Lecture 6: RNA-RNA interaction

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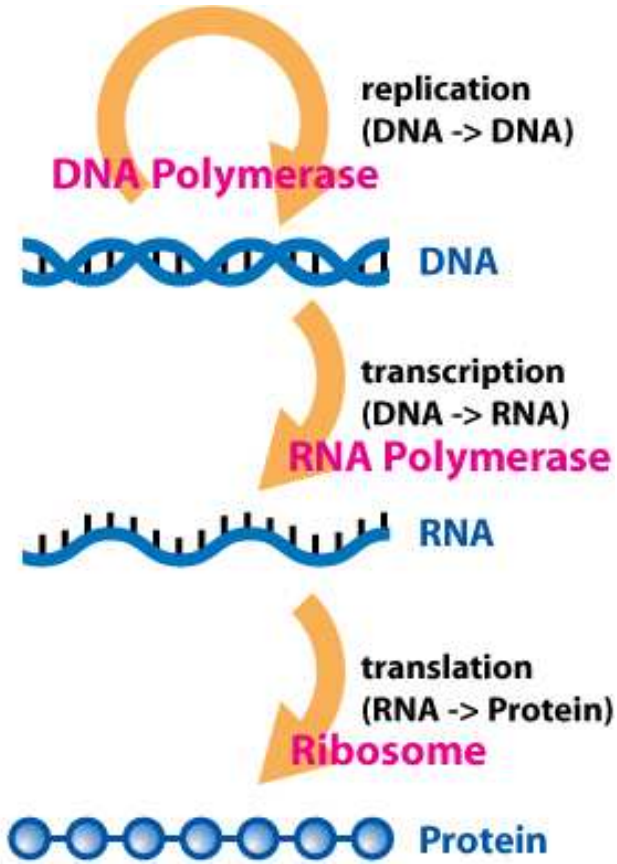
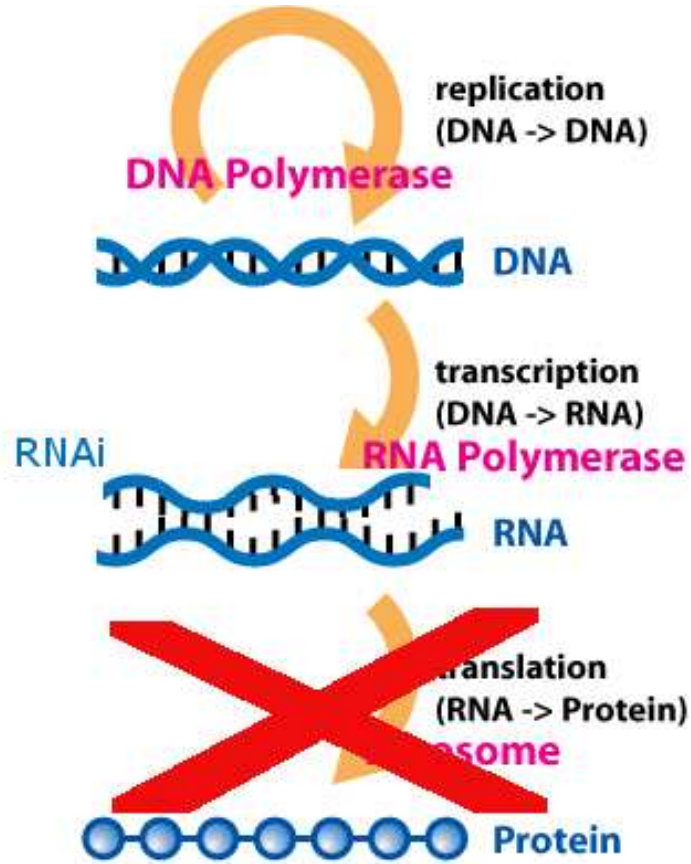
Central dogma

DNA → RNA → Protein



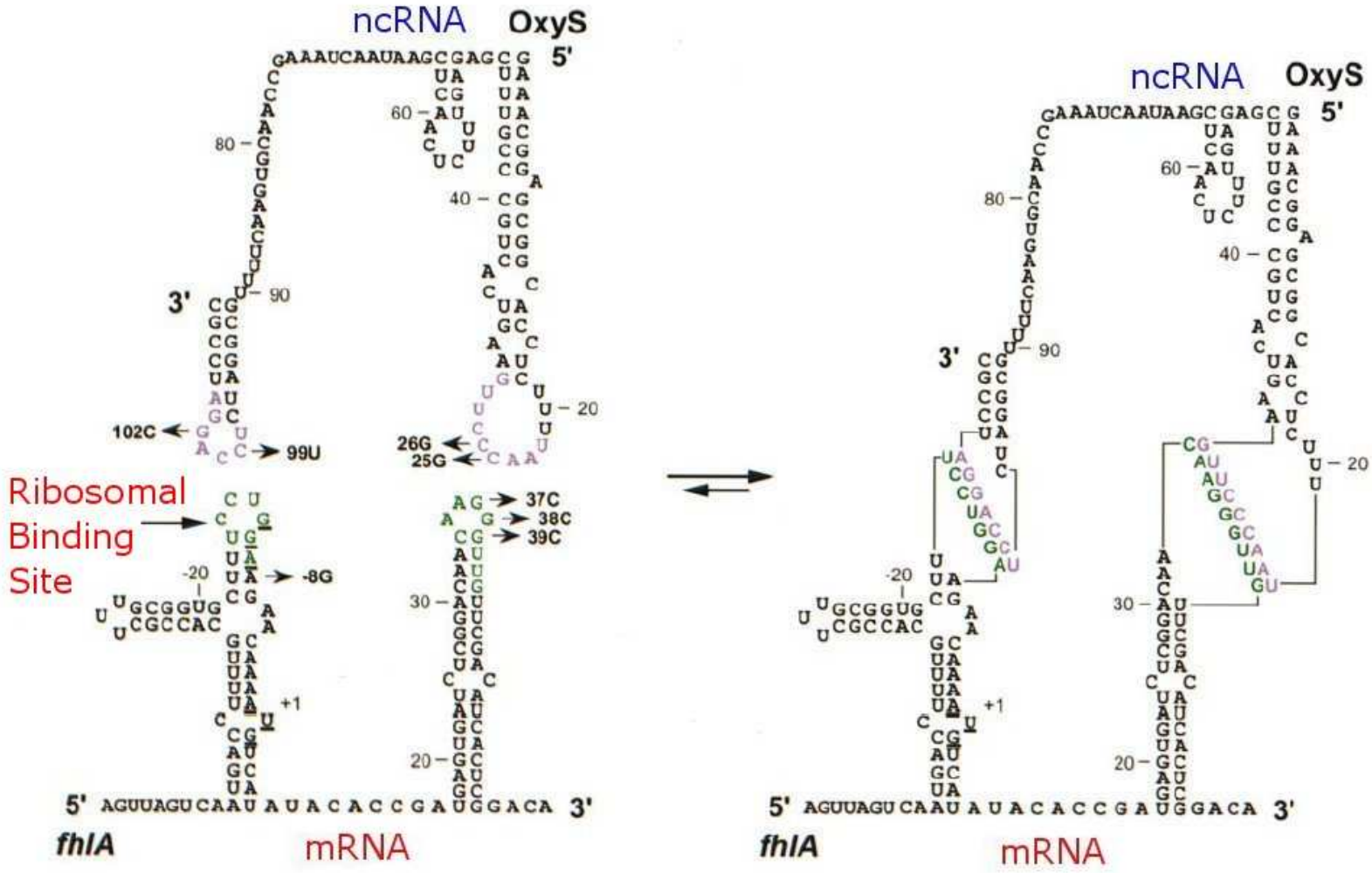
Motivation

Post-transcriptional regulation of gene expression



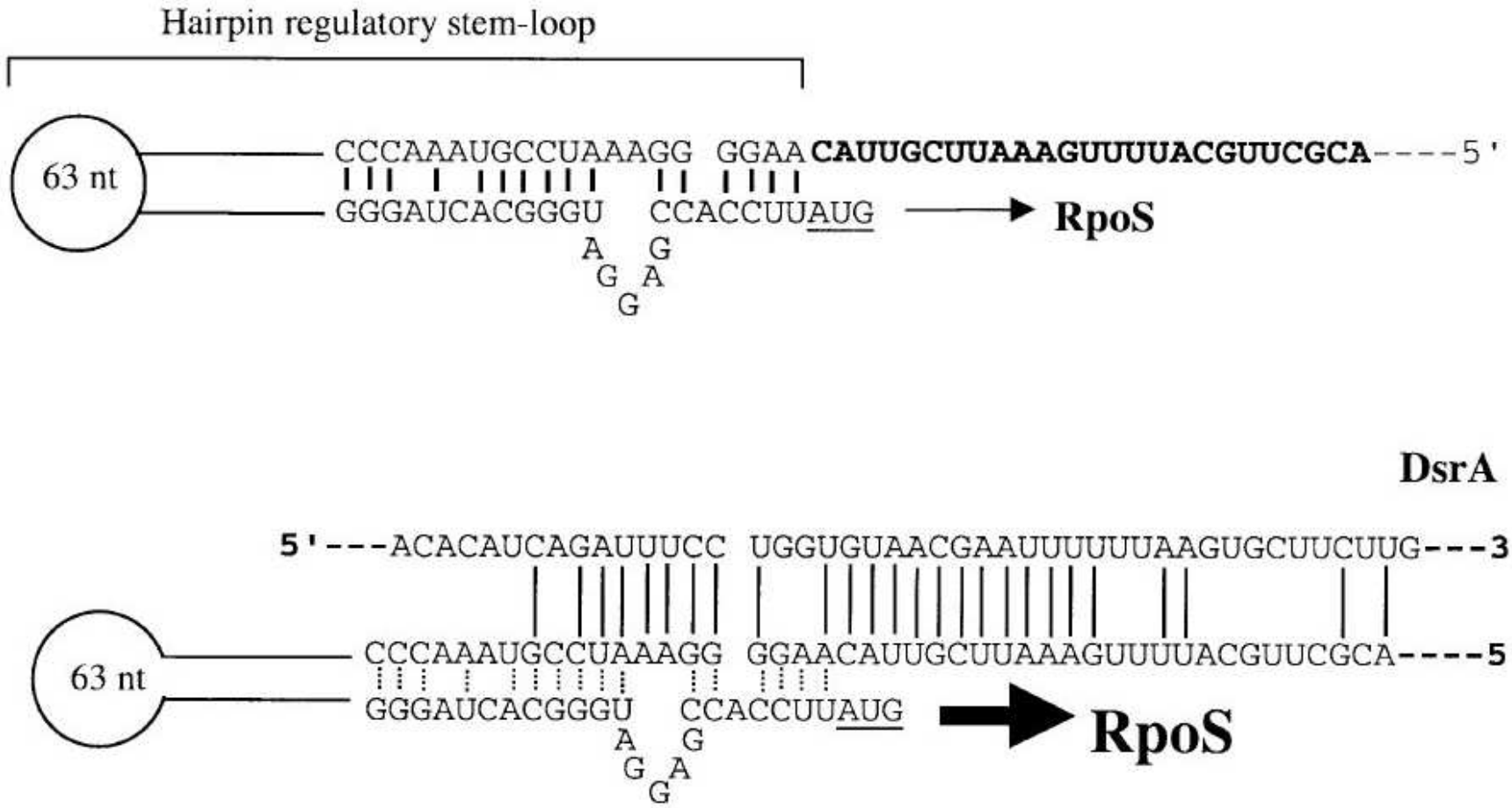
Regulatory RNA

Repression example (Argaman and Altuvia, J. Mol. Biol. 2000)



Regulatory RNA

Activation example (Repoila, Majdalani, and Gottesman, Mol. Microbiol. 2003)



Background

RNA-RNA MFE structure prediction

- Avoid intramolecular base pairing
  RNAhybrid (Rehmsmeier *et al.* 2004), **RNAduplex** (Bernhart *et al.* 2006), **UNAFold** (Markham *et al.* 2008)
  No internal structure
- Concatenate input sequences as a single strand; no pseudoknots
  PairFold (Andronescu *et al.* 2005), **RNAcofold** (Bernhart *et al.* 2006)
  No kissing hairpins
- Predict binding sites
  RNAup (Mückstein *et al.* 2008), **intaRNA** (Busch *et al.* 2008)
  Just one binding site not complete structure
- Concatenate input sequences; consider special pseudoknots
  NUPACK (Dirks *et al.* 2003,2007)

  Still no kissing hairpins!

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Background (continued)

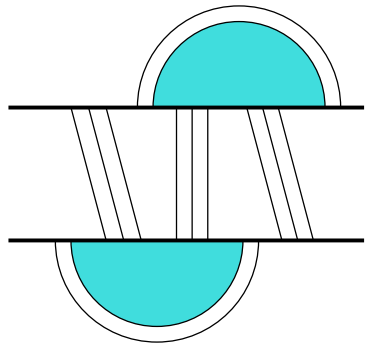
RNA-RNA MFE structure prediction

Consider inter- and intramolecular base pairing

IRIS (Pervouchine 2004), **inteRNA** (Alkan *et al.* 2005), **Grammatical Approach** (Kato *et al.* 2009)

Voilà, now we are talking business.

The problem is NP-Hard (Alkan *et al.* 2005); no surprise as pseudoknots are NP-Hard. Exclude *zigzags* and crossing interactions to lift the curse of complexity and obtain an exact $O(n^6)$-time $O(n^4)$-space DP algorithm (albeit for simple base-pair counting).



First order zigzag. A general zigzag involves an arbitrary number of kissing hairpins.

Ahhh...but MFE is often wrong!

Question: how about

1. computing base pairing probabilities,
2. sampling from the Boltzmann ensemble of interaction structures, clustering, centroids, etc.,
3. and computing equilibrium concentrations and melting temperature for RNA-RNA compounds?

Answer: the key enabling technology is the **partition function**. All of the above can be computed from the partition function.

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Partition function

$$Q(T) = \sum_{f \in F} e^{-G_f/RT},$$

$F =$ All permissible interaction structures,

$$p(f) \propto e^{-G_f/RT},$$

and Q is the normalizing factor. Also other thermodynamic quantities can be derived from Q.

