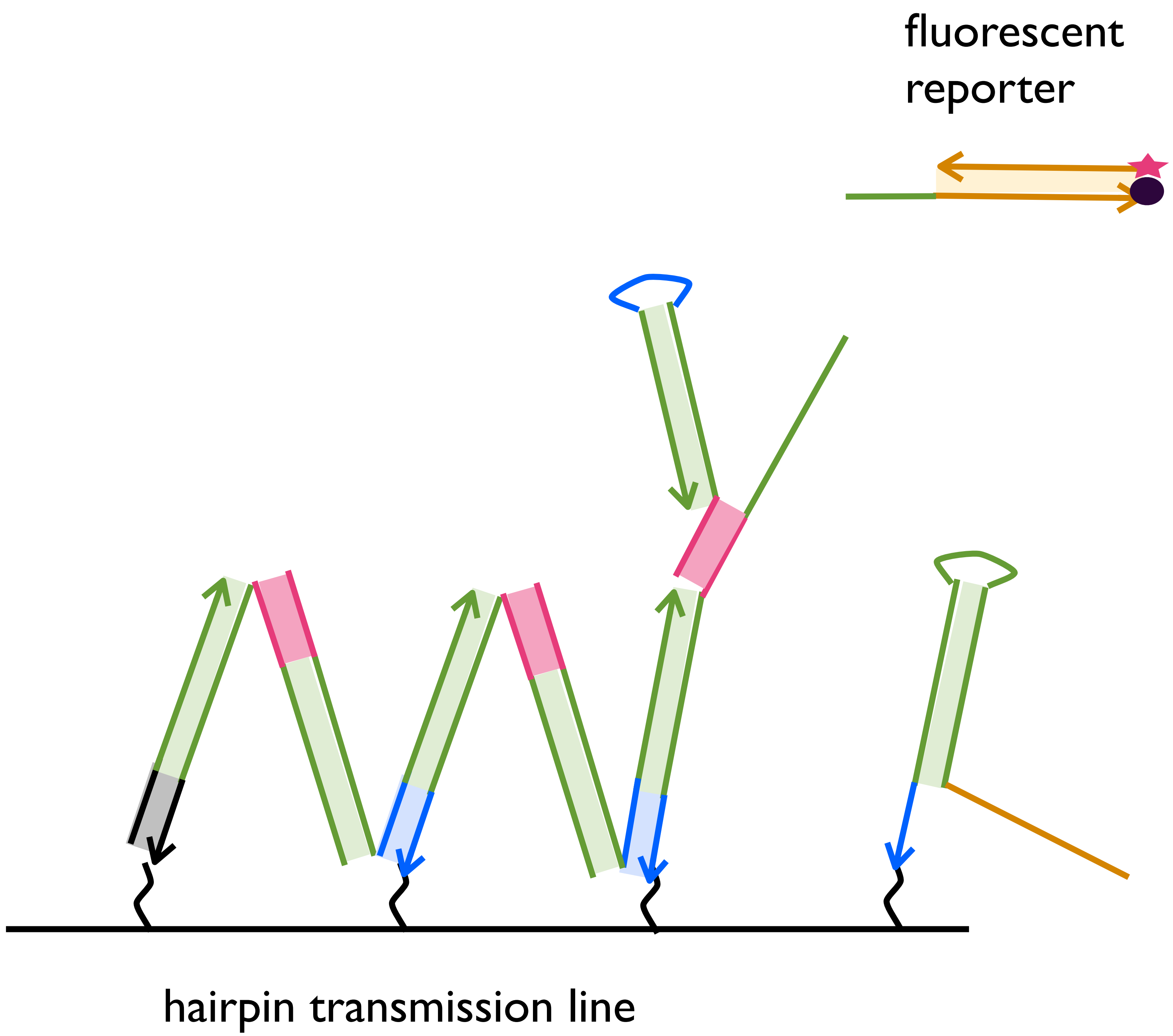

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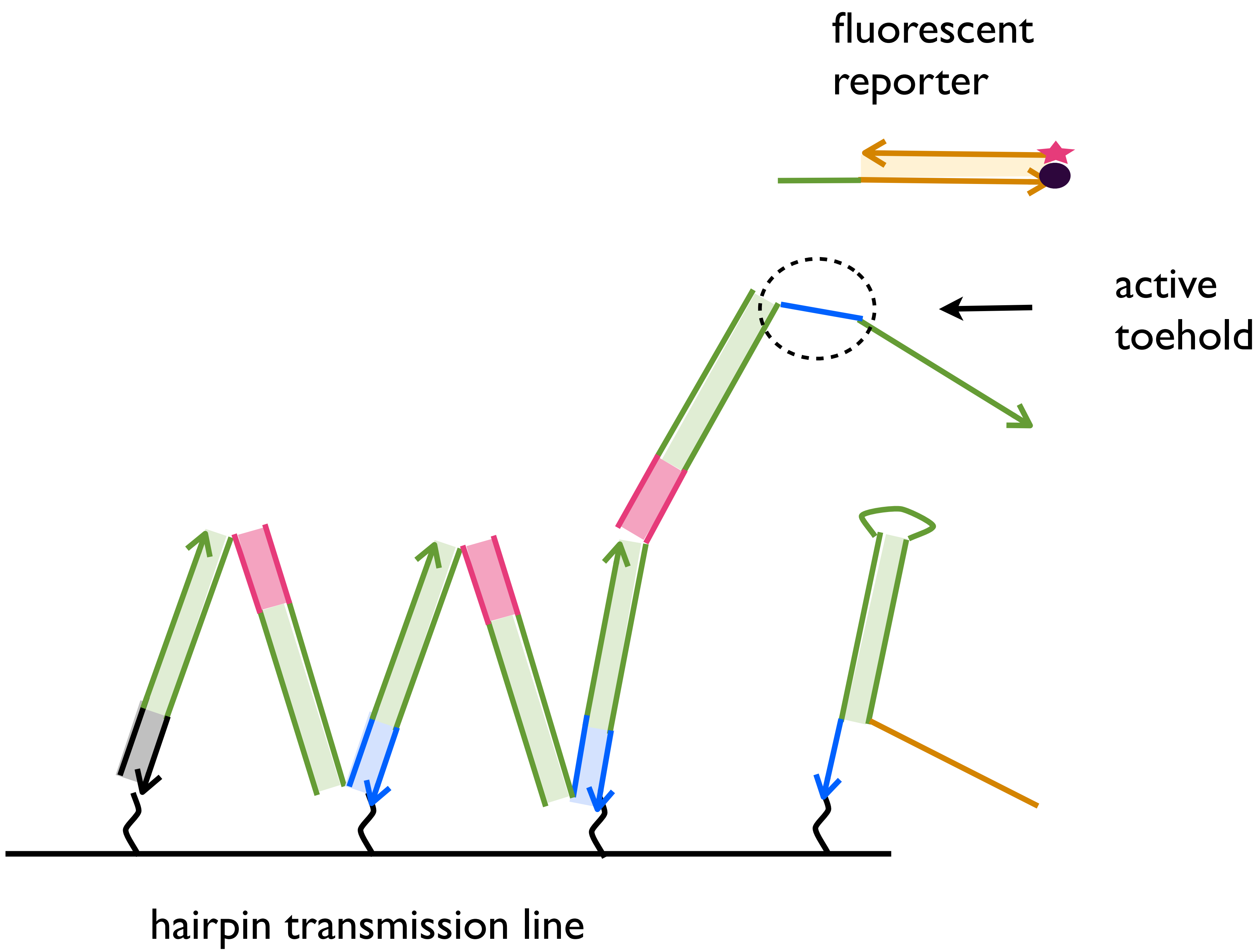

