Hybrid correction of long reads with a variable-order de Bruijn graph

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Plan

Next Generation Sequencing

- In 2005, Next Generation Sequencing (NGS) technologies started to develop
- Production of millions of short sequences (100-300 bases), called reads, useful to resolve various problems
- These reads contain sequencing errors ($\sim 1\%$)
- $\Rightarrow$ Efficient algorithms are required to process these reads
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Third Generation Sequencing

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- Two main technologies: Pacific Biosciences and Oxford Nanopore
- Allow the sequencing of longer reads (several thousand of bases)
- Very useful to resolve assembly problems for large and complex genomes
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- Various methods already exist for the correction of short reads, but are not applicable to long reads
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We developed a new hybrid method, HG-CoLoR, that:

- Combines different approaches from the state-of-the-art:
  - Short reads alignment
  - Use of a short reads de Bruijn graph
- Follows a seed-and-extend approach:
  1. Align the short reads to the long reads $\Rightarrow$ find seeds
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de Bruijn graph

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- de Bruijn graphs are widely used for assembly and correction...
- ...But face difficulties:
  - Large $k \Rightarrow$ Missing edges in insufficiently covered regions
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Solutions

- Build multiple de Bruijn graphs of different orders
- Requires a different graph for each order
- Consumes large amounts of time and memory

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Represent all the de Bruijn graphs, up to a maximum order K, in a single data structure

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Theoretical methods, or unsatisfying implementations

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Our representation

- Relies on PgSA [Kowalski et al., 2015]
- The K-mers from the reads are stored in the index
- The index is queried in order to retrieve the edges

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PgSA [Kowalski et al., 2015] is a data structure that allows the indexing of a set of reads, in order to answer the following queries on the reads, for a given string f:

1. In which reads does f occur?
2. In how many reads does f occur?
3. What are the occurrences positions of f?
4. What is the number of occurrences of f?
5. In which reads does f occur only once?
6. In how many reads does f occur only once?
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Index construction

- Concatenation of all the reads ⇒ Pseudogenome (Pg)
- Construction of the sparse Suffix Array (SA) of the obtained pseudogenome
- Construction of an auxiliary array

Queries

Queries are handled by a binary search over the suffix array, and with the help of the auxiliary array

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Our representation

- Define a maximum order K
- Extract the K-mers of the reads
- Build the PgSA index of the K-mers
- Query the index, looping over the third query (what are the occurrences positions of f?), to retrieve the edges

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Example

Let $S = \{\text{AGCTTACA}, \text{CTTACGTA}\}$

To build the variable-order de Bruijn graph of maximum order $K = 6$, we index the 6-mers of the reads:

K-mers set
1: AGCTTA
2: CTTACA
3: CTTACG
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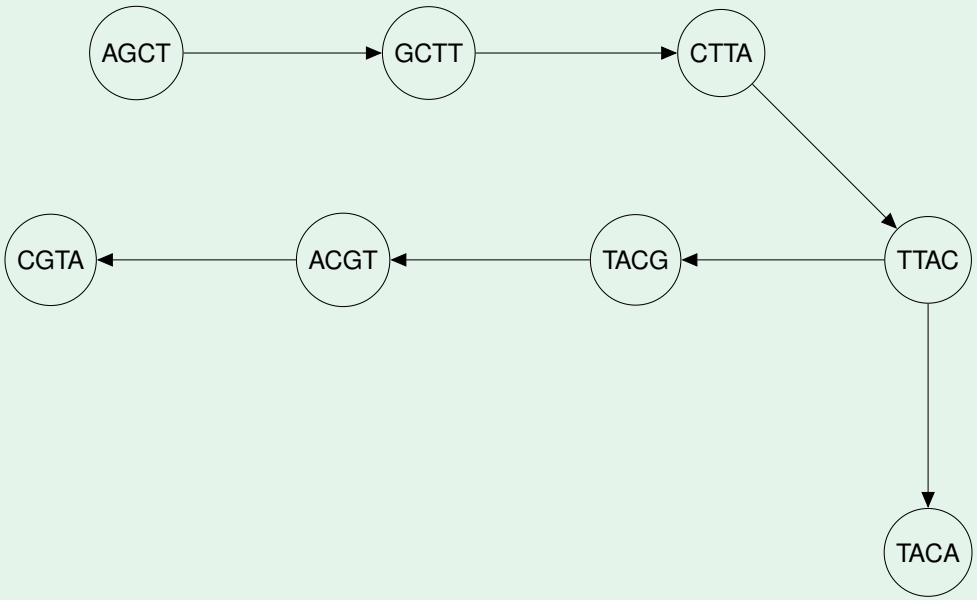

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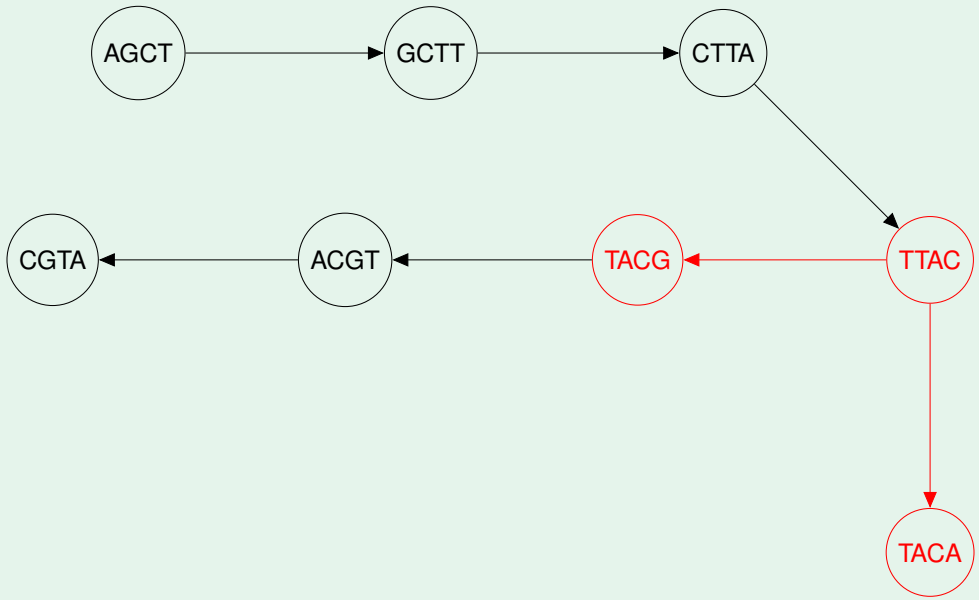

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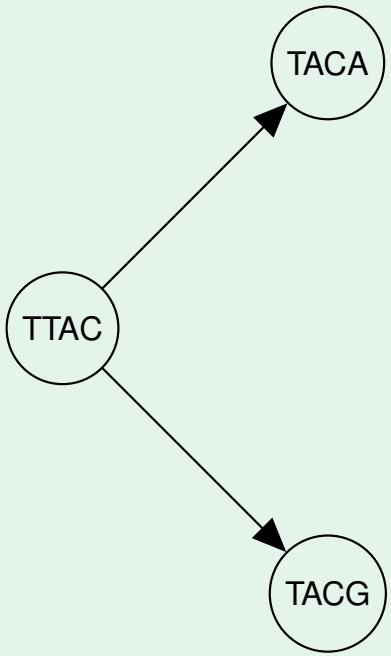

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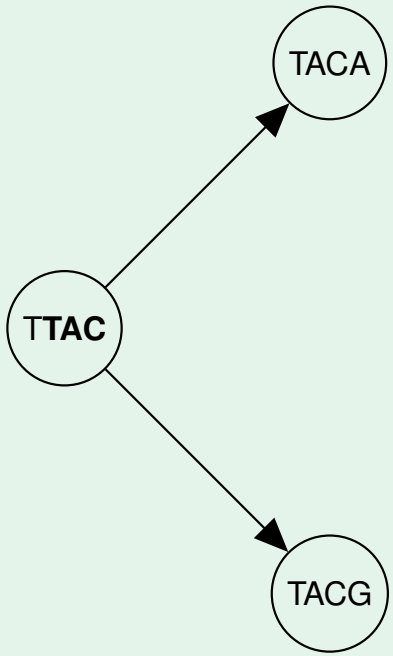

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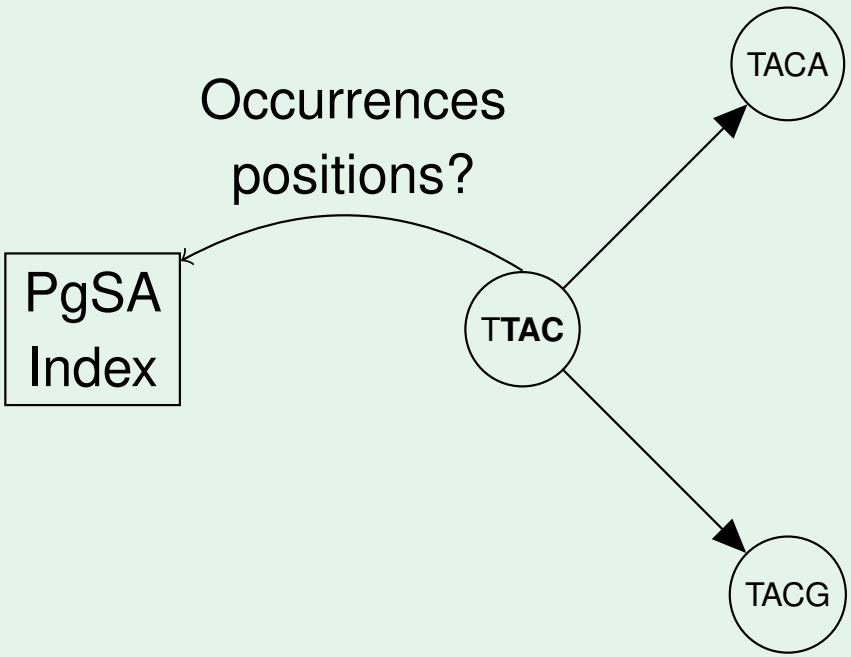

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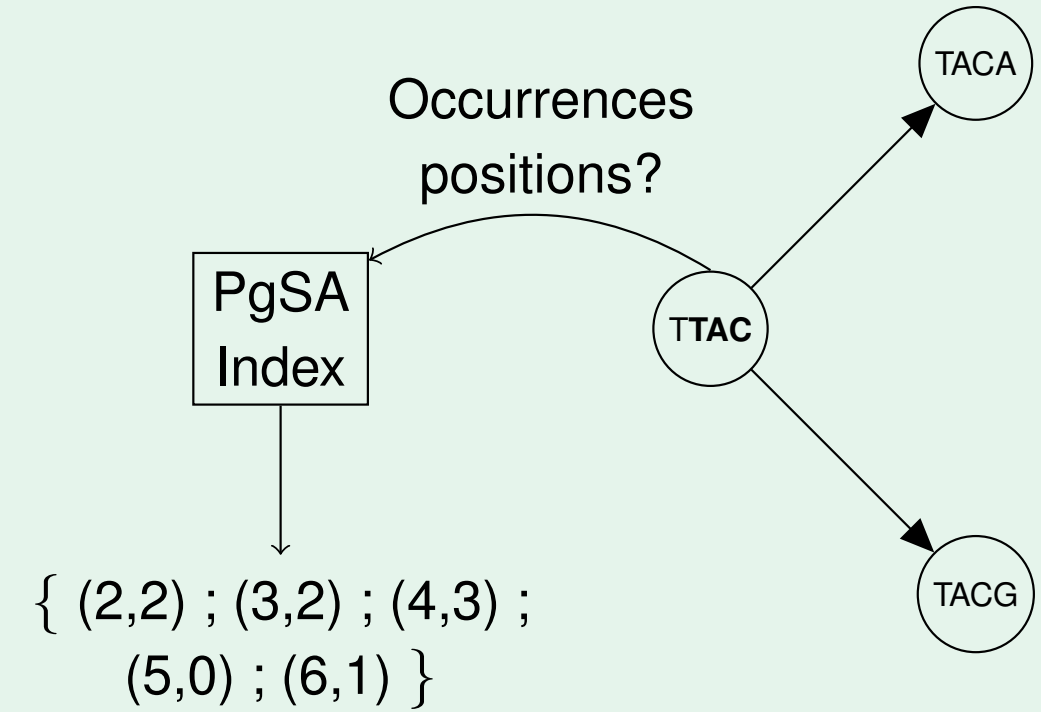

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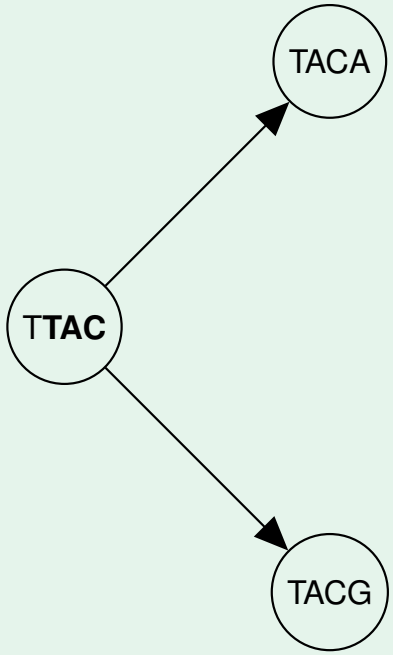