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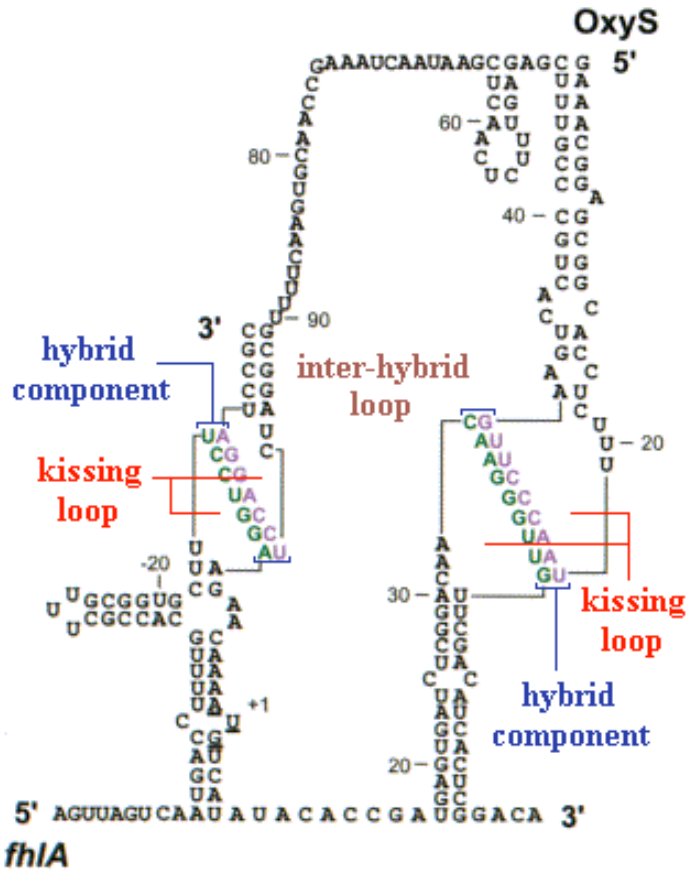
Our extension of the Turner model

Chitsaz *et al.*, Bioinformatics 25(12): i365-i373

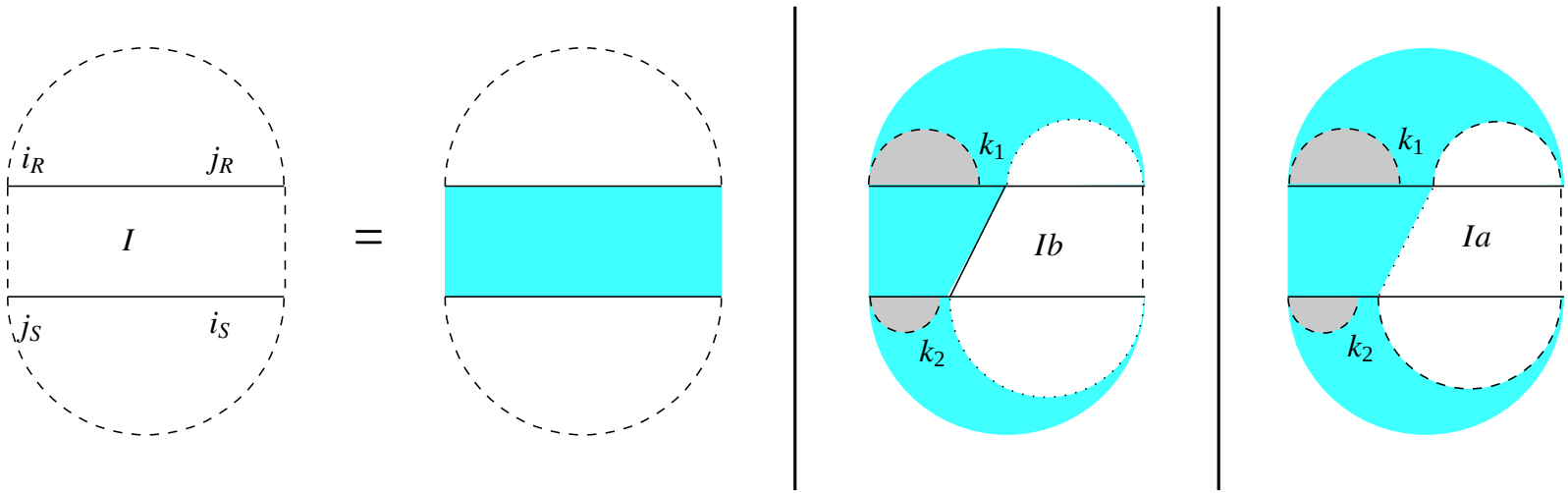


Hybrid component: as if intramolecular, with penalties.

Kissing loop: like multibranch loop.

Partition function for two strands

straight vertical line: intermolecular bond
solid: a base pair
dotted: not a base pair
dashed: either of those two



$$Q^I_{i_R,j_R,i_S,j_S} = Q_{i_R,j_R} Q_{i_S,j_S} + \sum_{\substack{i_R \le k_1 < j_R \\ i_S < k_2 \le j_S}} Q_{i_R,k_1-1} Q_{k_2+1,j_S} Q^{Ib}_{k_1,j_R,i_S,k_2} +$$

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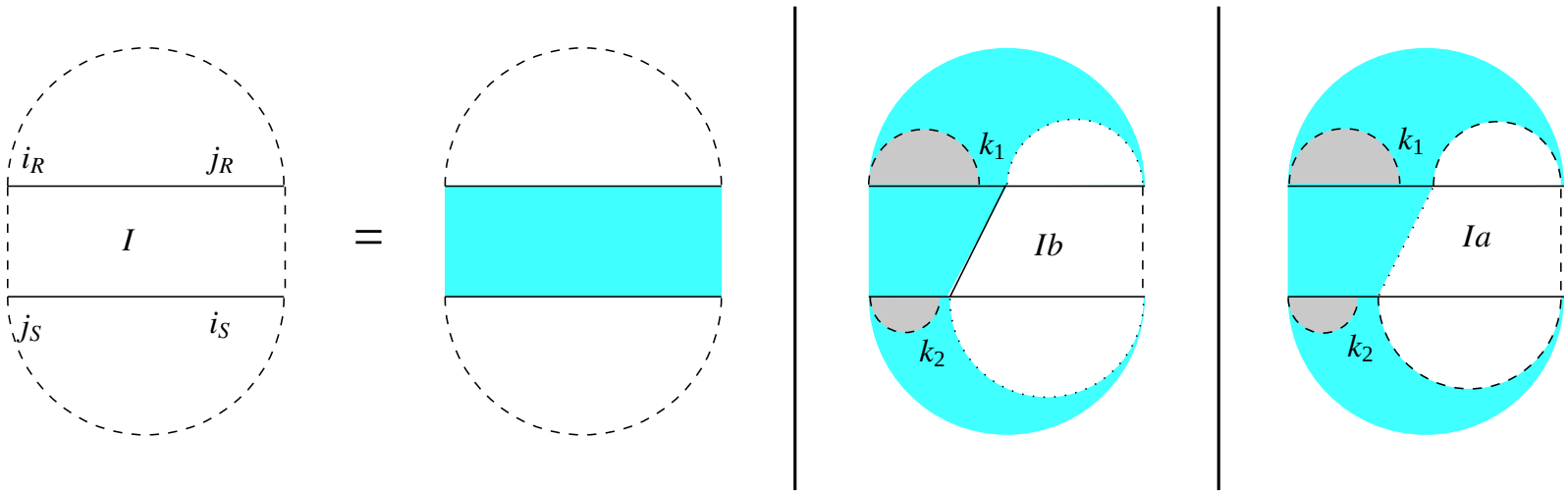

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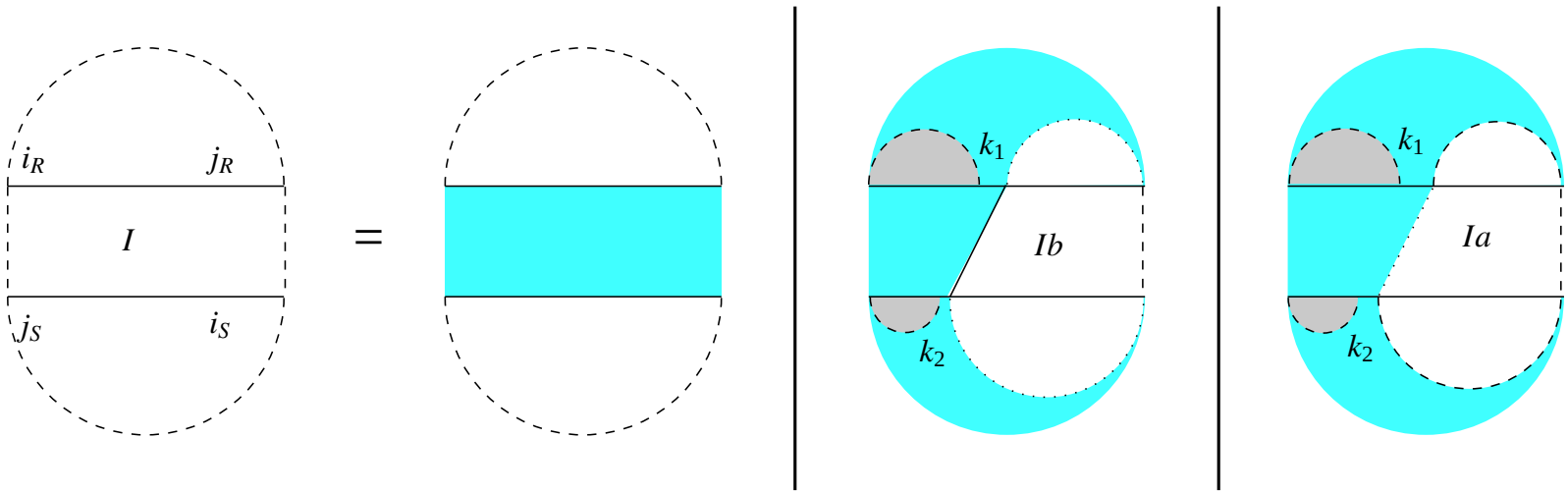

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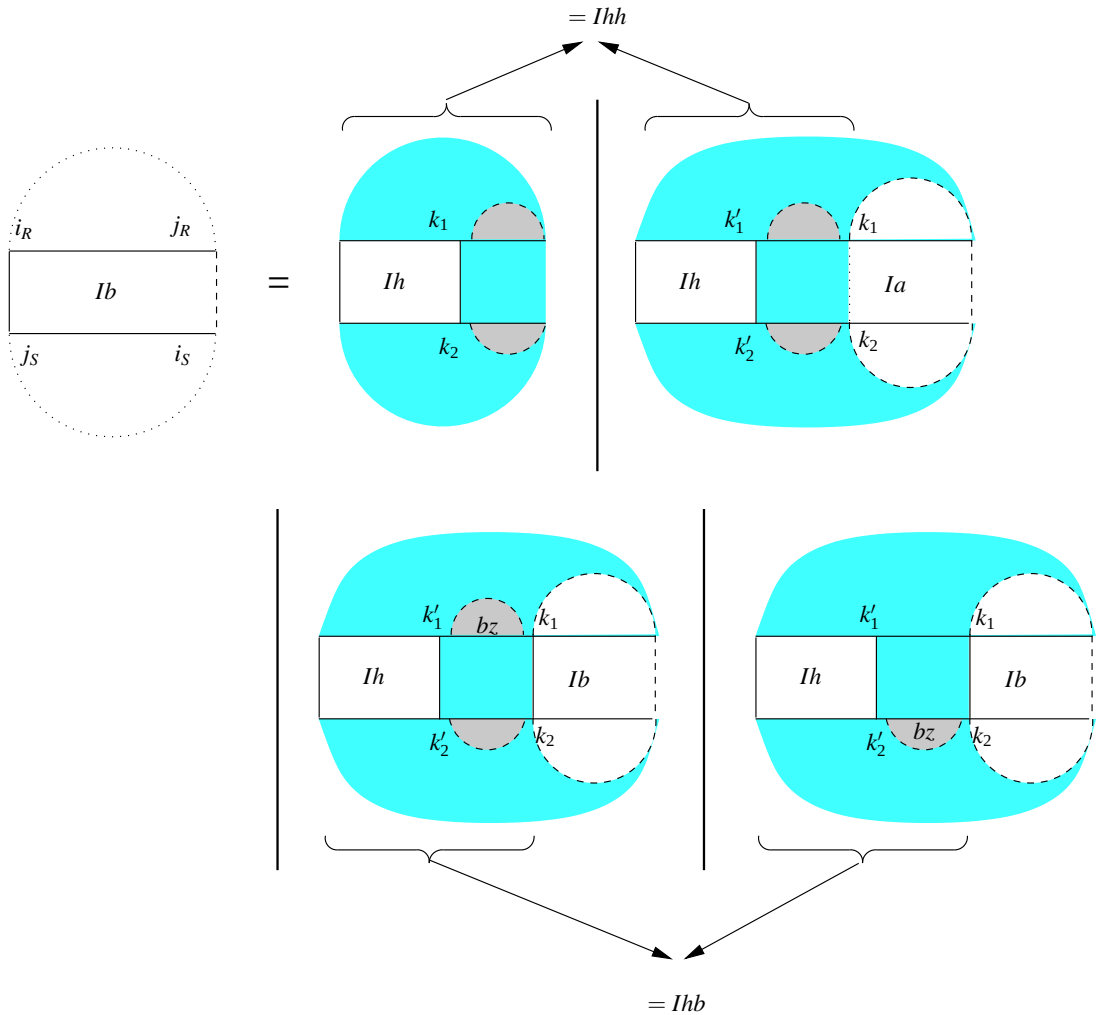
Q^{Ib}