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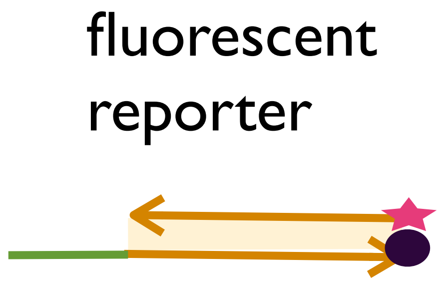

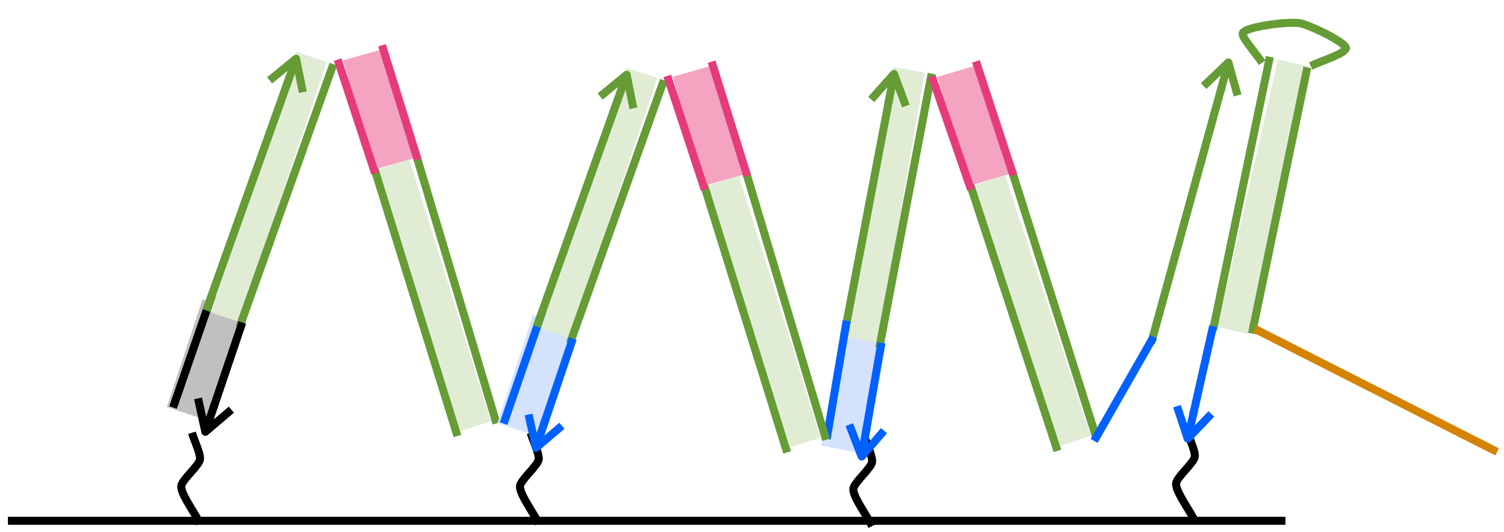

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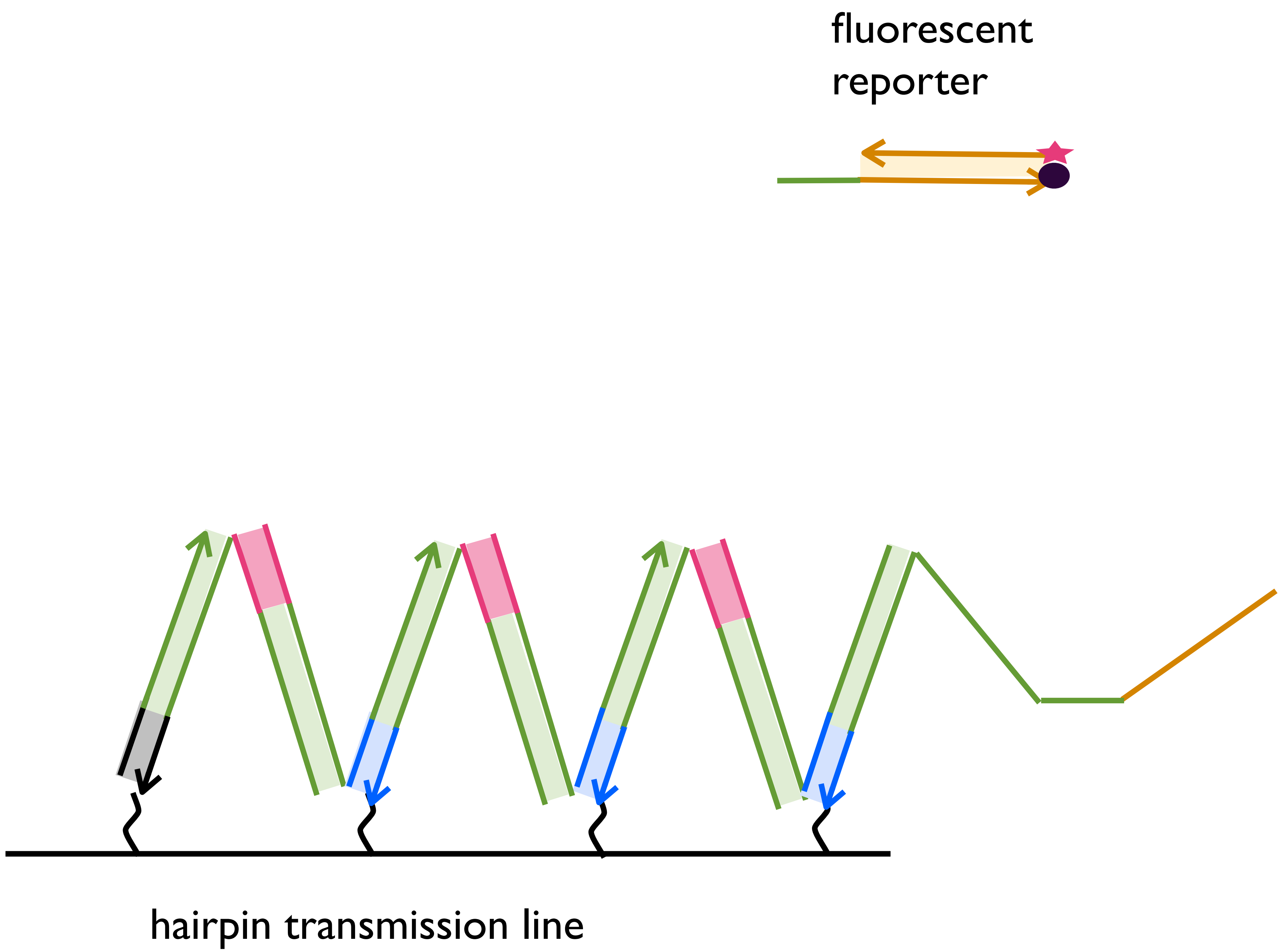

