Accurate Detection of Tandem Repeats from Error-Prone Sequences with EquiRep

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PennState College of Engineering | ELECTRICAL ENGINEERING AND COMPUTER SCIENCE

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- Approximate: ACTTACTACGTCCGTACGGT

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Tandem **repeats generated by certain technologies** such as those used for circular molecules can be useful for full-length circular RNA assembly.

Applications

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Study of Satellite DNAs

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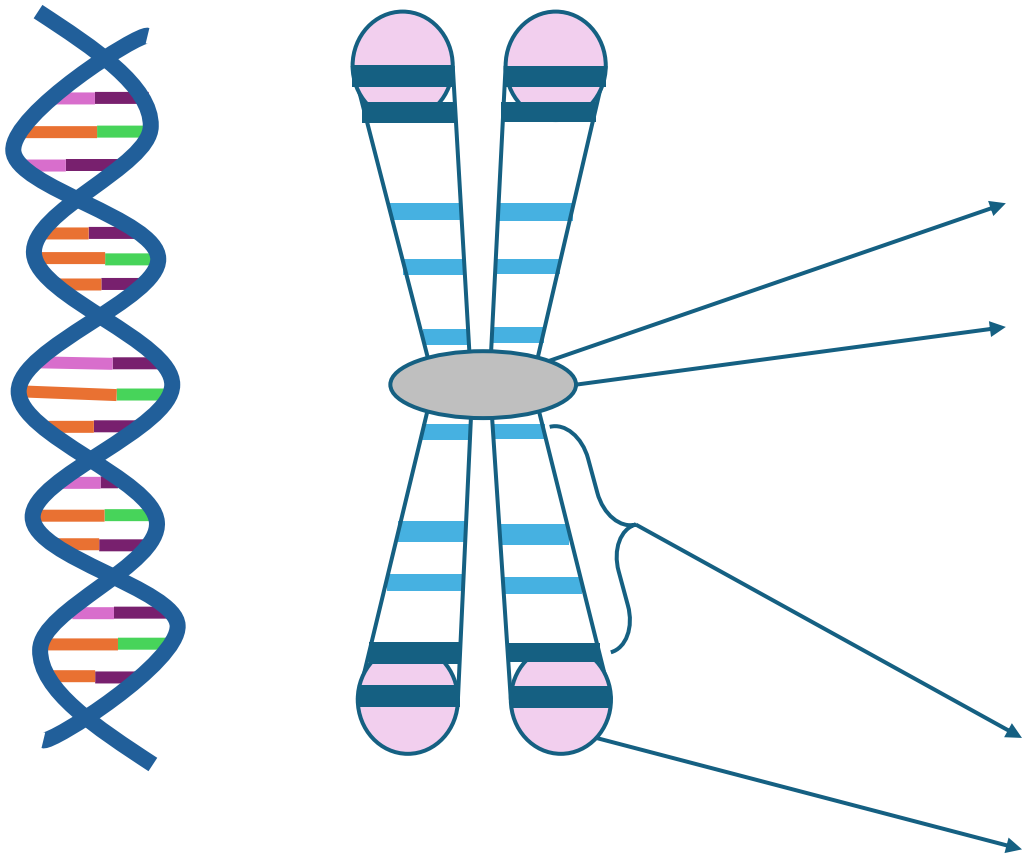

Satellite Family	Size of Repeat Unit (bp)	Location in Human Chromosome
α	170	Centromeres of all chromosomes
β	68	Centromeres of chromosomes 1, 9 13, 14, 15, 21, 22, and Y
Satellite 1	25-48	Centromeres and other regions in heterochromatin of most chromosomes
Satellite 2	5	Most chromosomes
Satellite 3	5	Most chromosomes
Microsatellites	1-10	Widely distributed throughout the chromosome
Minisatellites	10-60	Telomeres of many chromosomes

https://en.wikipedia.org/wiki/Satellite_DNA

Applications

Assemble Circular RNAs from Rolling Circular Reads

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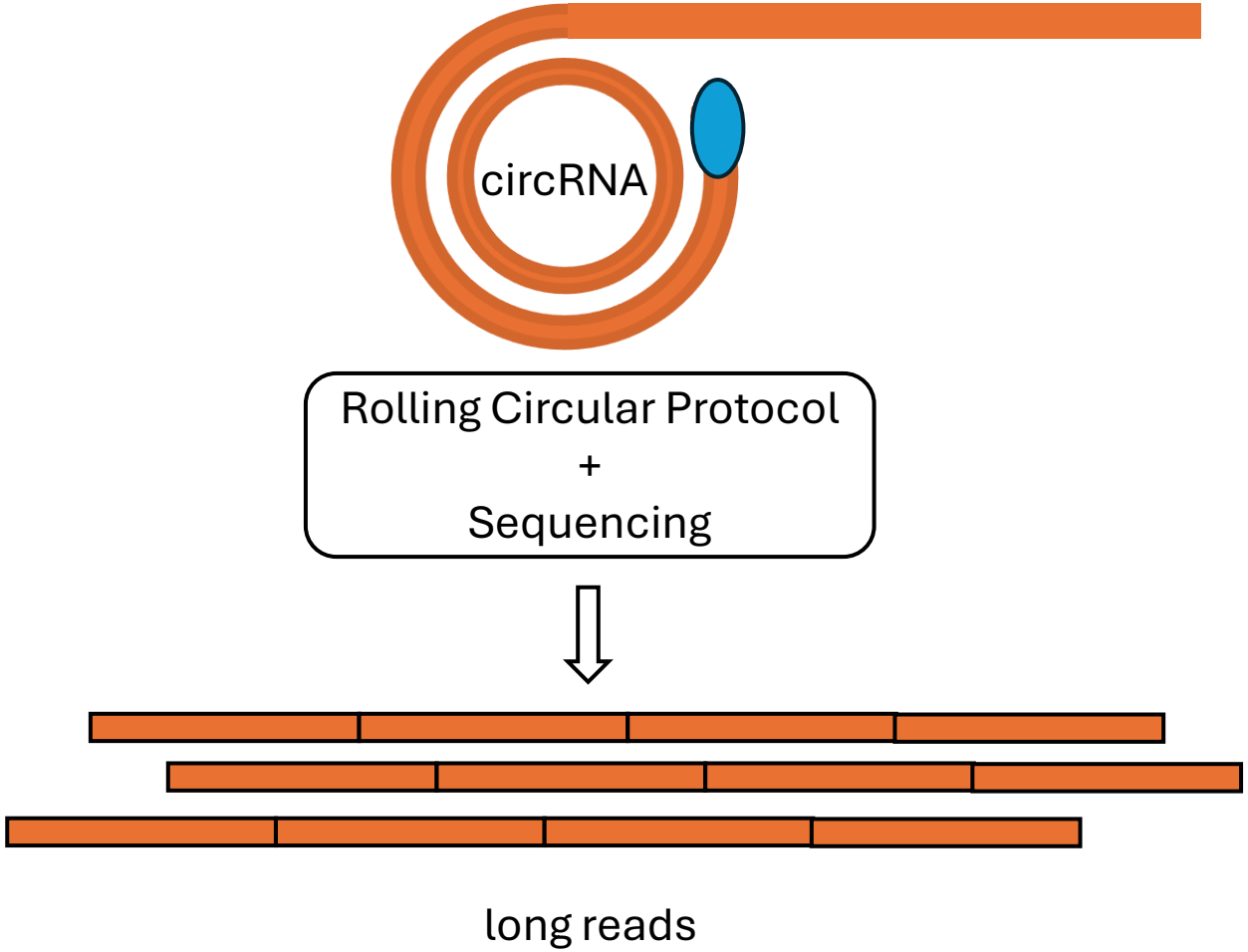

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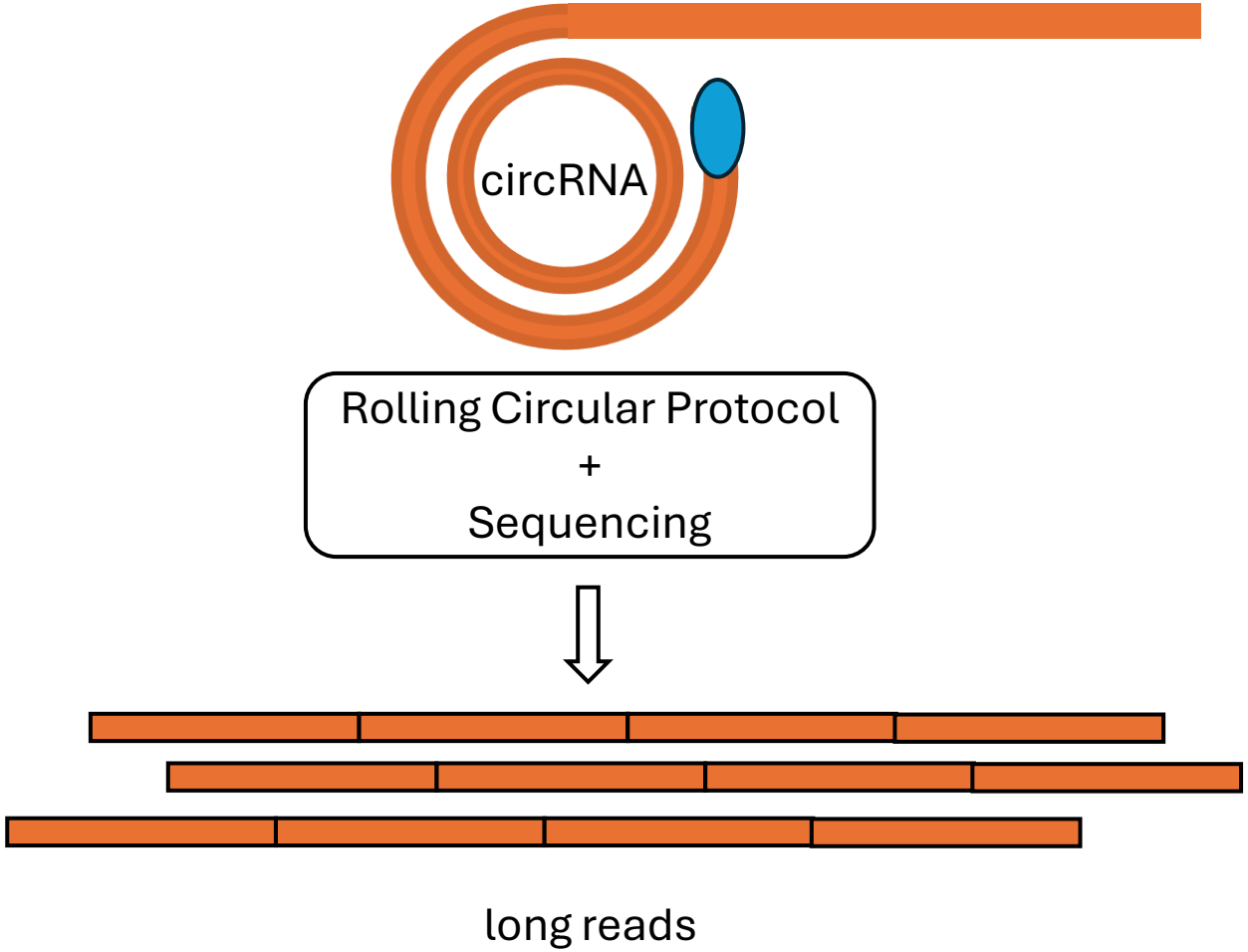

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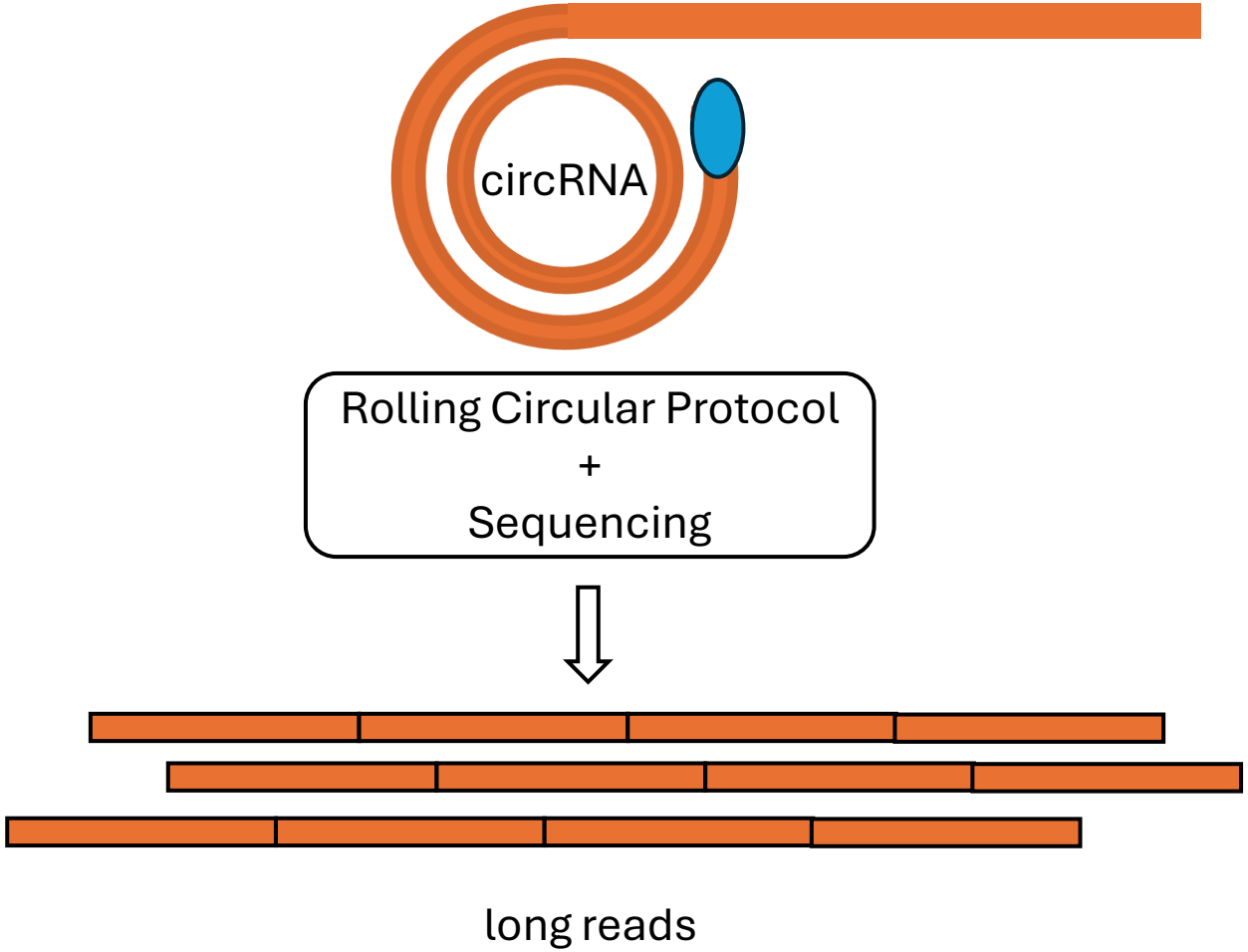

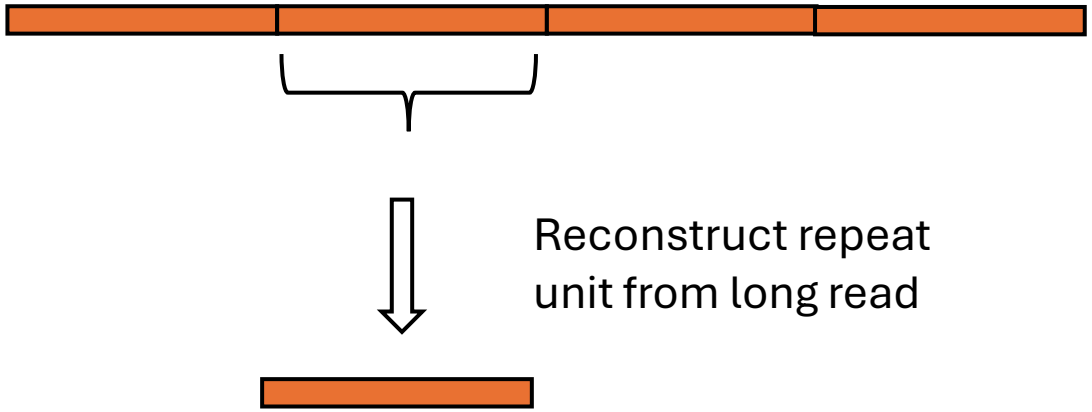

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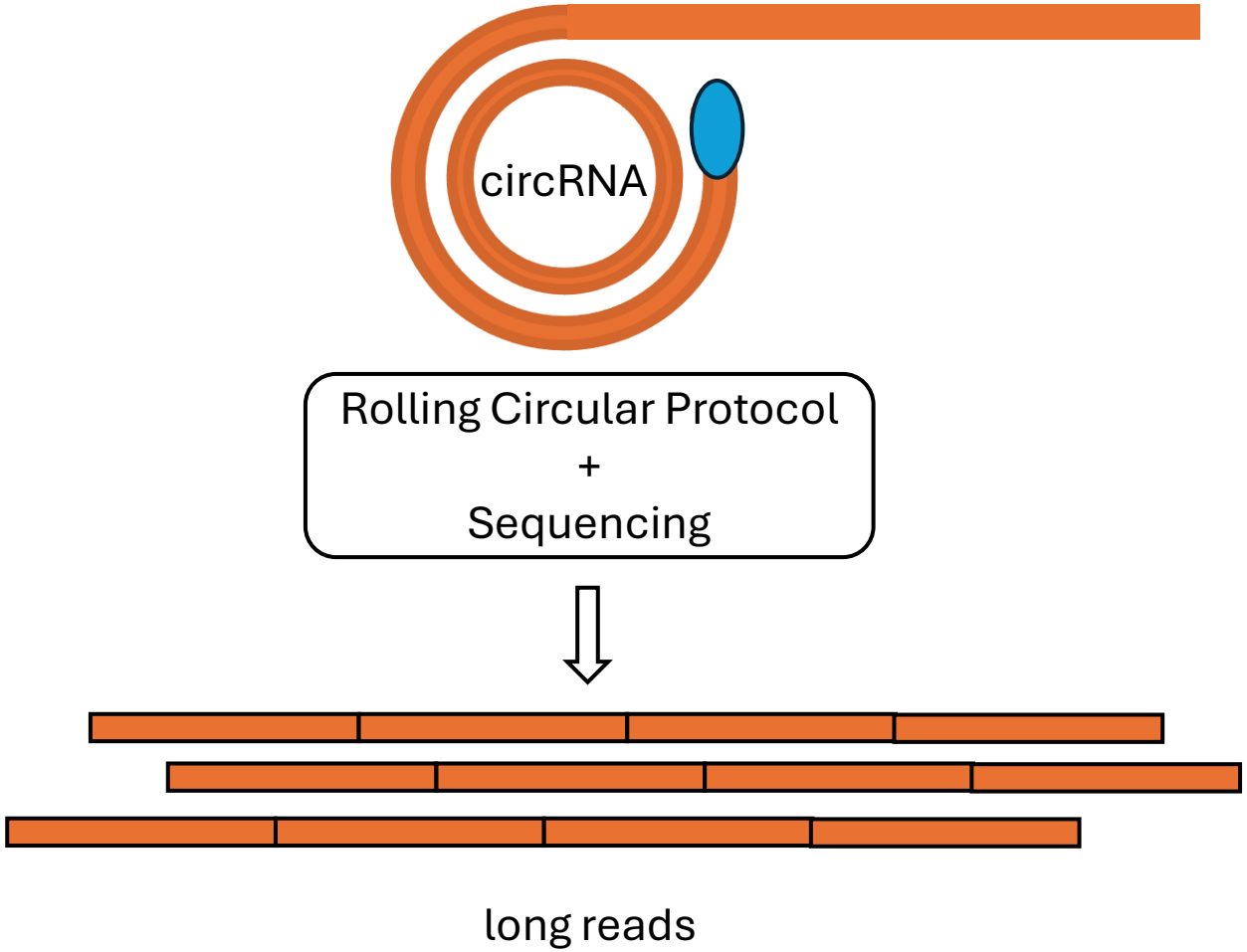