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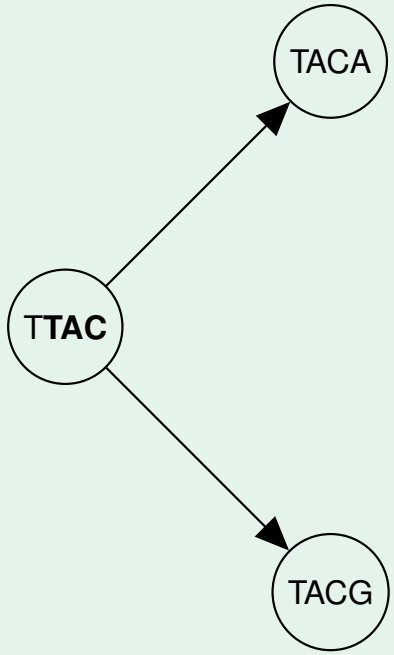

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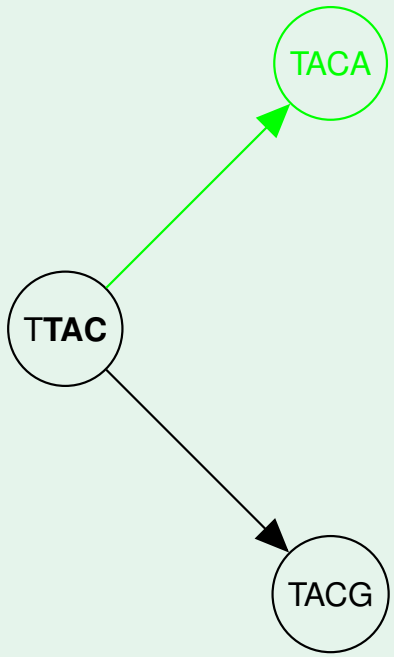

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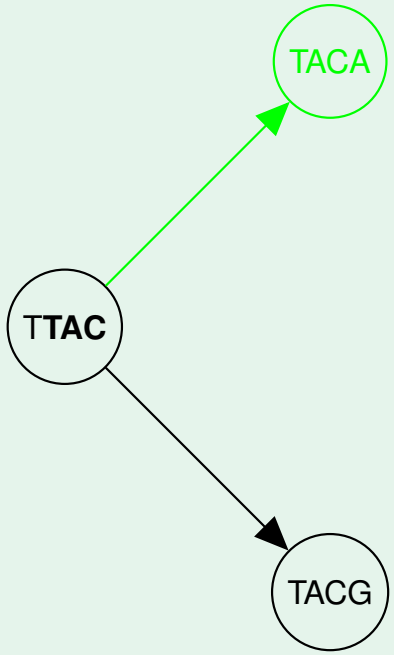

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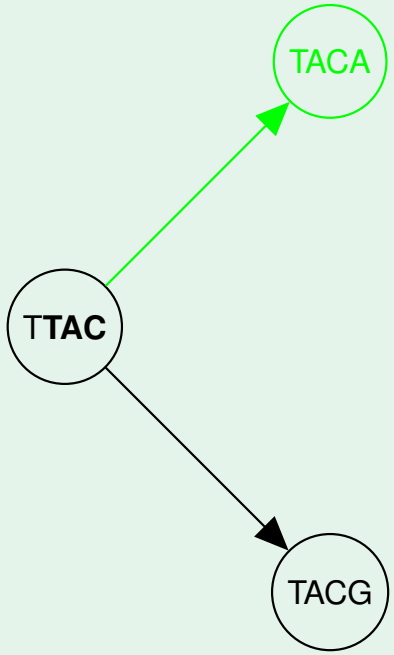

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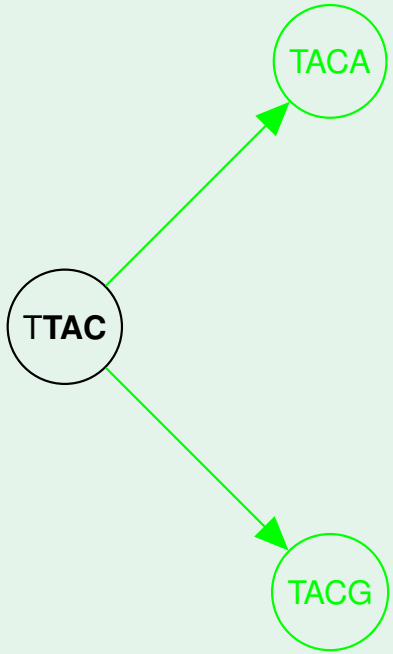

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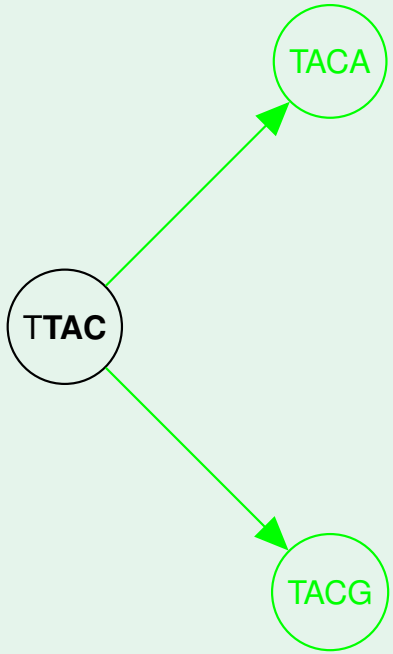

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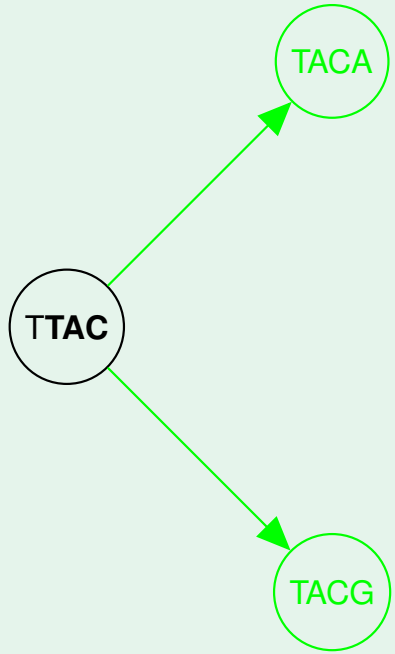

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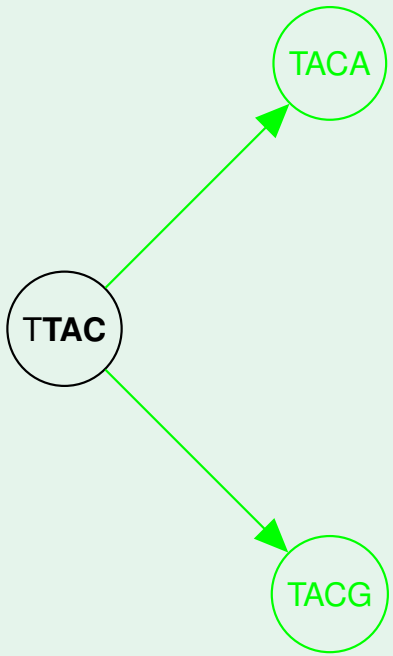

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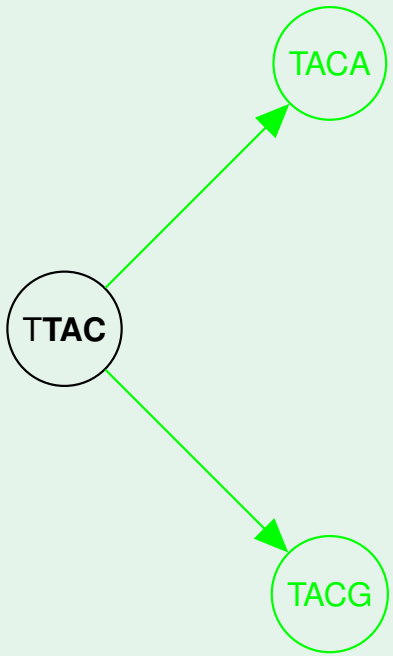

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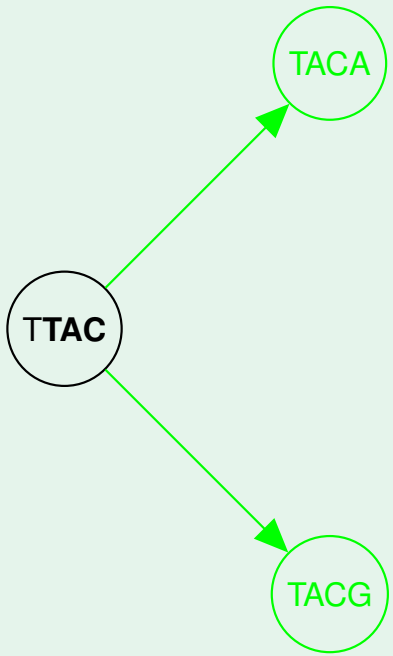
Example

k-mers set

1: AGCTTA
2: CTTACA
3: CTTACG
4: GCTTAC
5: **TAC**G**T**A
6: TTACGT

PgSA Index

{ (2,2) ; (3,2) ; (4,3) ;
(5,0) ; (6,1) }



Our representation

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k-mers set

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4: GCTTAC
5: TACGTA
6: T**TAC**GT

PgSA Index

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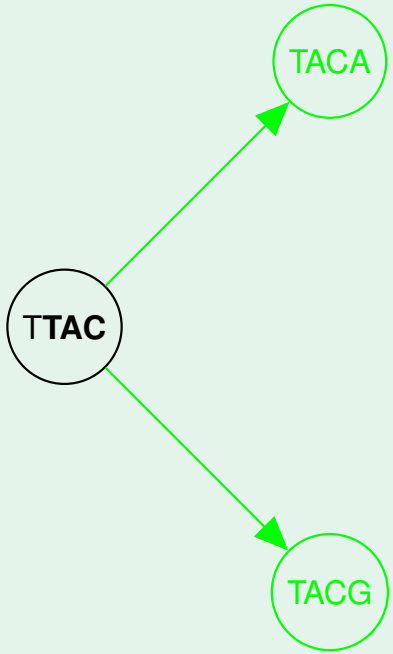
(5,0) ; **(6,1)** }



Our representation

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6: T**TACG**T

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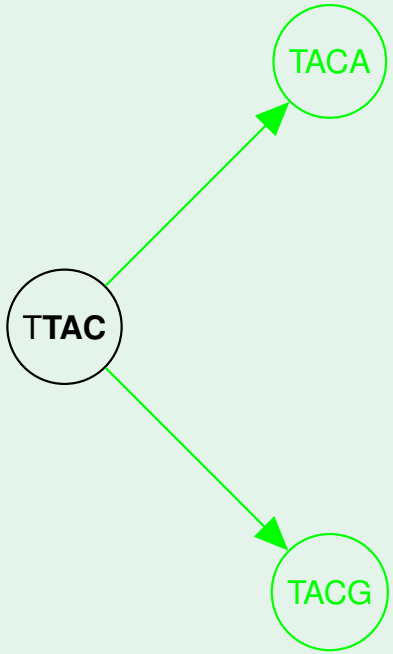

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PgSA Index

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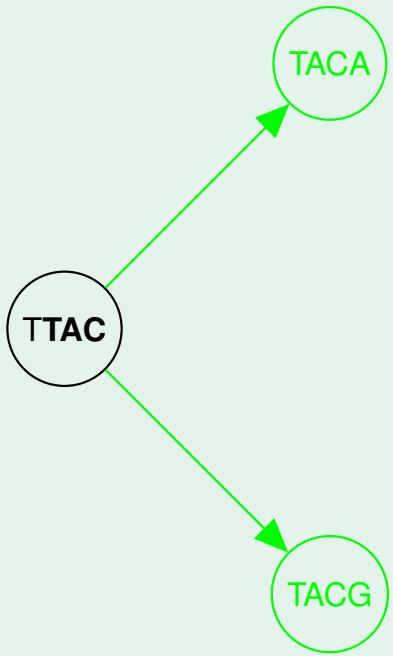

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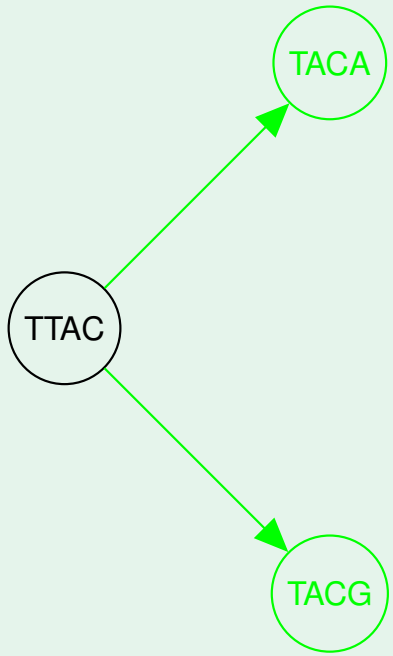