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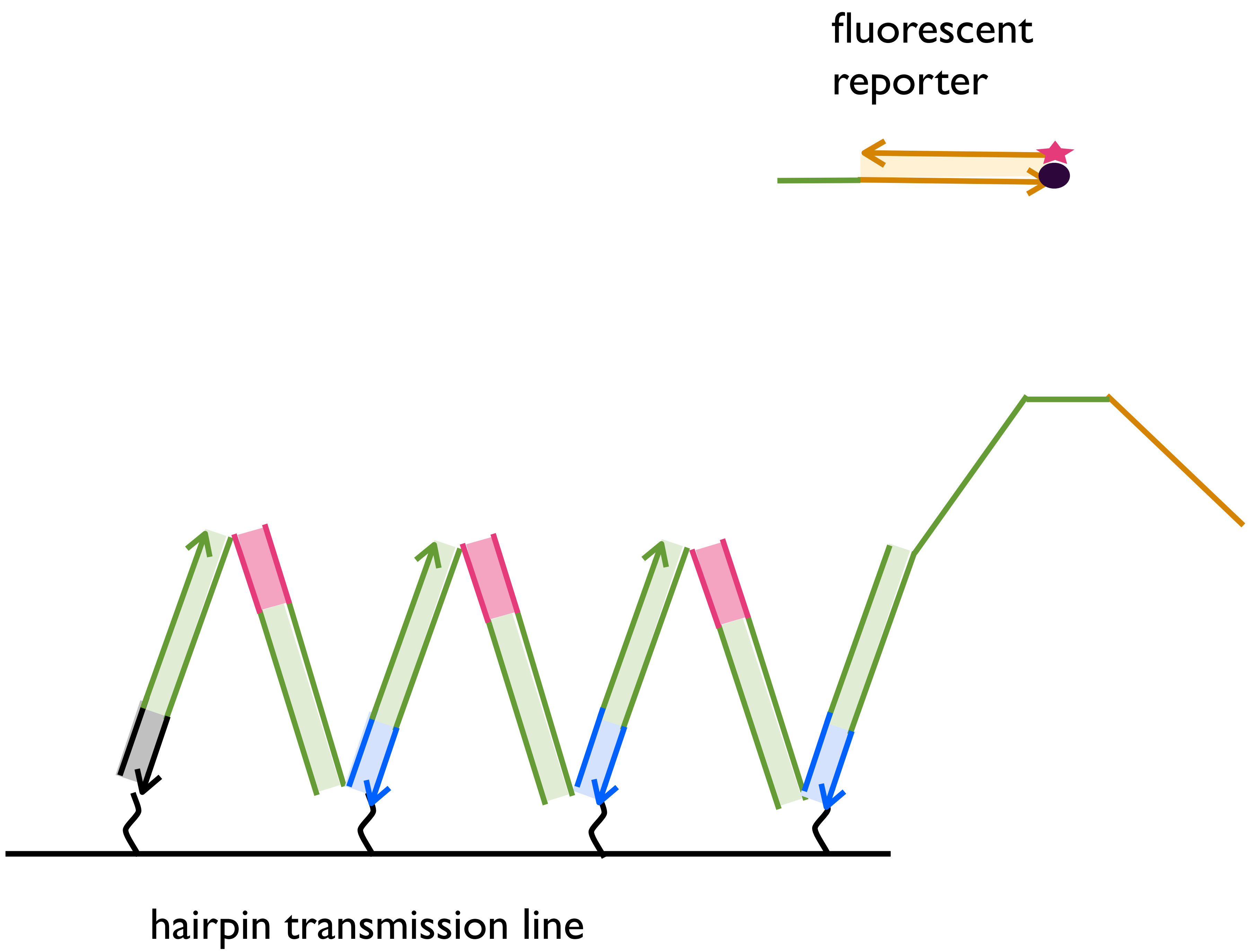

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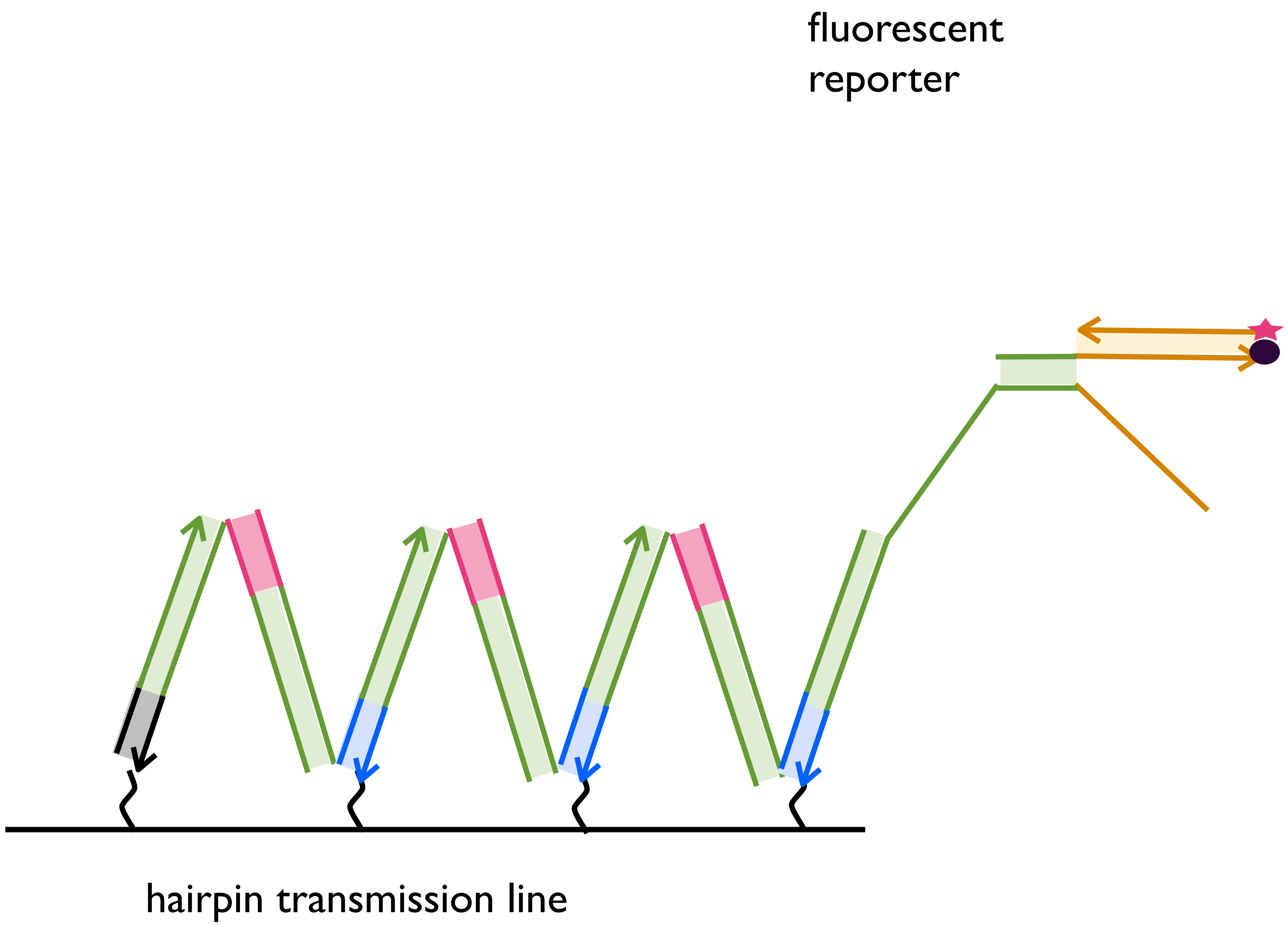