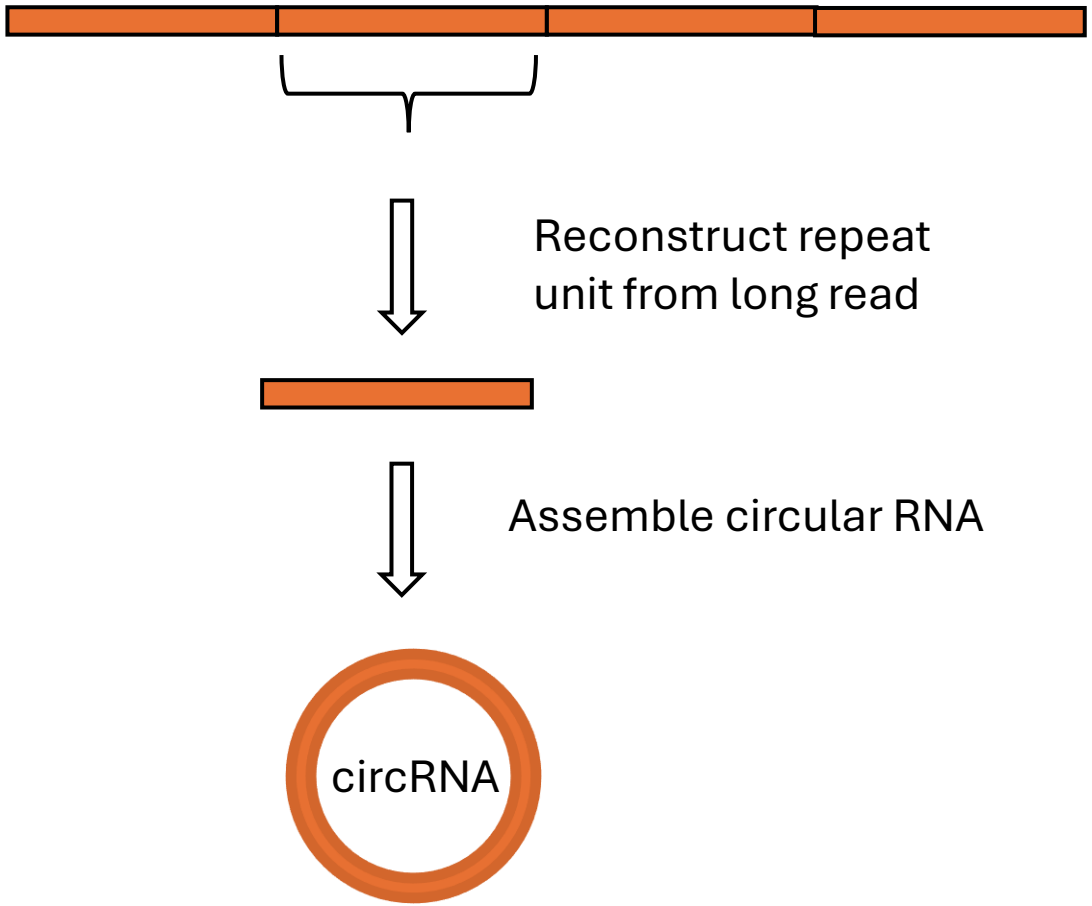

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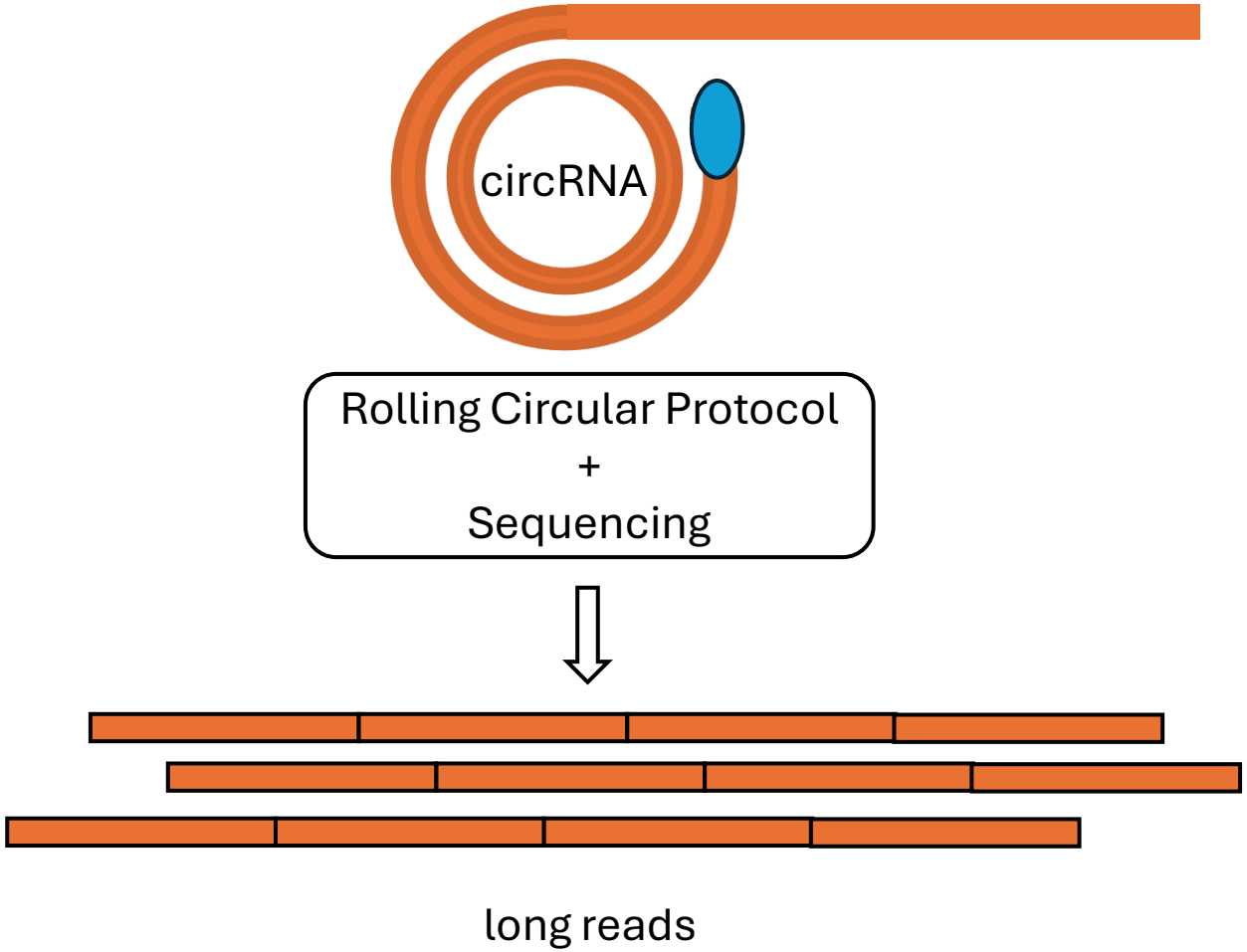

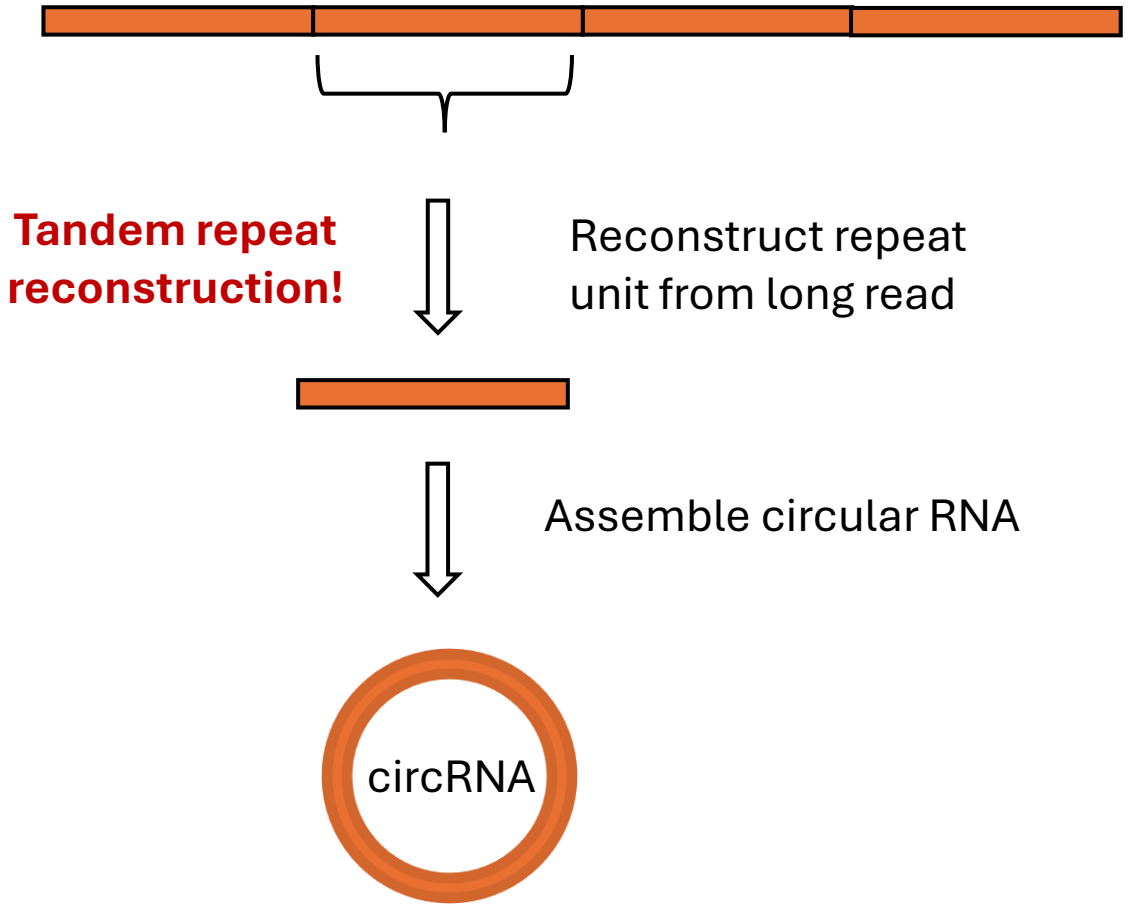

Tandem Repeat Reconstruction

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Input: an error-prone (long) sequence/read.

ACTTACTACGTCCGTACGGT

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Output: tandem repeat unit (if any).

ACGT

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- Most tools are designed for reconstruction of short units from relatively low error data.
  - mreps, dot2dot.
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EquiRep: a new tool for reconstructing tandem repeat units from error-prone sequences.
- Robust against errors.
- Effective in detecting repeats of large length and low frequency.

Definitions

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- **Equivalent positions**: i ~ j, if R[i] and R[j] originate from the same letter in the true unit U.

Erroneous Sequence (R)

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

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Repeat Unit (U)

A C G T

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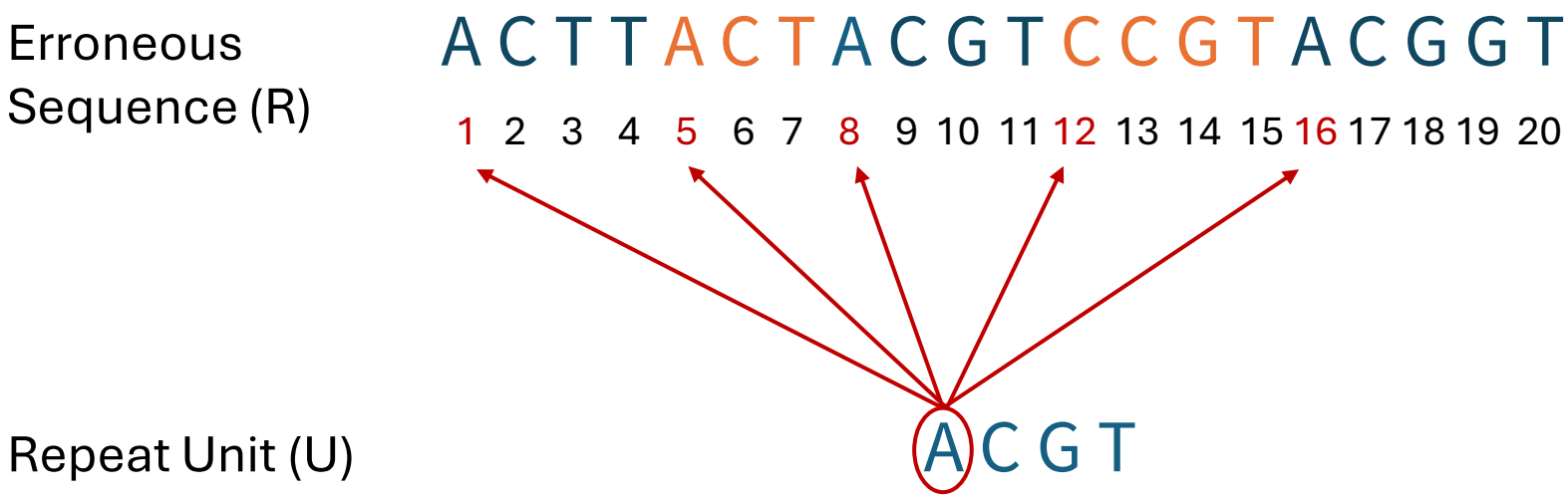

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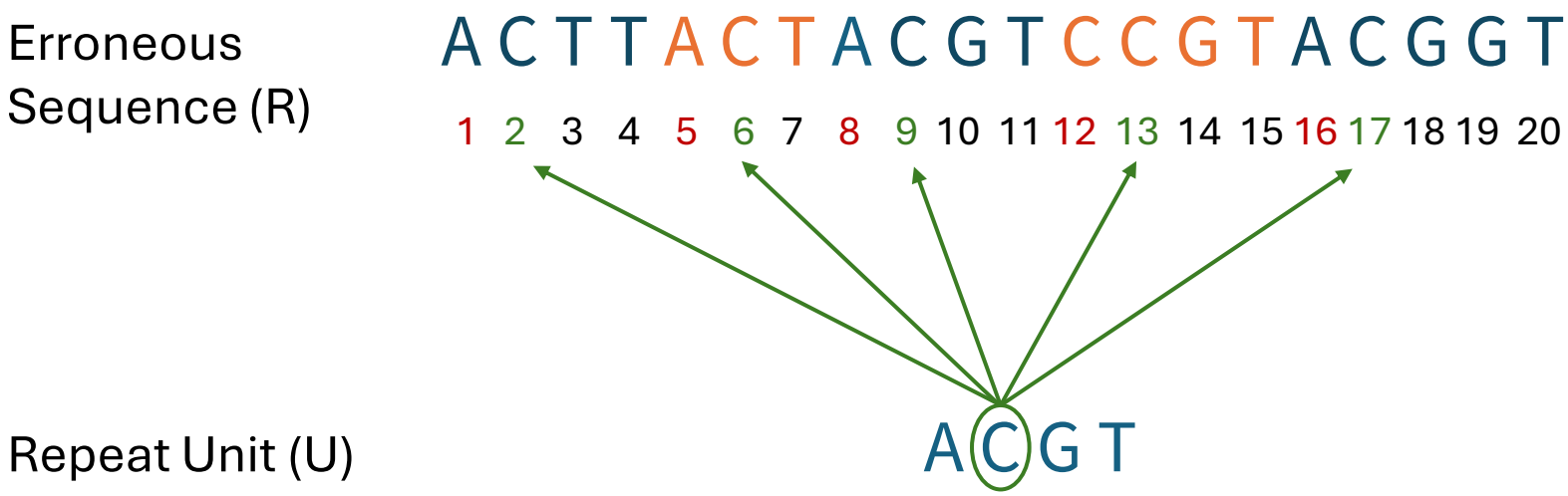

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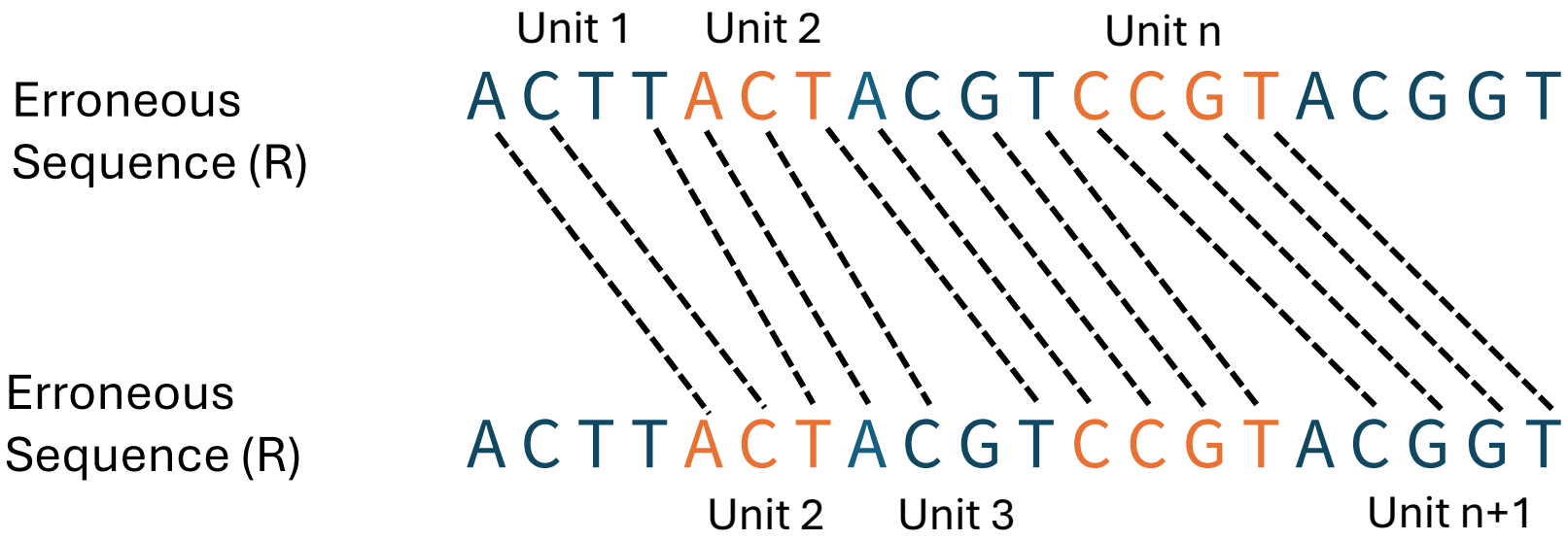
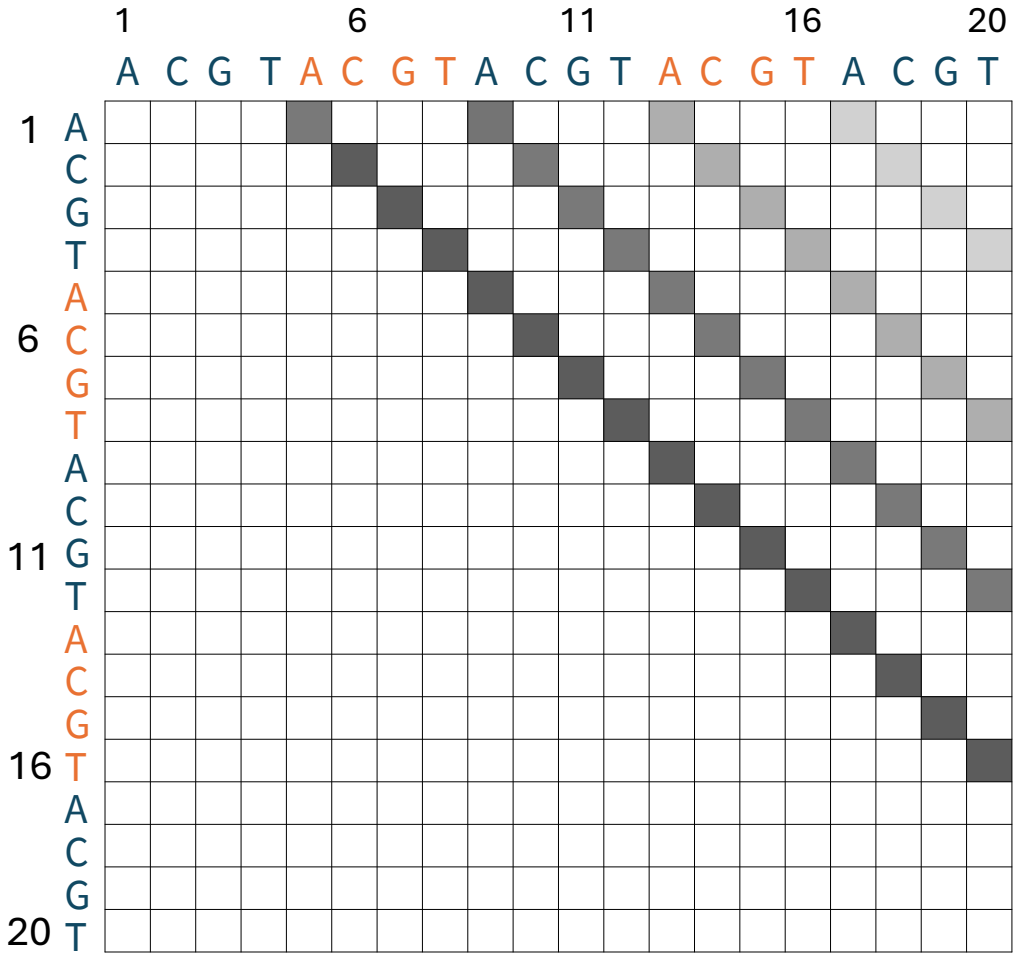


Diagonal-free Self-alignment (Ideal)



Ideal DP Table

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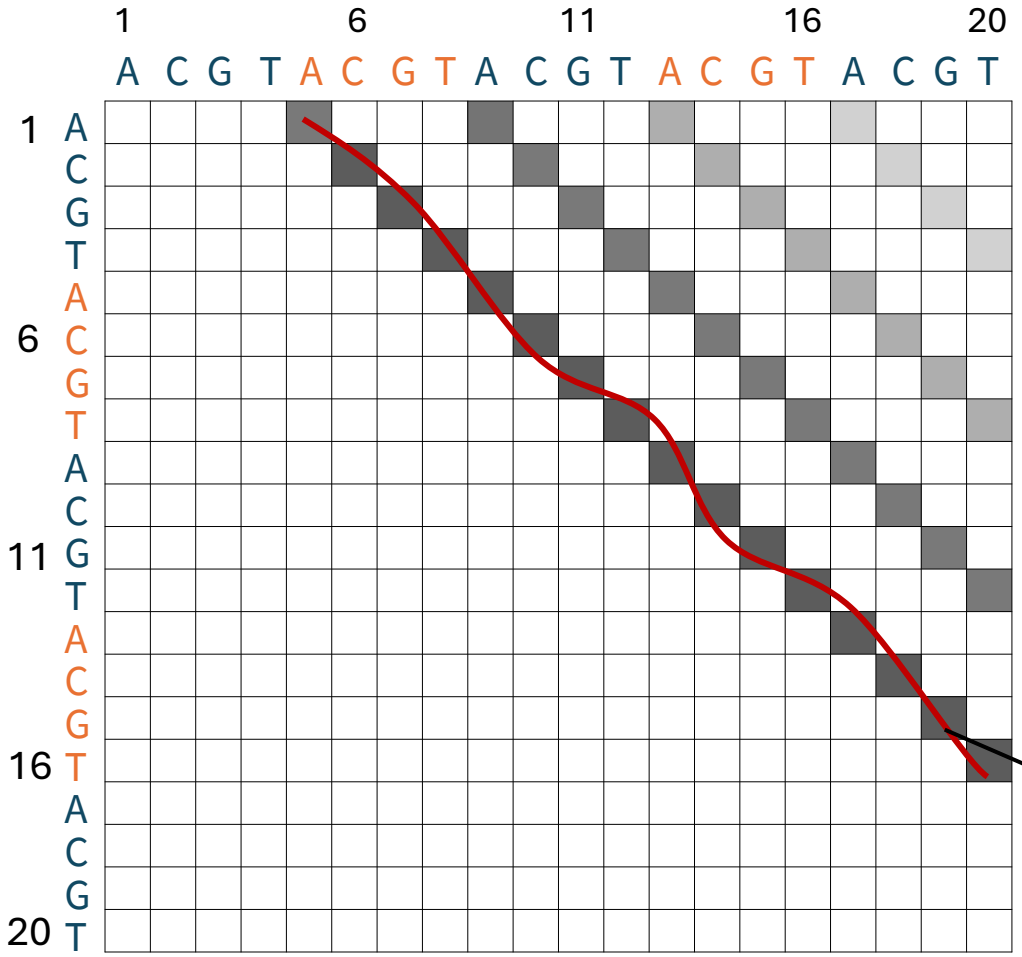