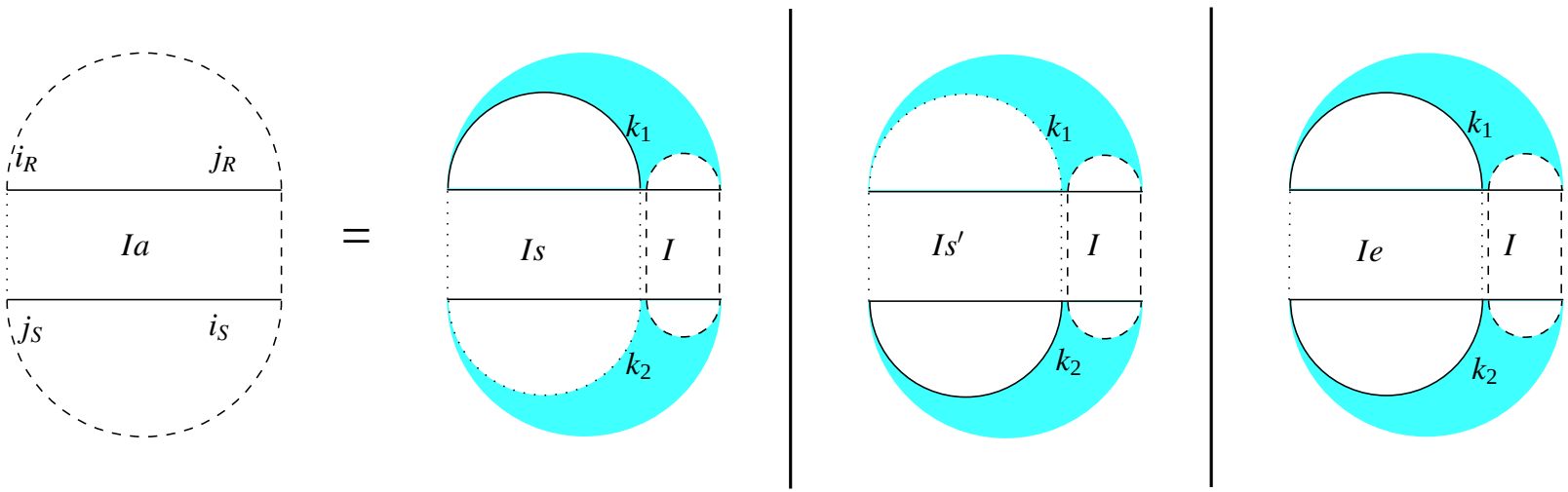
b: stands for bond

Q^{Ia}

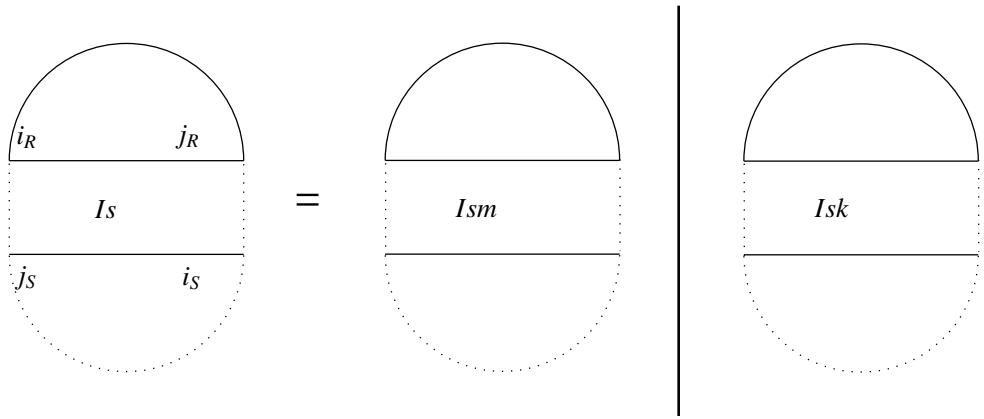
a: stands for arc

s: stands for subsume

e: stands for equivalent



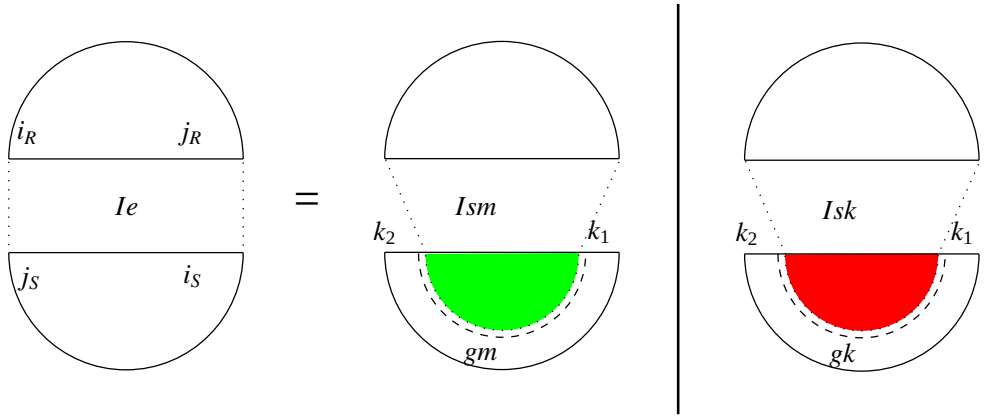
Q^{Is} and Q^{Ie}



s: stands for subsume

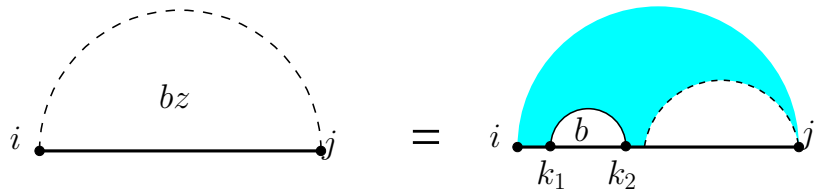
k: stands for kissing-loop

m: stands for multi-loop



e: stands for equivalent

All tables



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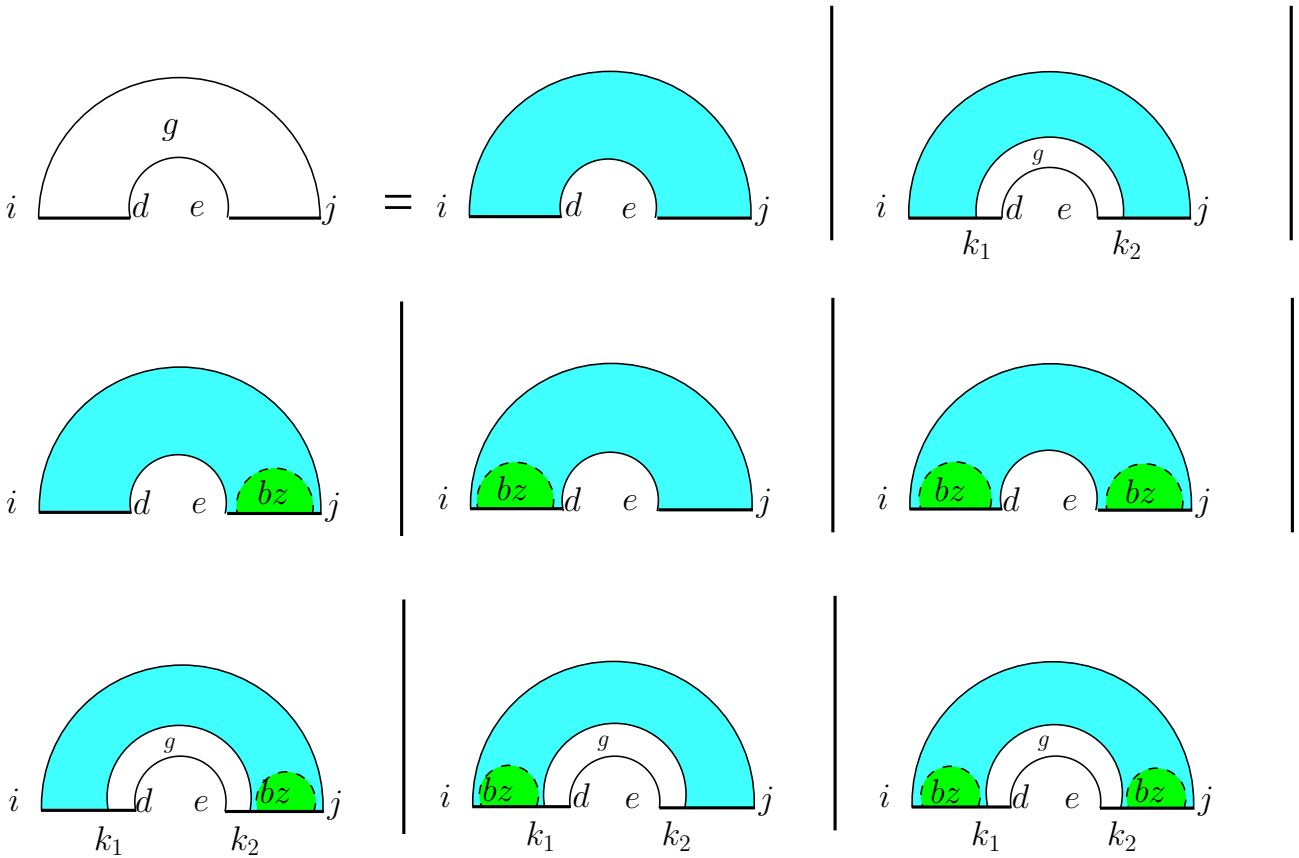
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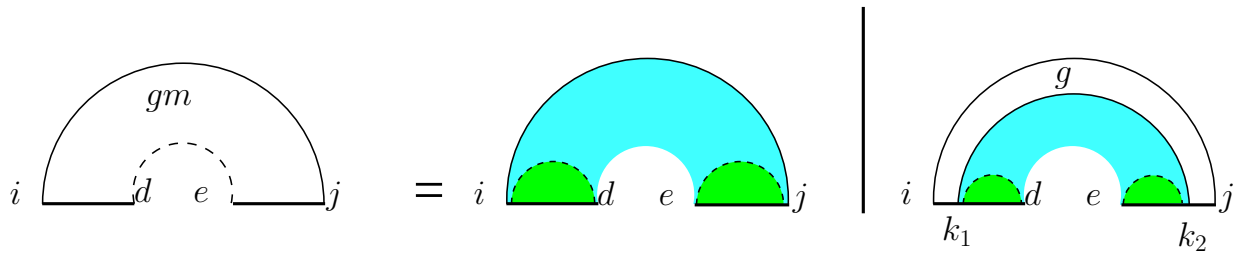

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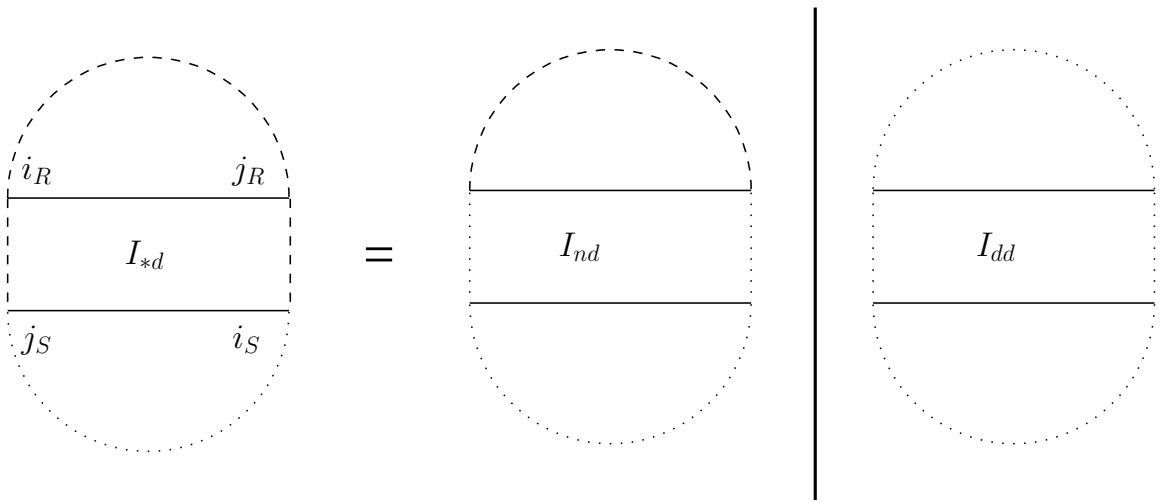

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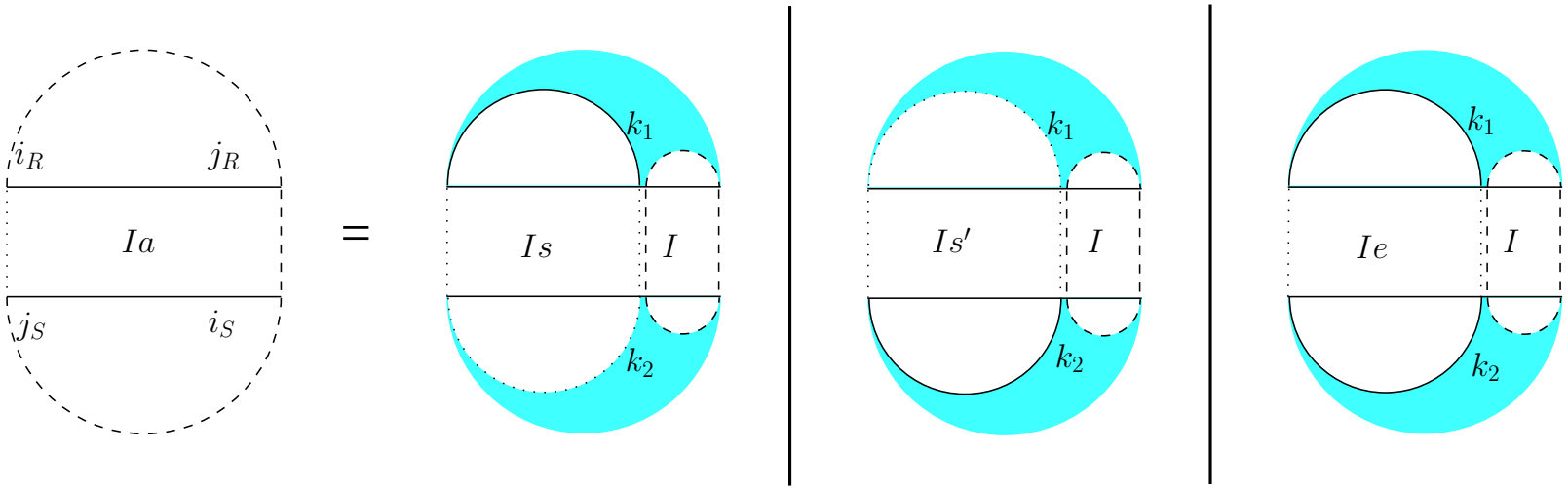