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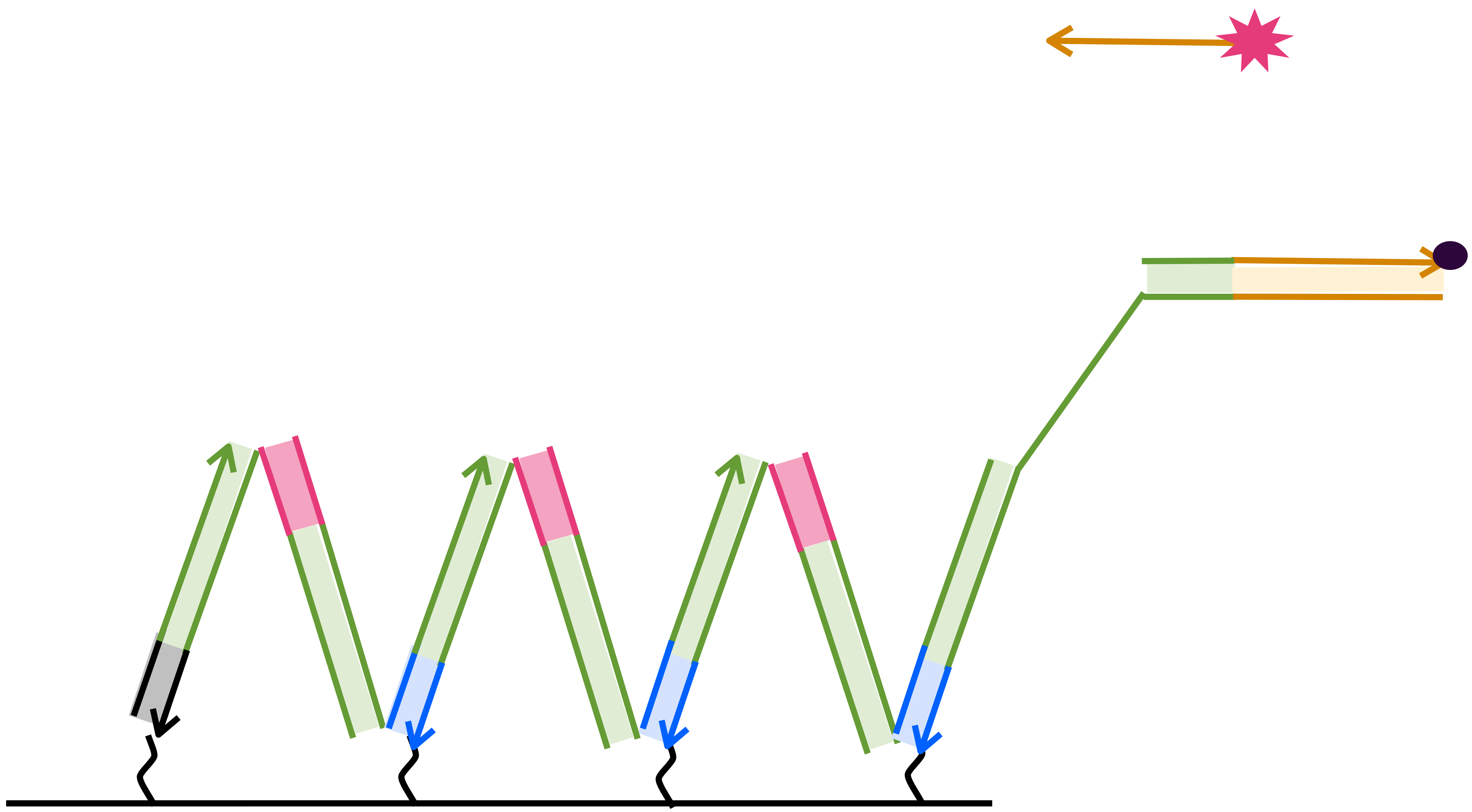
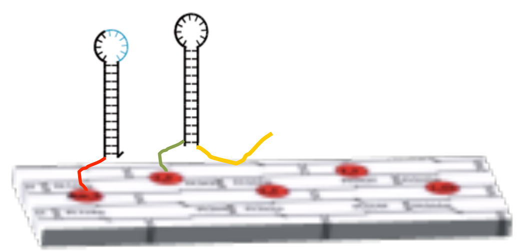
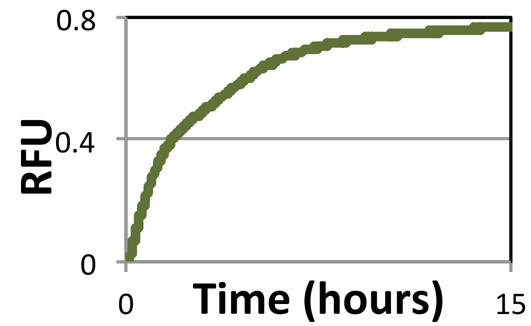