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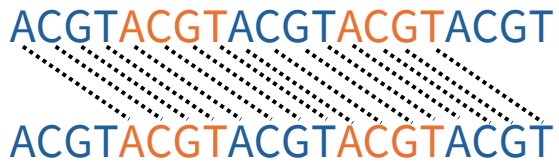

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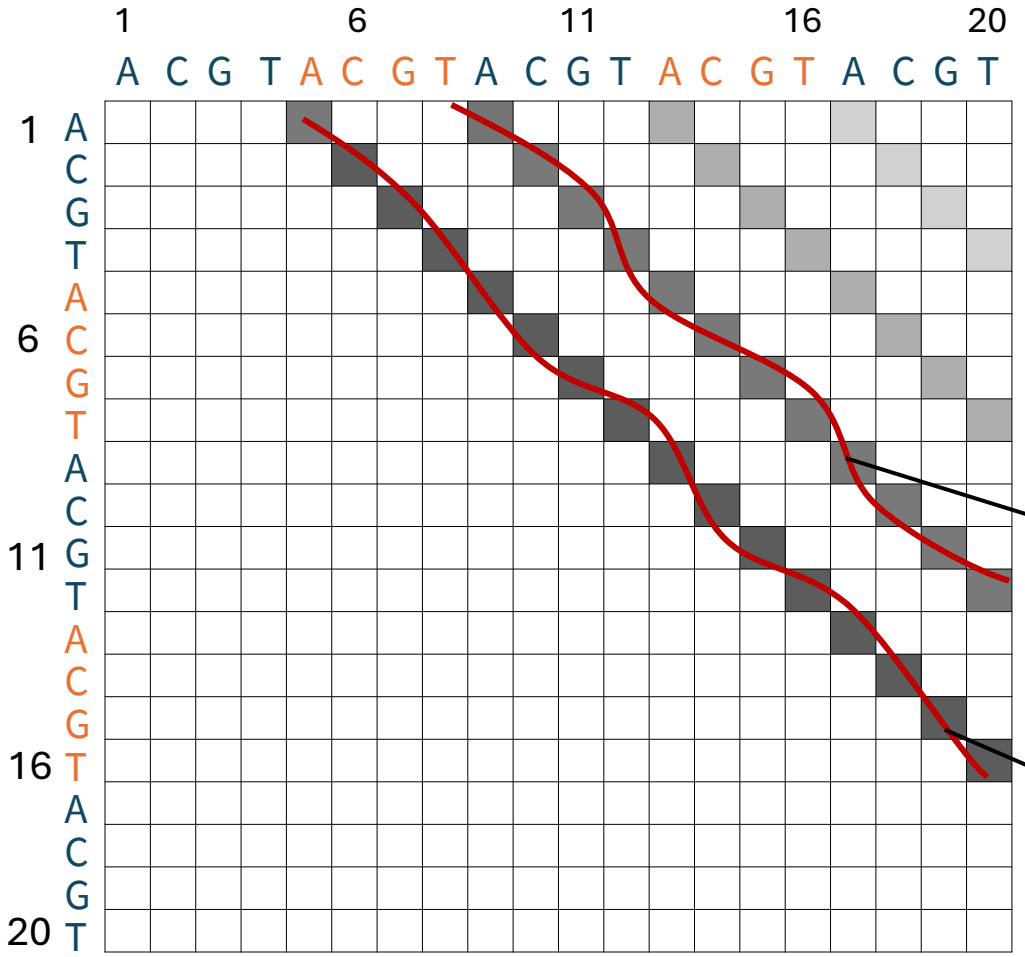

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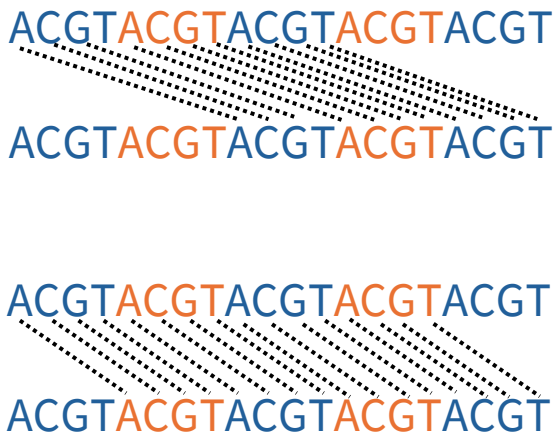

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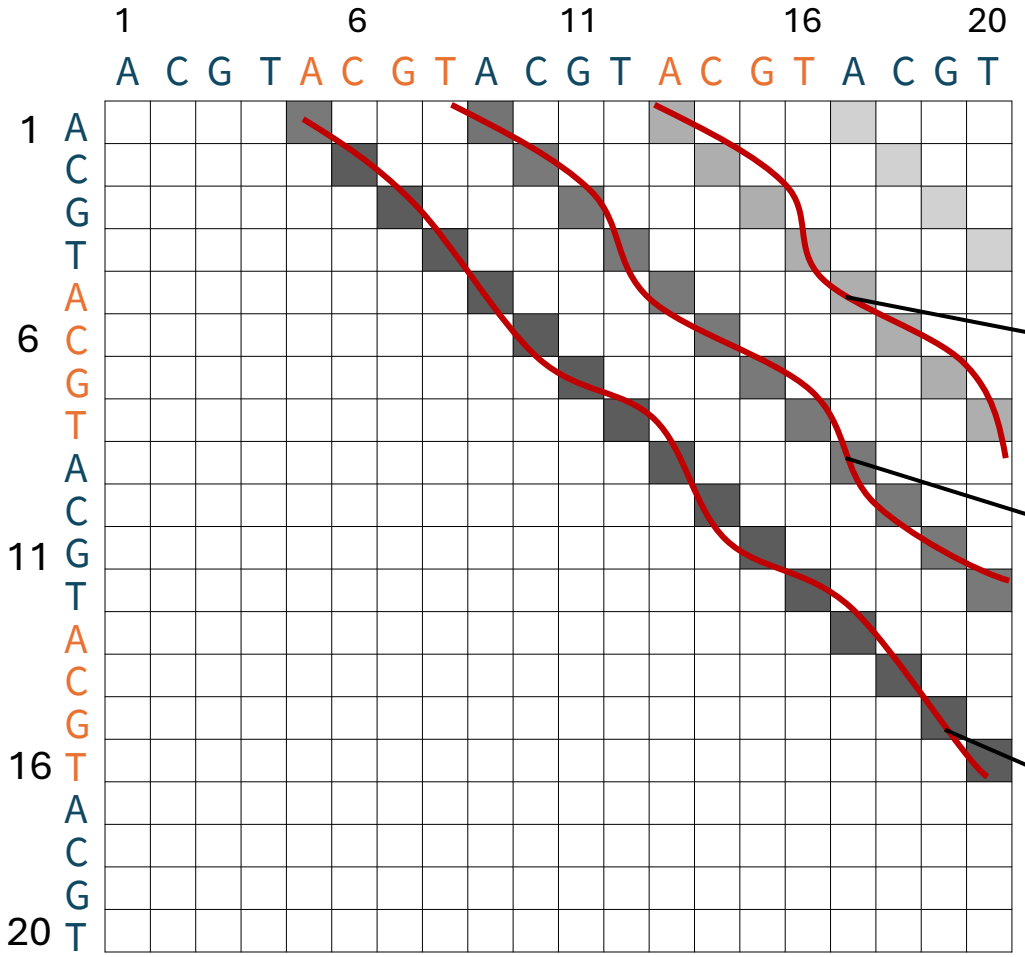

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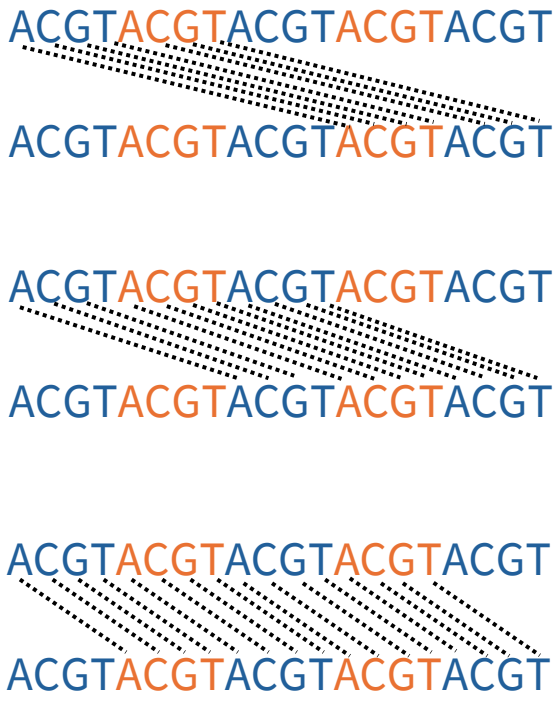

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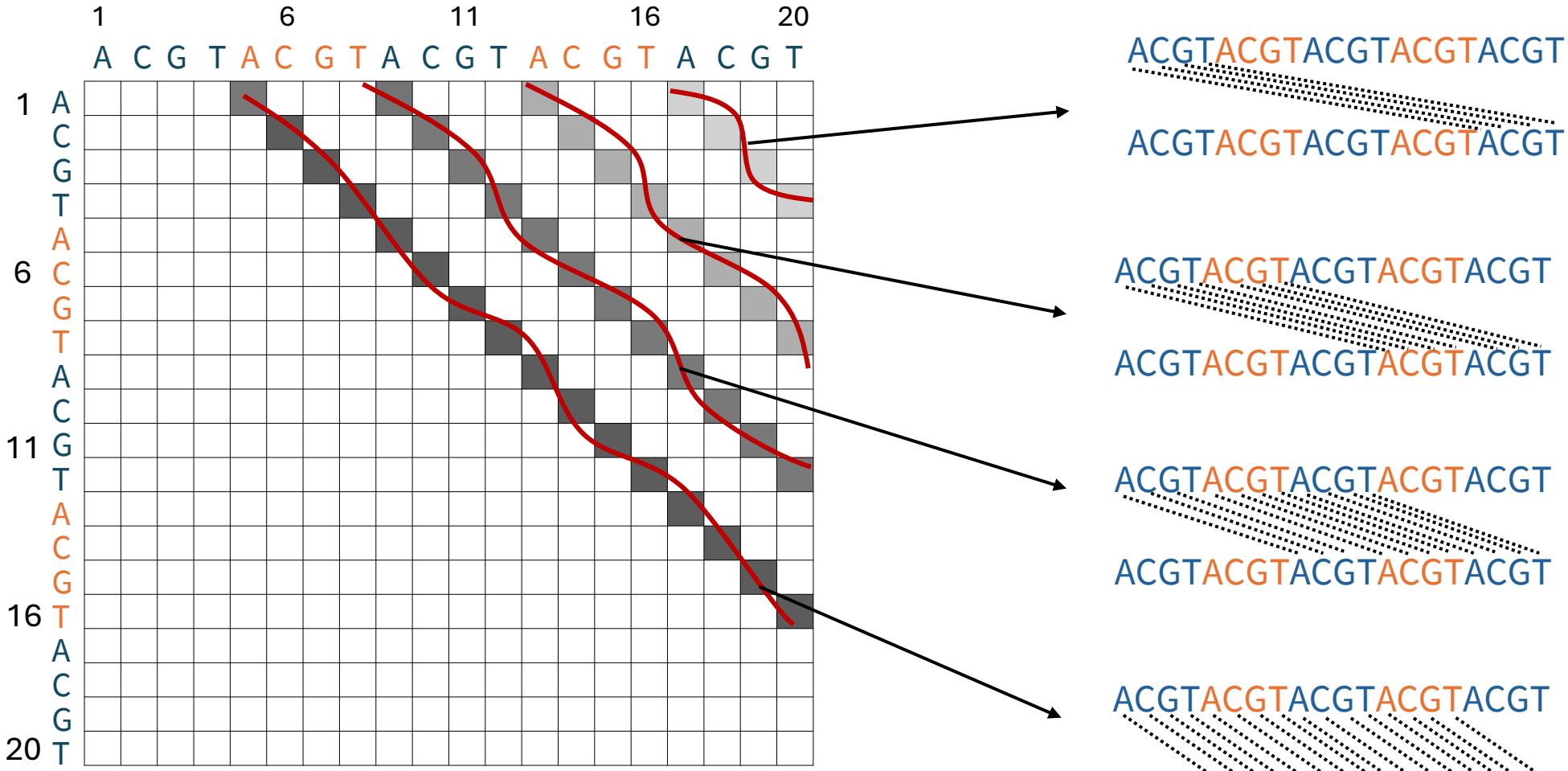

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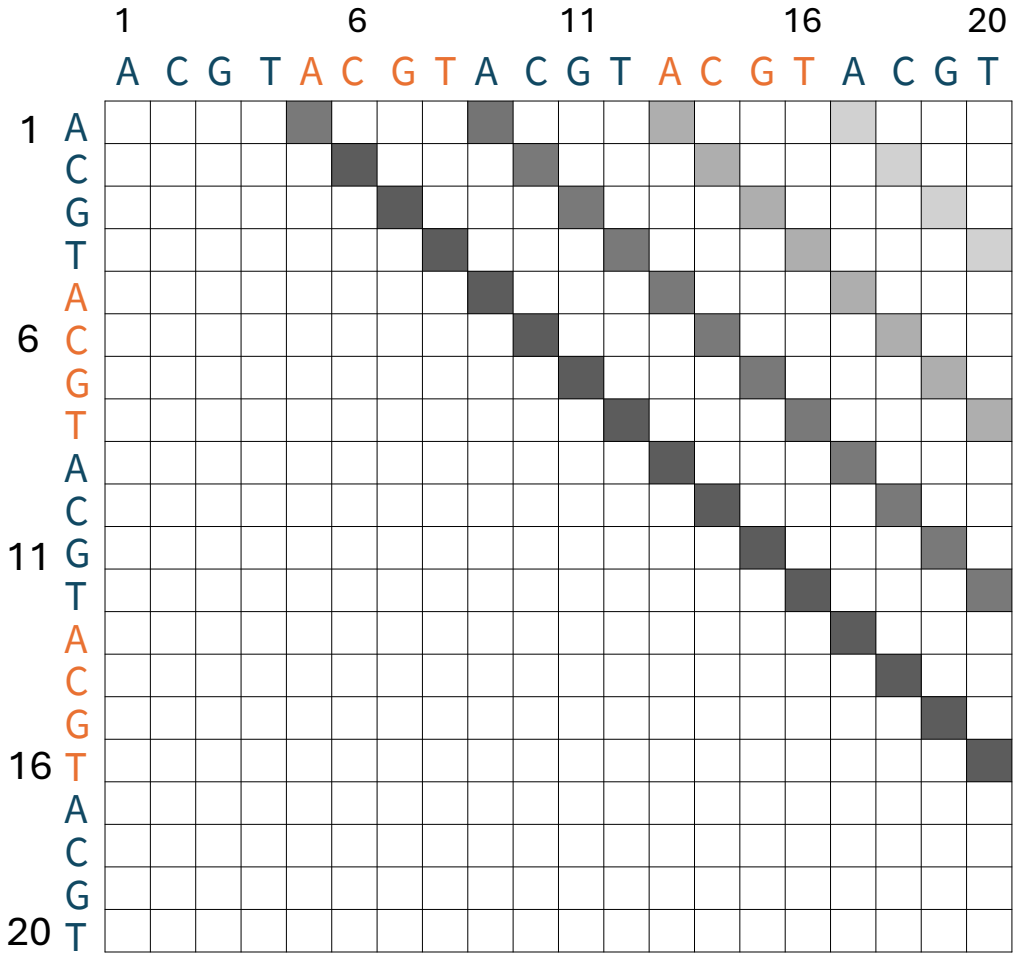

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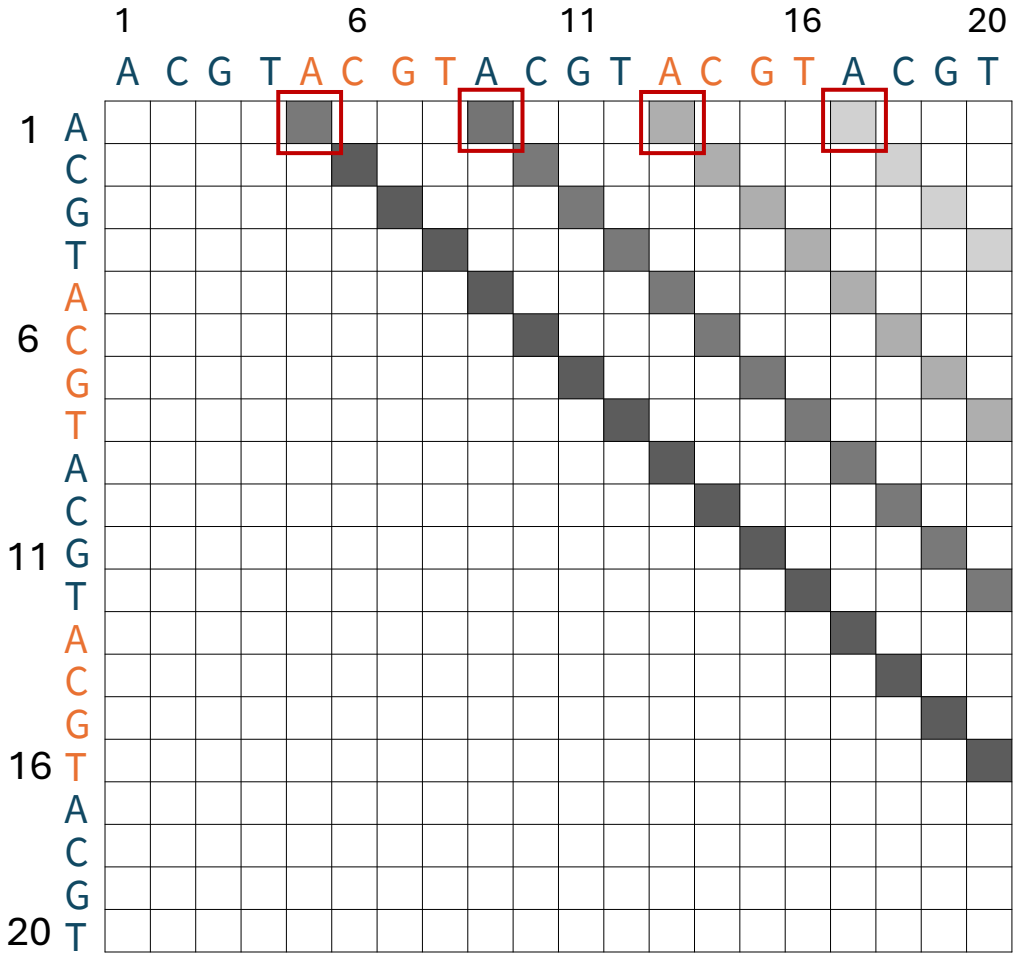