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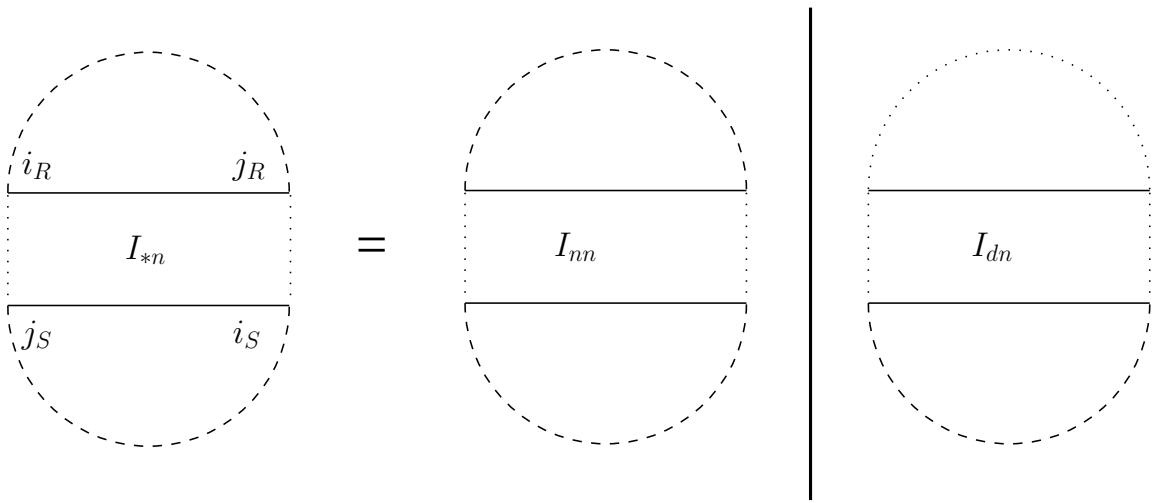

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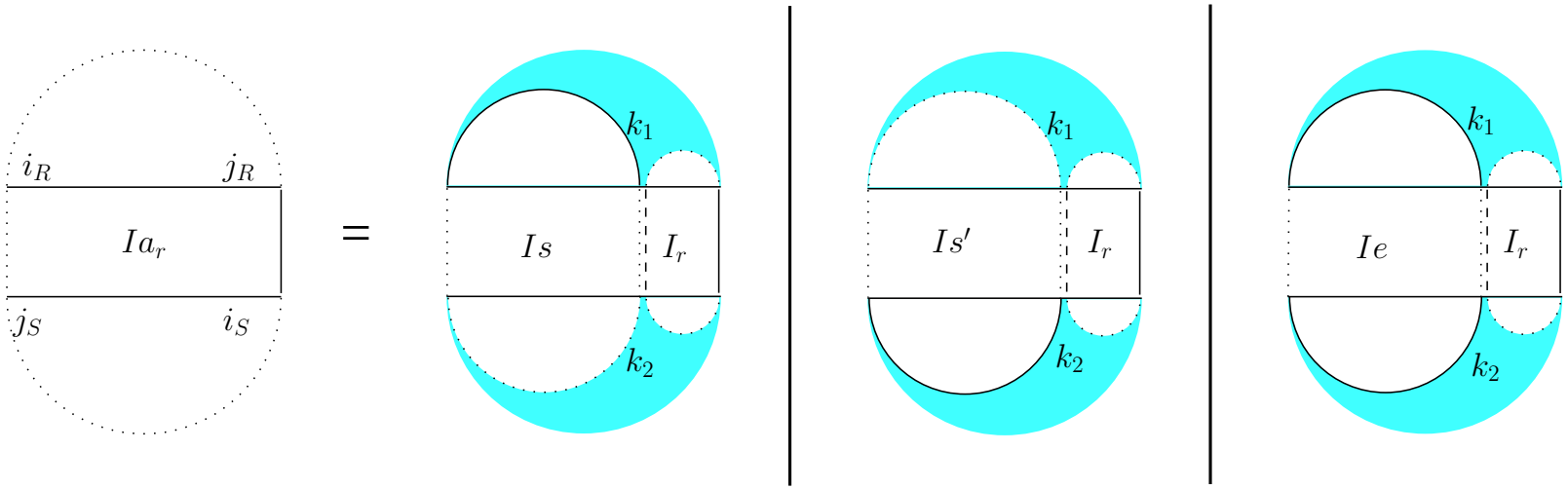

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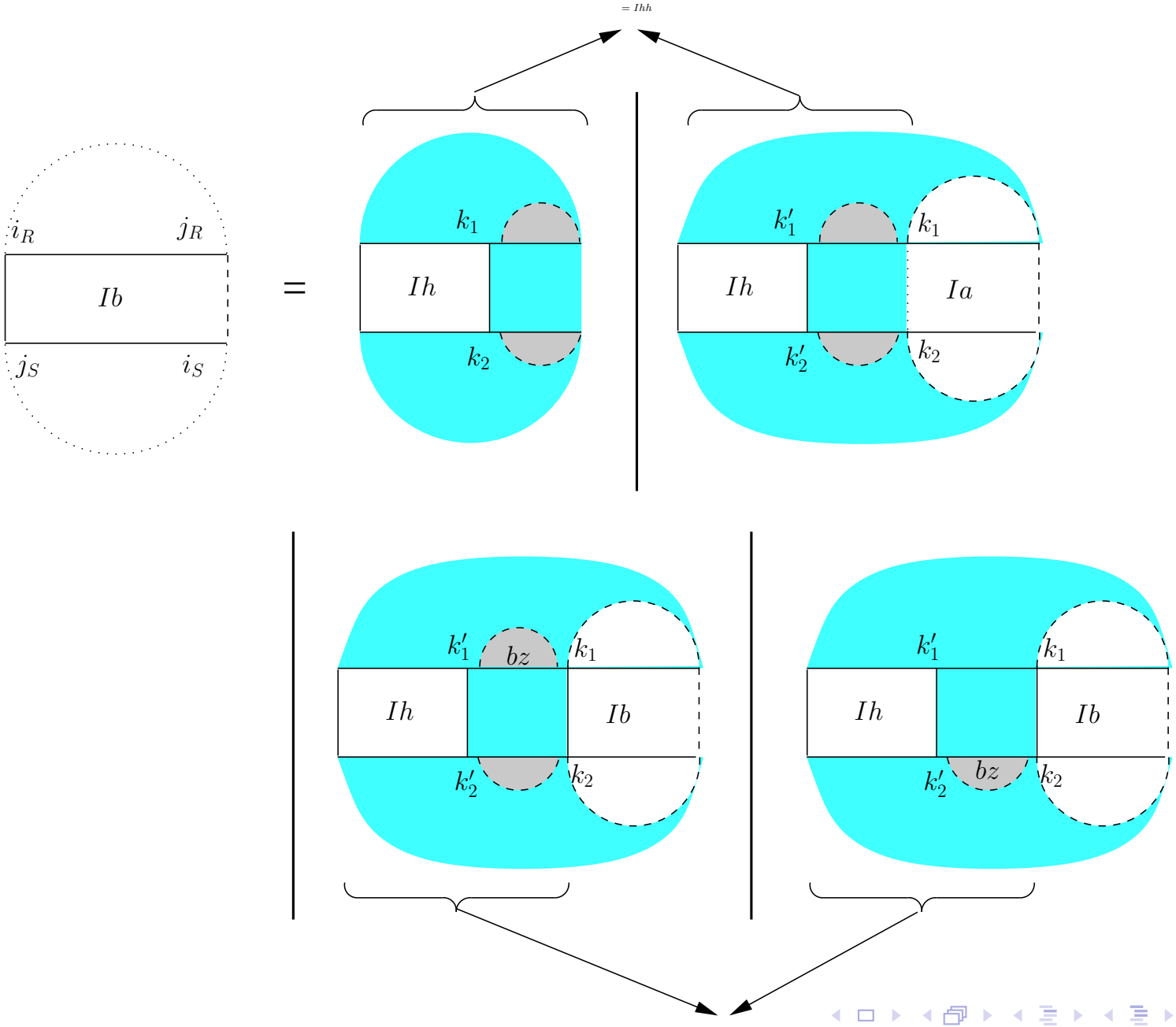
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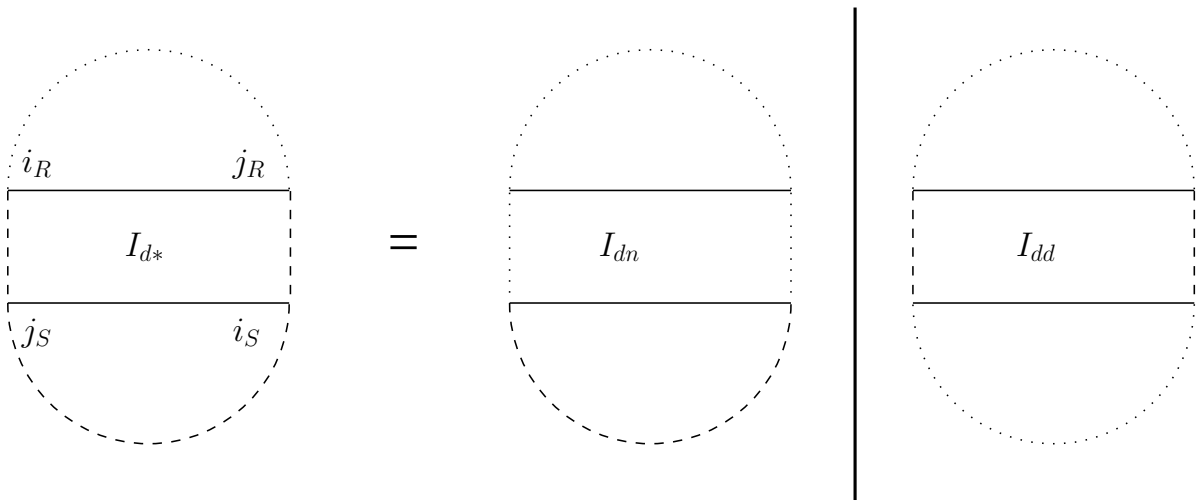
All tables



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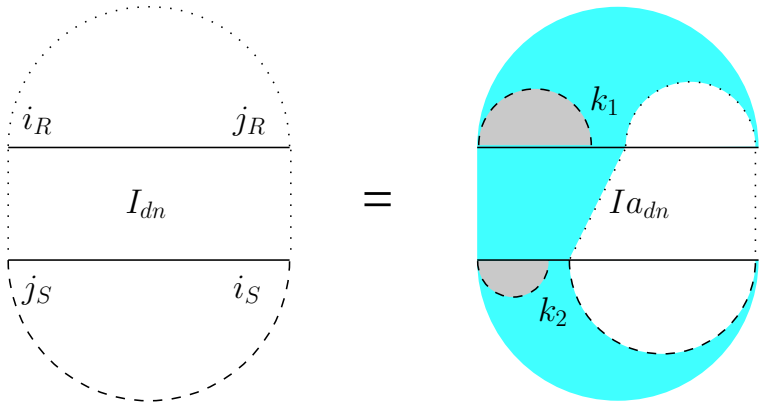

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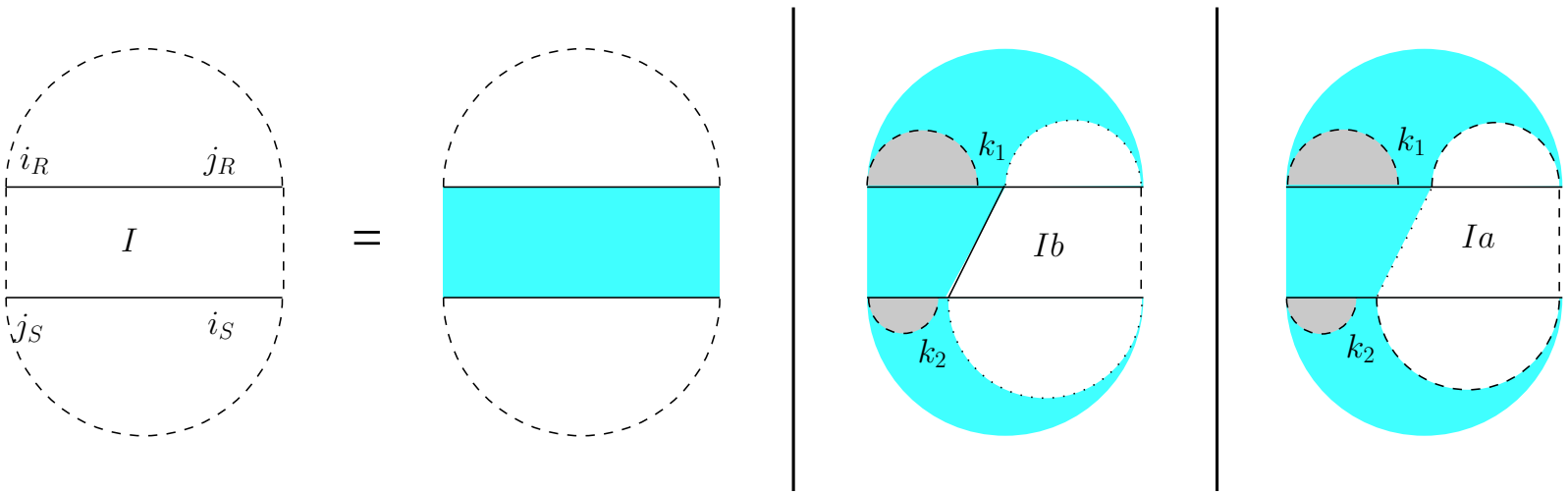