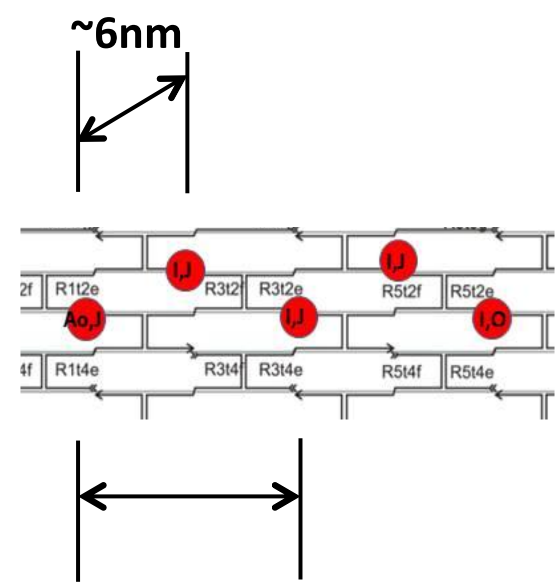
hairpin transmission line

Experimental validation

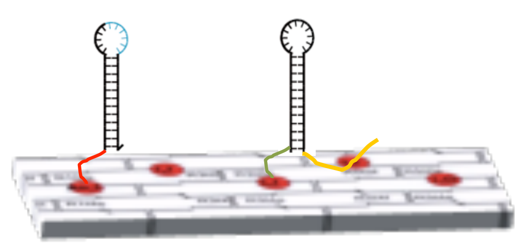
single spacing

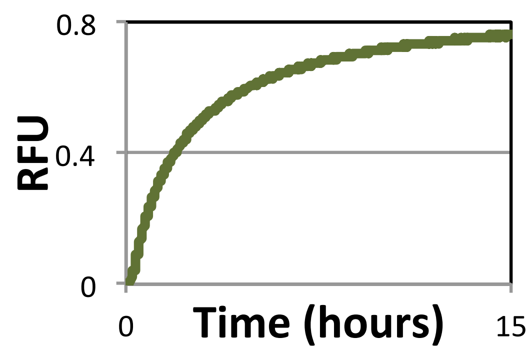




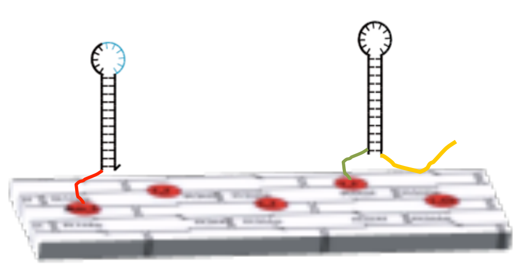


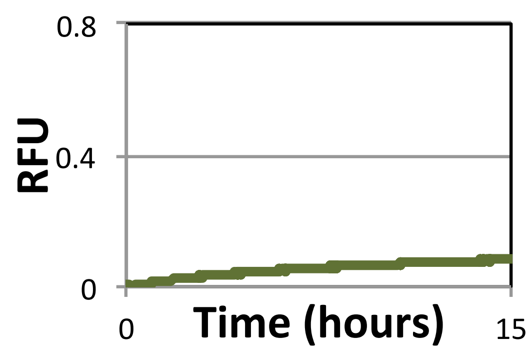
double spacing





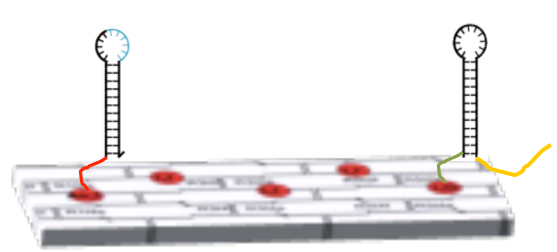
triple spacing

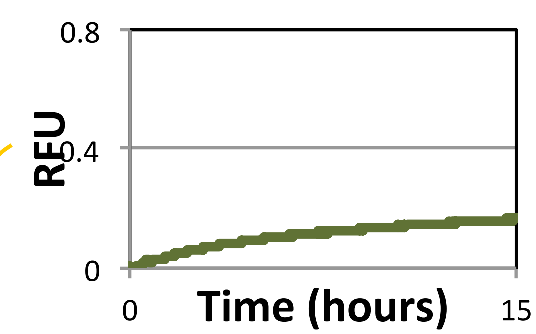