Ideal DP Table

Class 1: {1,5,9,13,17}

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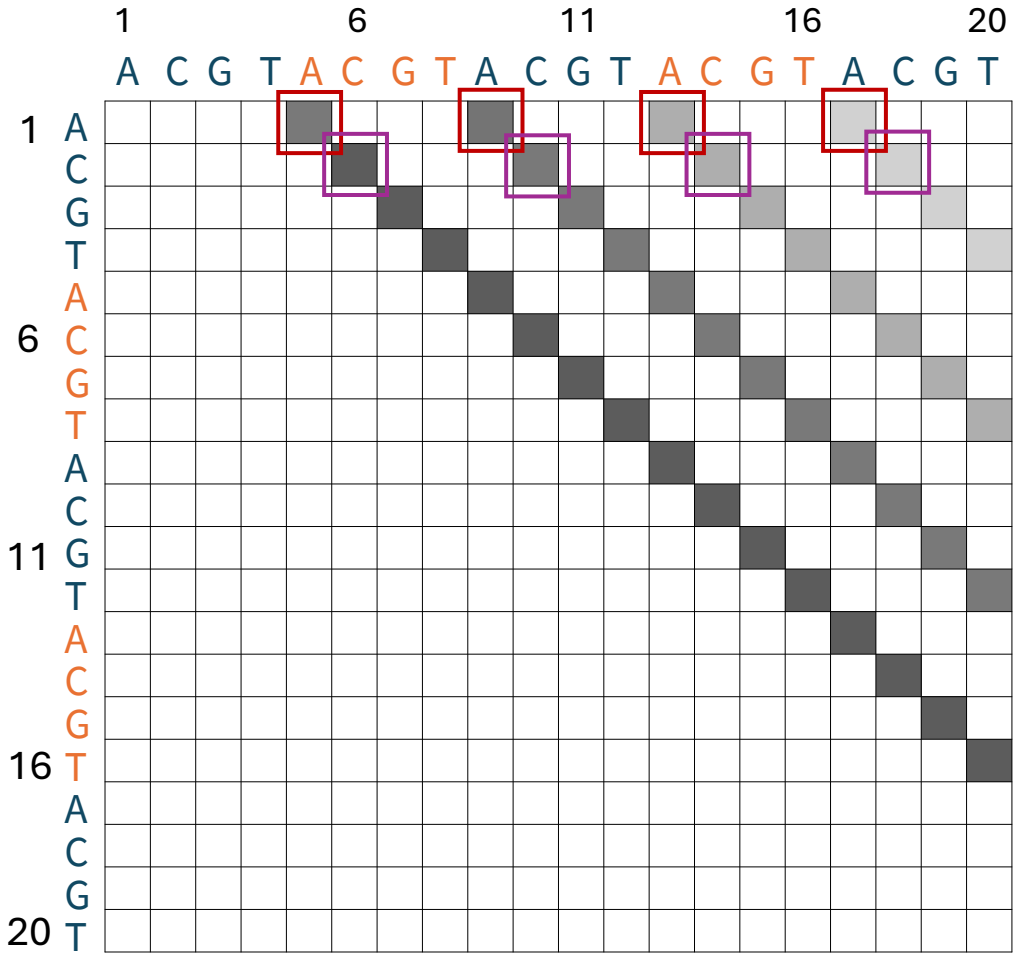
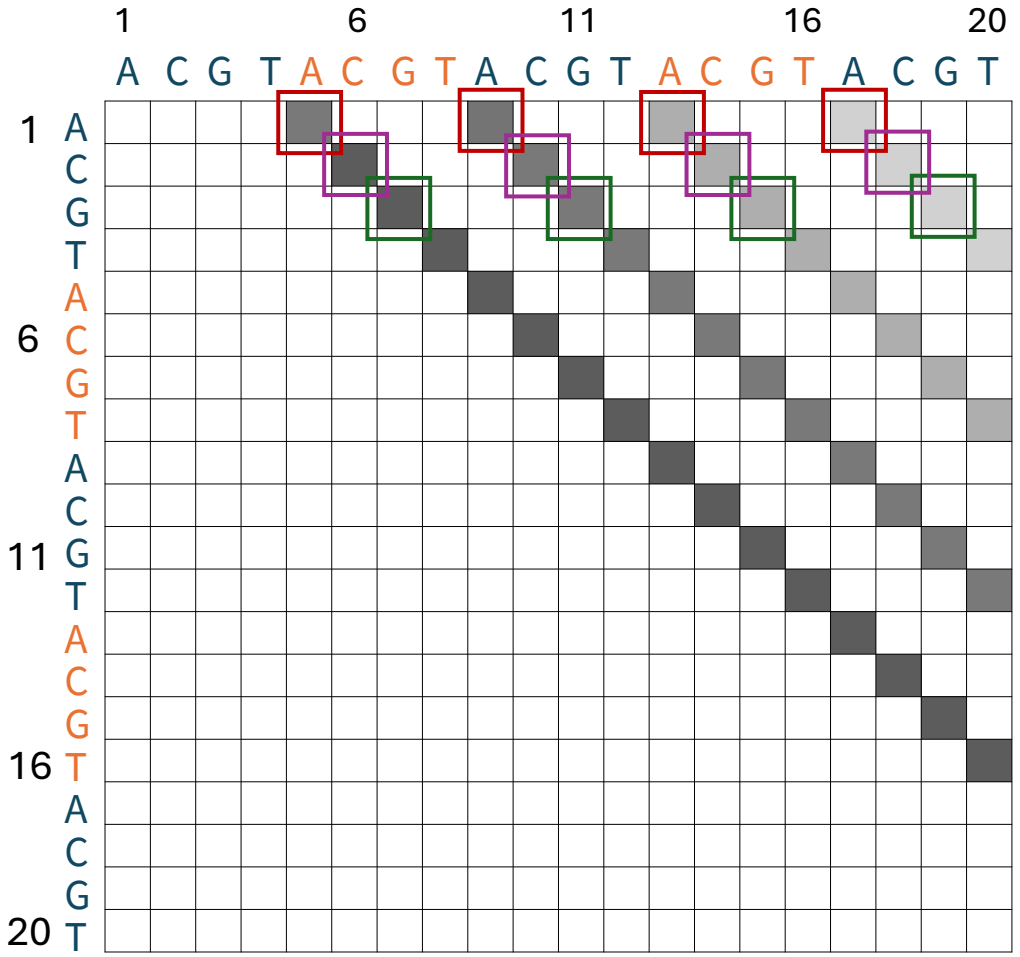


Ideal DP Table

Class 1: {1,5,9,13,17}

Class 2: {2,6,10,14,18}

Diagonal-free Self-alignment (Ideal)



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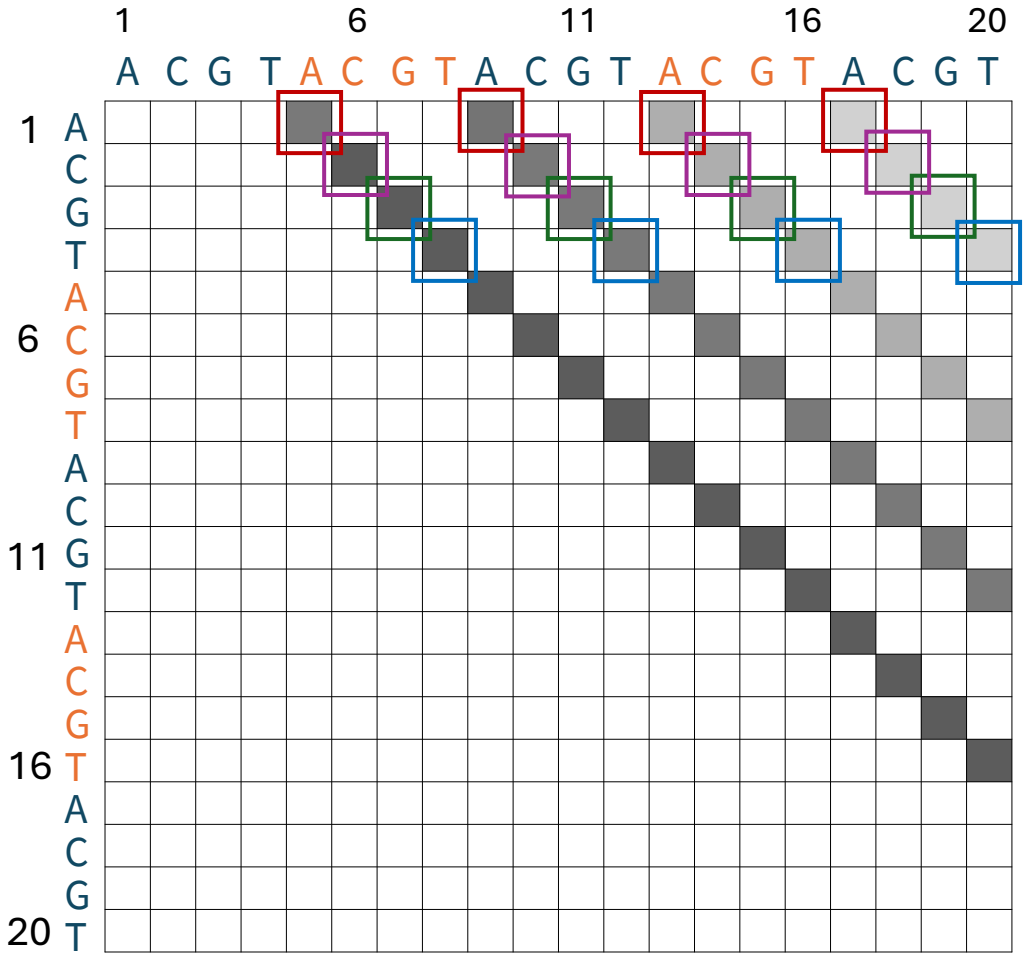
Class 3: {3,7,11,15,19}

Diagonal-free Self-alignment (Ideal)



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Class 1: {1,5,9,13,17}

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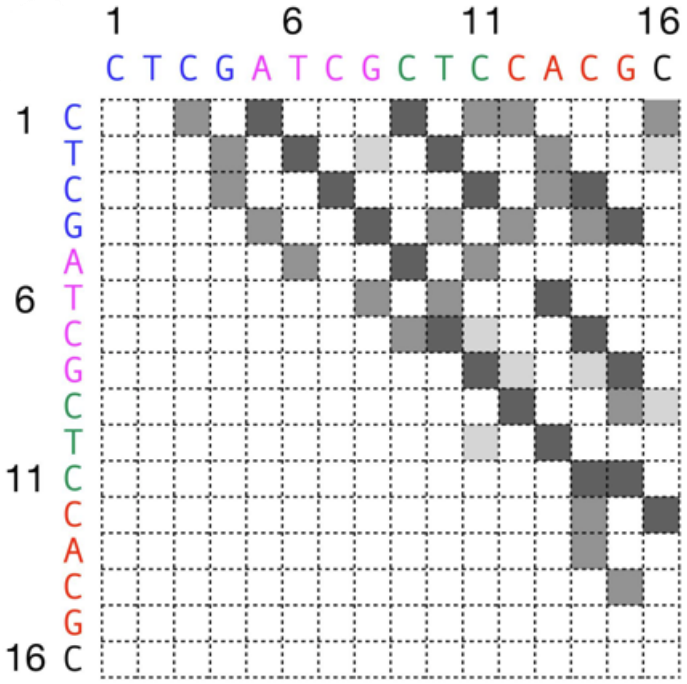
Class 3: {3,7,11,15,19}

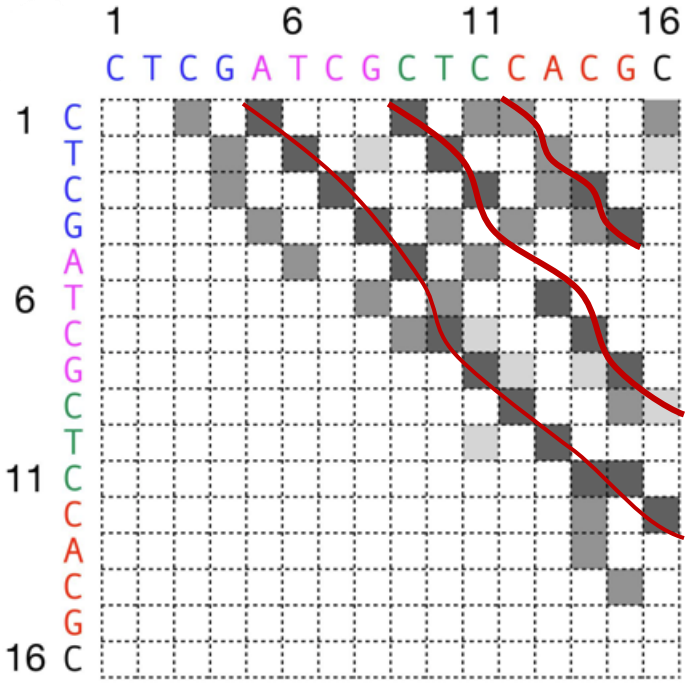
Class 4: {4,8,12,16,20}

Diagonal-free Self-alignment (Actual)



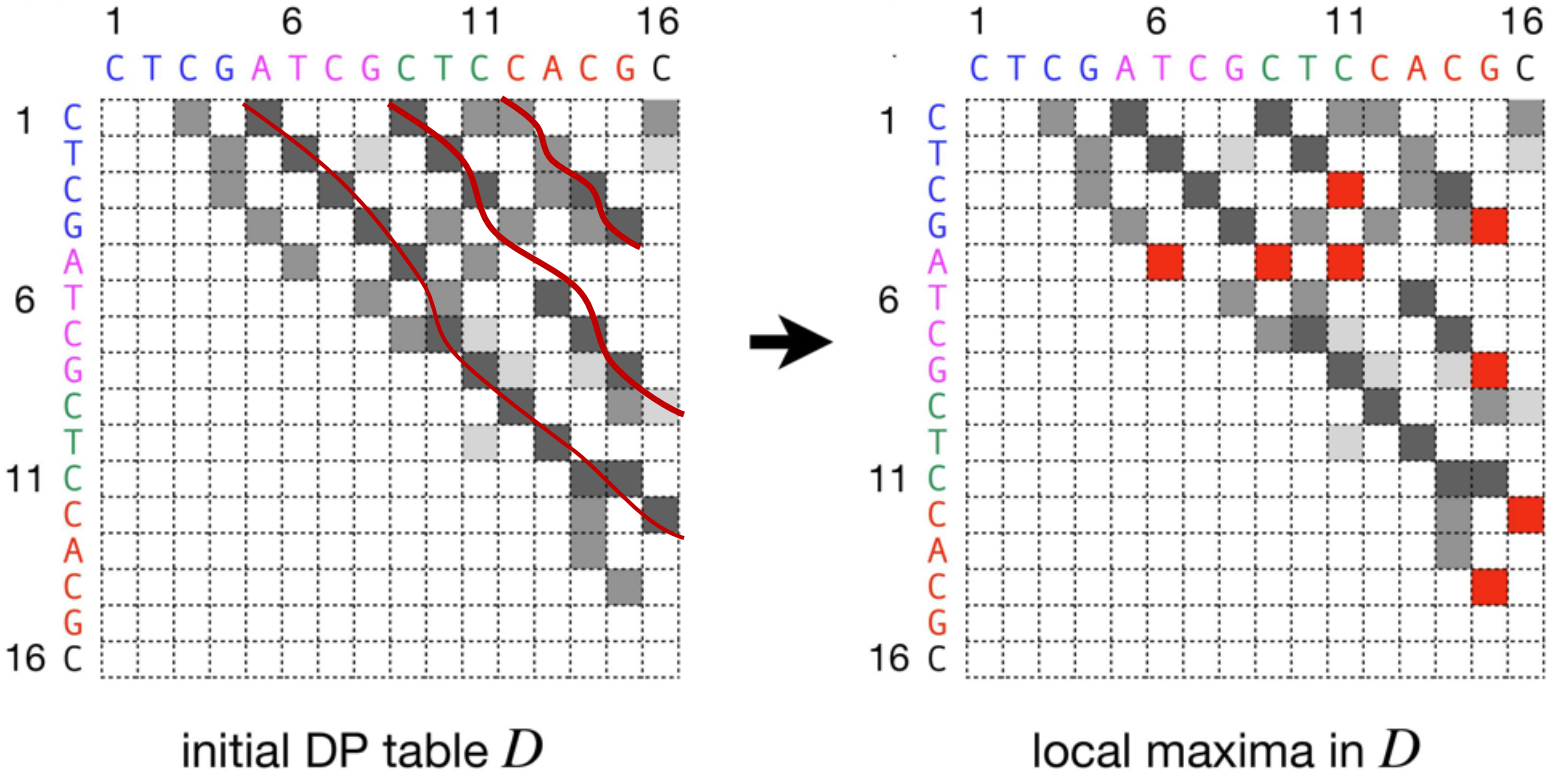
initial DP table D

Diagonal-free Self-alignment (Actual)



initial DP table D

Constructing Initial Matrix M



initial DP table D

local maxima in D

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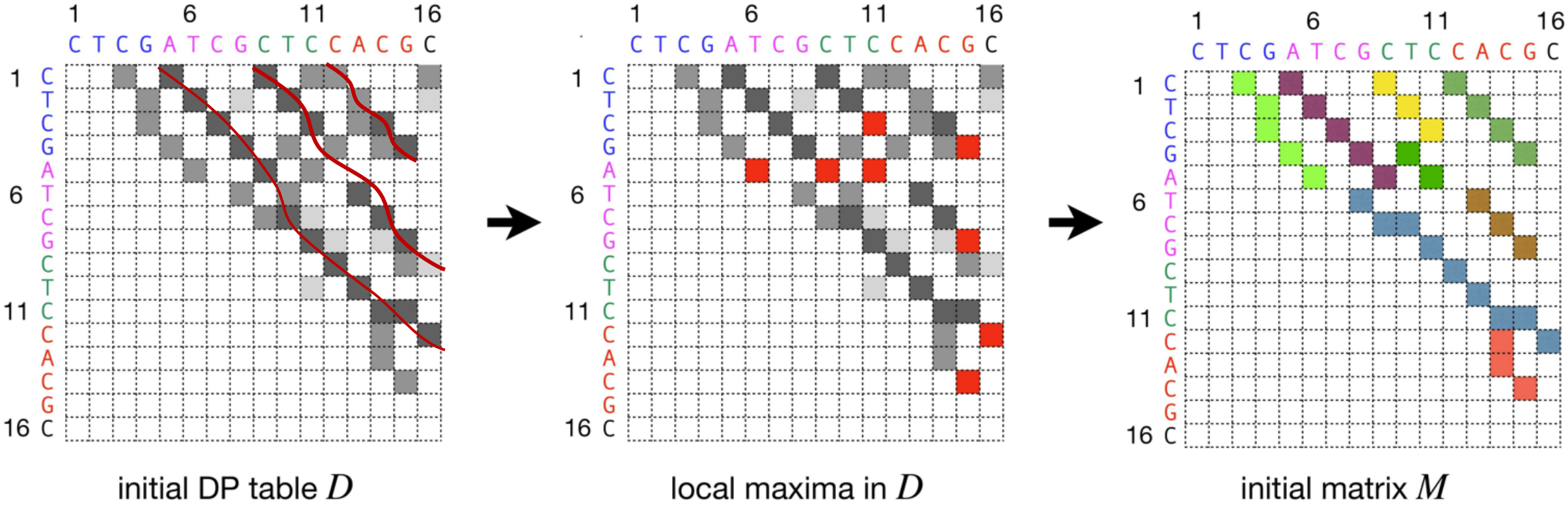
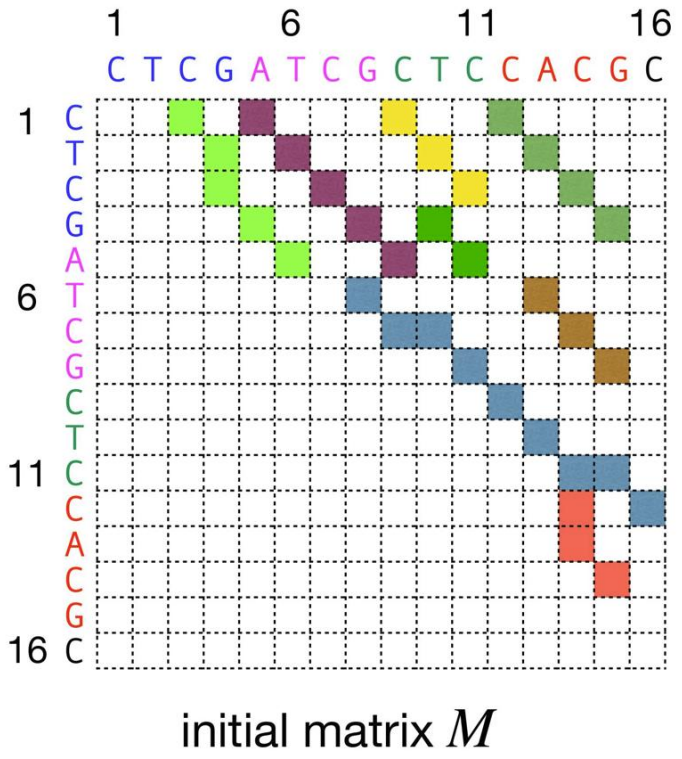


Constructing Refined Matrix M’



initial matrix M

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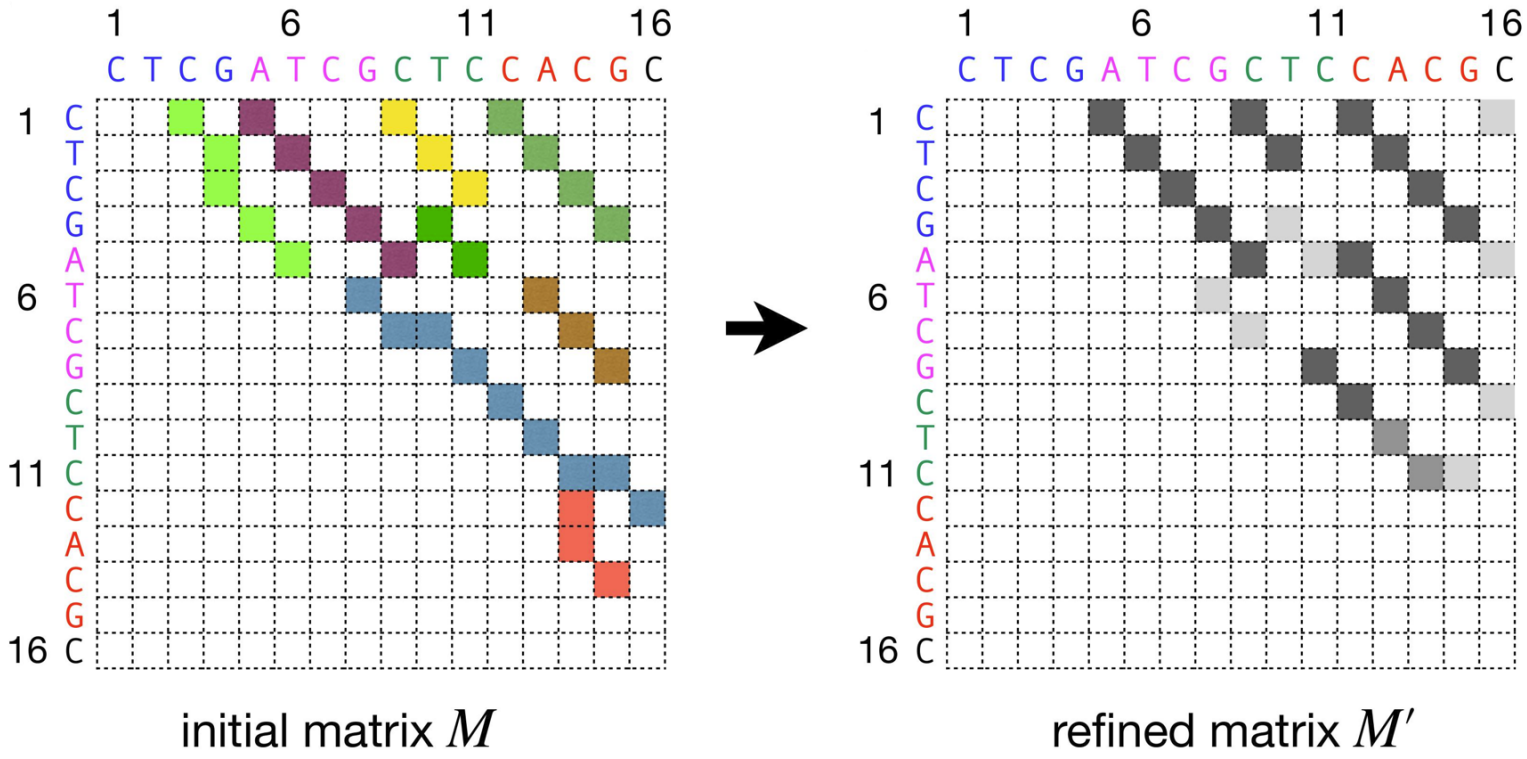

initial matrix M refined matrix M'