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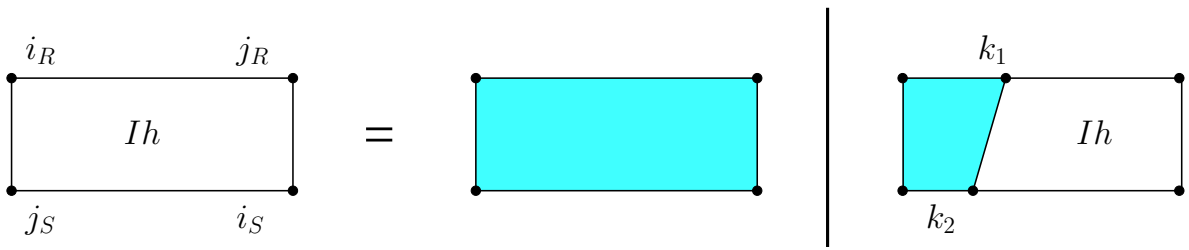

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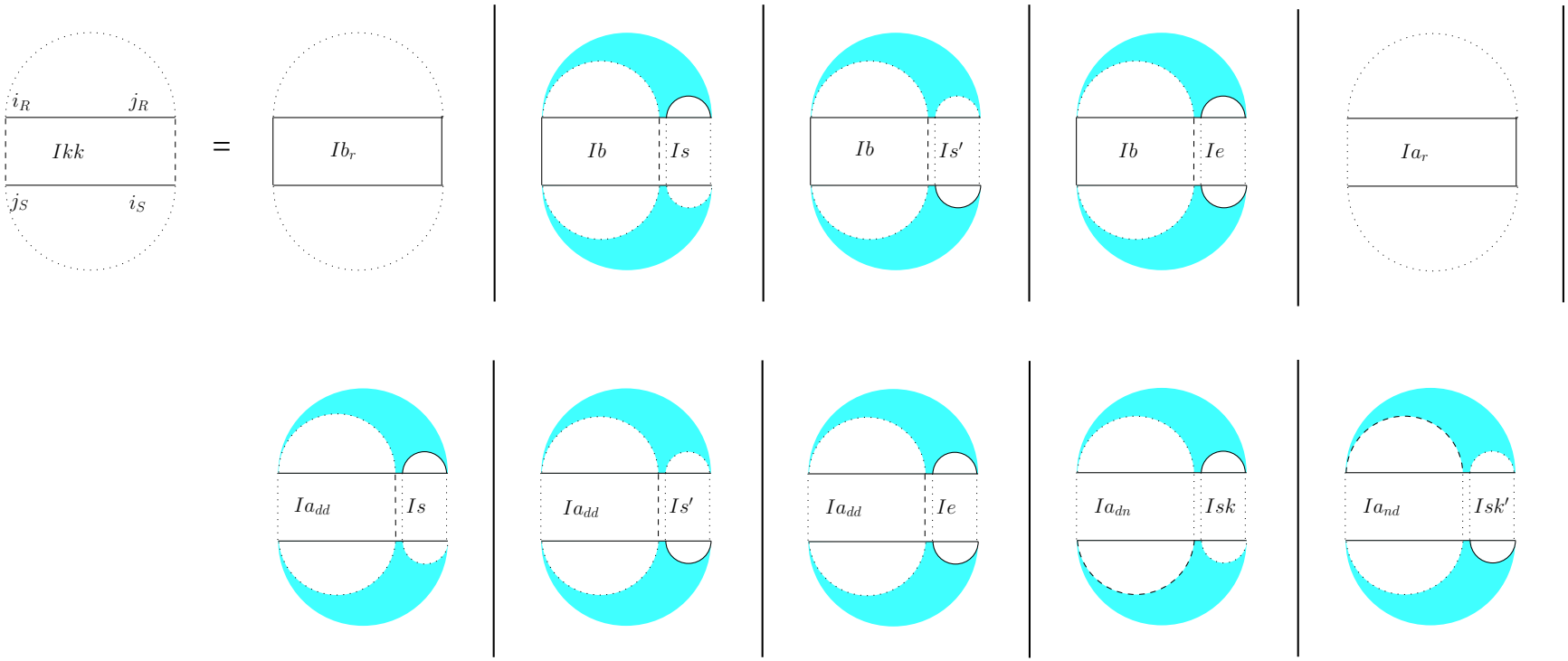
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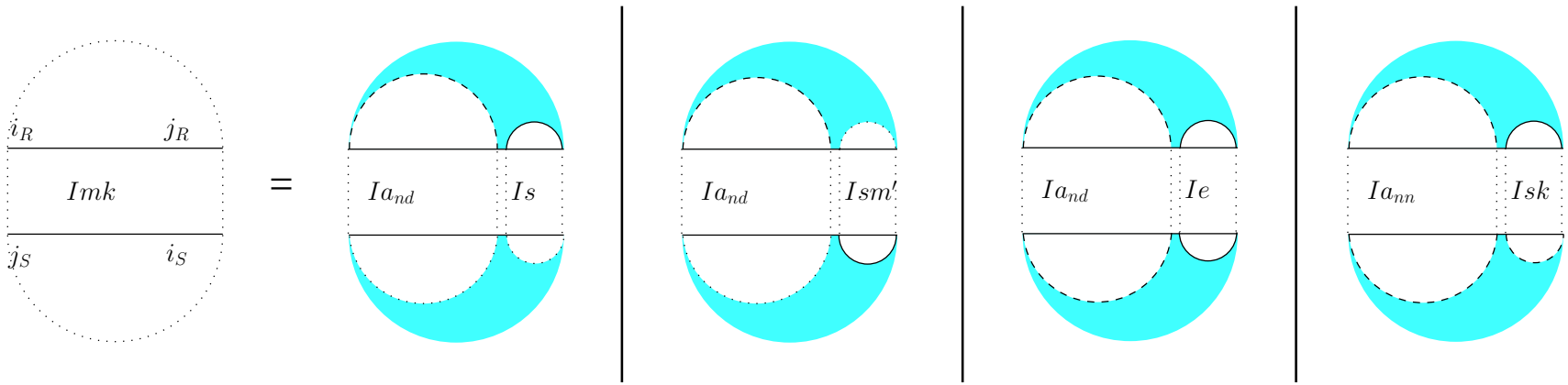

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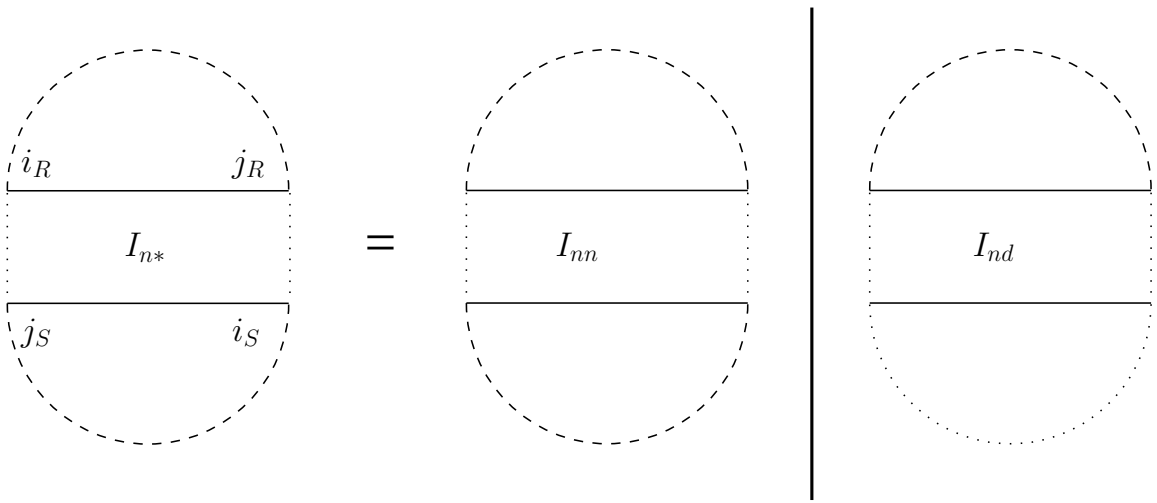

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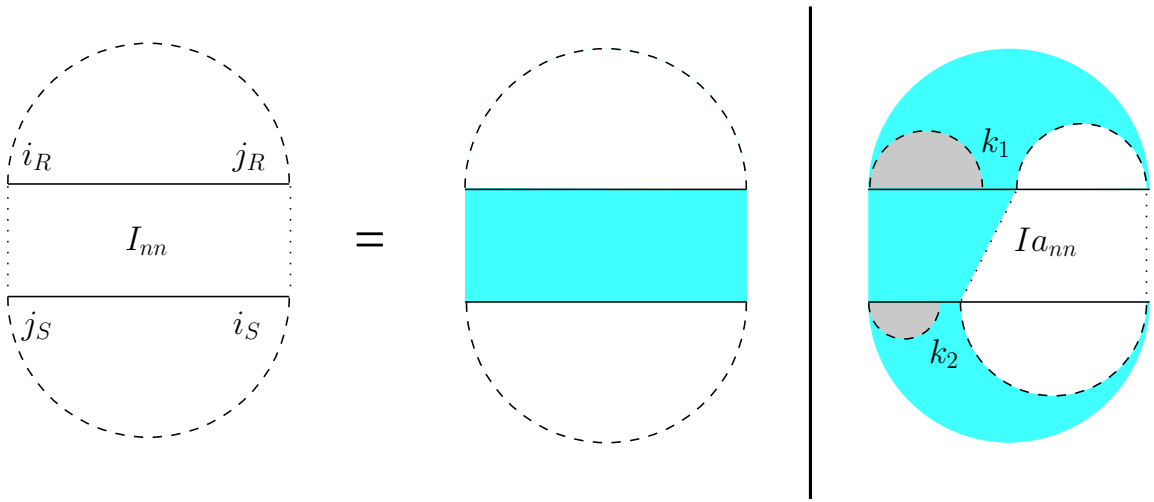

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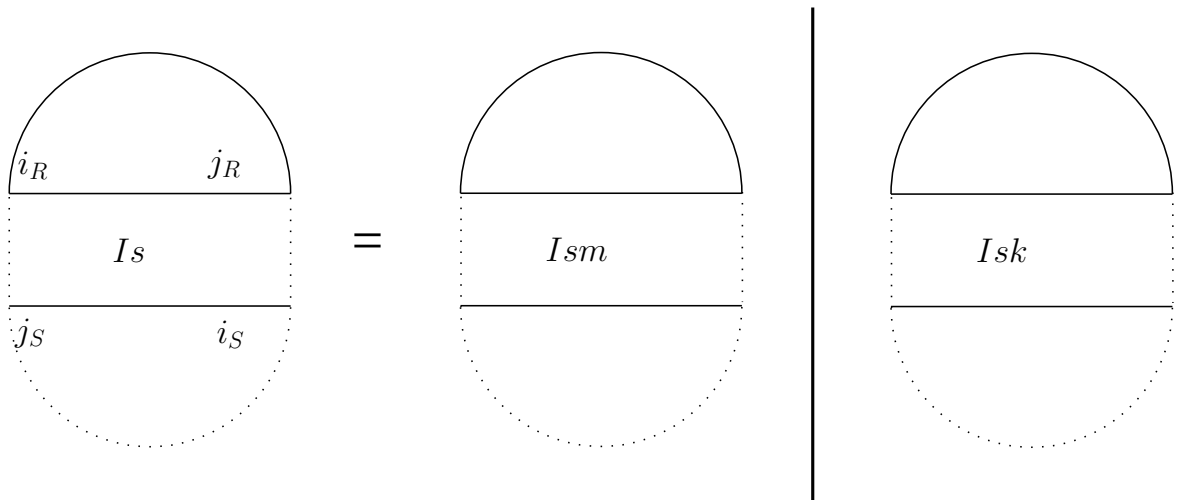

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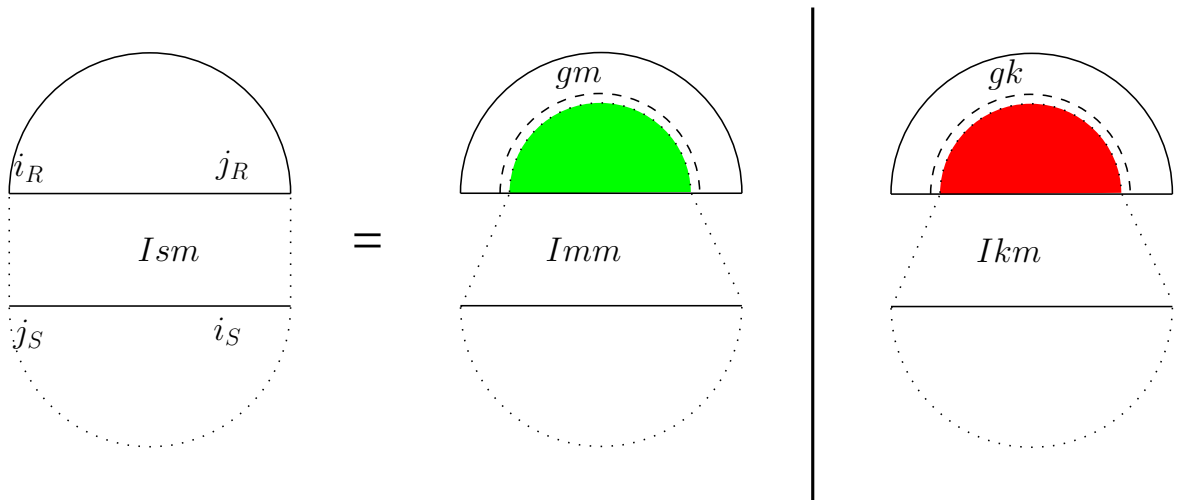

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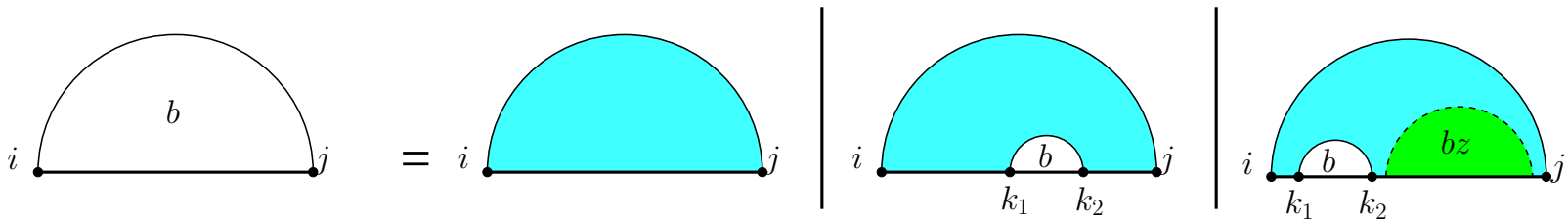