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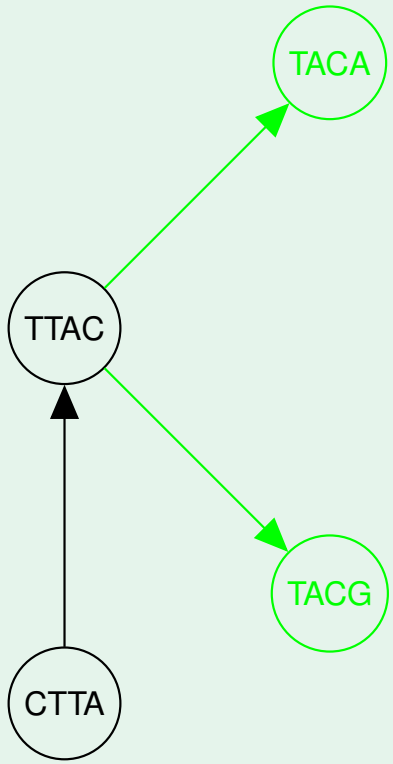
Index



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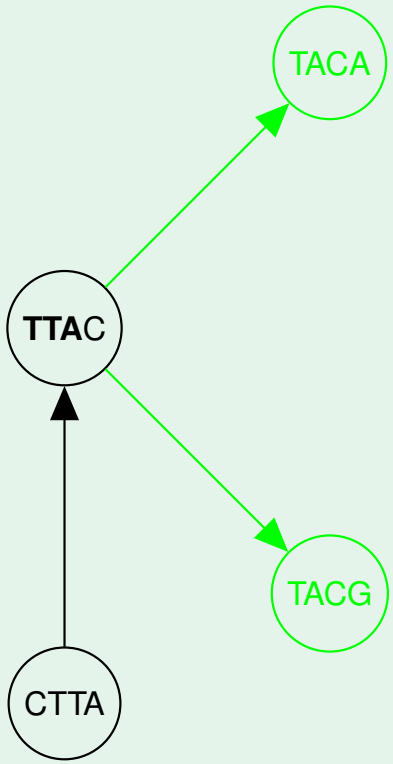

Our representation

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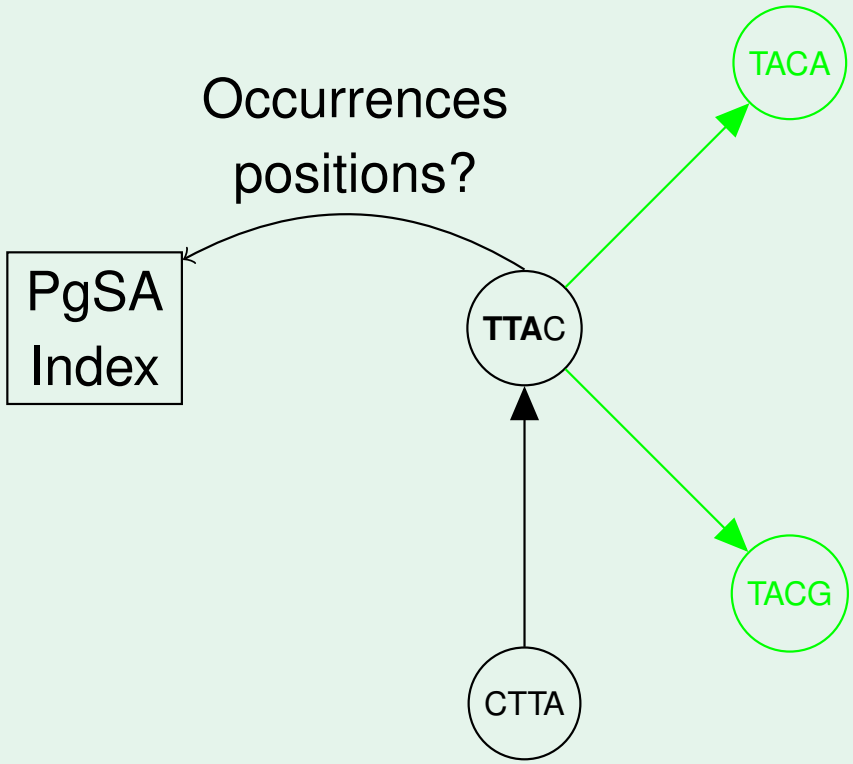

Our representation

Example

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1: AGCTTA
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3: CTTACG
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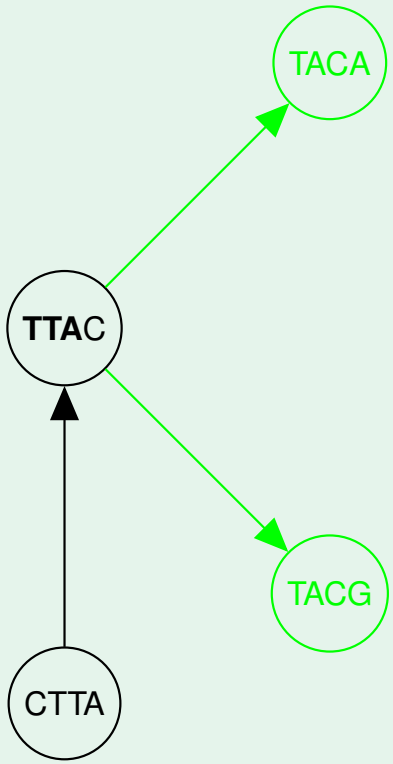
6: TTACGT

PgSA Index

{ (1,3) ; (2,1) ; (3,1) ; (4,2) ; (6,0) }



Our representation

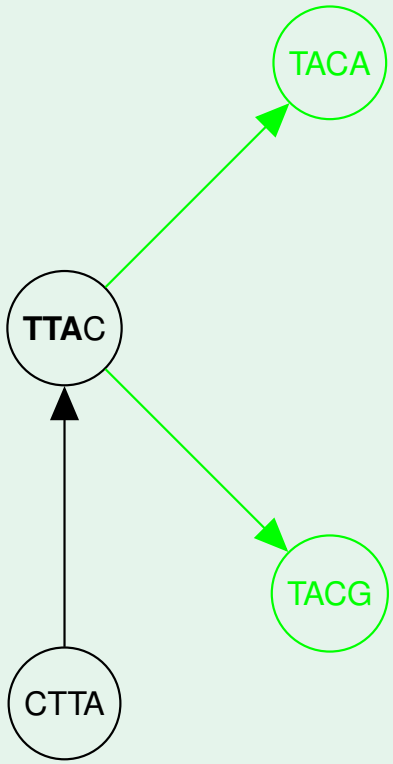
Example

k-mers set

1: AGC**TTA**
2: CTTACA
3: CTTACG
4: GCTTAC
5: TACGTA
6: TTACGT

PgSA Index

{ **(1,3)** ; (2,1) ; (3,1) ; (4,2) ; (6,0) }



Our representation

Example

k-mers set

1: AG**CTTA**
2: CTTACA
3: CTTACG
4: GCTTAC
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PgSA Index

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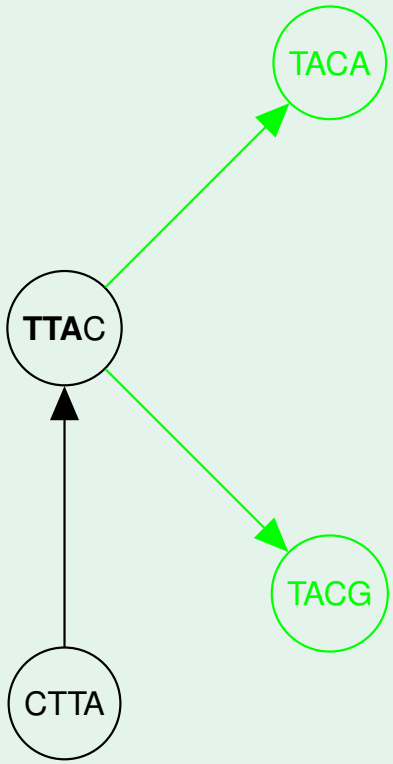

Our representation

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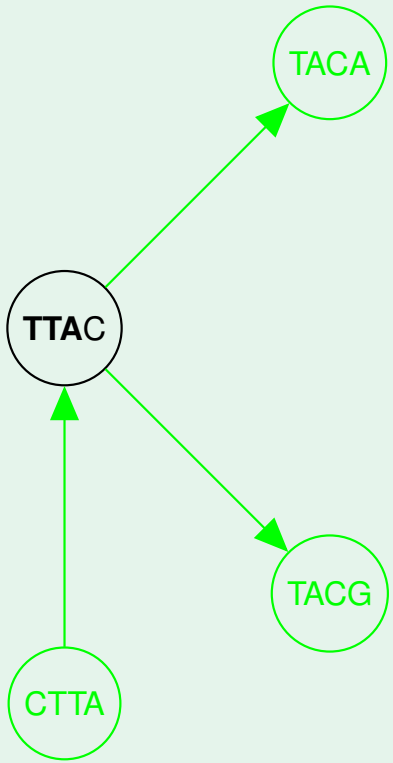

Our representation

Example

k-mers set

1: AGCTTA
2: C**TTA**CA
3: CTTACG
4: GCTTAC
5: TACGTA
6: TTACGT

PgSA
Index

{ (1,3) ; **(2,1)** ; (3,1) ;
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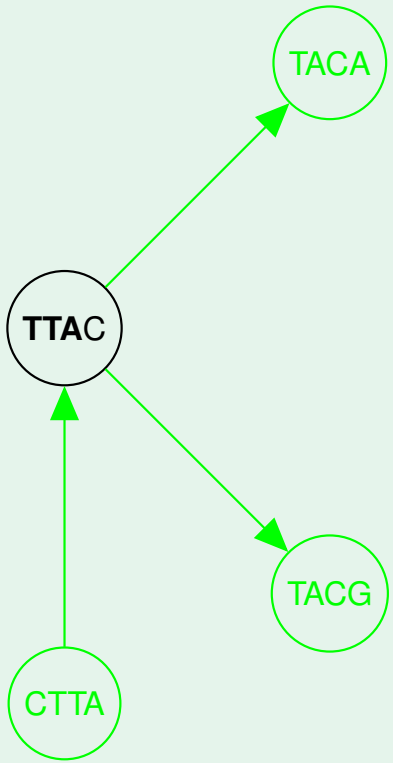

Our representation

Example

k-mers set

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4: GCTTAC
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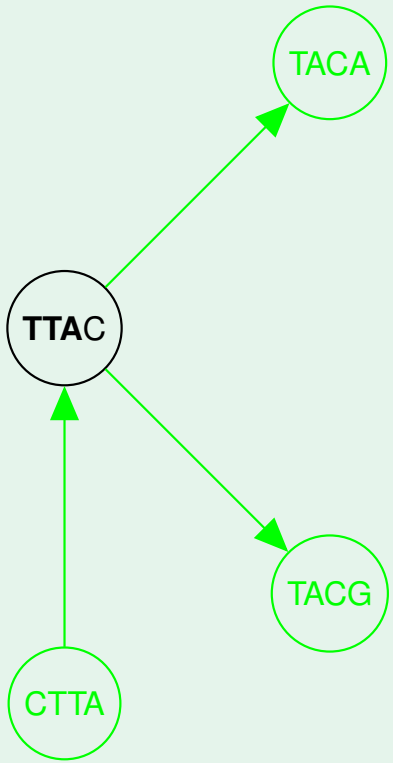
PgSA Index

{ (1,3) ; **(2,1)** ; (3,1) ; (4,2) ; (6,0) }



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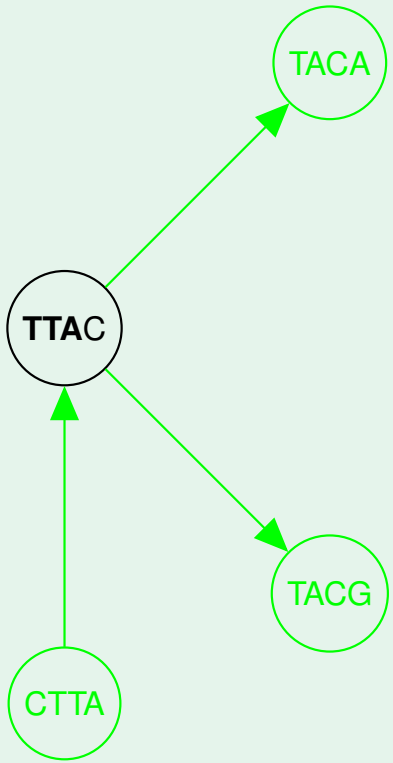

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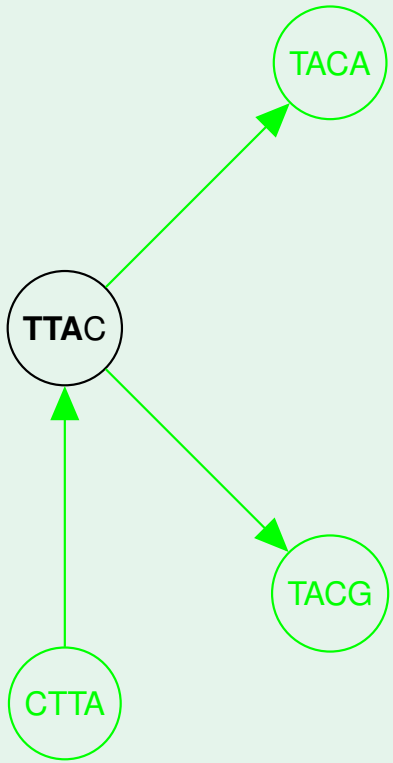