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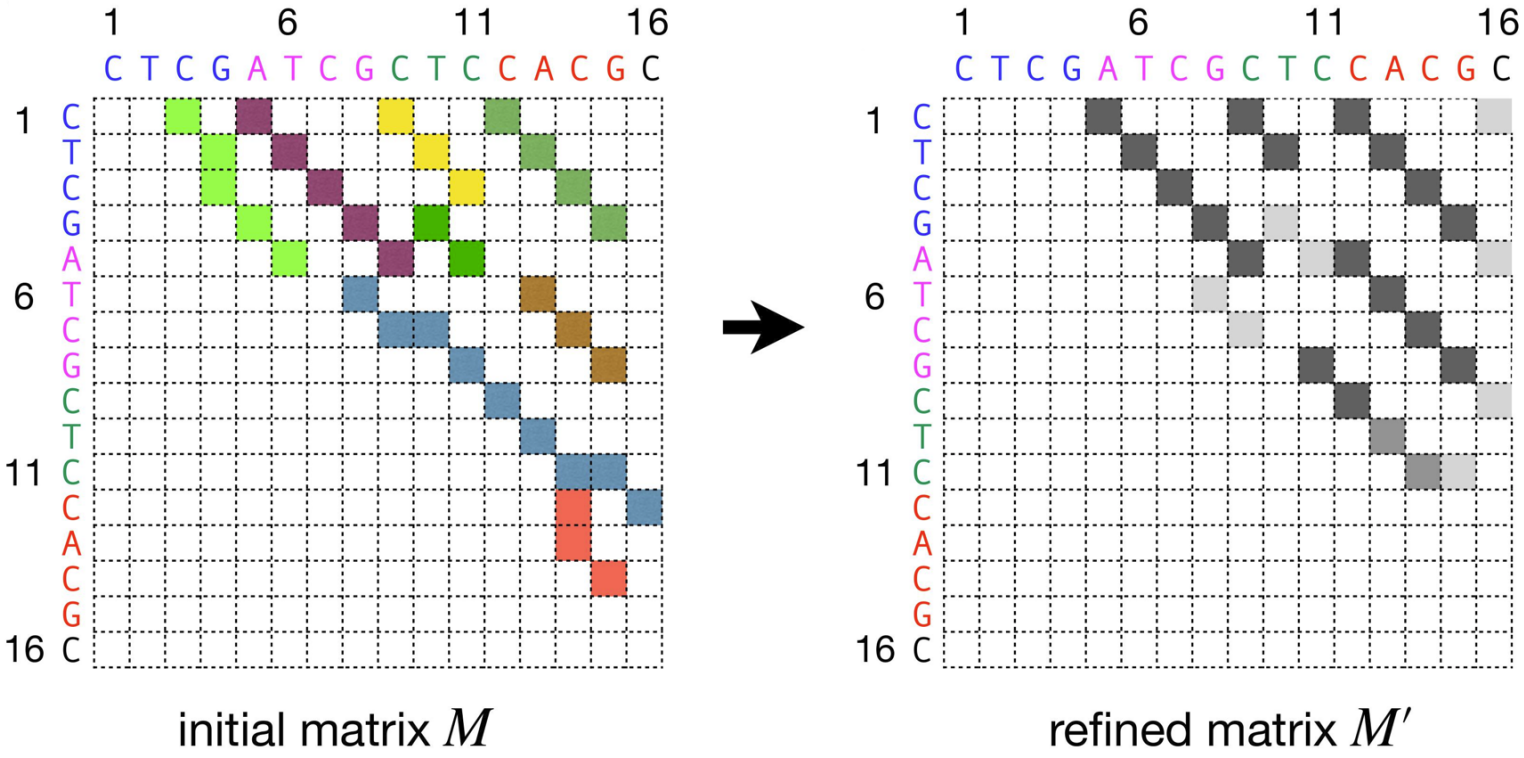
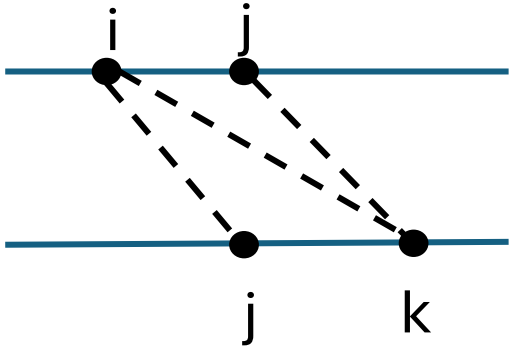


initial matrix M

refined matrix M'



$$\delta \leftarrow \min\{M[i,j], M[i,k], M[j,k]\}$$
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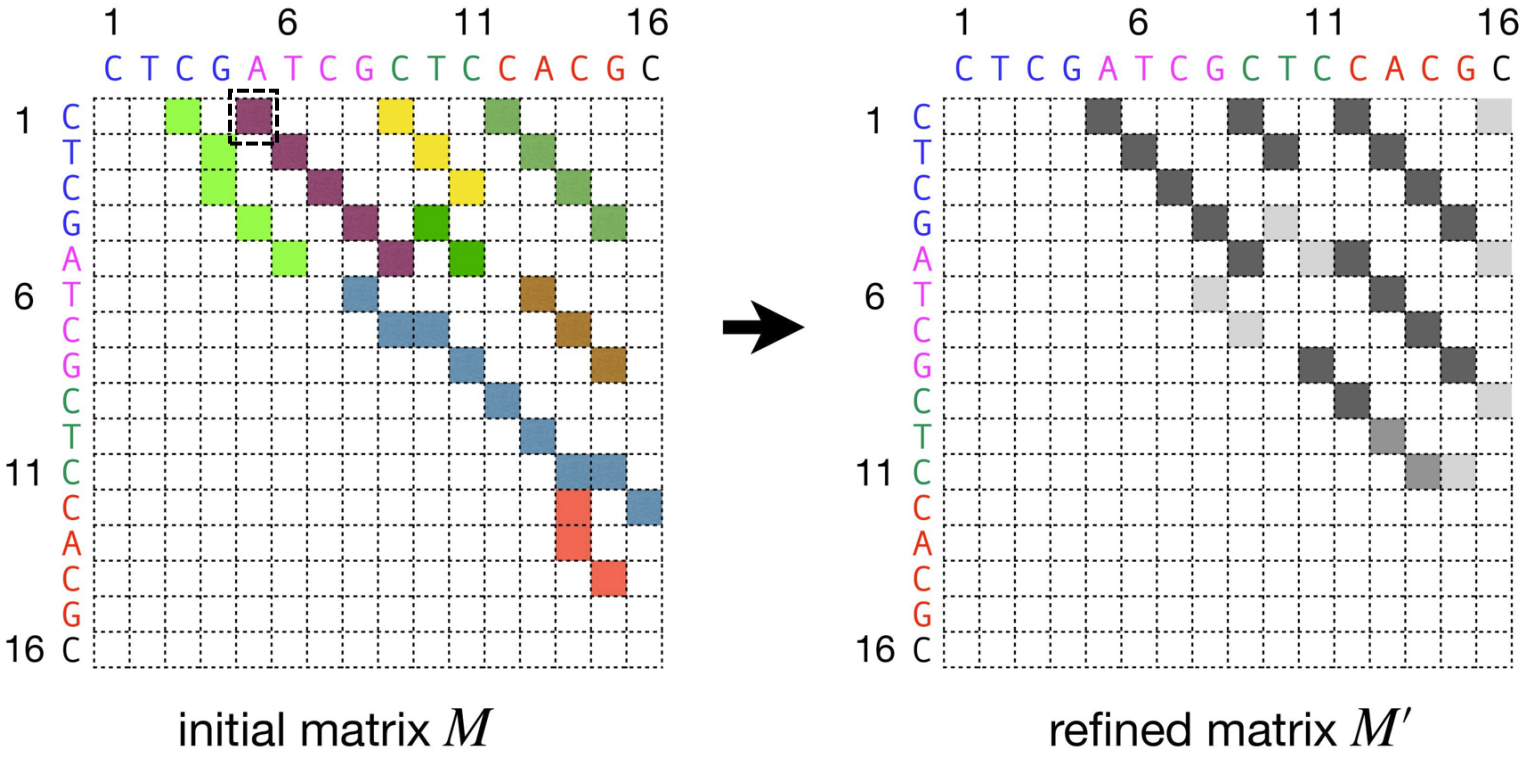
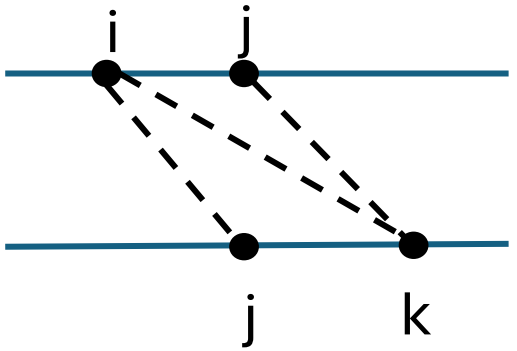


initial matrix M

refined matrix M'

$M\,[1, 5] > 0$



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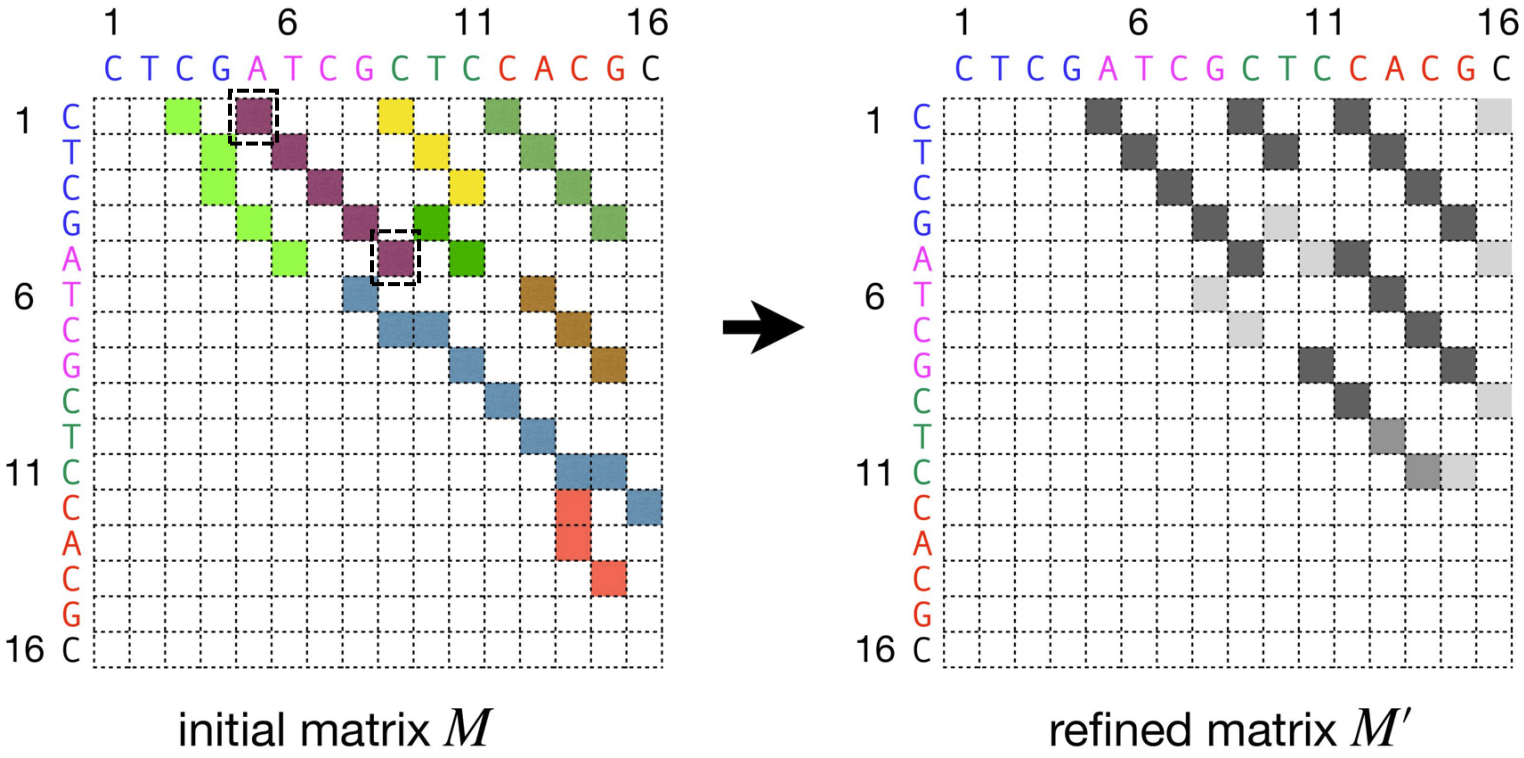

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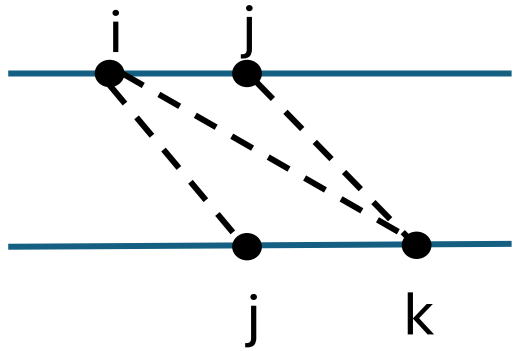

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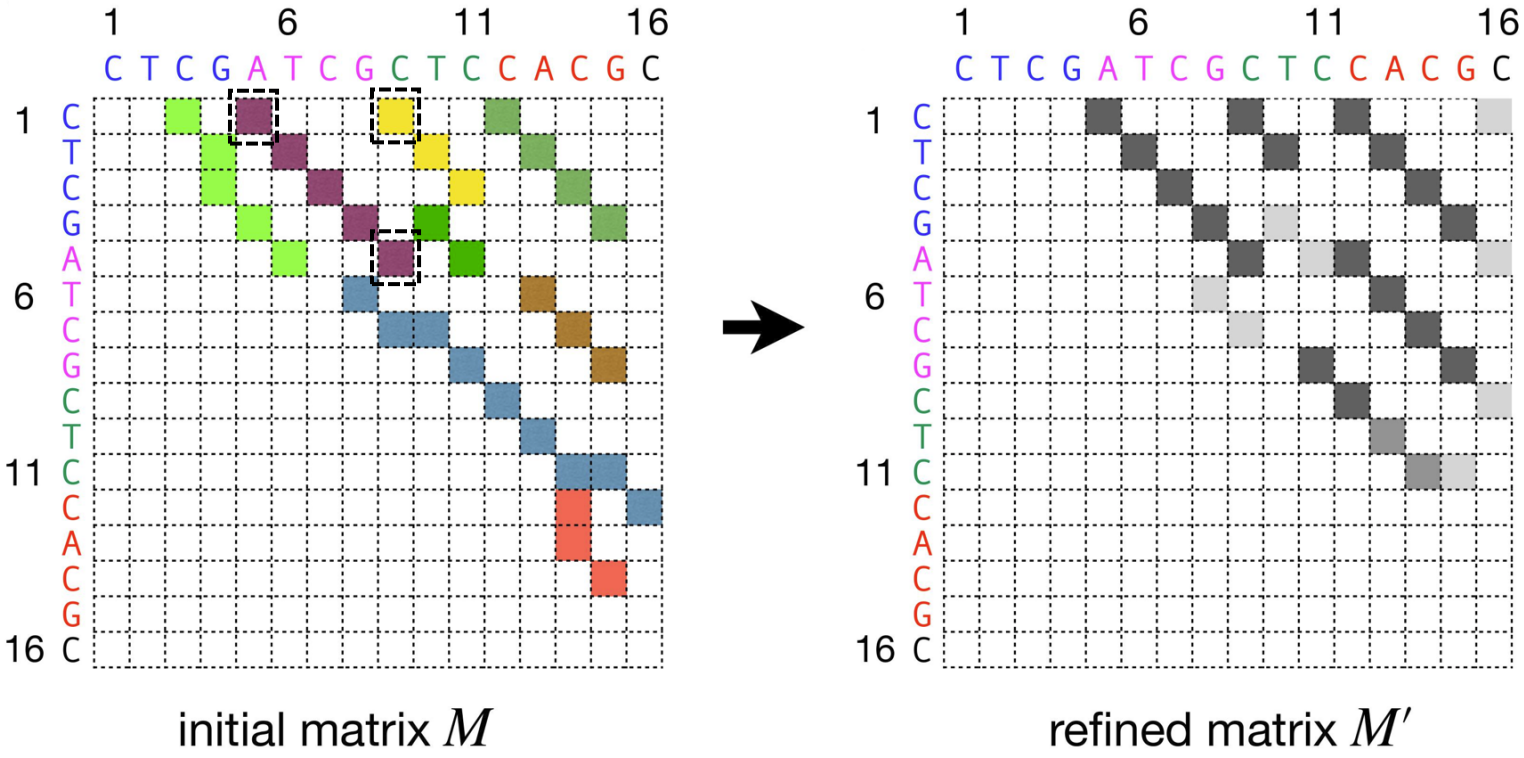

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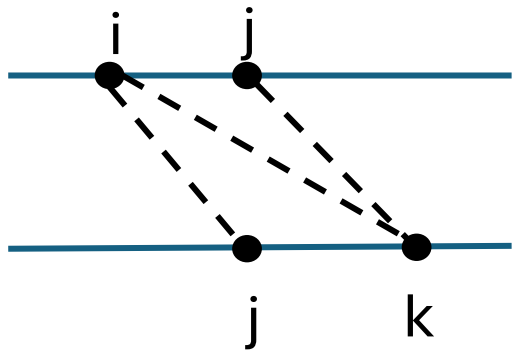

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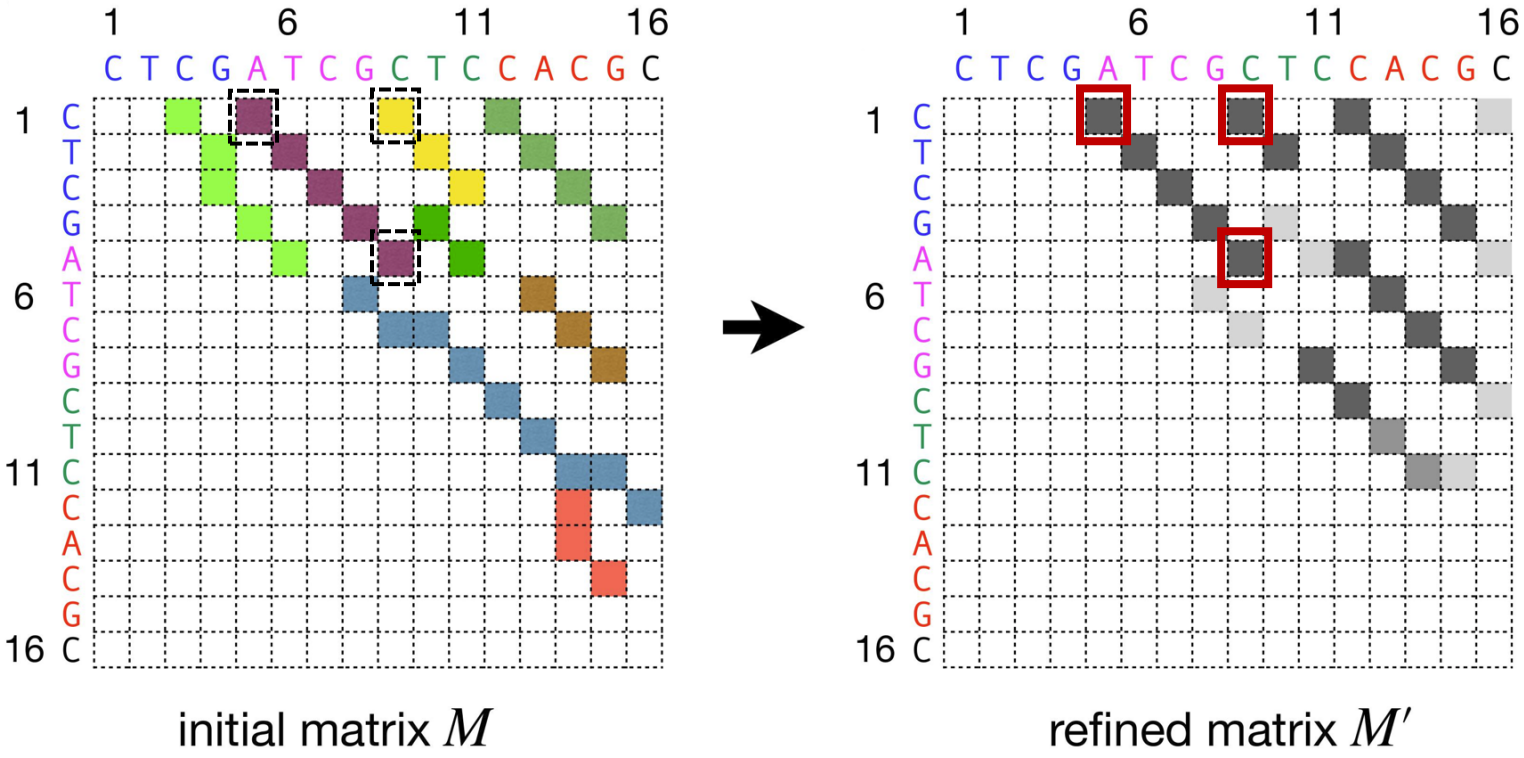