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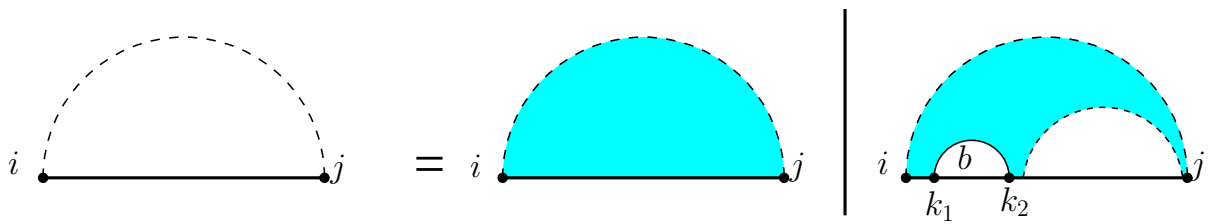

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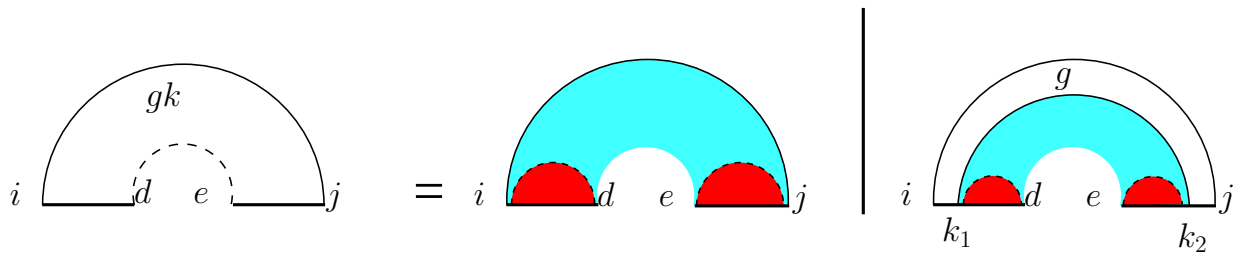

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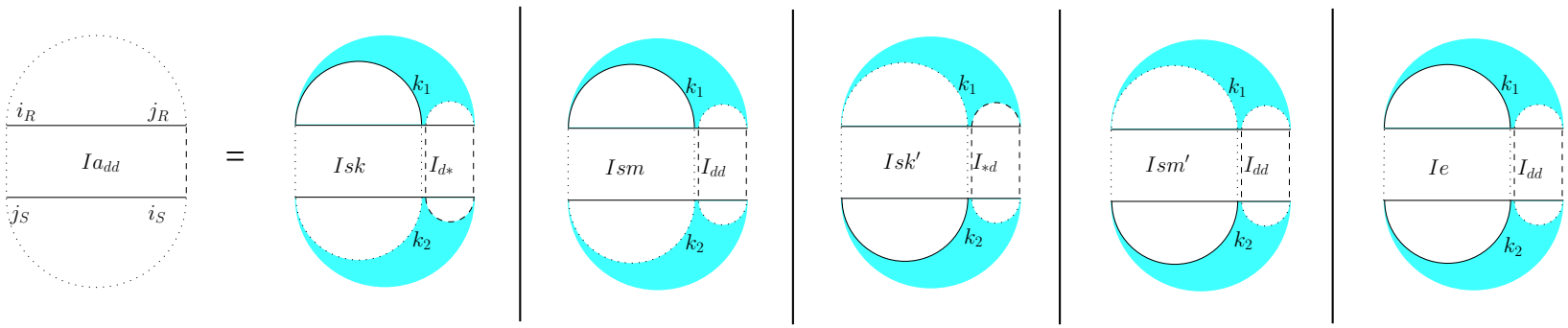
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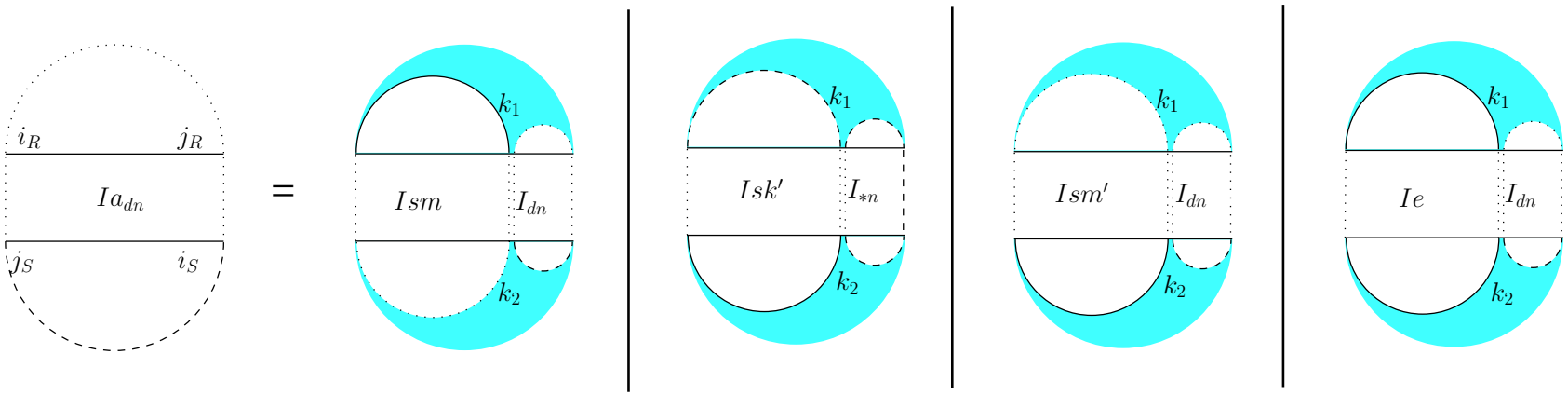
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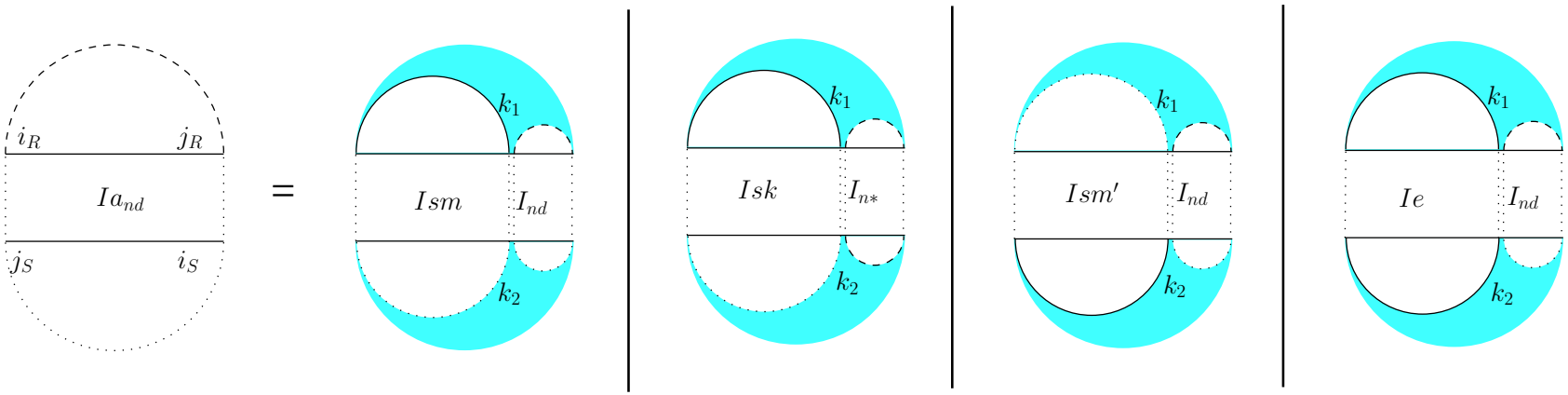
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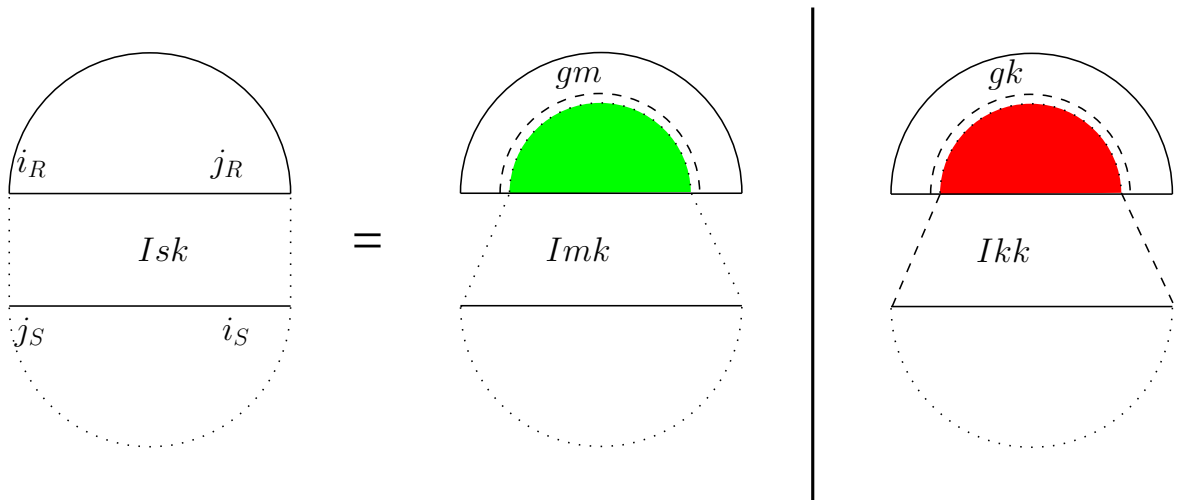

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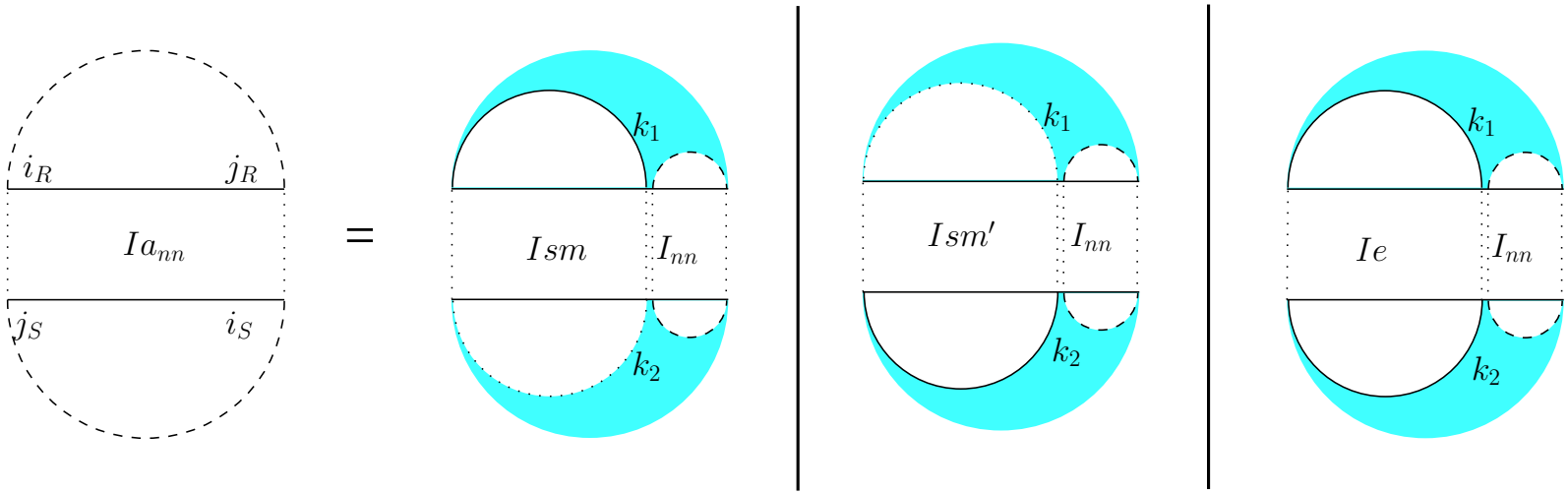

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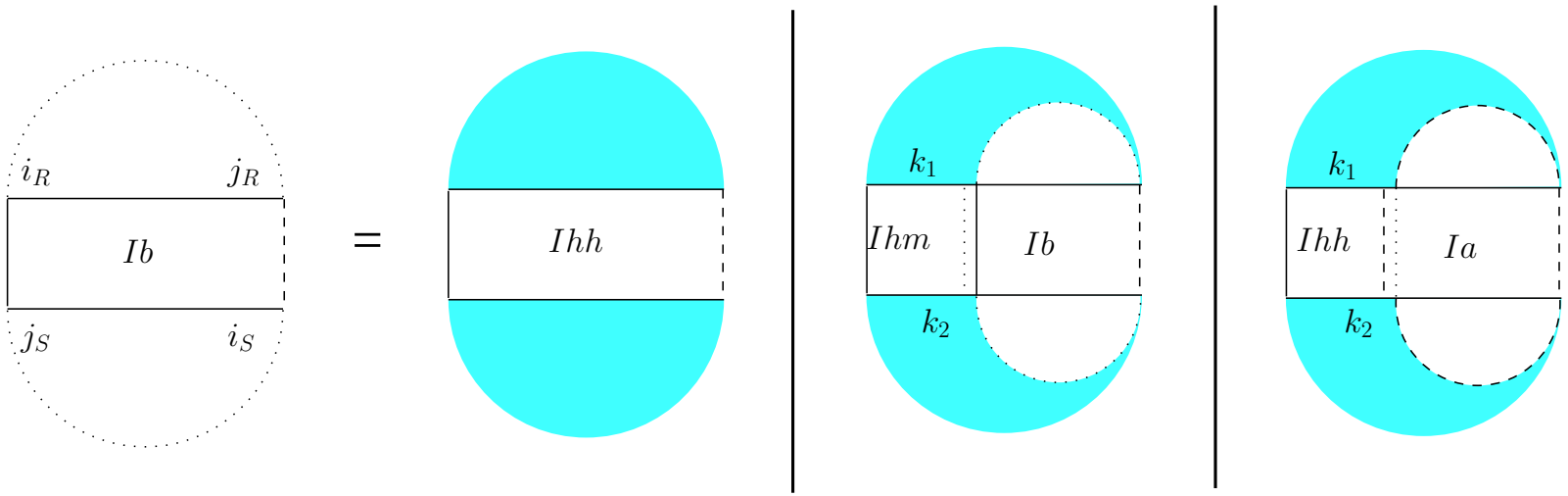