Reaction conditions:
~10nM origami, 20nM probe, 200nM input, 200nM fuel

quadruple spacing

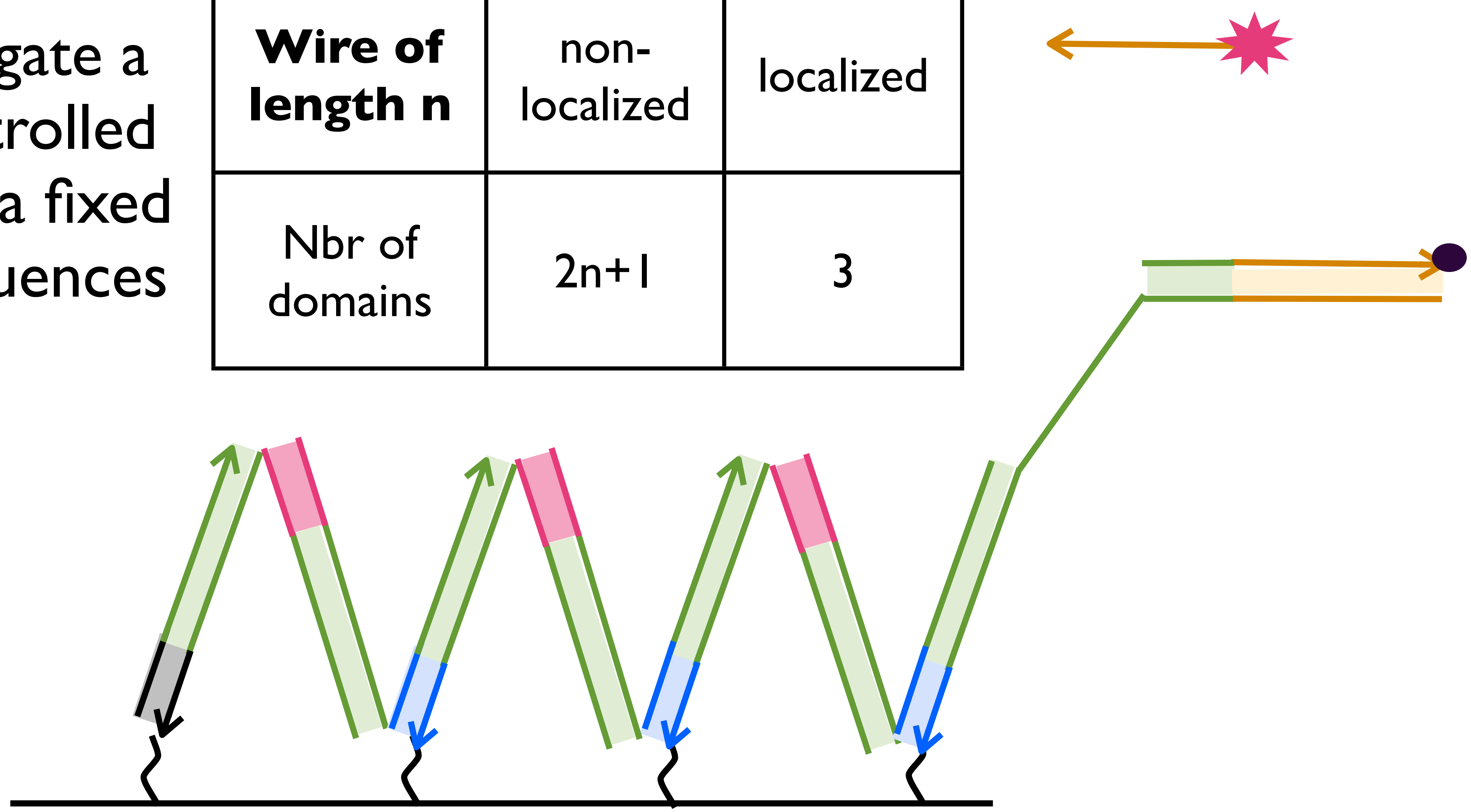




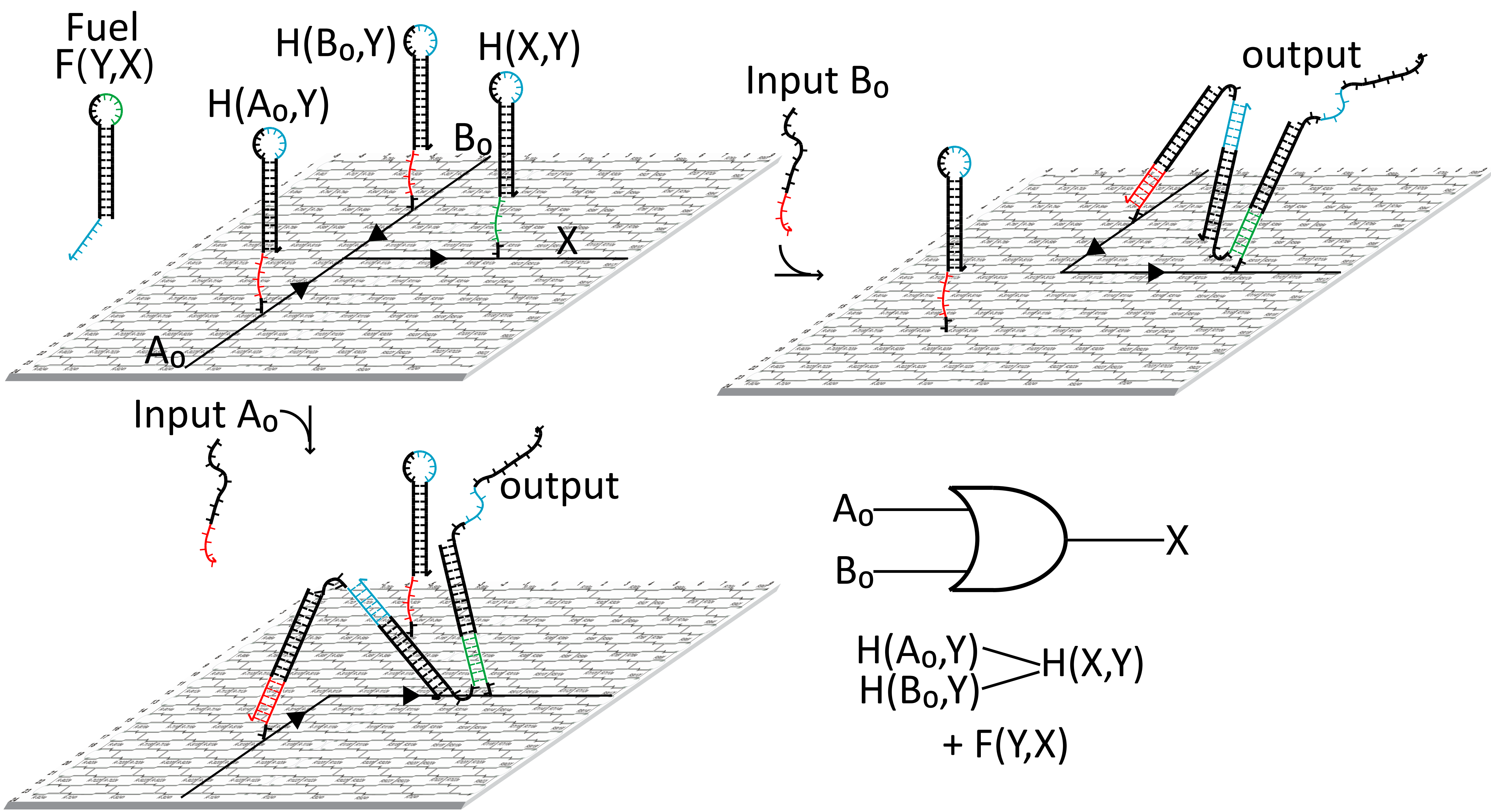
Take-home message

We can propagate a signal in a controlled way using only a fixed number of sequences

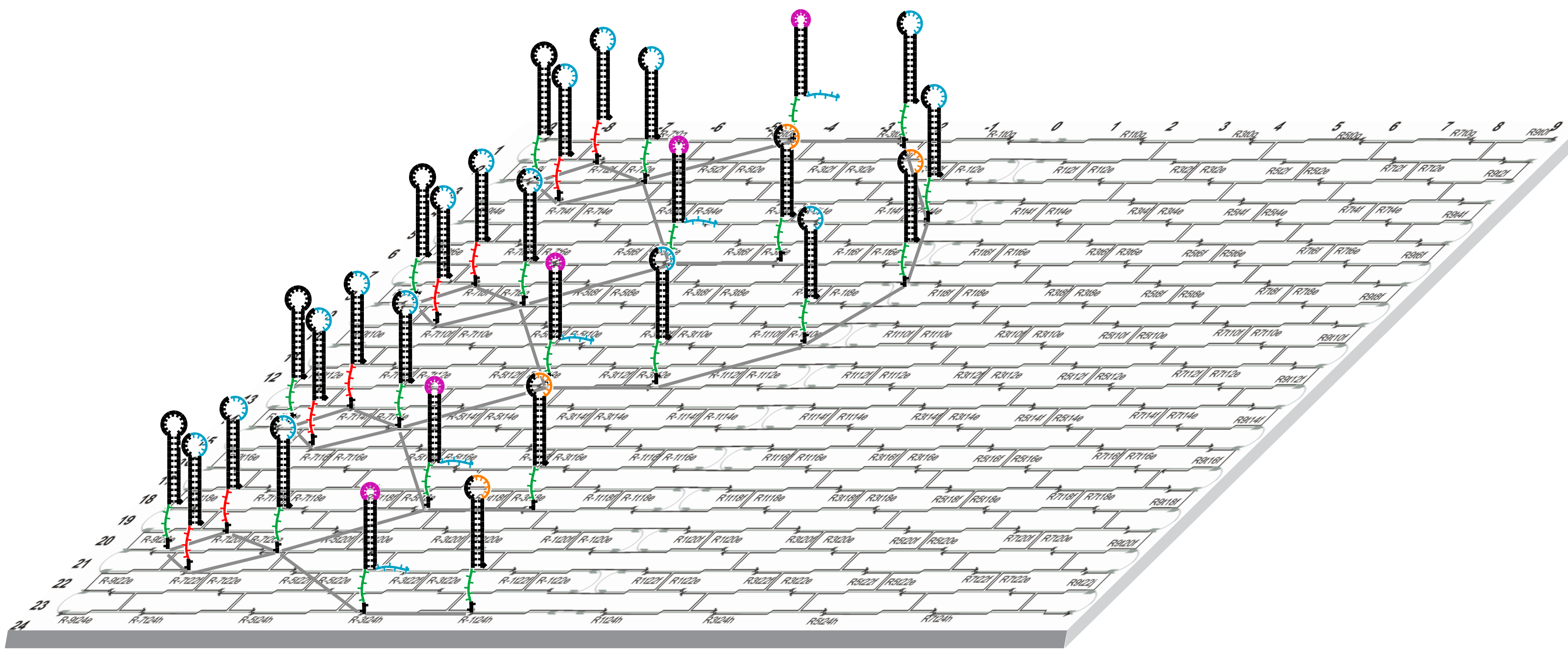
Wire of length n	non-localized	localized
Nbr of domains	2n+1	3