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refined matrix M'

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$$M\,[5,9] > 0$$
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$$M'\,[1,5] \leftarrow M'\,[1,5] + \delta$$
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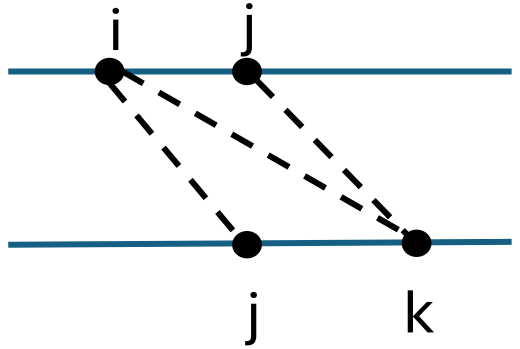

$$\delta \leftarrow \min\{M\,[i,j], M\,[i,k], M\,[j,k]\}$$
$$M'\,[i,j] \leftarrow M'\,[i,j] + \delta$$
$$M'\,[j,k] \leftarrow M'\,[j,k] + \delta$$
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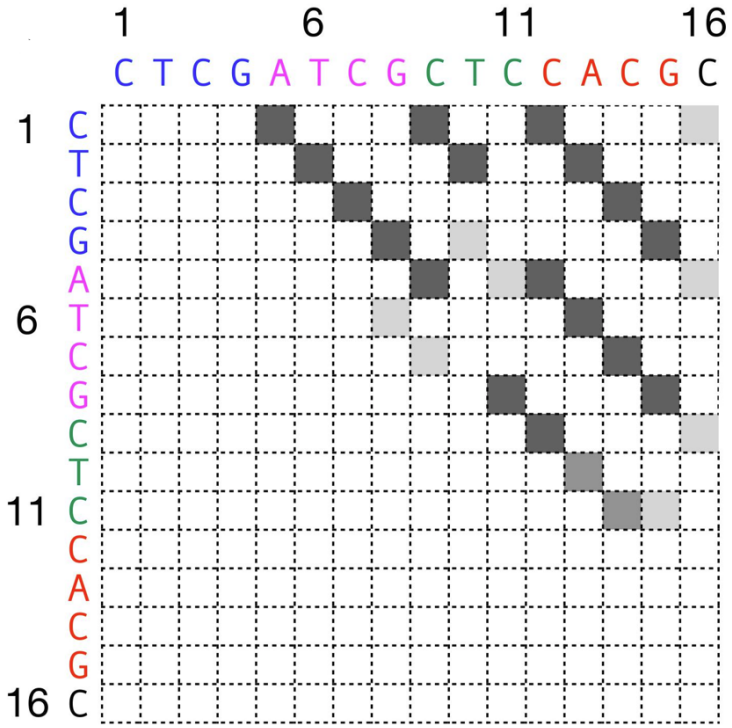
Constructing Equivalent Positions



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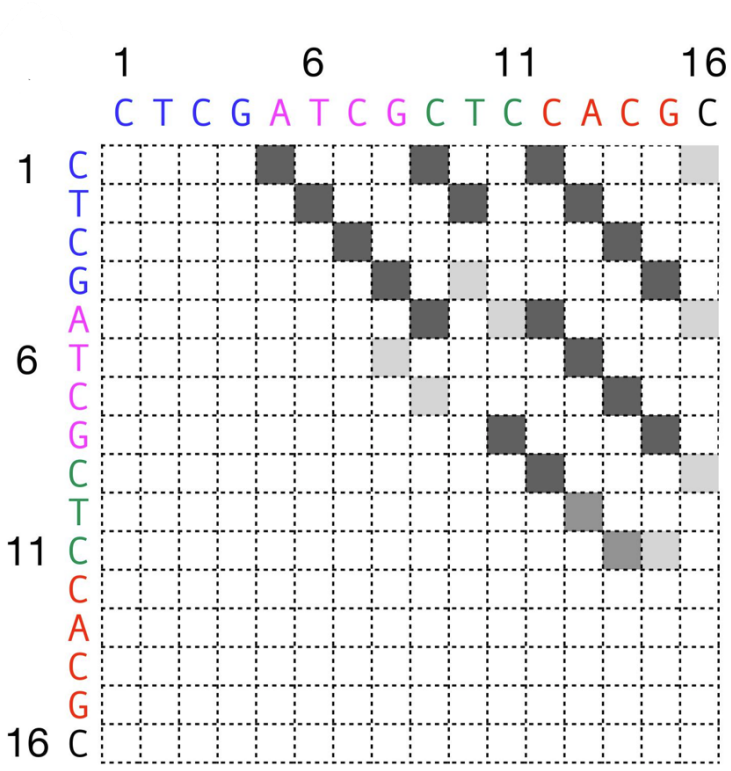

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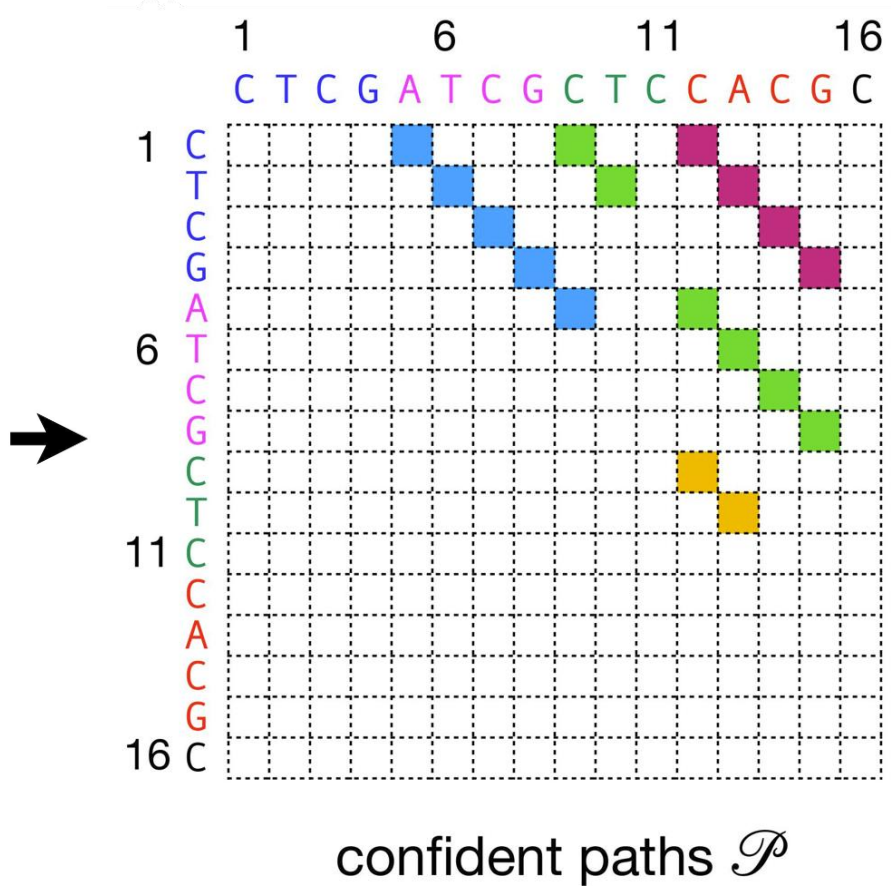

confident paths $\mathscr{P}$

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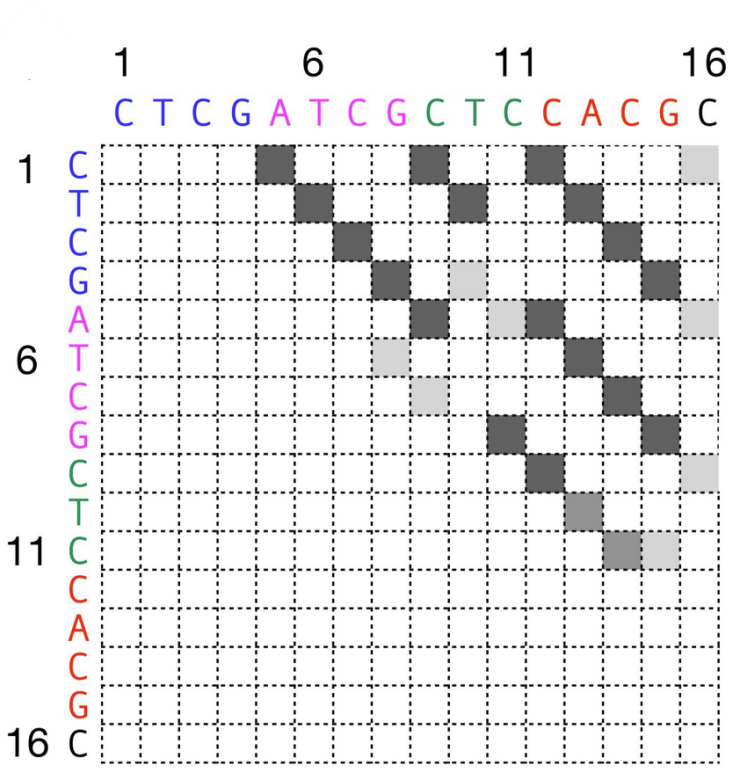

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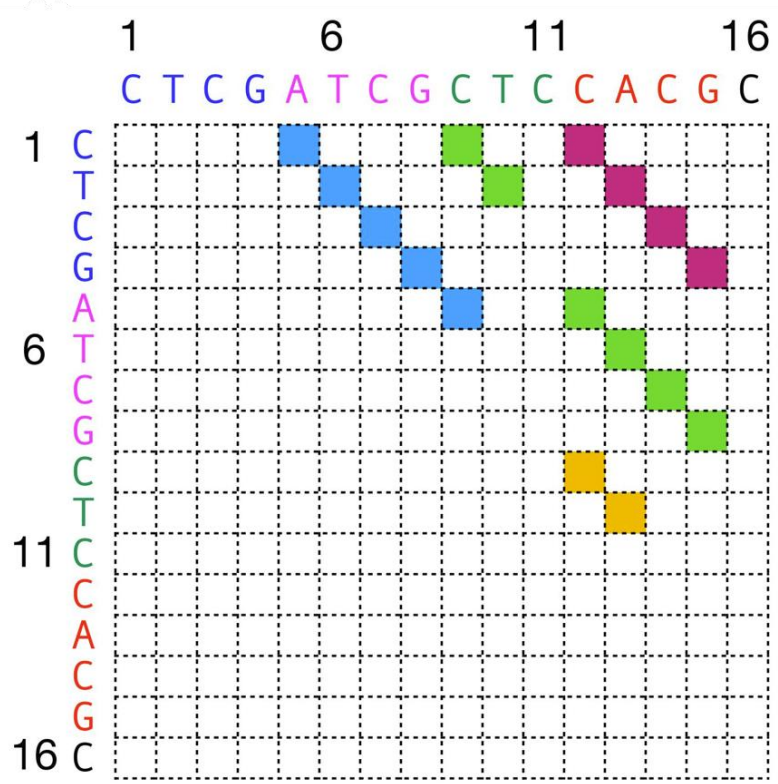


confident paths $\mathscr{P}$

1,5,9,12 (C)

2,6,10,13 (T)

3,7,14 (C)

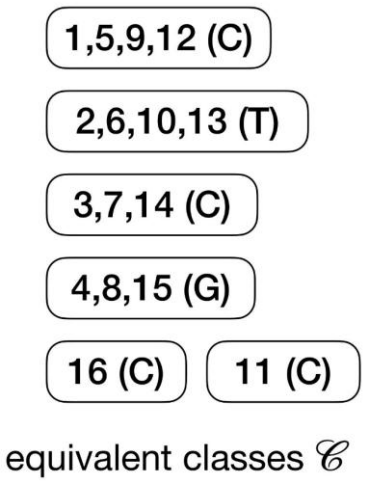
4,8,15 (G)

11 (C)

16 (C)

equivalent classes $\mathscr{C}$

Building Weighted Graph



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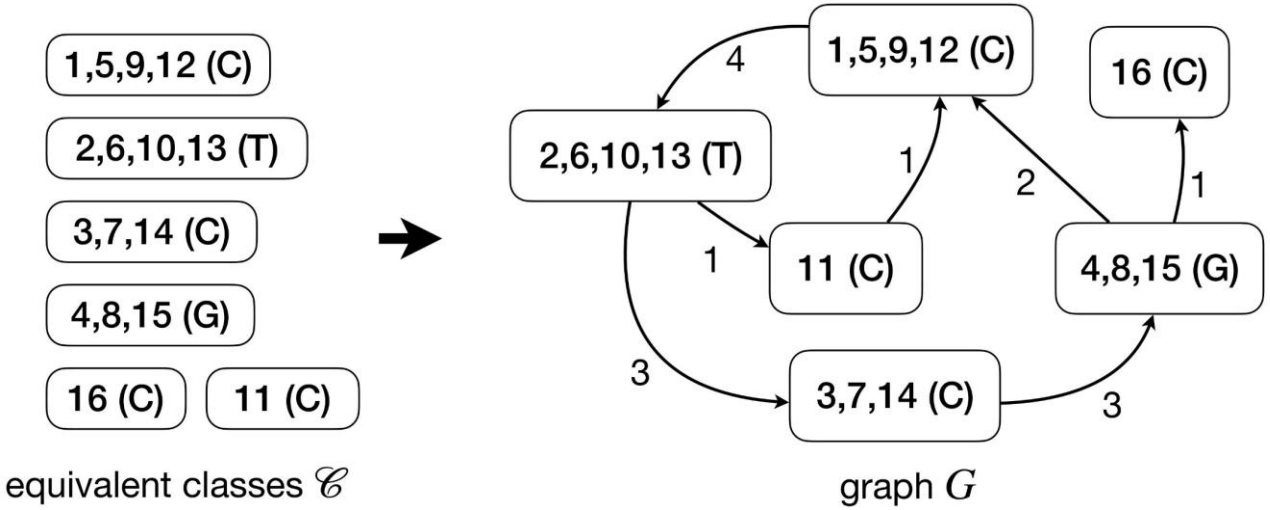

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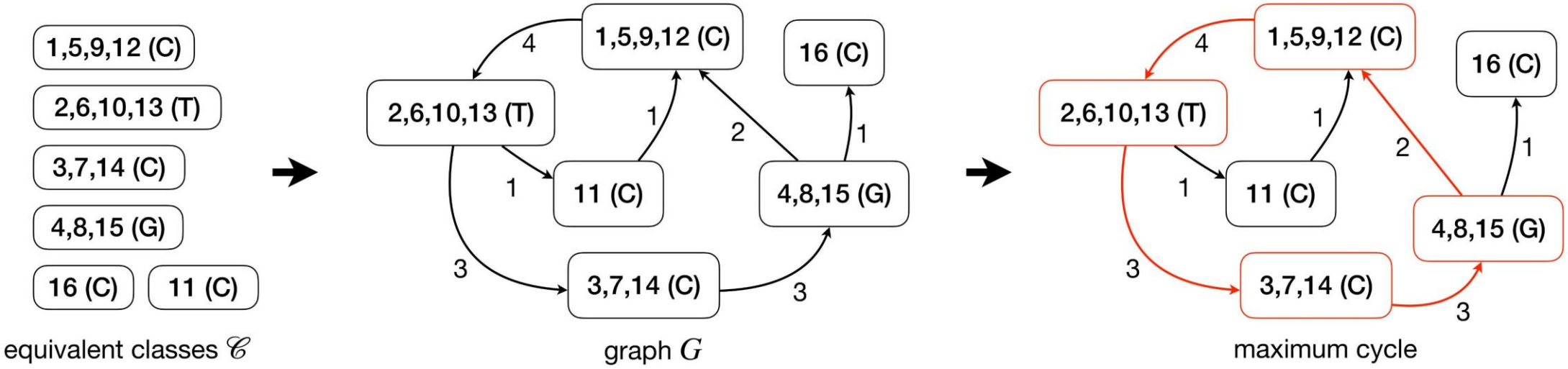

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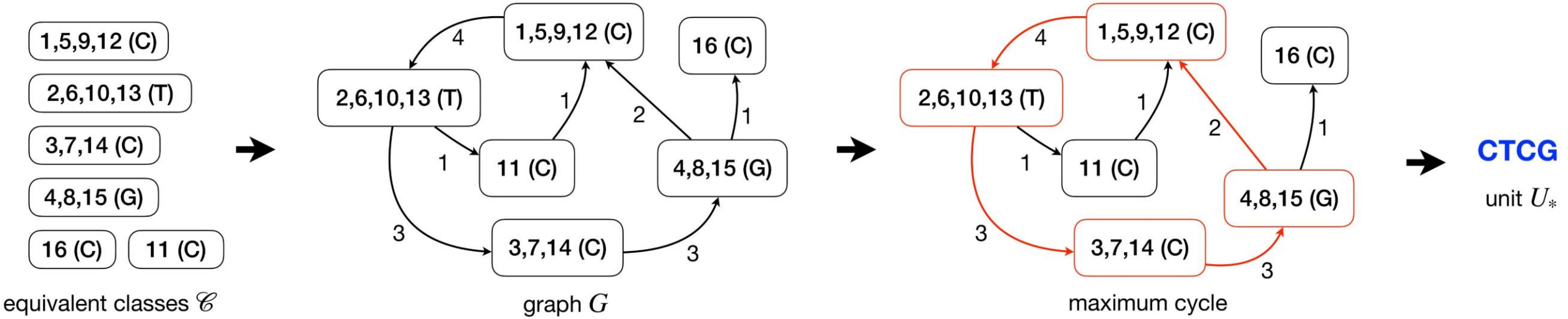

Experimental Setup: Simulations

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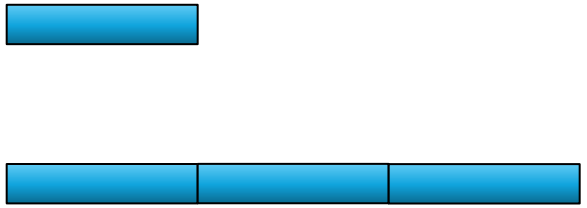

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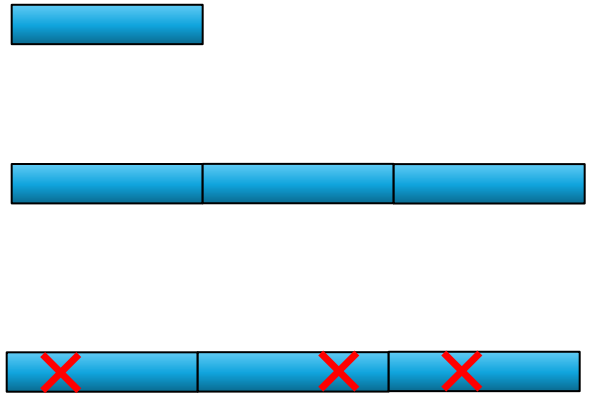

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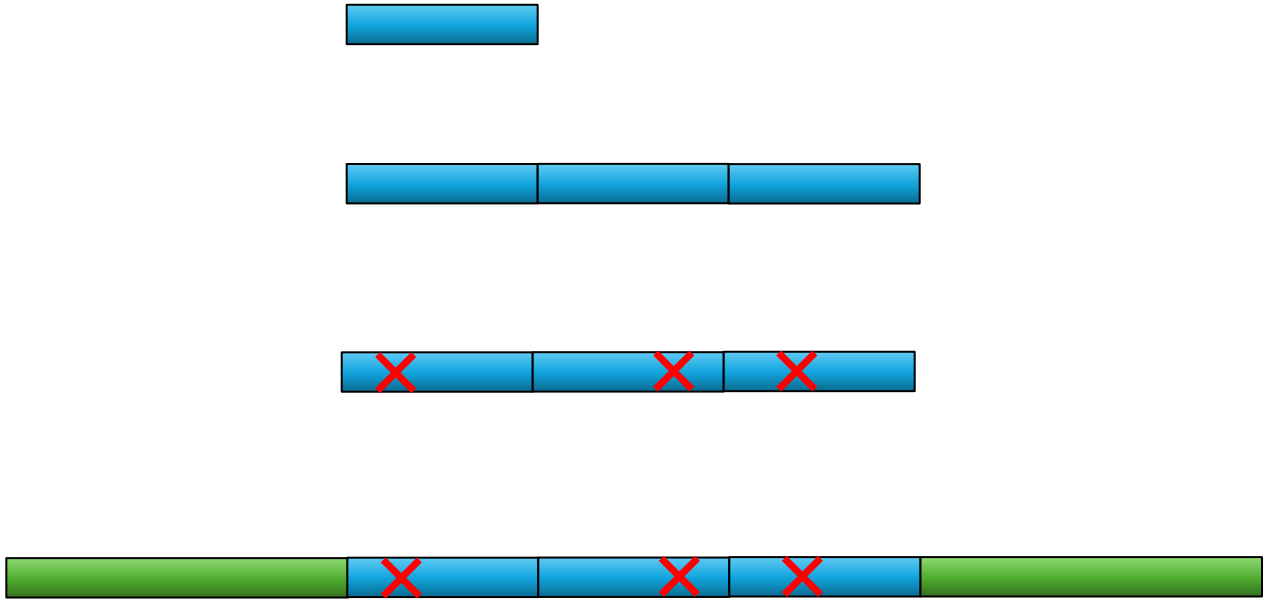

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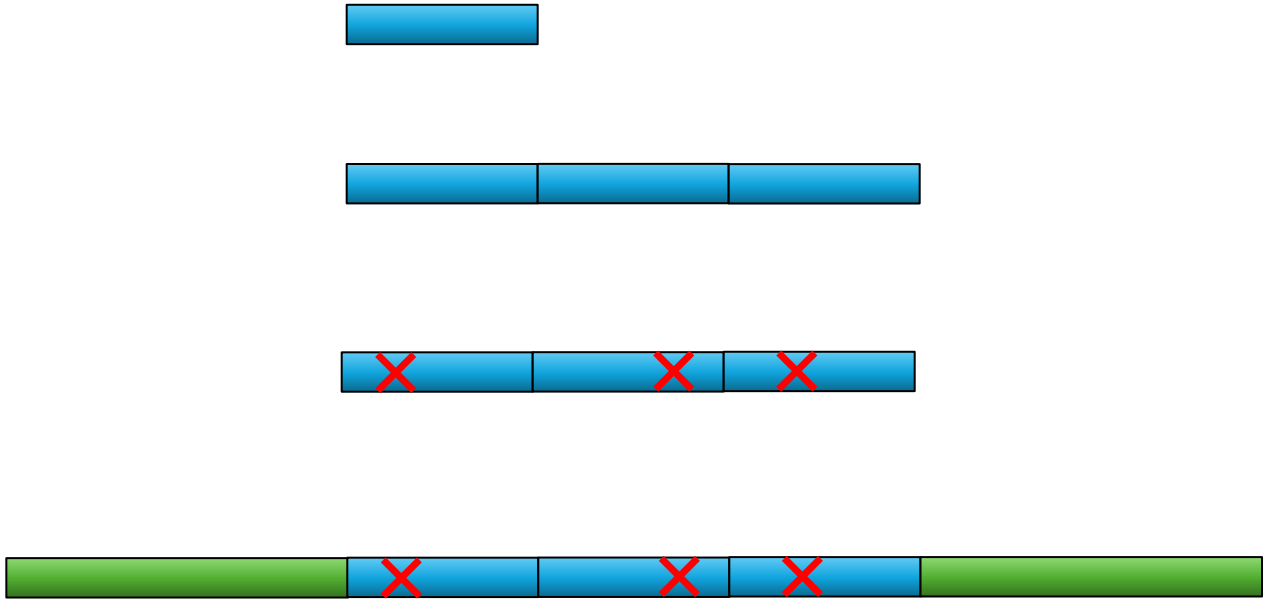
- Generate data for different combinations of L, F, R.