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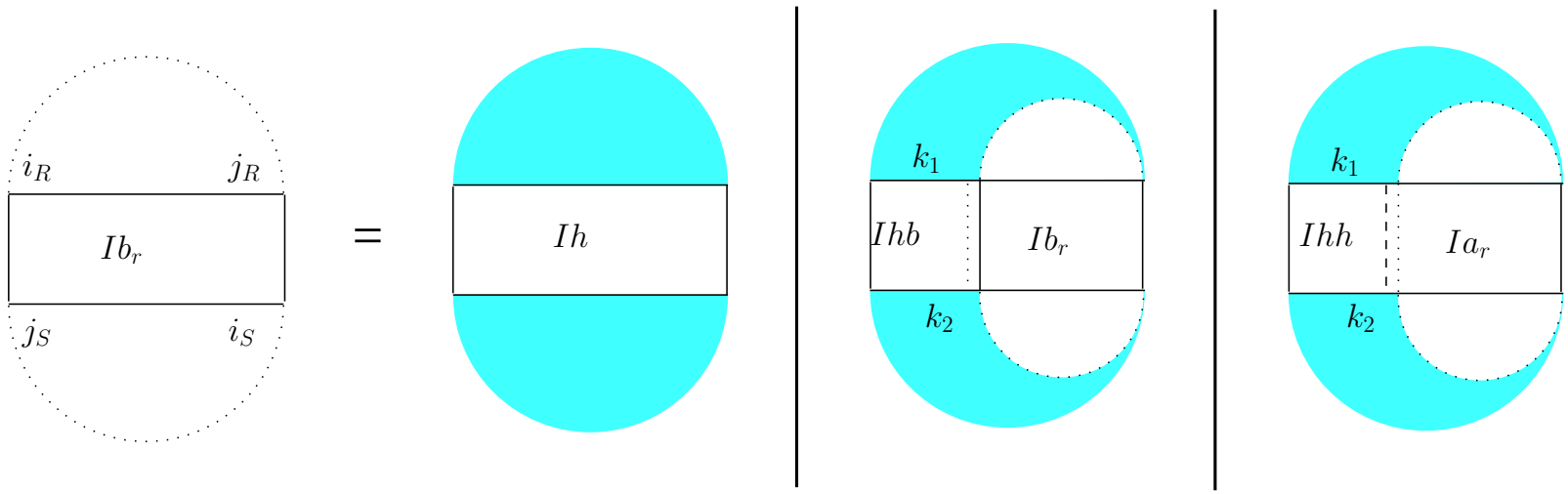

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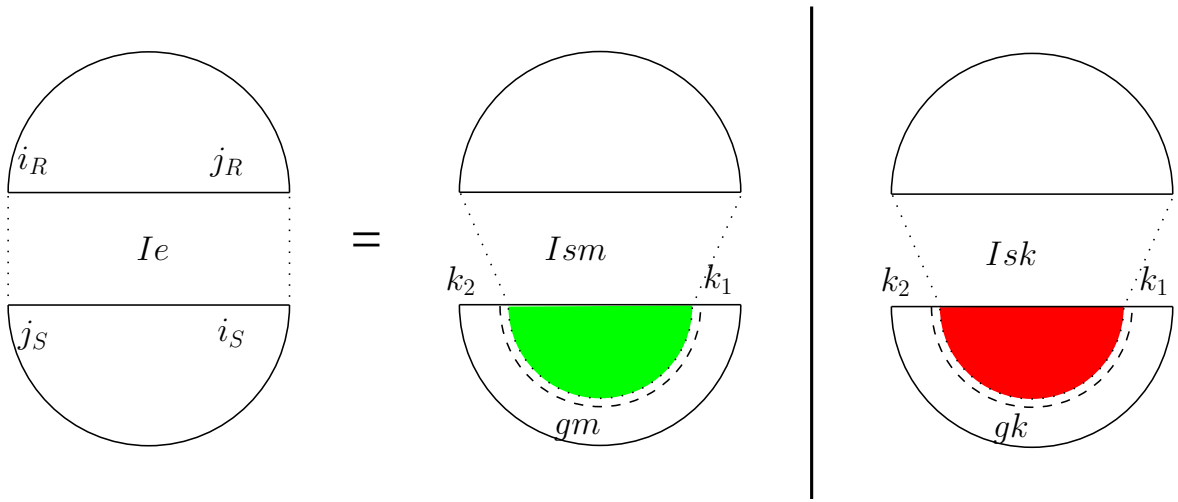

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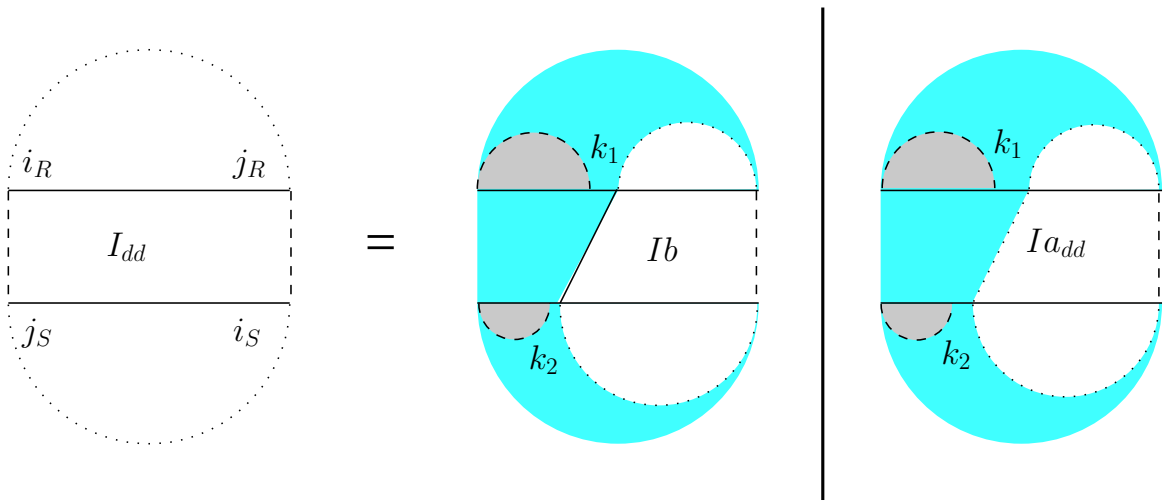

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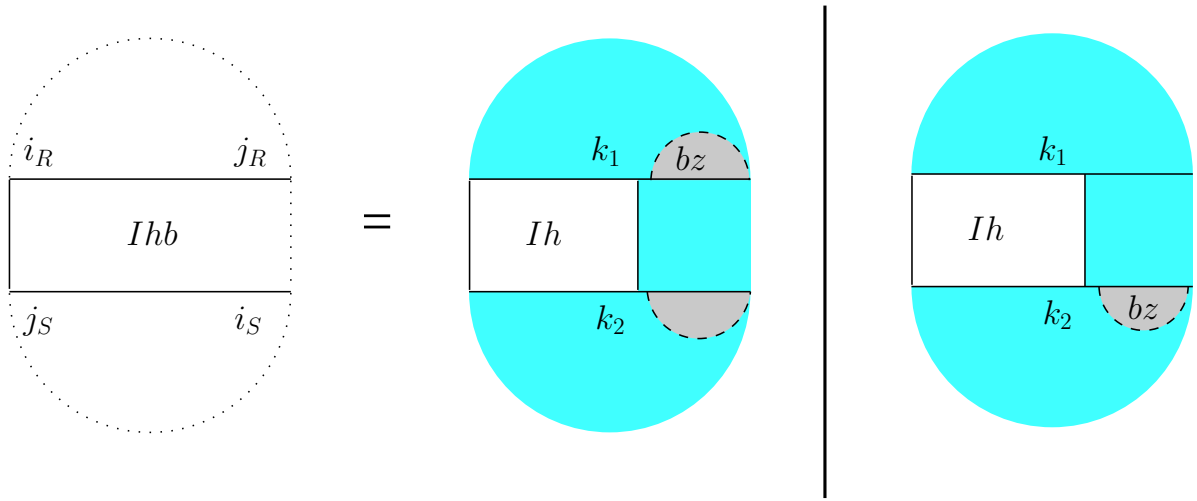

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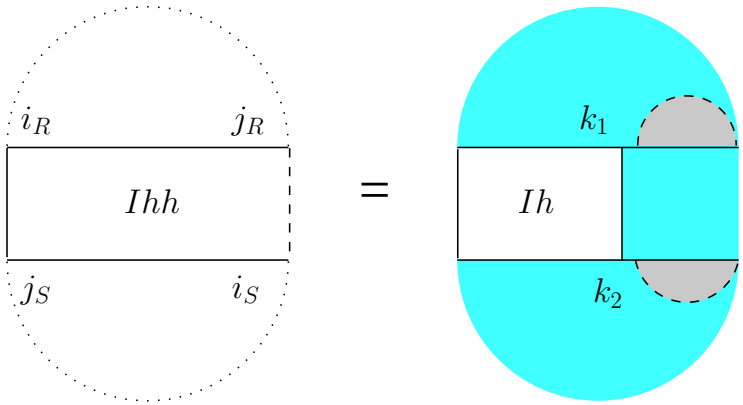

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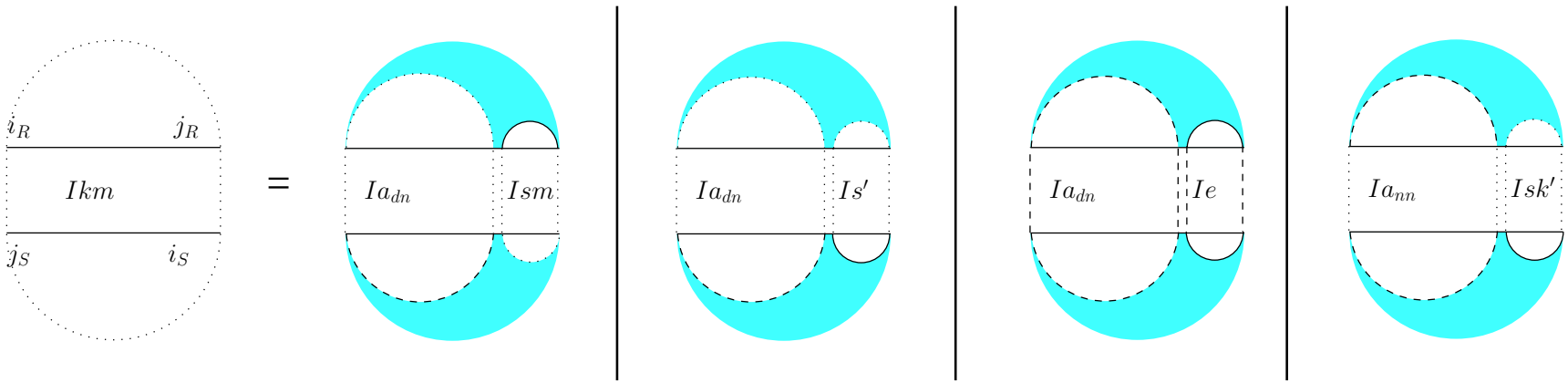

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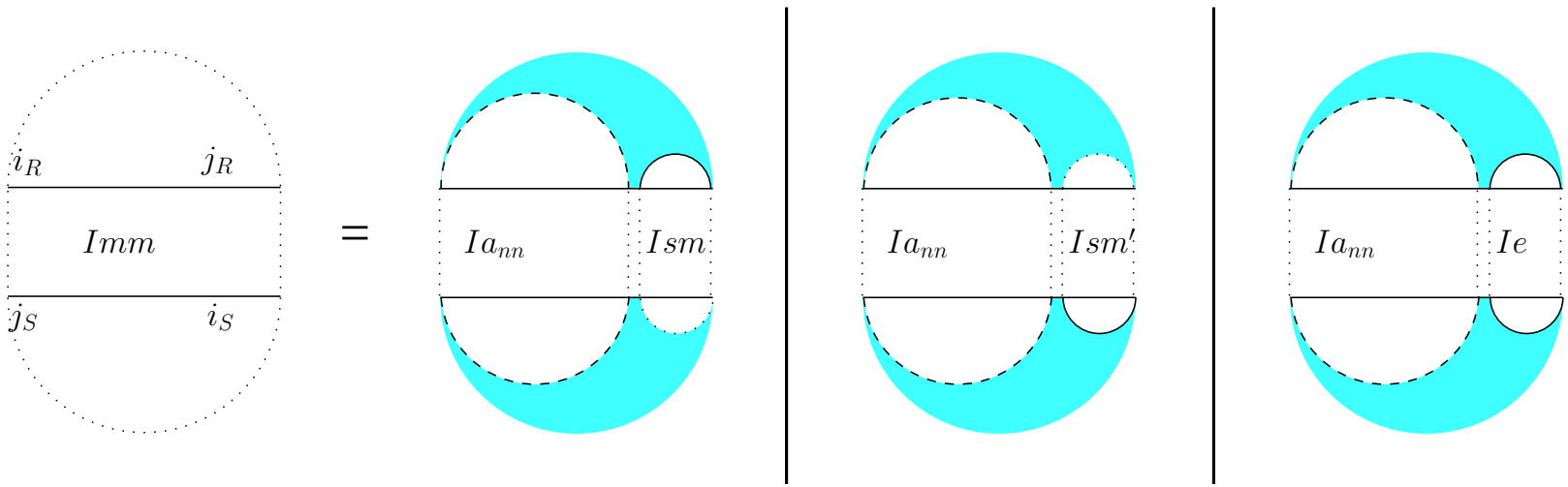