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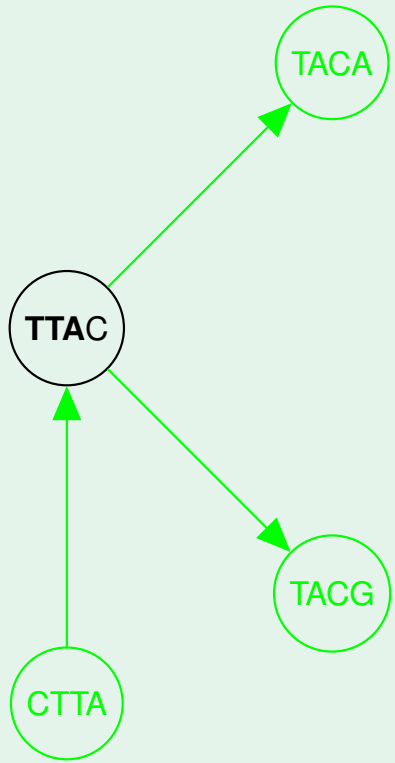

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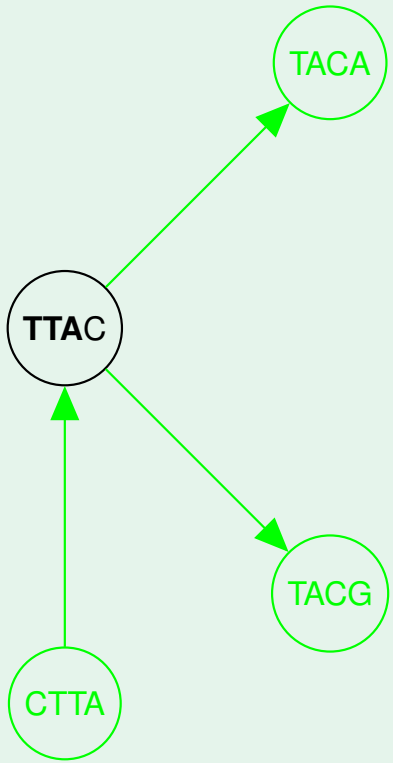

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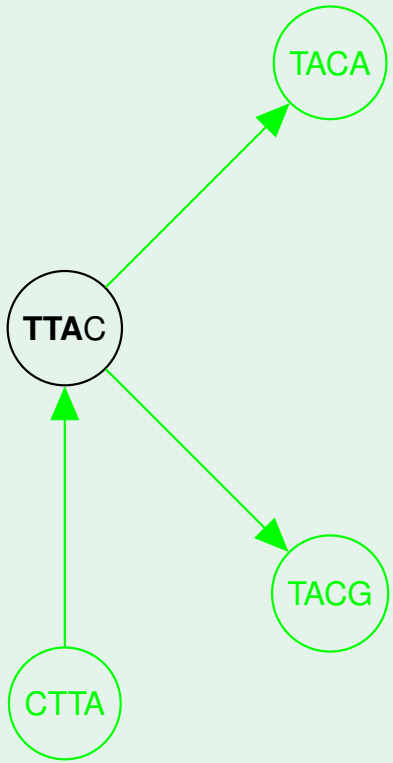

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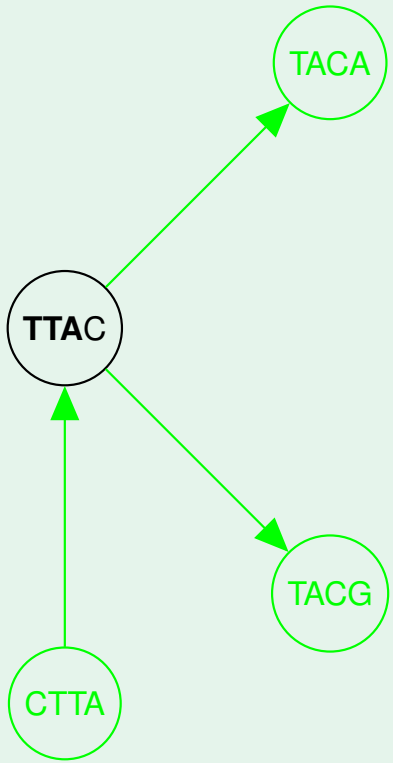

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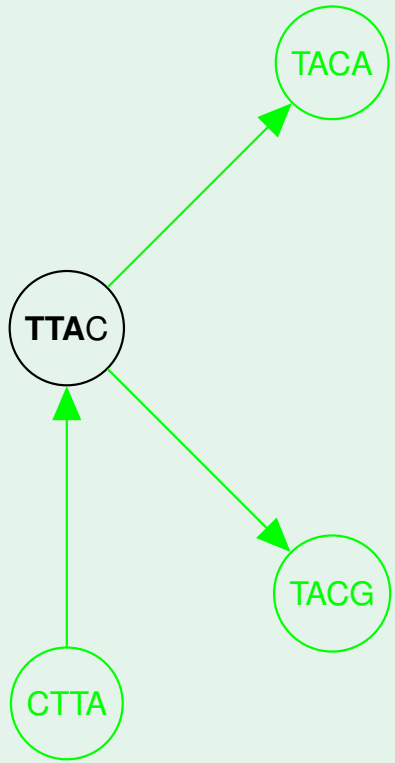

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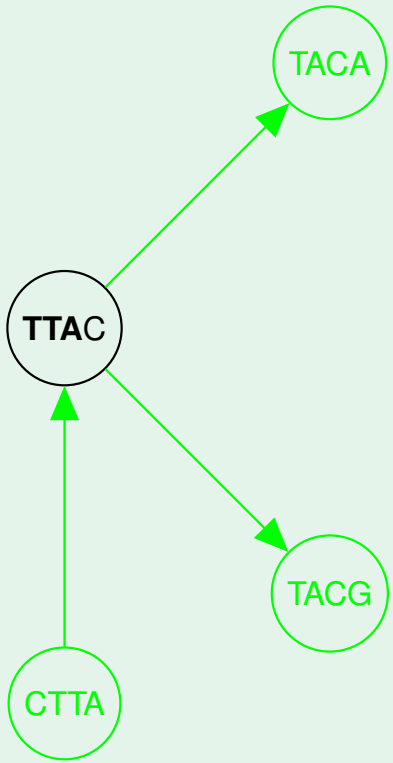

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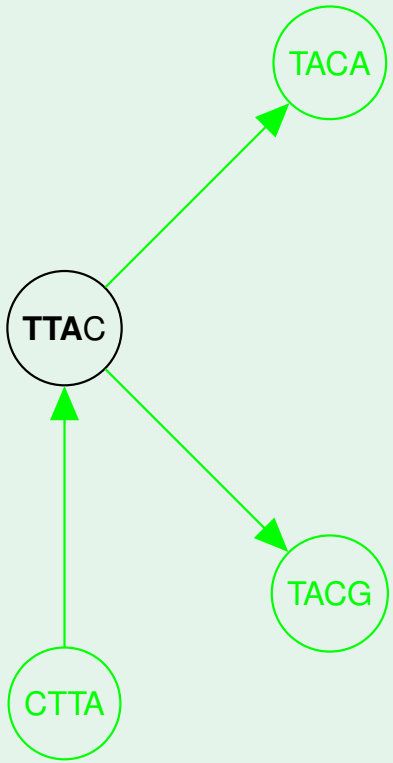

Workflow

5 steps:

1. Correct the short reads (with QuorUM [Marçais et al., 2015])
2. Filter out corrected short reads containing weak K-mers, and index solid K-mers with PgSA
3. Align the remaining short reads to the long reads, to find seeds (with BLASR [Chaisson and Tesler, 2012])
4. Merge the overlapping seeds, and link them together, by traversing the graph
5. Extend the obtained corrected long read, on the left (resp. right) of the leftmost (resp. rightmost) seed

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- Process the seeds with overlapping mapping positions:
  - Perfect overlap: merge
  - Otherwise: keep the best seed
- Seeds are used as anchor points on the graph
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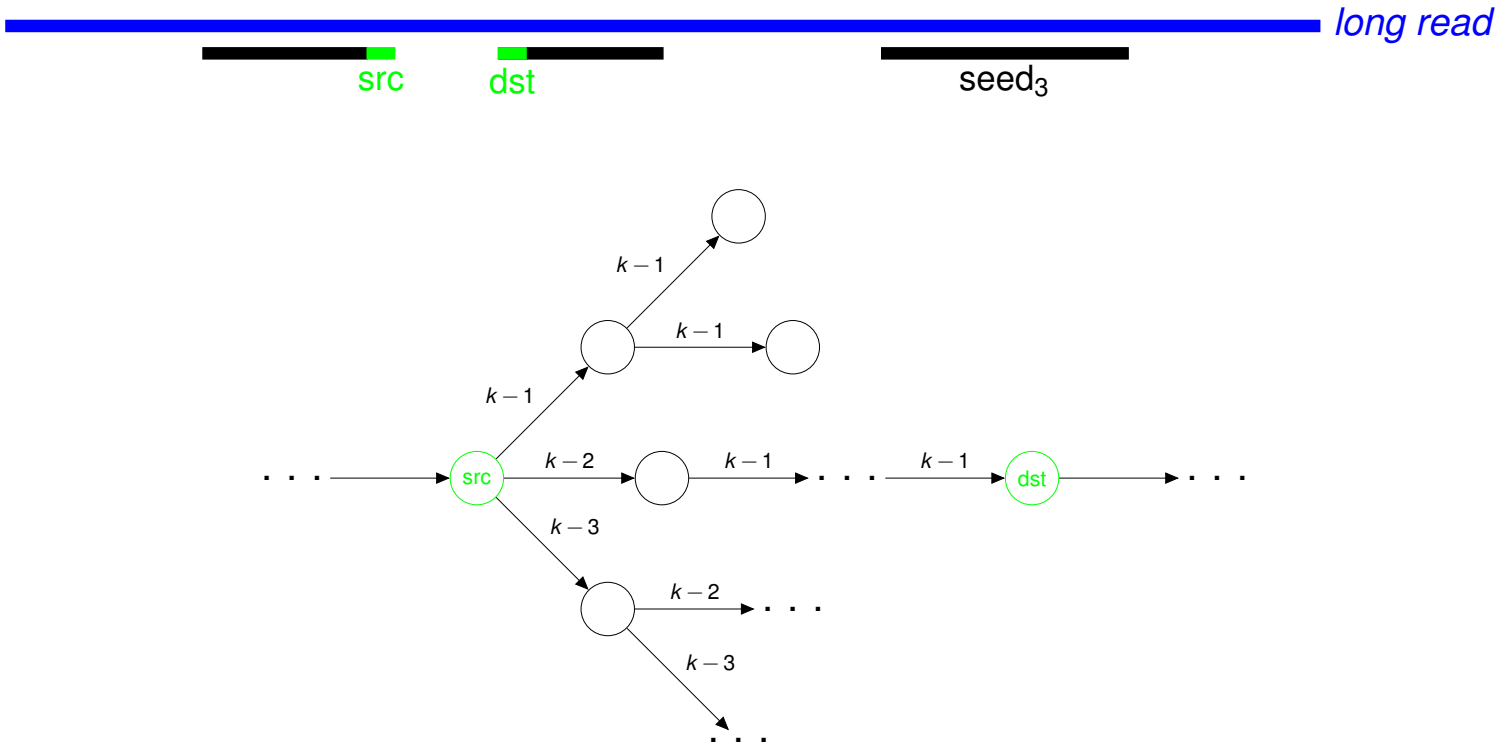