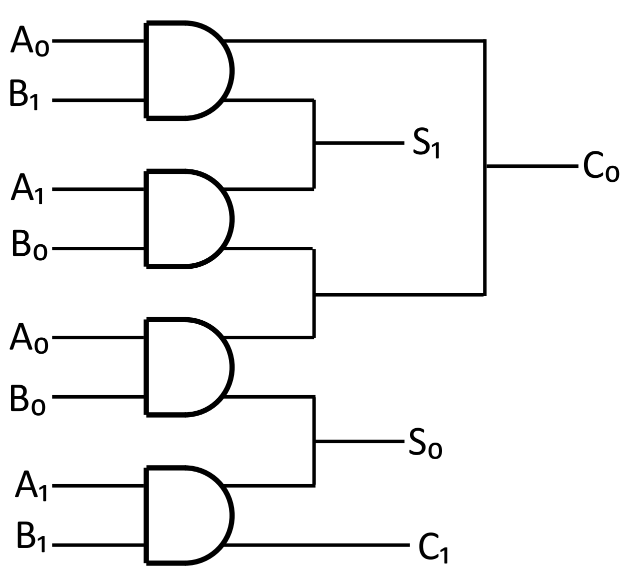
Localized OR gates

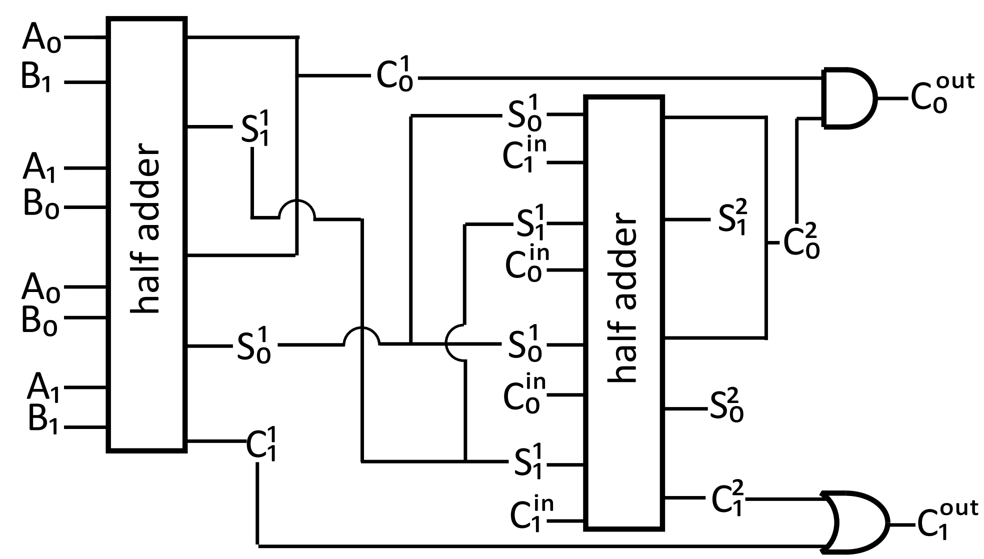


Localized adder circuits



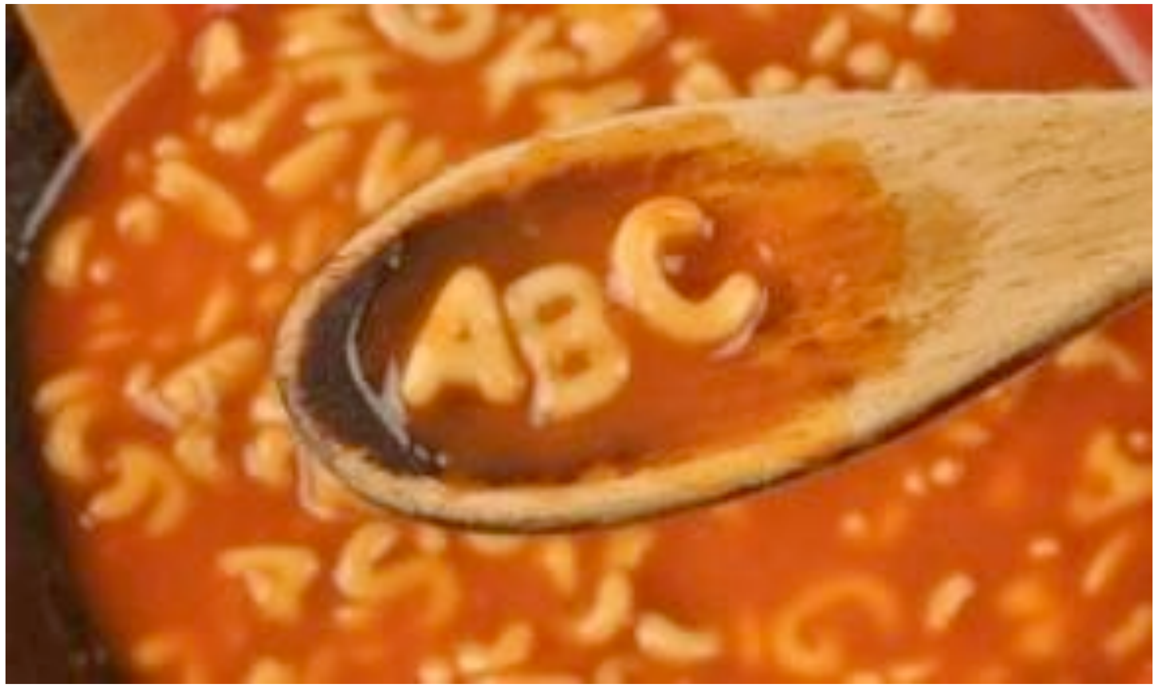
Basic circuits elements:
OR
AND
fan-out
wire crossings
(input/output hairpins)