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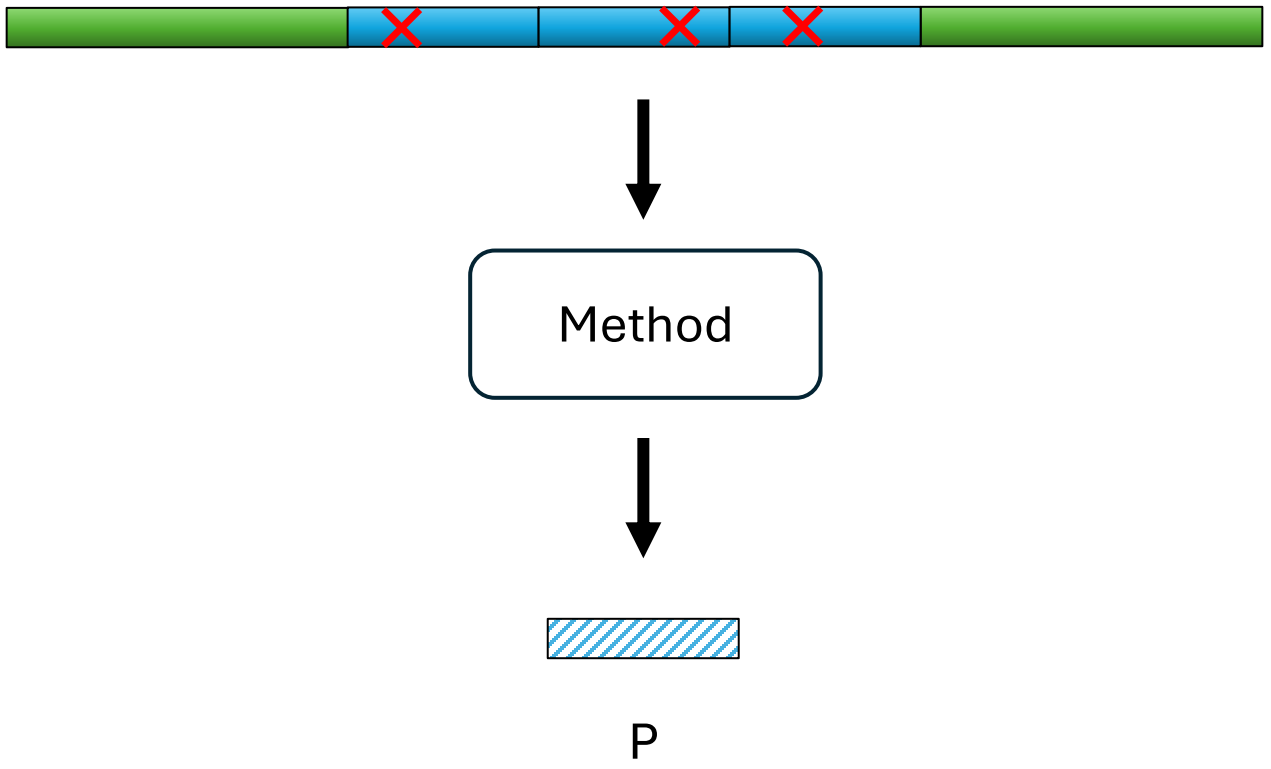

Evaluation

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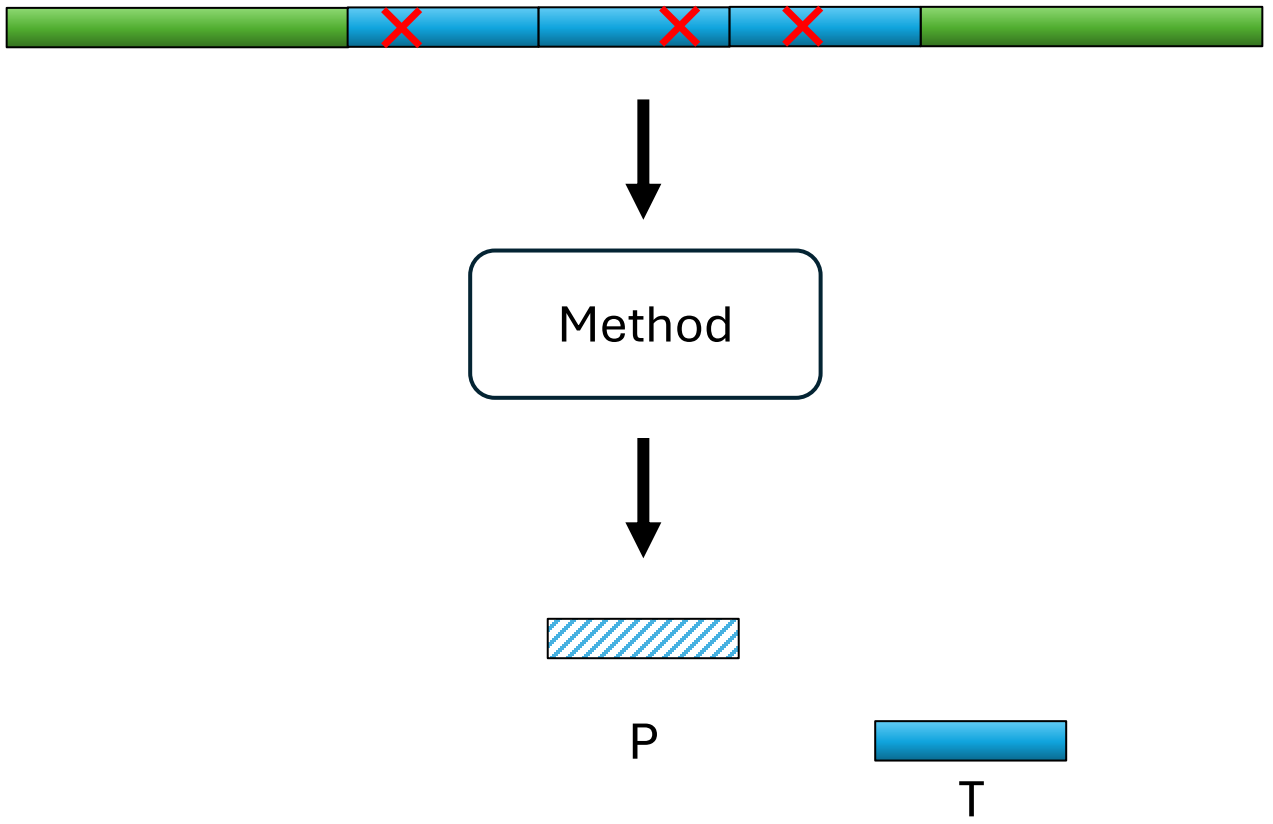

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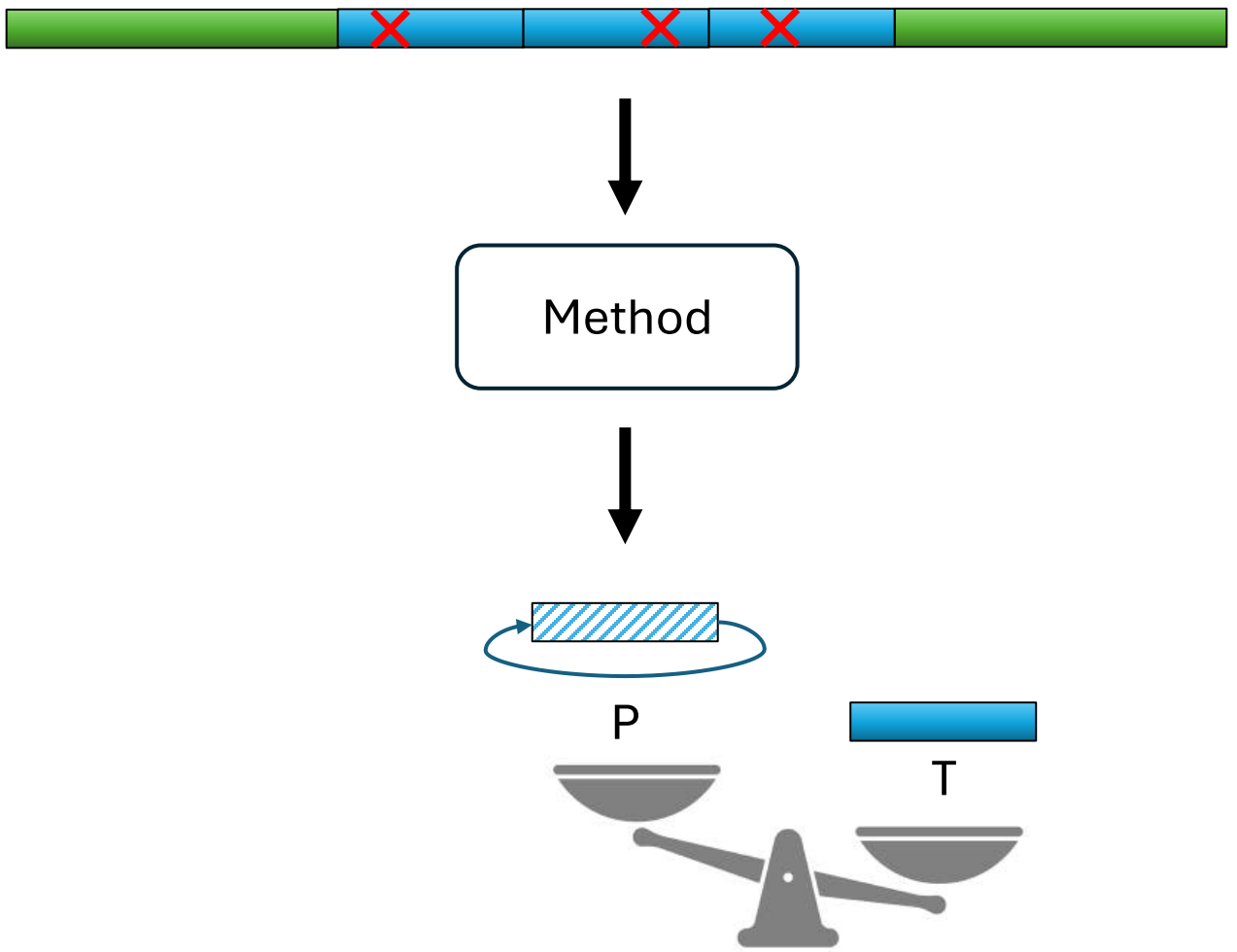

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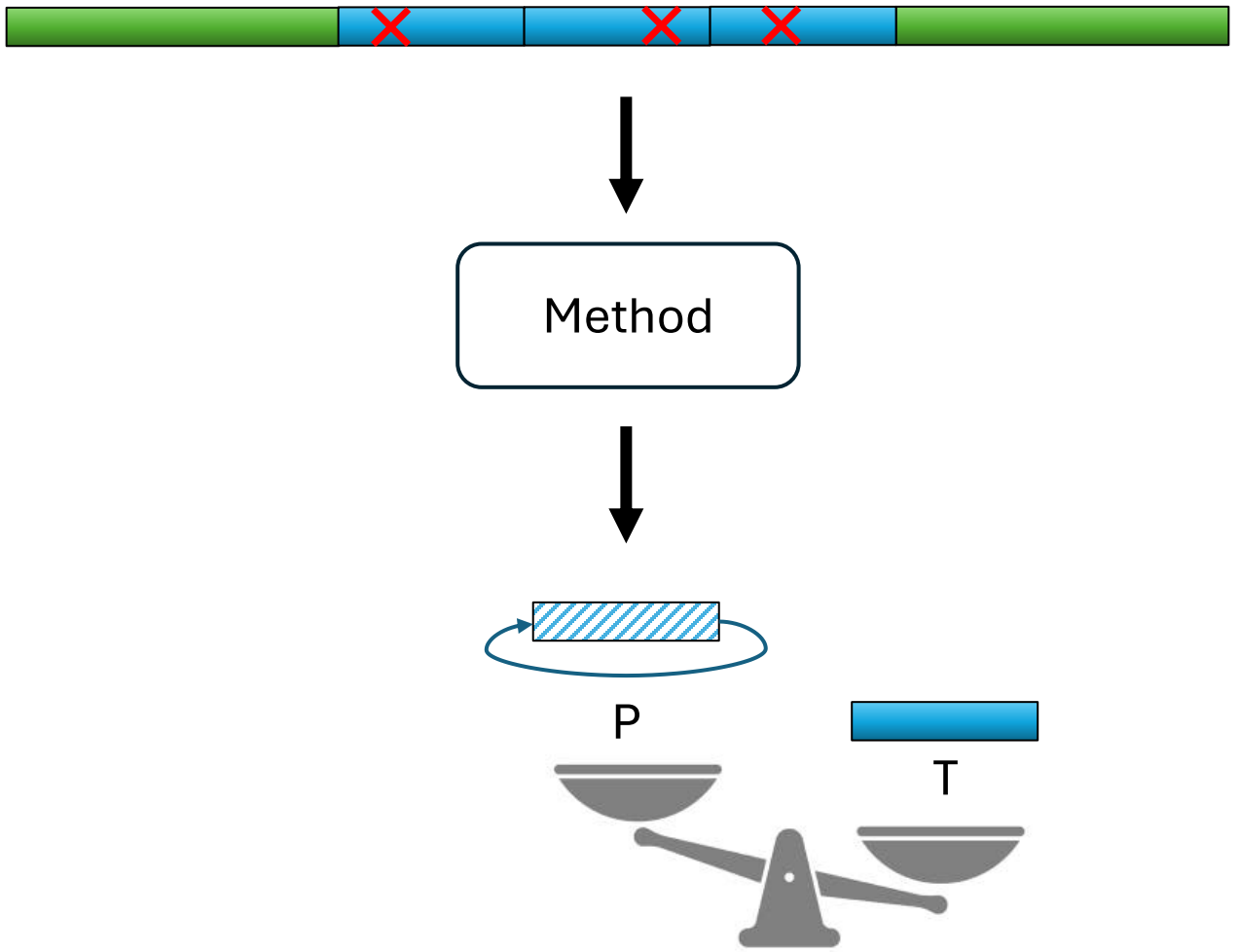
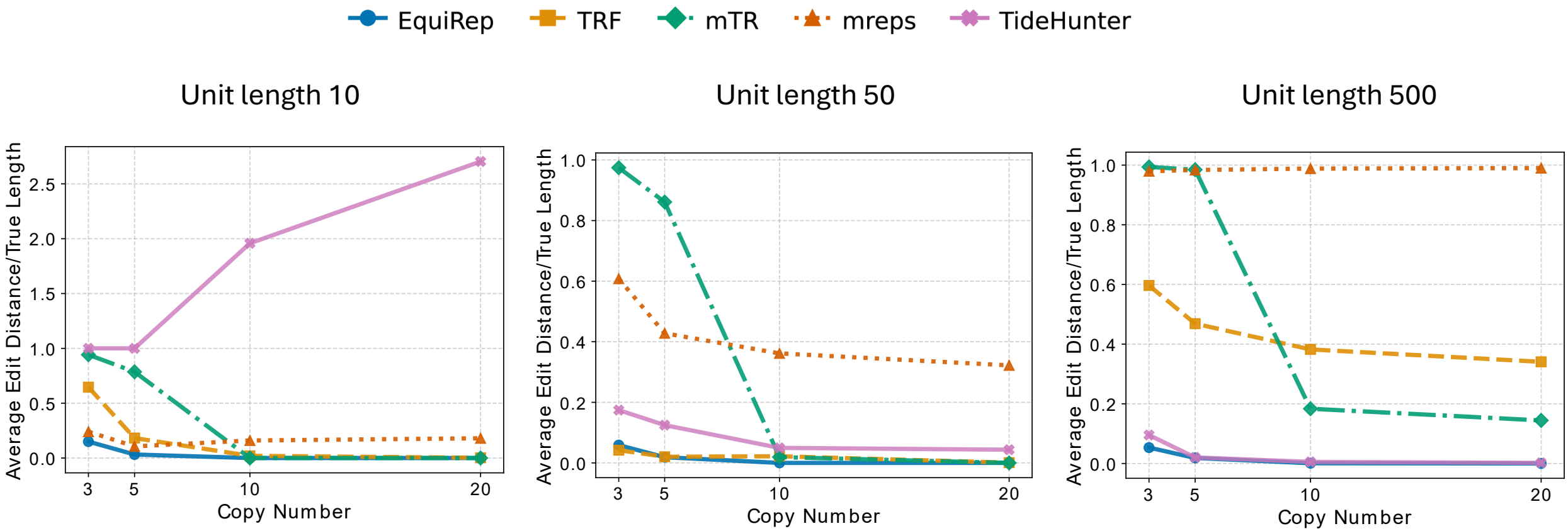
  - We divide the minimum distance by the true unit length for normalization.



Results on Simulations



Average normalized rotation-aware edit distance at 10% error rate

Experimental Setup: C. elegans Centromere

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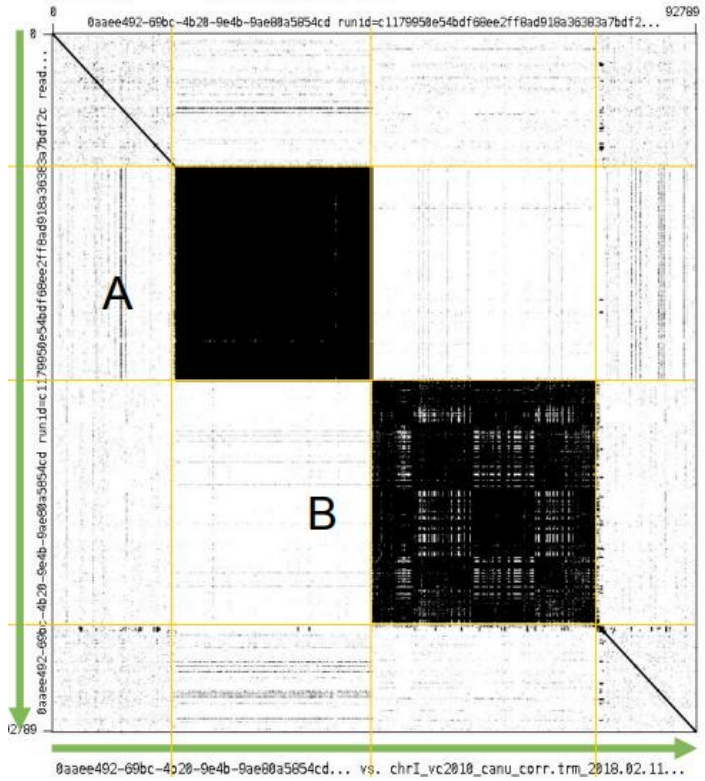

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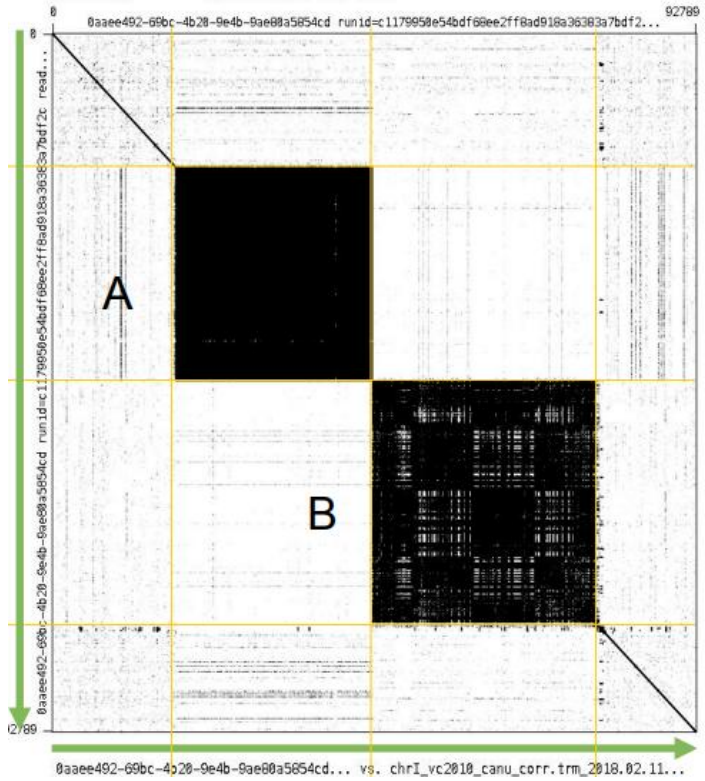