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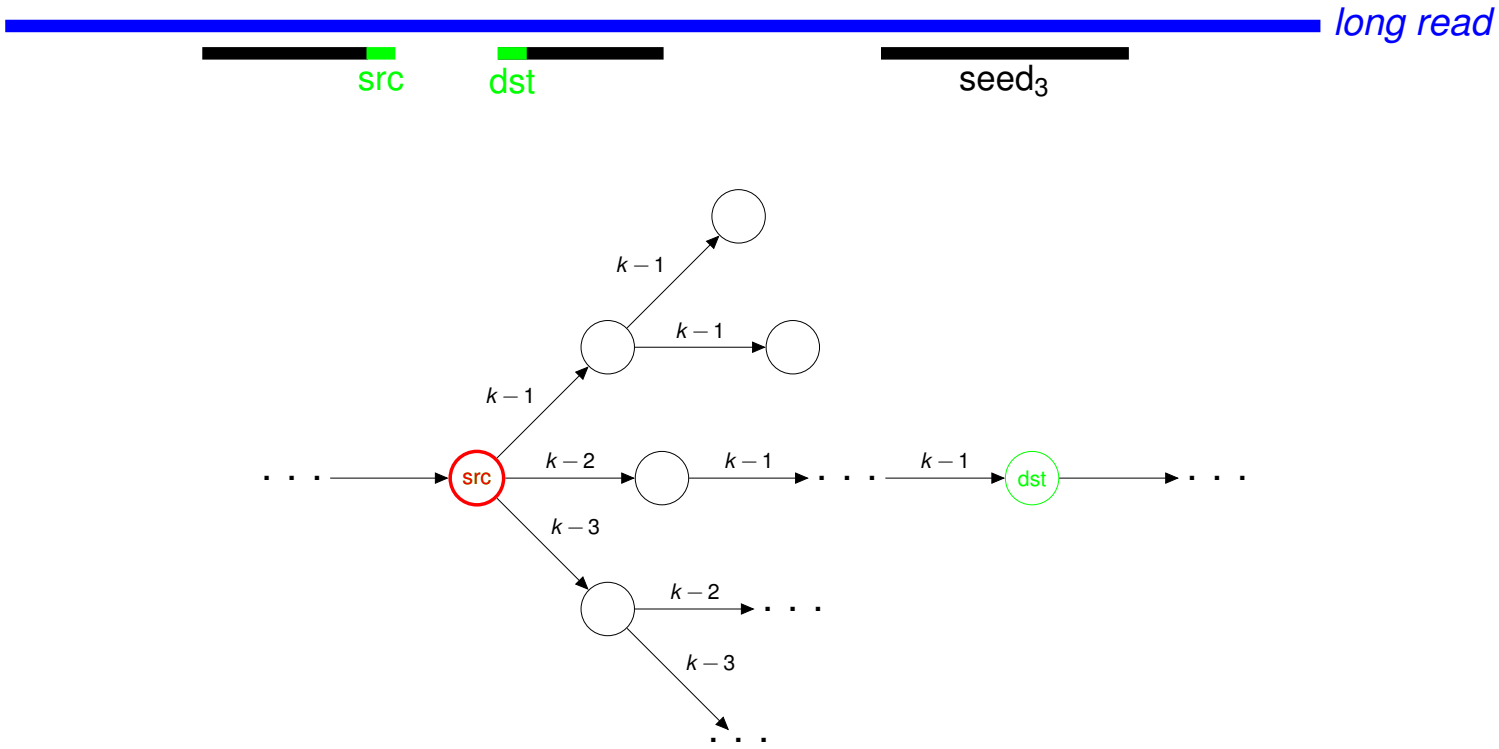

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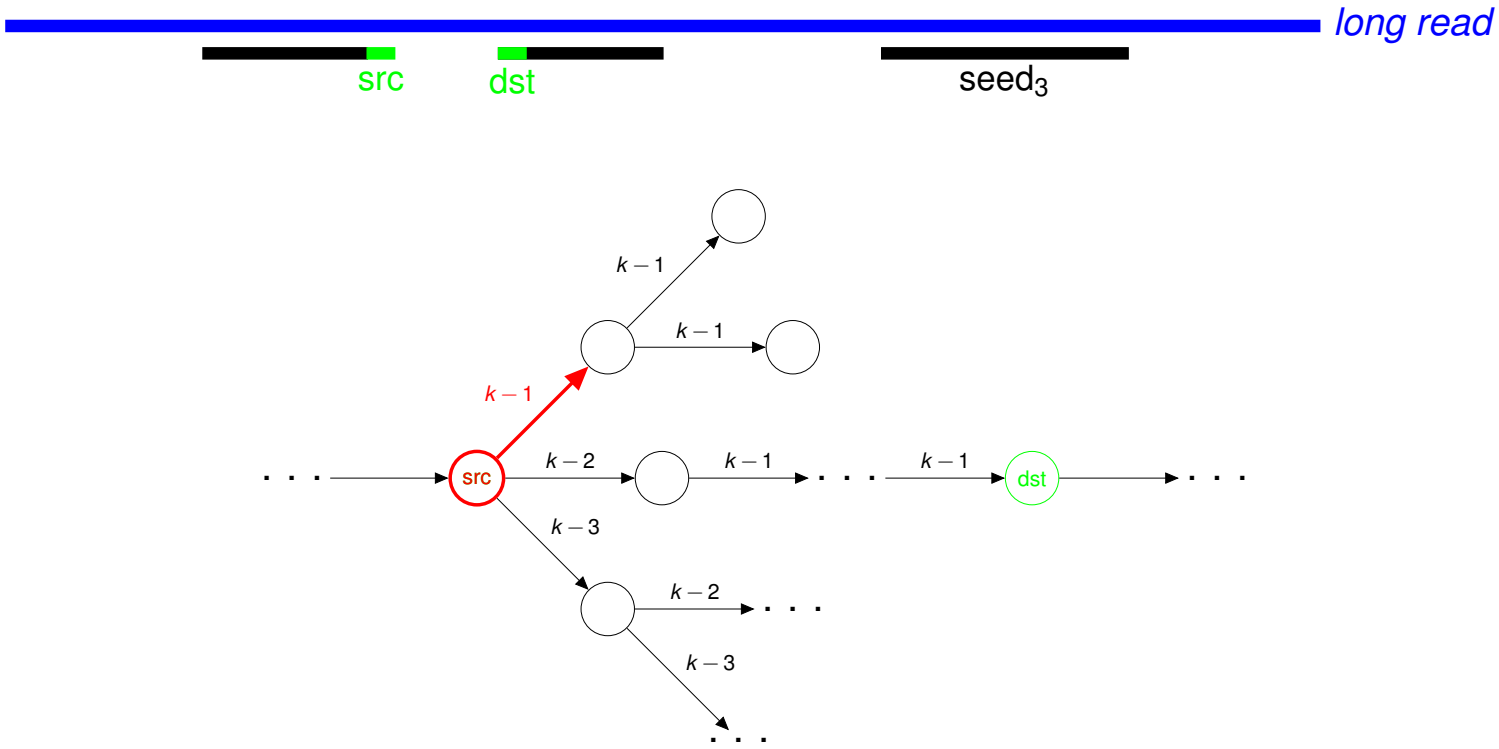

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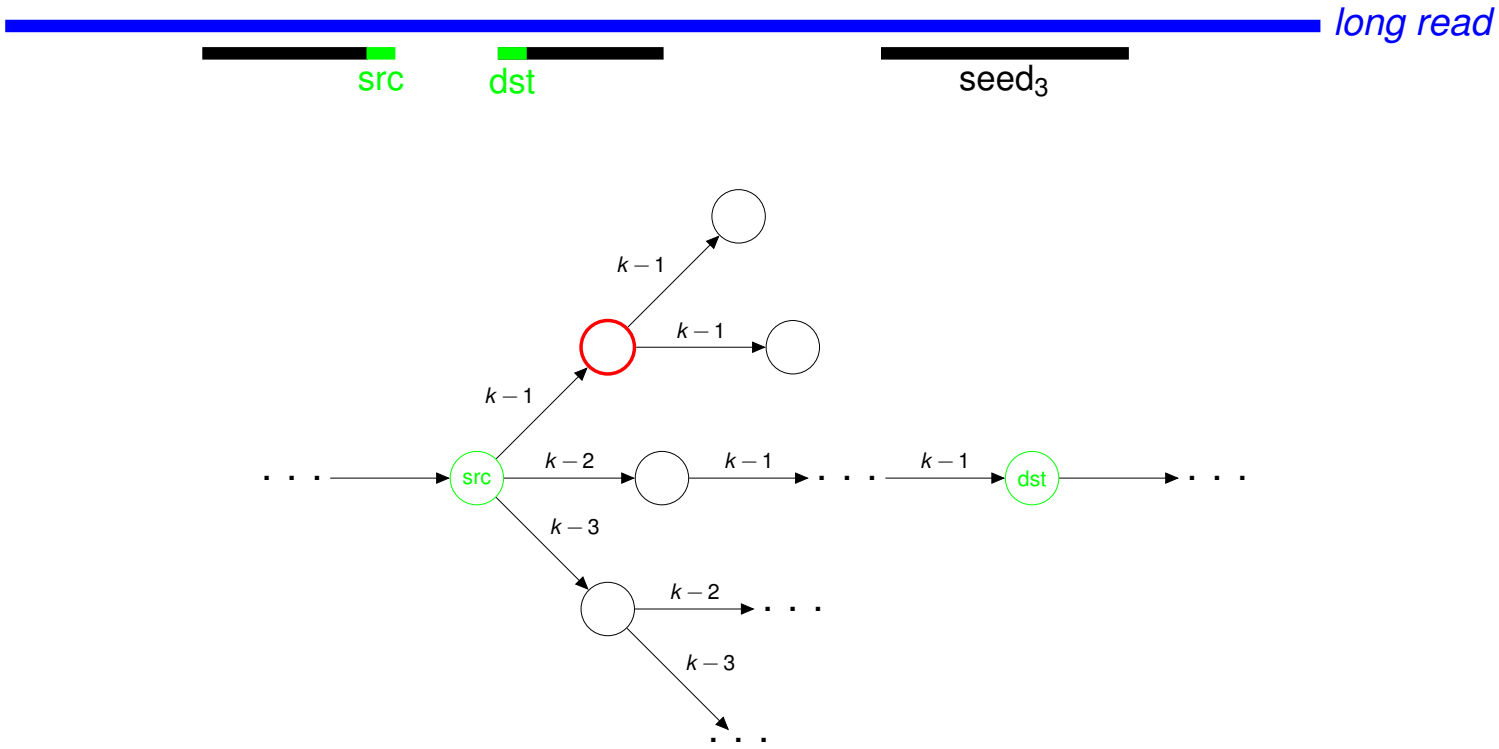

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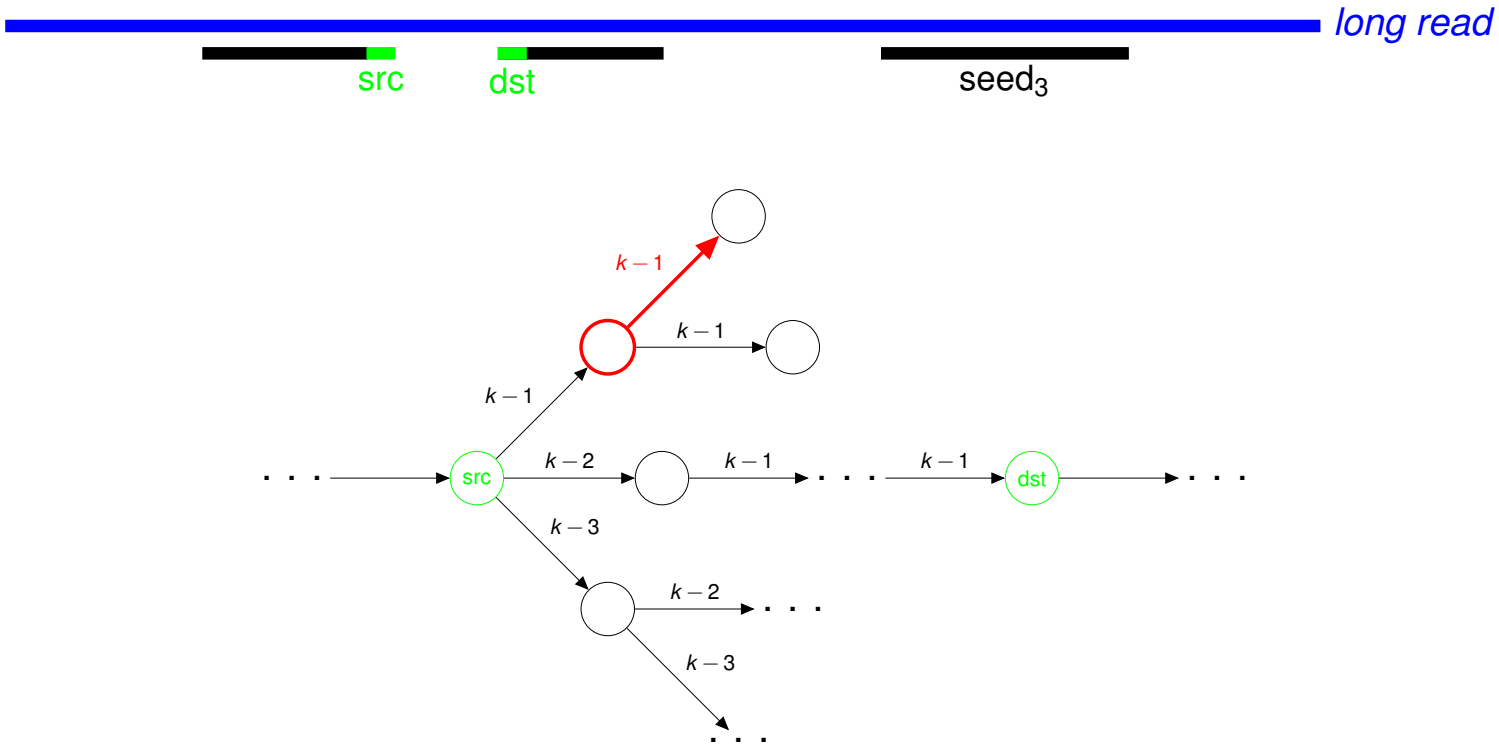