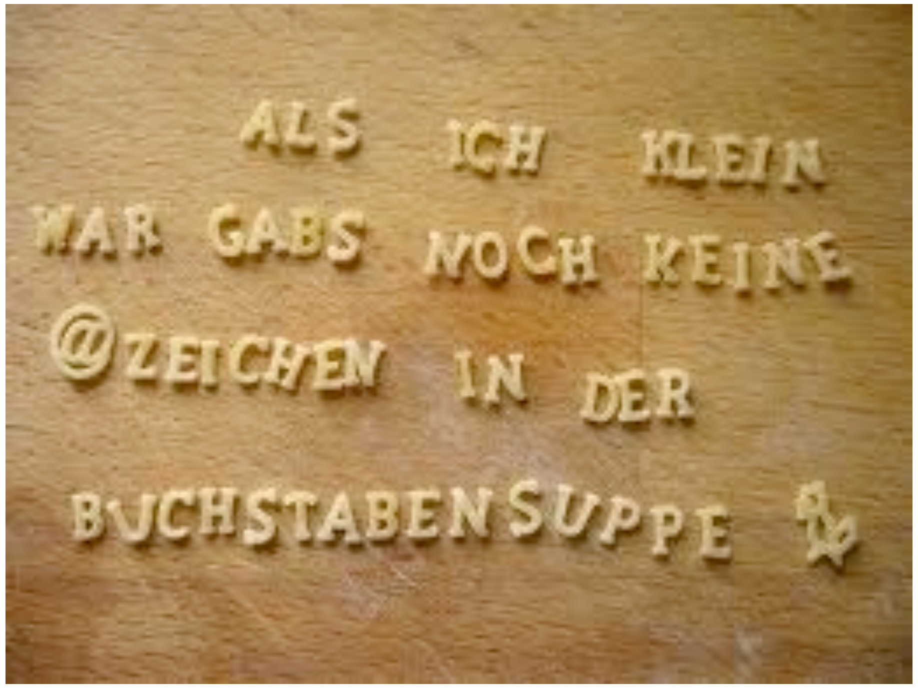




Take home message

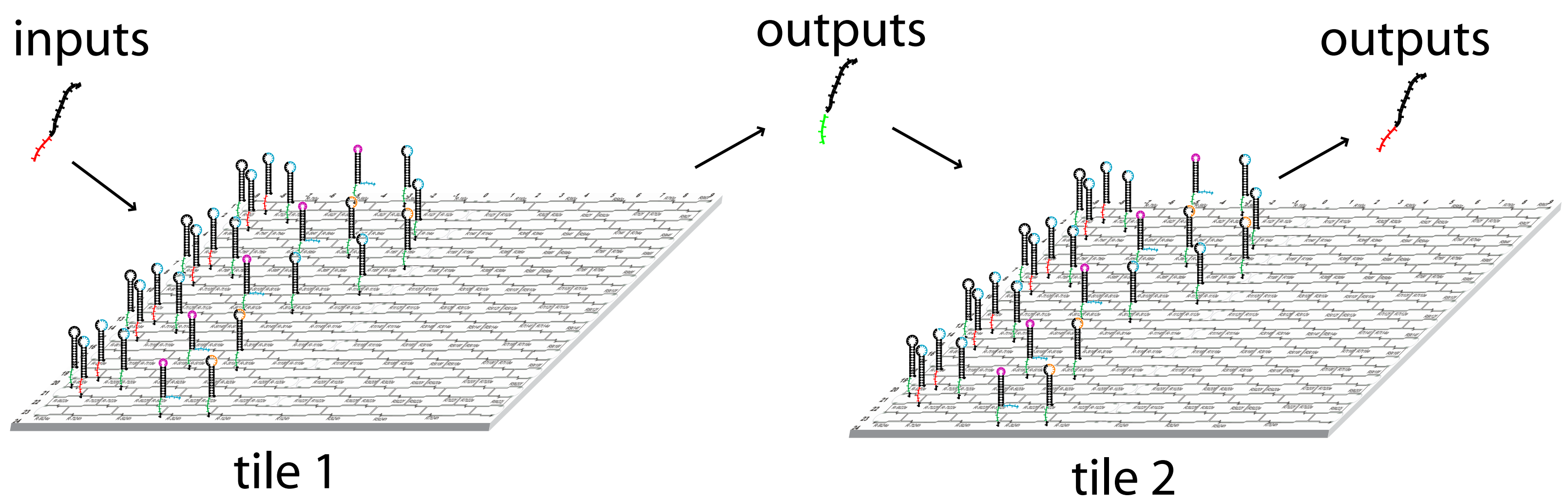
Localization enables composability of DNA circuits



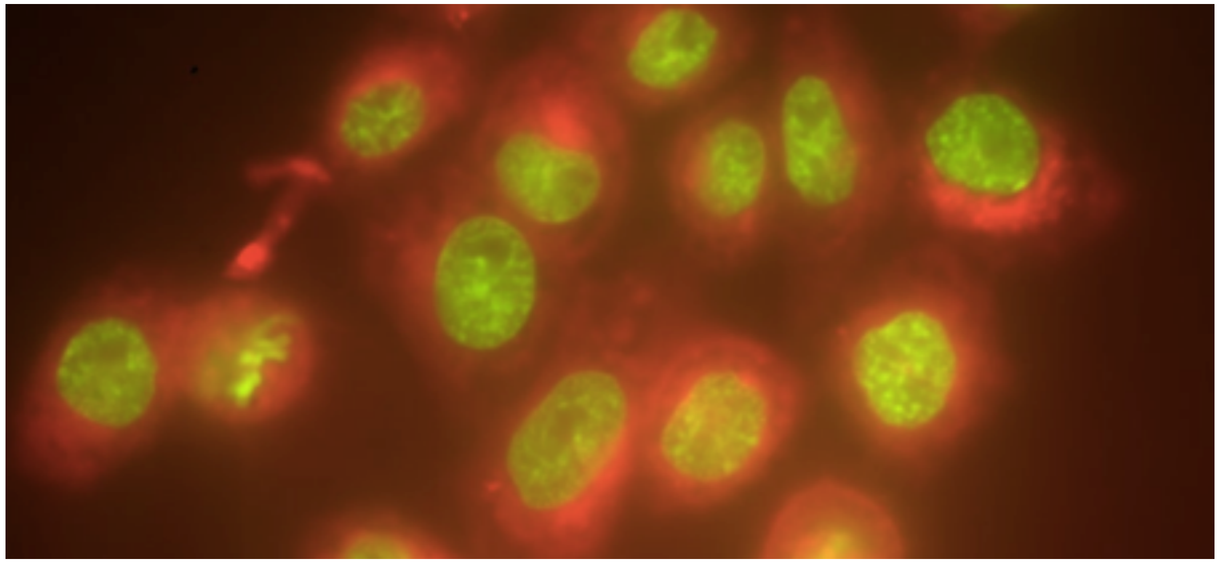


Outlook and future work

1. Communication between multiple origami enables circuits scale-up



2. Testing circuits in live cells



Summary

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3. DNA strand displacement circuits are the largest rationally designed molecular circuits so far but size and reliability are limited by the need to make sequences of all components orthogonal.

Summary

1. Circuits that can work in cells and other "wet" environments have interesting applications as therapeutics and diagnostics.

2. Synthetic DNA is an engineering material for the construction of nanoscale structures and circuits.

3. DNA strand displacement circuits are the largest rationally designed molecular circuits so far but size and reliability are limited by the need to make sequences of all components orthogonal.

4. Spatial isolation allows us to organize the flow of information in a better way and makes it much easier to design and compose large circuits.