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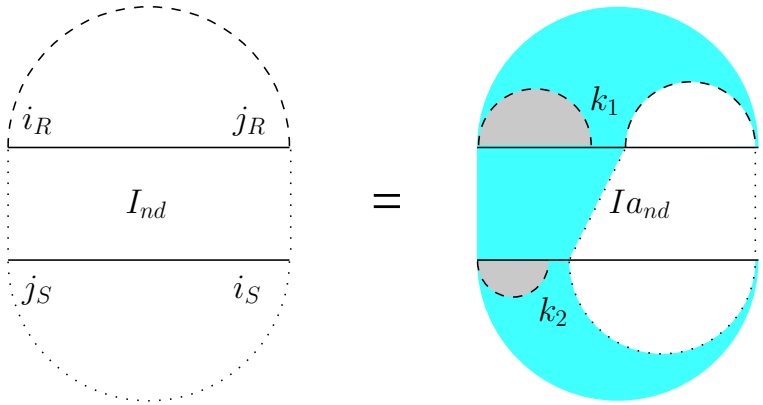

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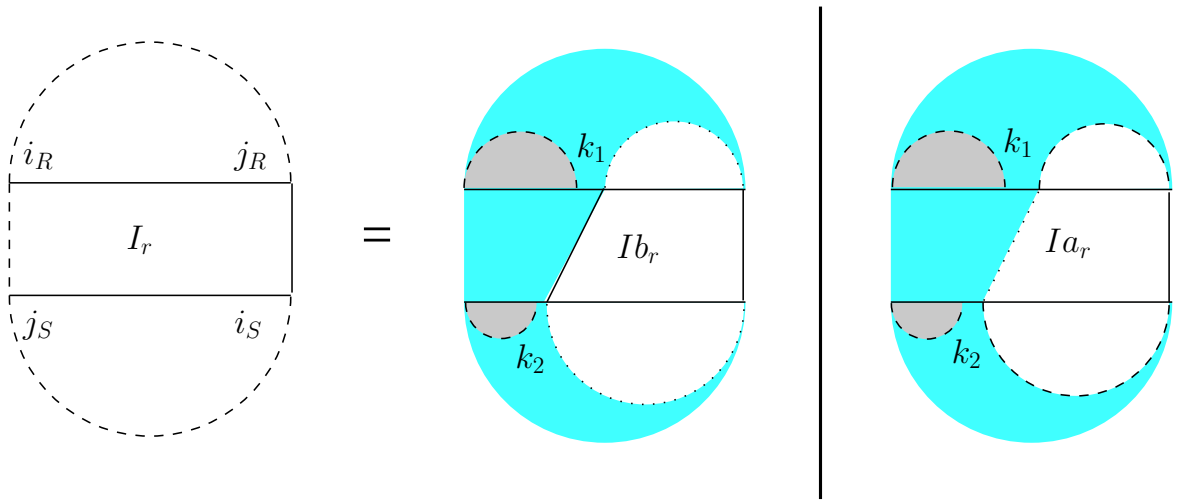


Equilibrium concentrations

For two RNAs $\mathbf{R}$ and $\mathbf{S}$

Assume five types of chemical compounds: **R**, **S**, **RR**, **SS**, **RS**.
Solve

$$K_{\mathbf{R}} = \frac{Q^I_{\mathbf{RR}}}{Q^2_{\mathbf{R}}} = \frac{N_{\mathbf{RR}}}{N^2_{\mathbf{R}}},$$

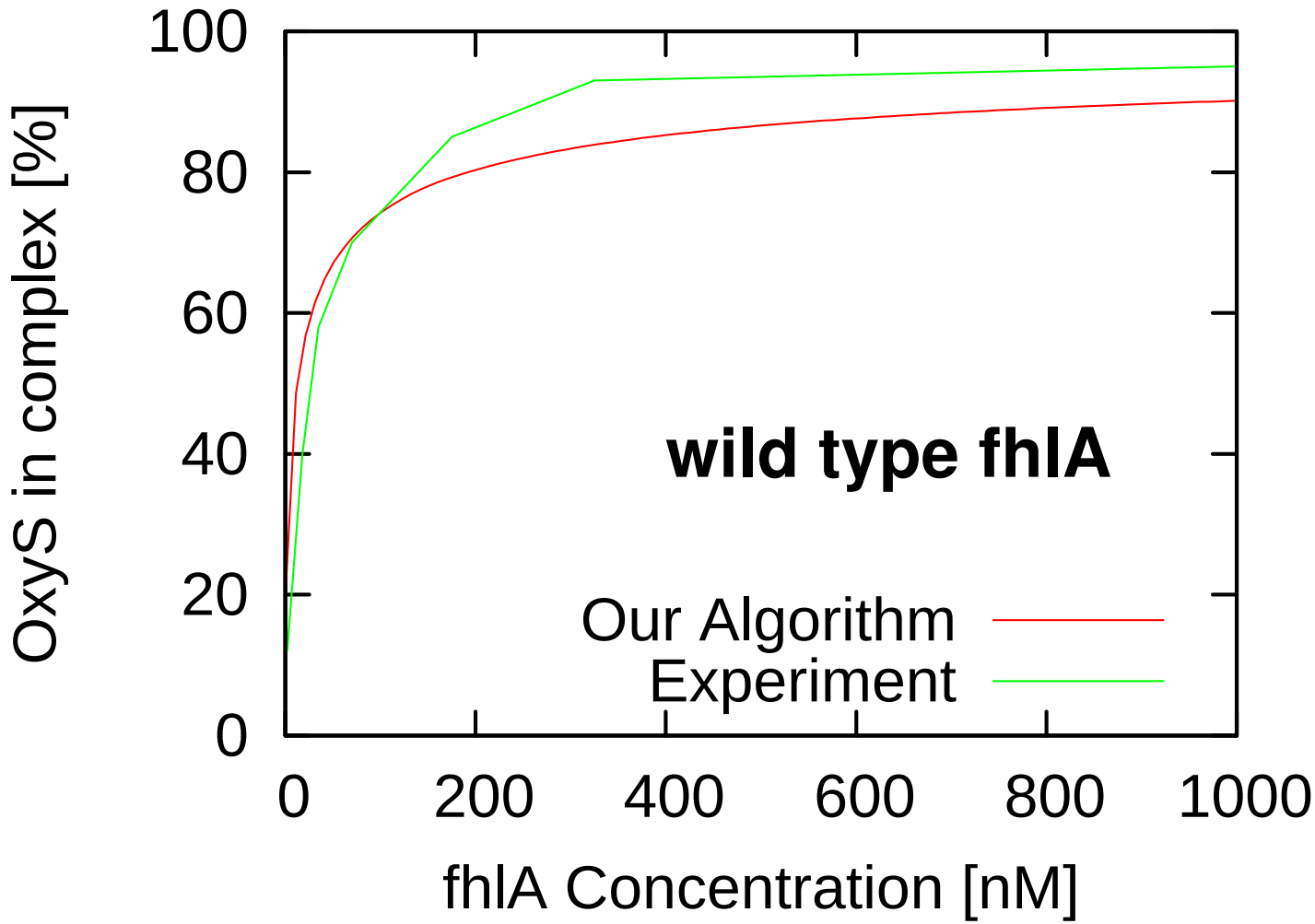
$$K_{\mathbf{S}} = \frac{Q^I_{\mathbf{SS}}}{Q^2_{\mathbf{S}}} = \frac{N_{\mathbf{SS}}}{N^2_{\mathbf{S}}},$$

$$K_{\mathbf{RS}} = \frac{Q^I_{\mathbf{RS}}}{Q_{\mathbf{R}} Q_{\mathbf{S}}} = \frac{N_{\mathbf{RS}}}{N_{\mathbf{R}} N_{\mathbf{S}}},$$

$$N_{\mathbf{RS}} = N^0_{\mathbf{R}} - 2N_{\mathbf{RR}} - N_{\mathbf{R}} = N^0_{\mathbf{S}} - 2N_{\mathbf{SS}} - N_{\mathbf{S}},$$

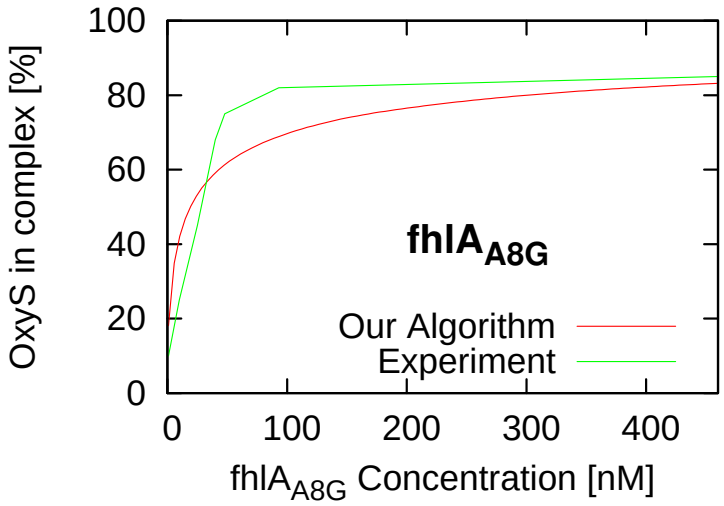
to obtain the equilibrium concentrations N. N^0 are the initial concentrations of single strands.

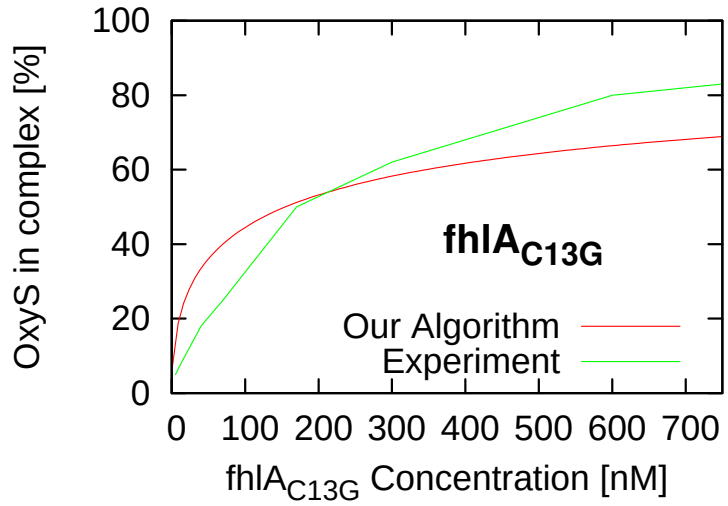
Equilibrium concentration of OxyS with wild type fhlA

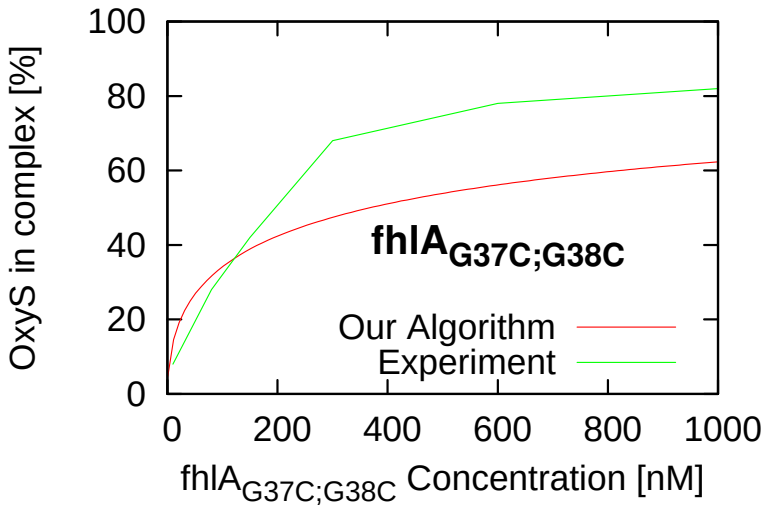


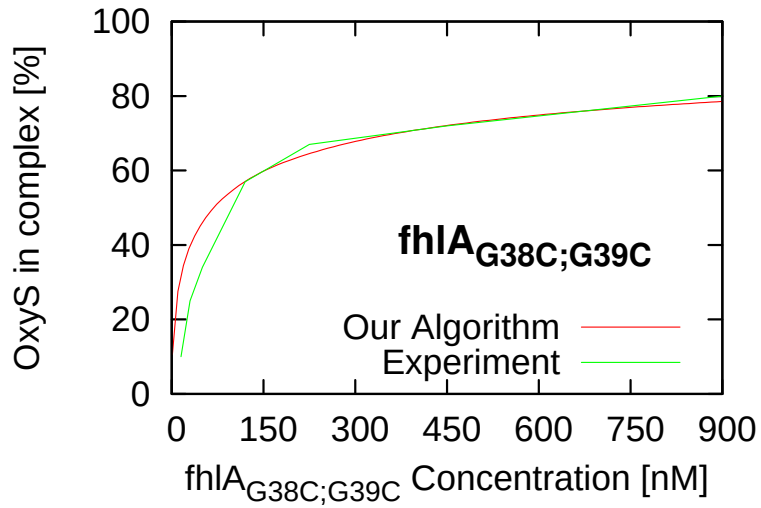
Init. [OxyS] = 2nM, [fhlA] = 0 to 1000nM

Equilibrium concentration of OxyS with fhlA mutants









Melting temperature prediction

Comparison of piRNA results over three data sets

Set	Size	Length	Avg error		
			piRNA	RNAcofold	UNAFold
I	9 short pairs	5-7nt	**1.48**°C	9.35°C	8.55°C
II	12 pairs	$\sim$ 20nt	**4.86**°C	22.97°C	9.12°C
III	62 pairs	$22-40$nt	**1.91**°C	14.34°C	26.53°C

Set	Size	Length	Spearman rank correlation		
			piRNA	RNAcofold	UNAFold
I	9 short pairs	5-7nt	**0.97**	**0.97**	0.57
II	12 pairs	$\sim$ 20nt	**0.41**	-0.03	0.1
III	62 pairs	$22-40$nt	**0.3**	-0.04	0.24