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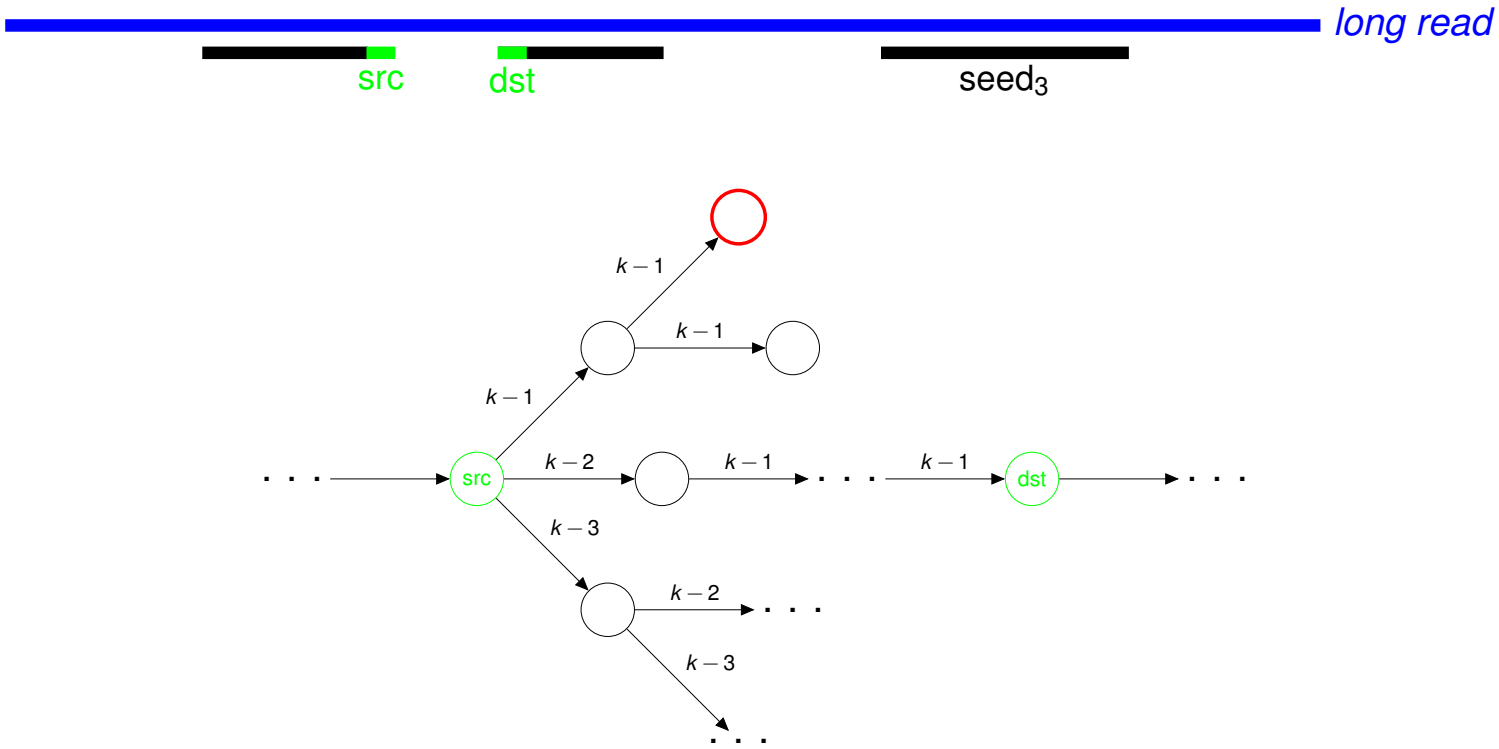

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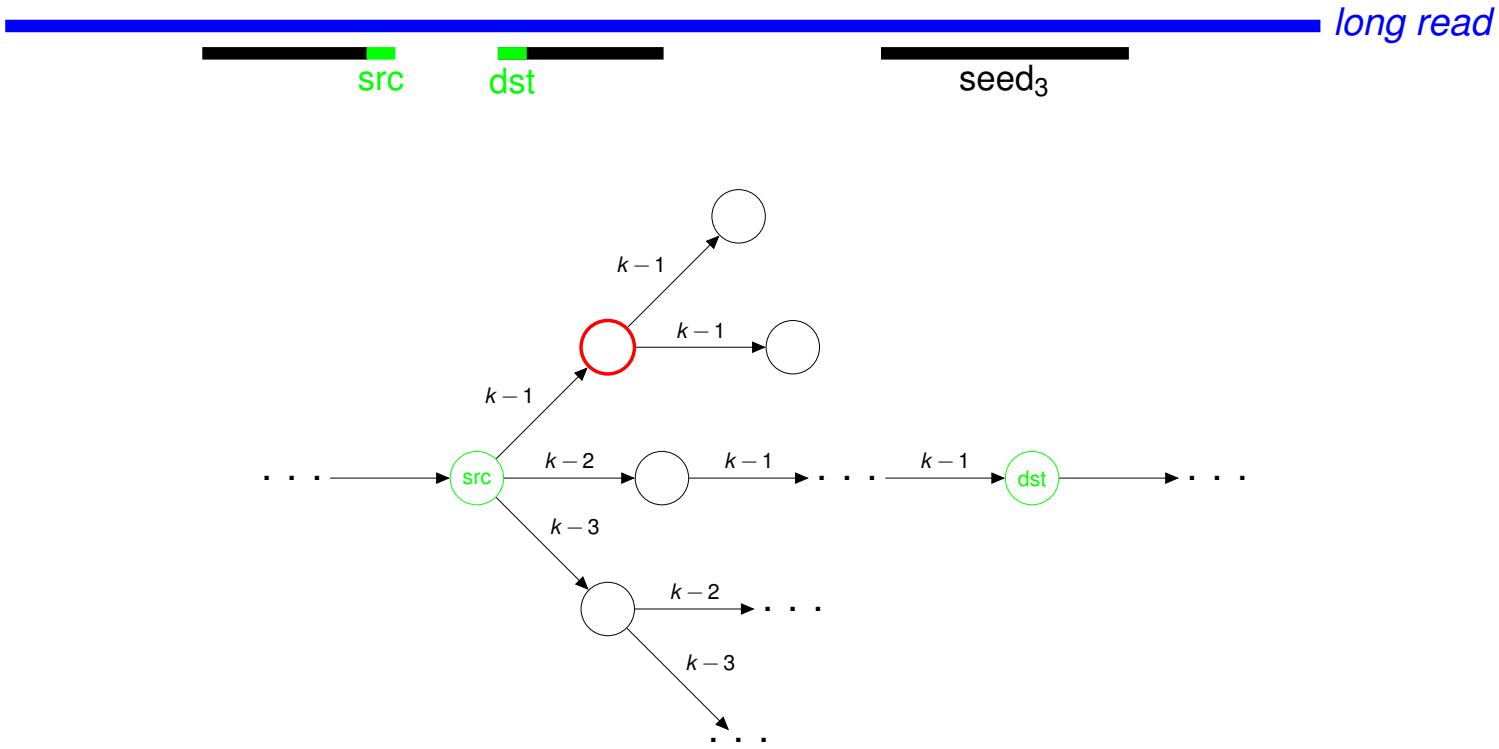

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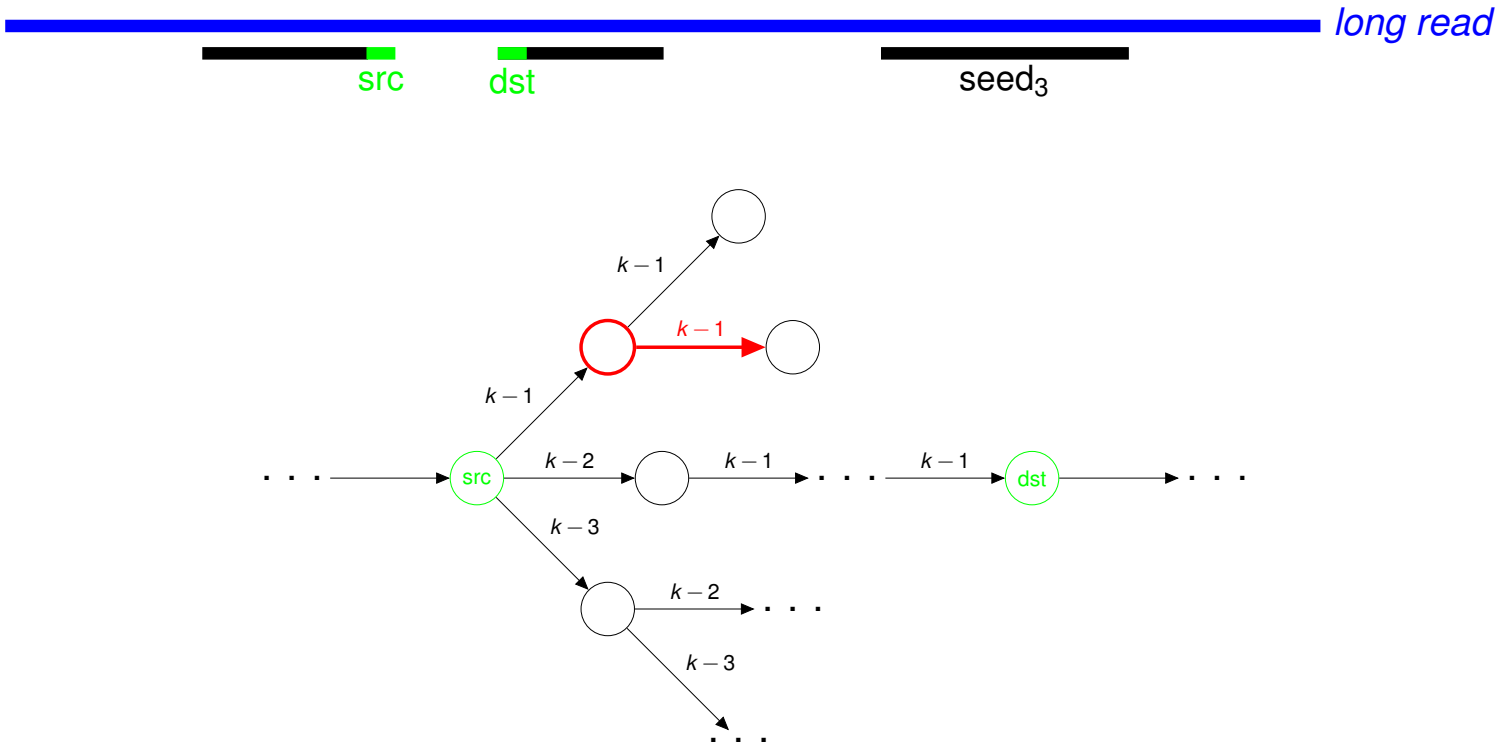

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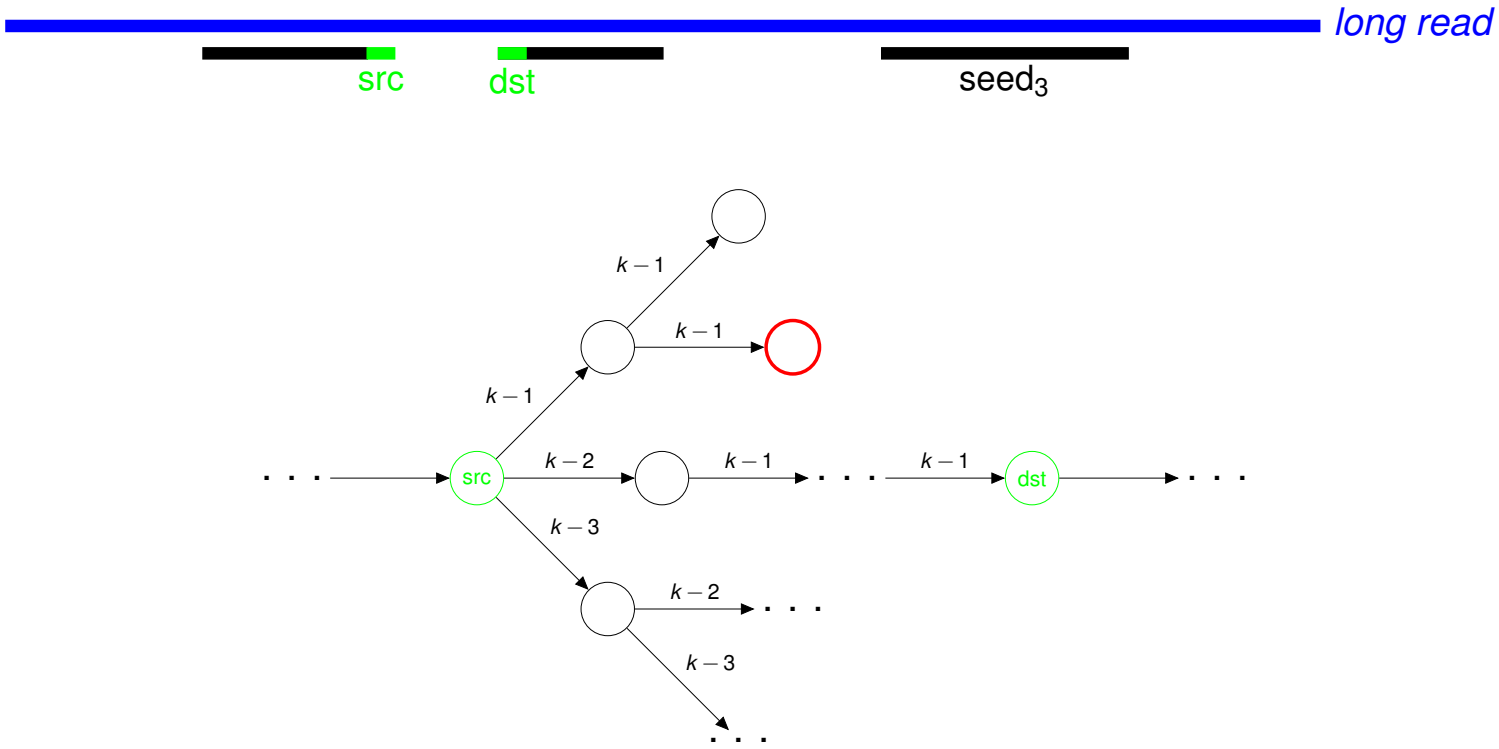