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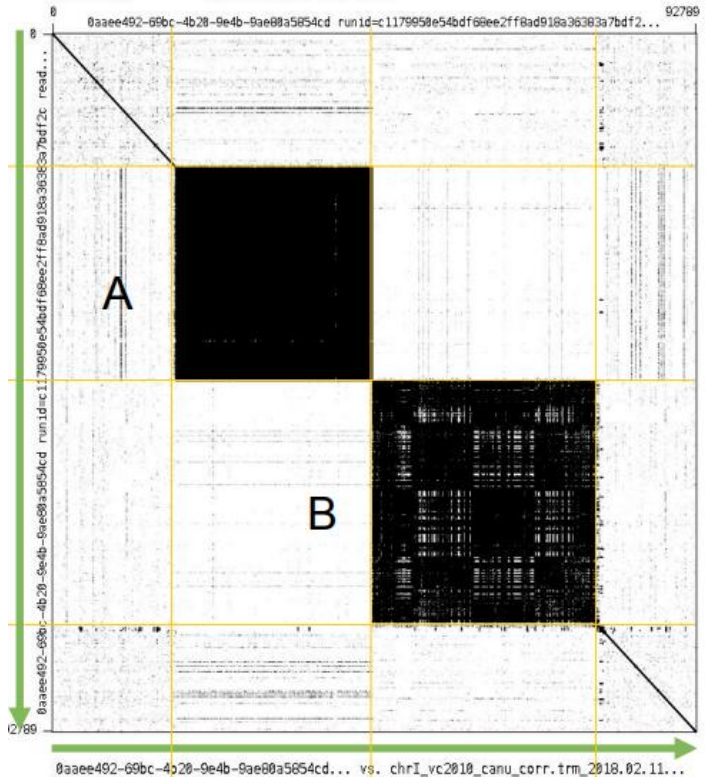

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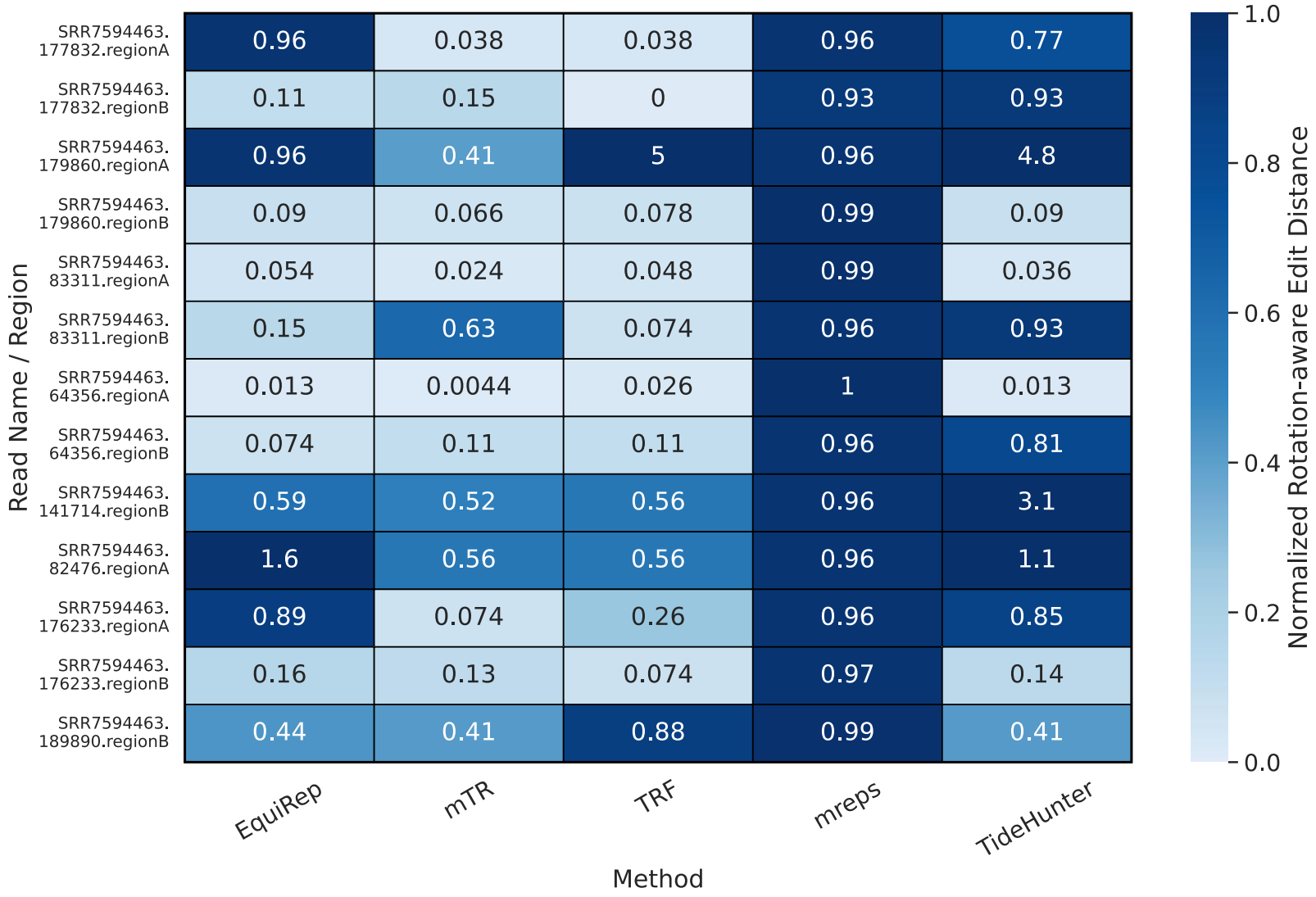
Results on C. elegans Centromere Data



Experimental Setup: RCA Human Tissue

- This set of real data is a Rolling Circle Amplification based Nanopore sequencing protocol from *Xin et al*.

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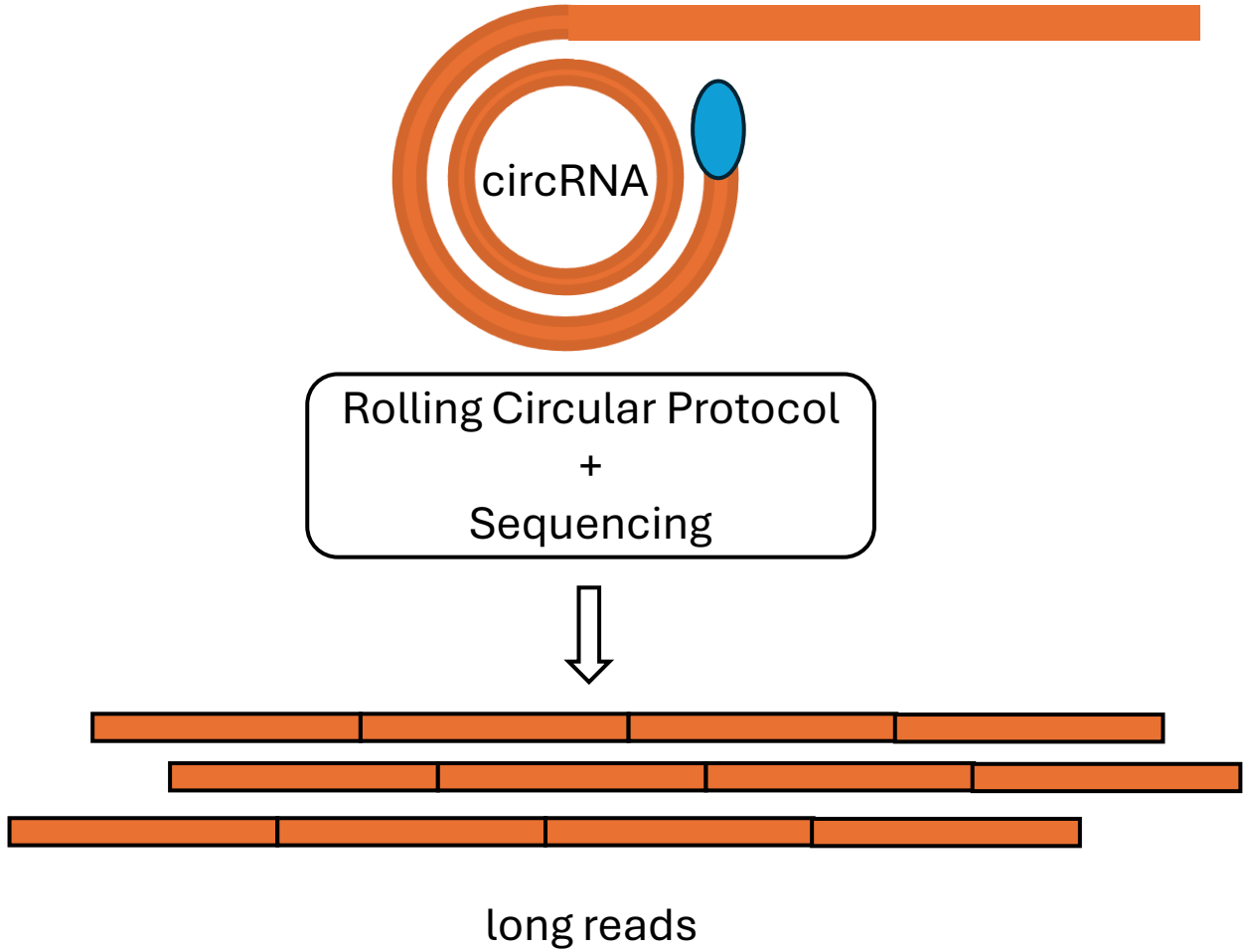

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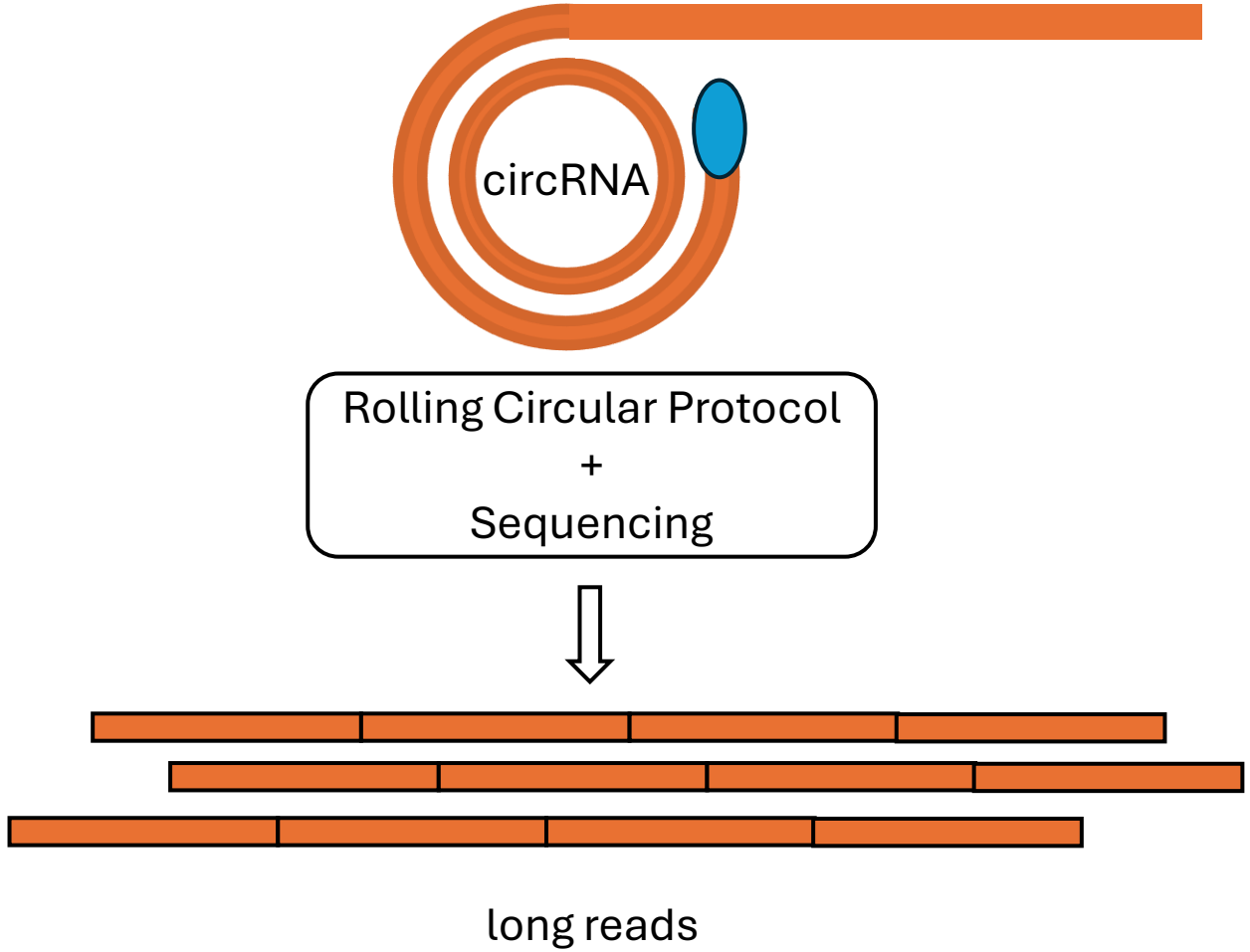

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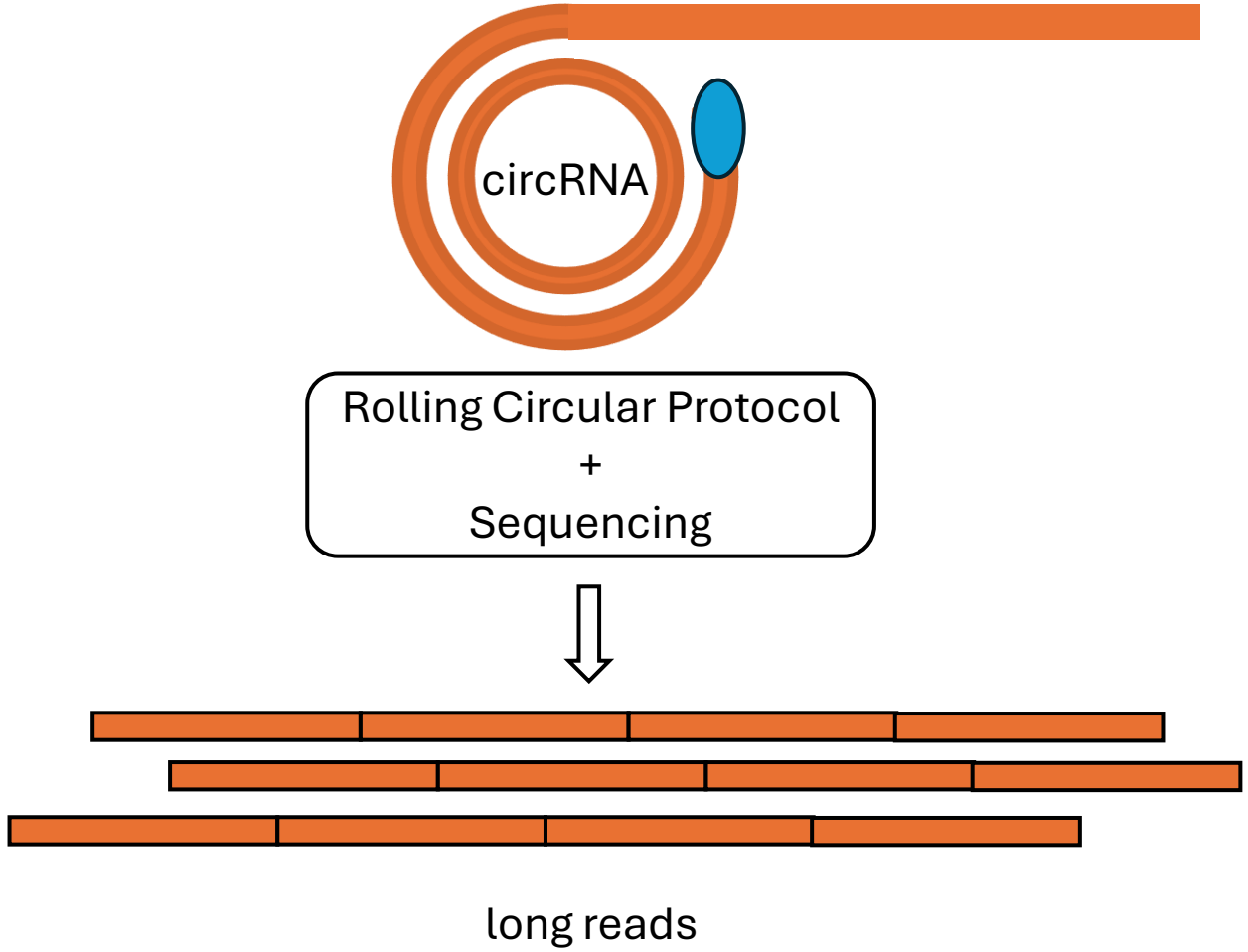

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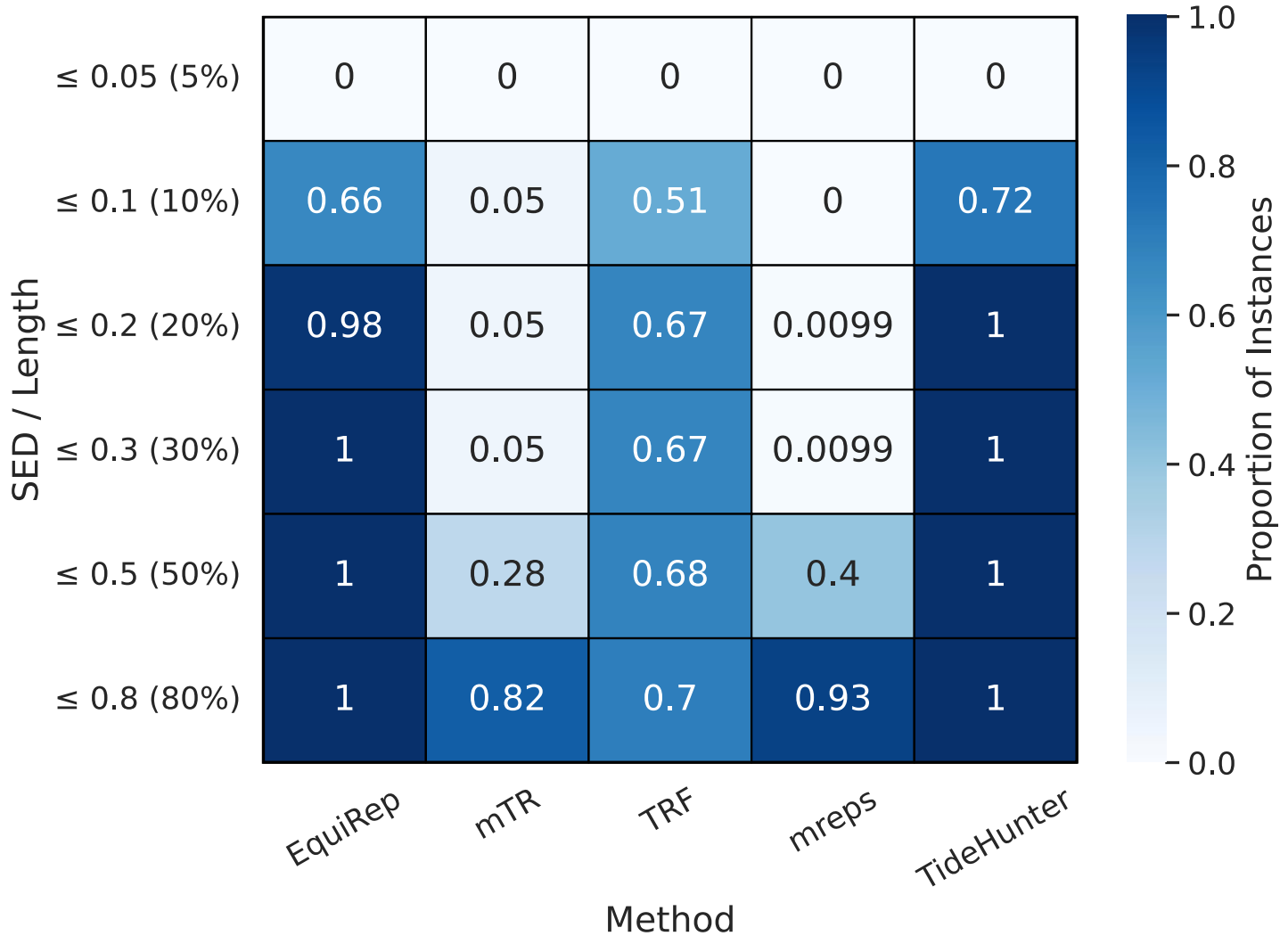
Results on RCA Data



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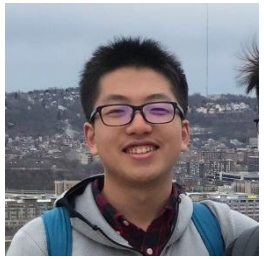
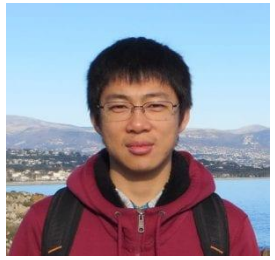
- Tool availability: https://github.com/Shao-Group/EquiRep.

Acknowledgements

- Co-authors


Zhezheng Song


Xiang Li


Mingfu Shao

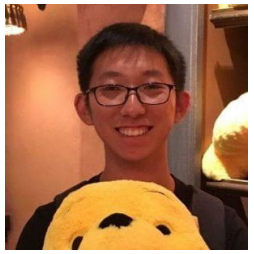
- Funding support

- Members of Shao Group


Ke Chen


Xin Yuan


Qian Shi


Carl Zang


Aaryan Mahesh


Ajmain Yasar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Abhishek Talesara