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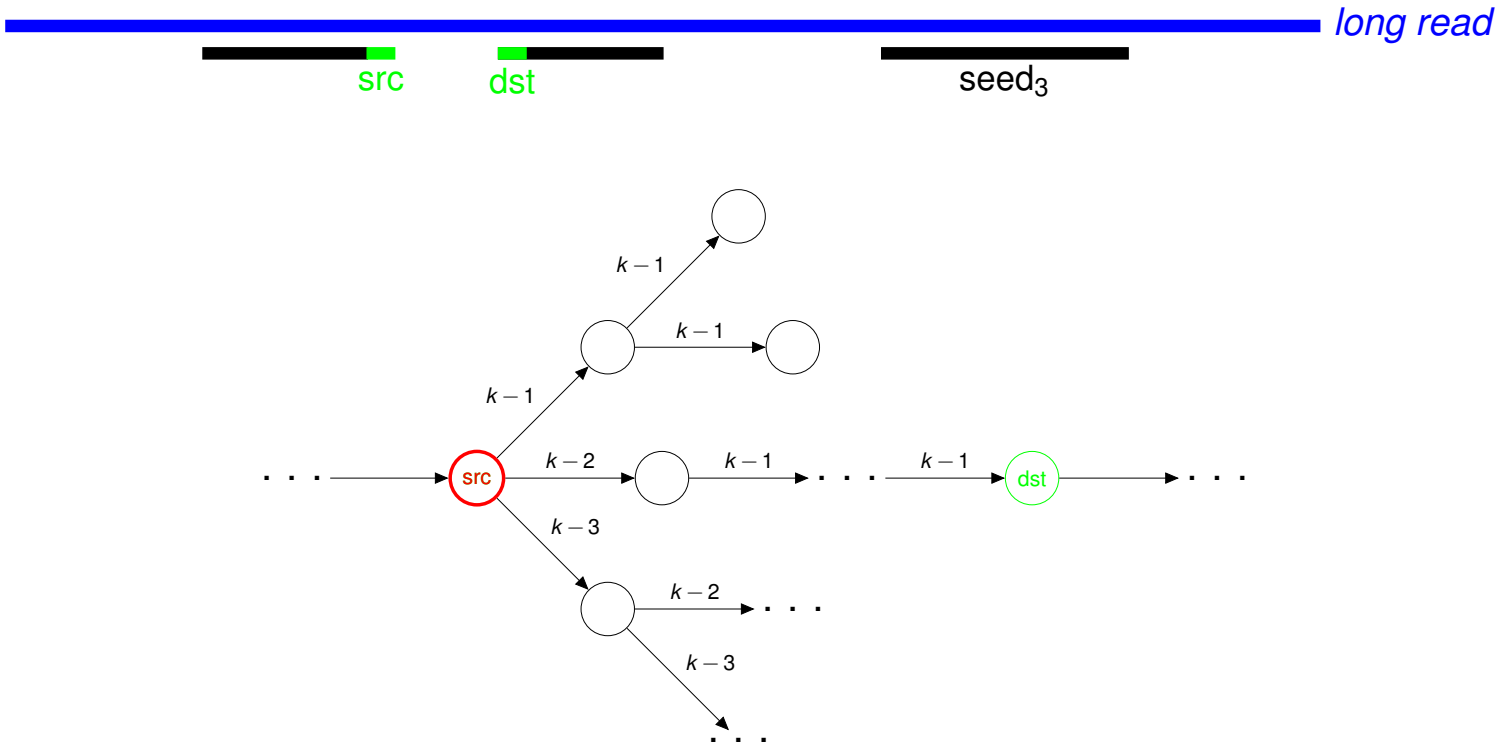

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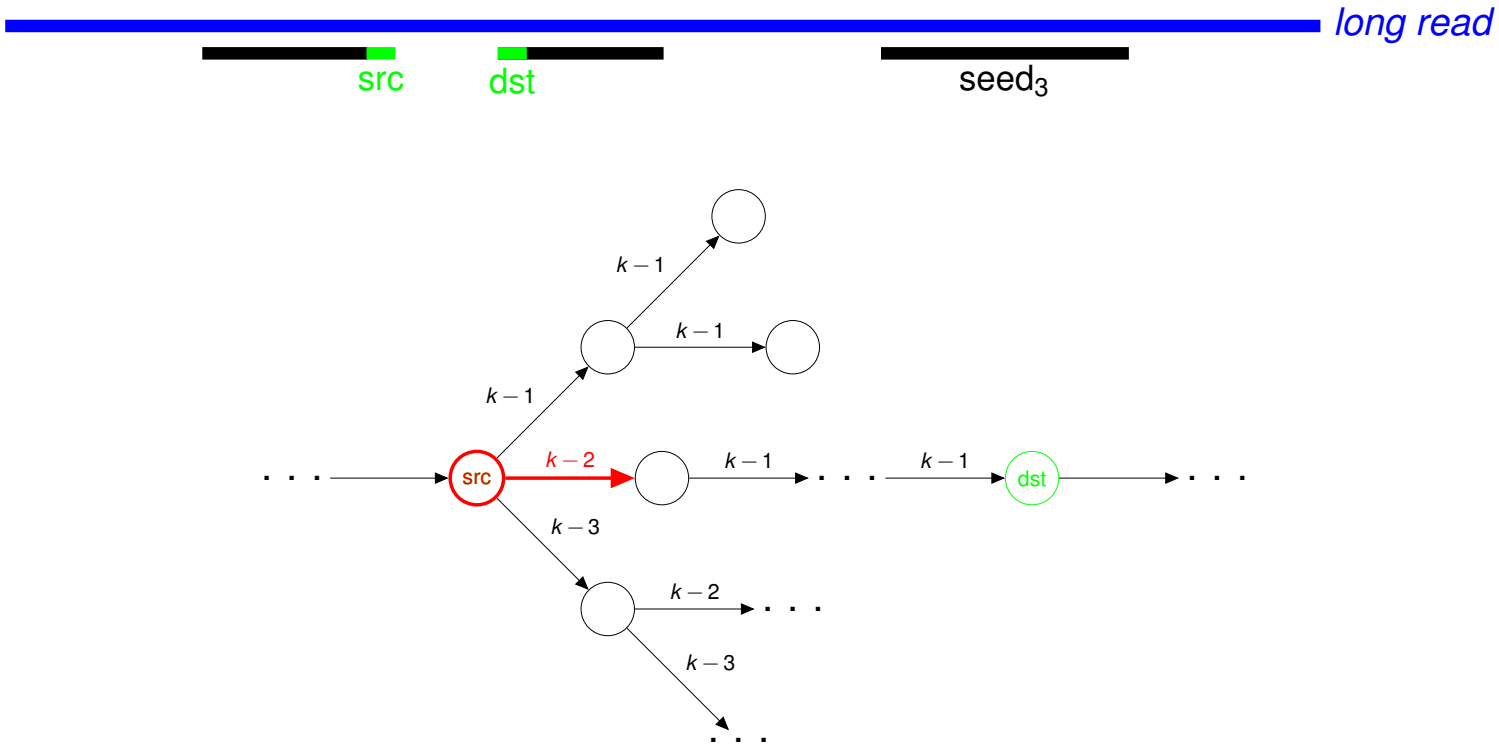

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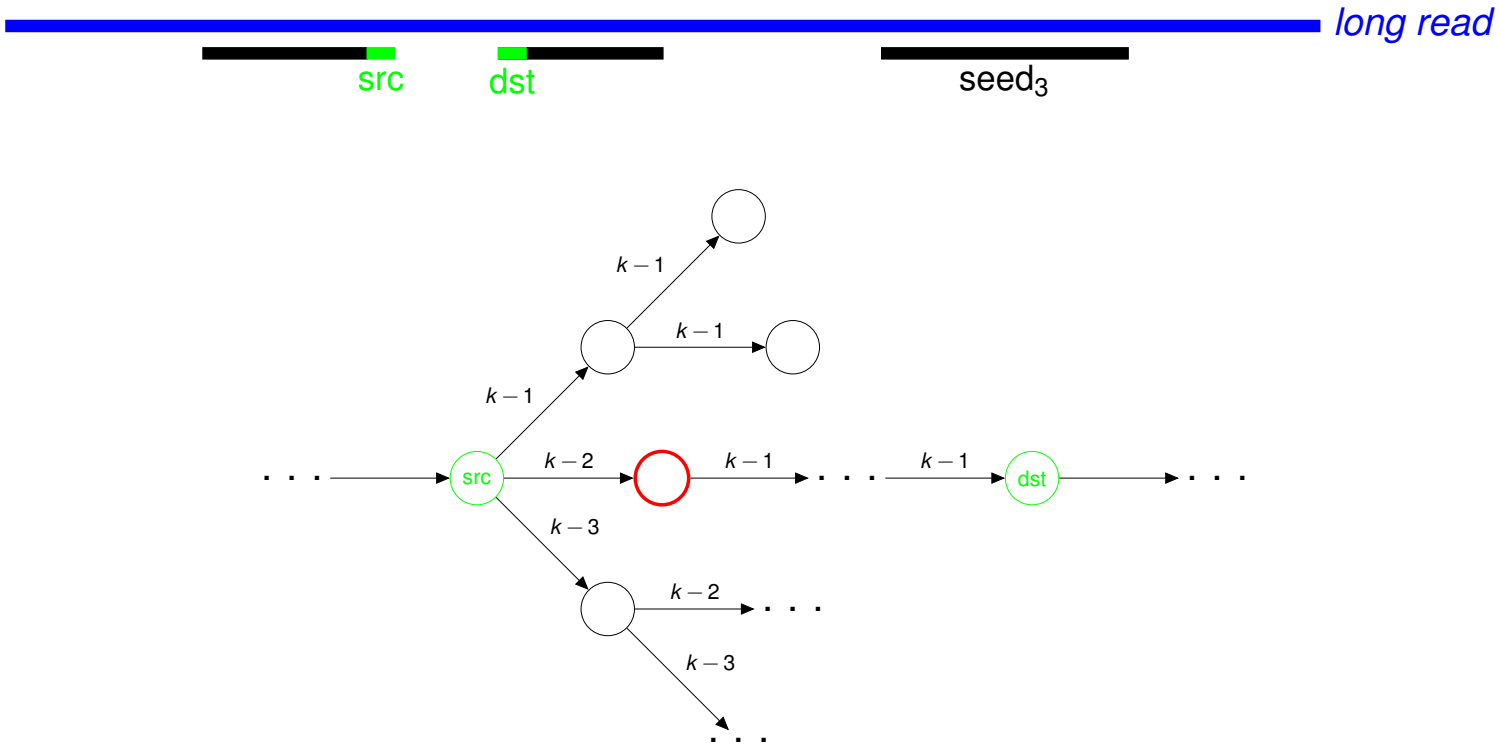

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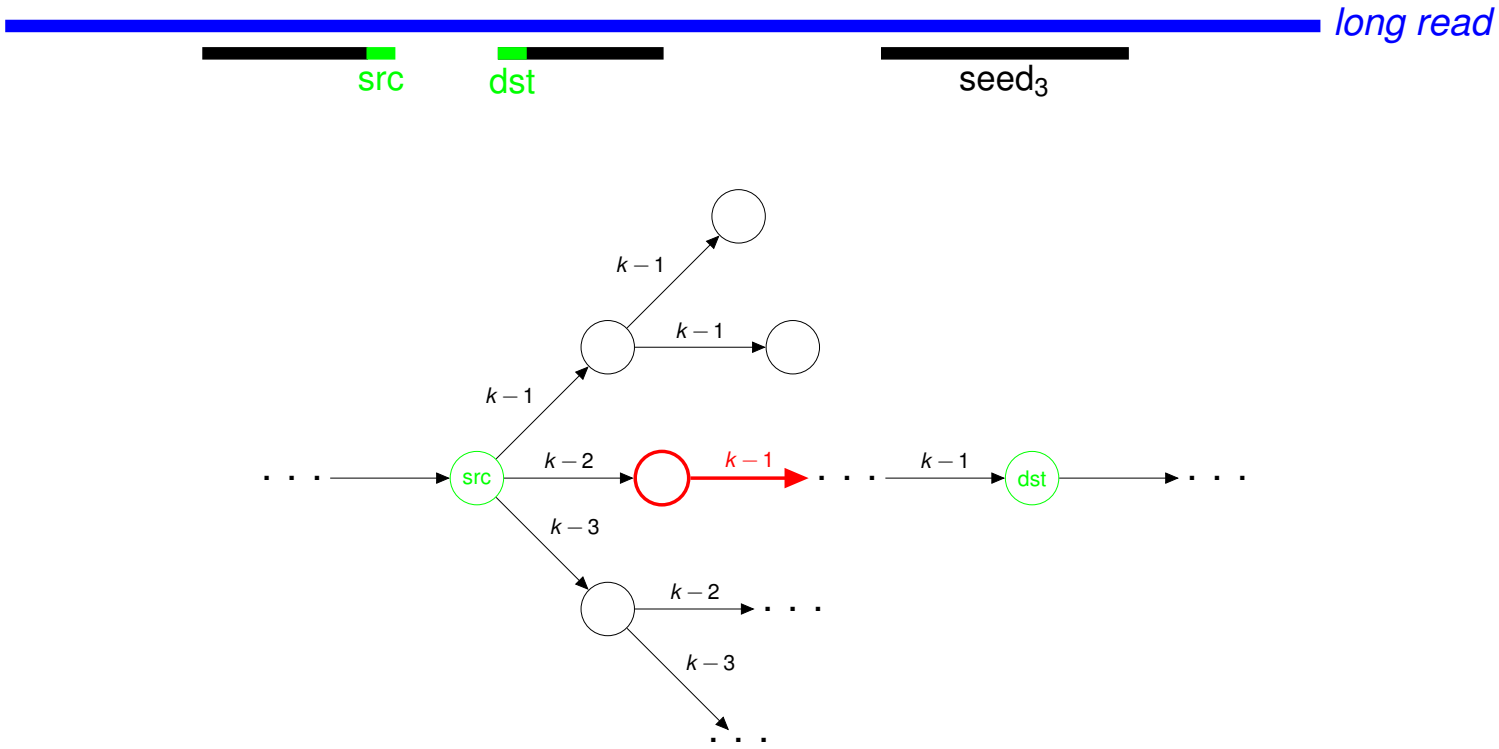

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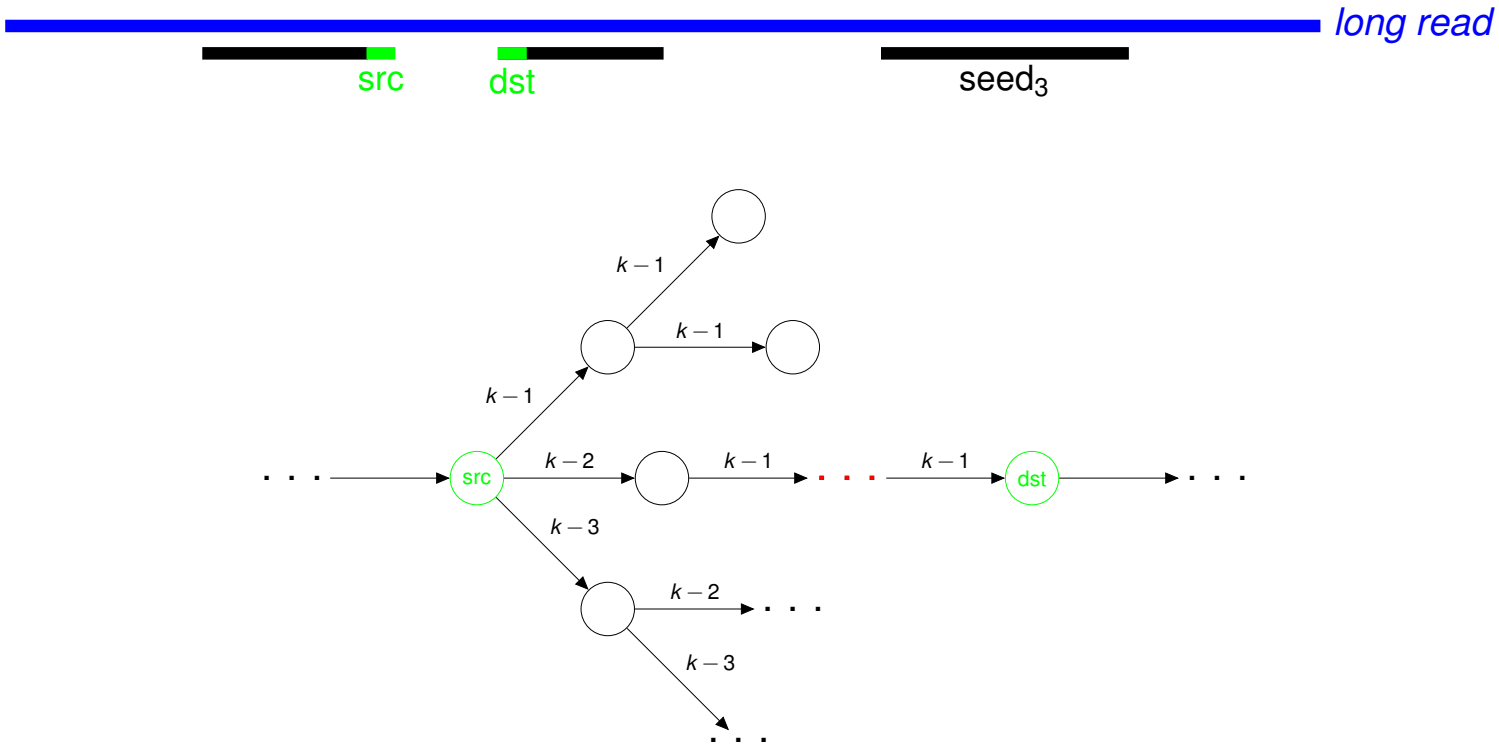

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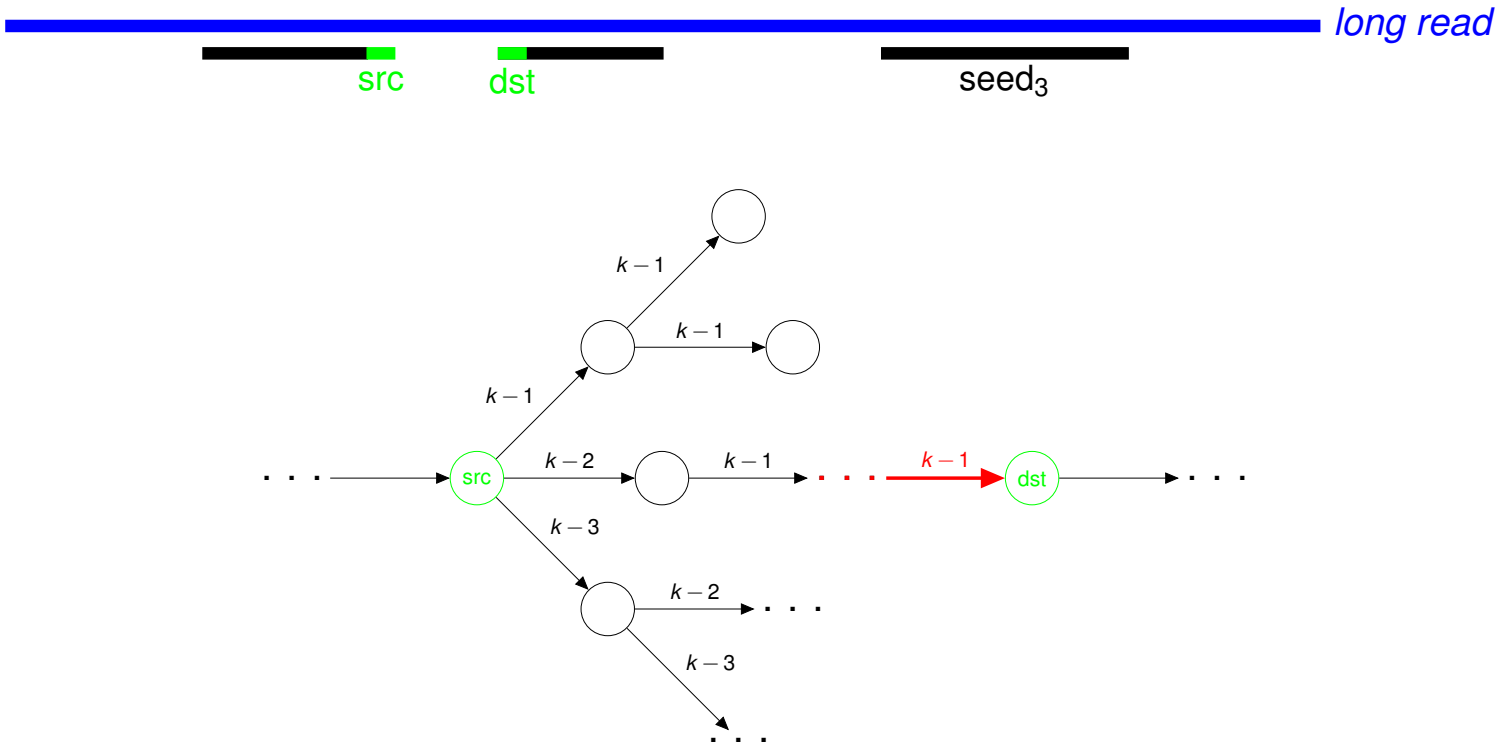

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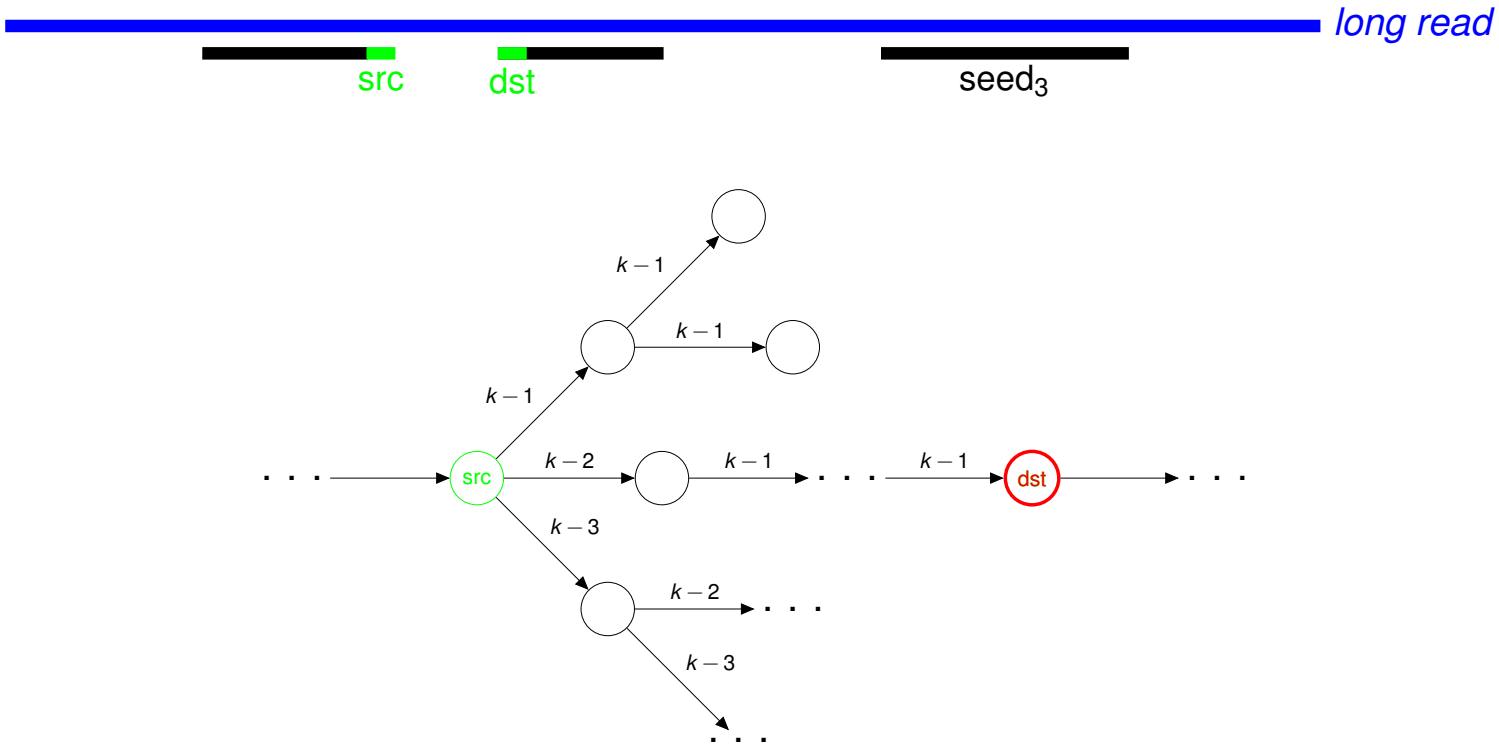

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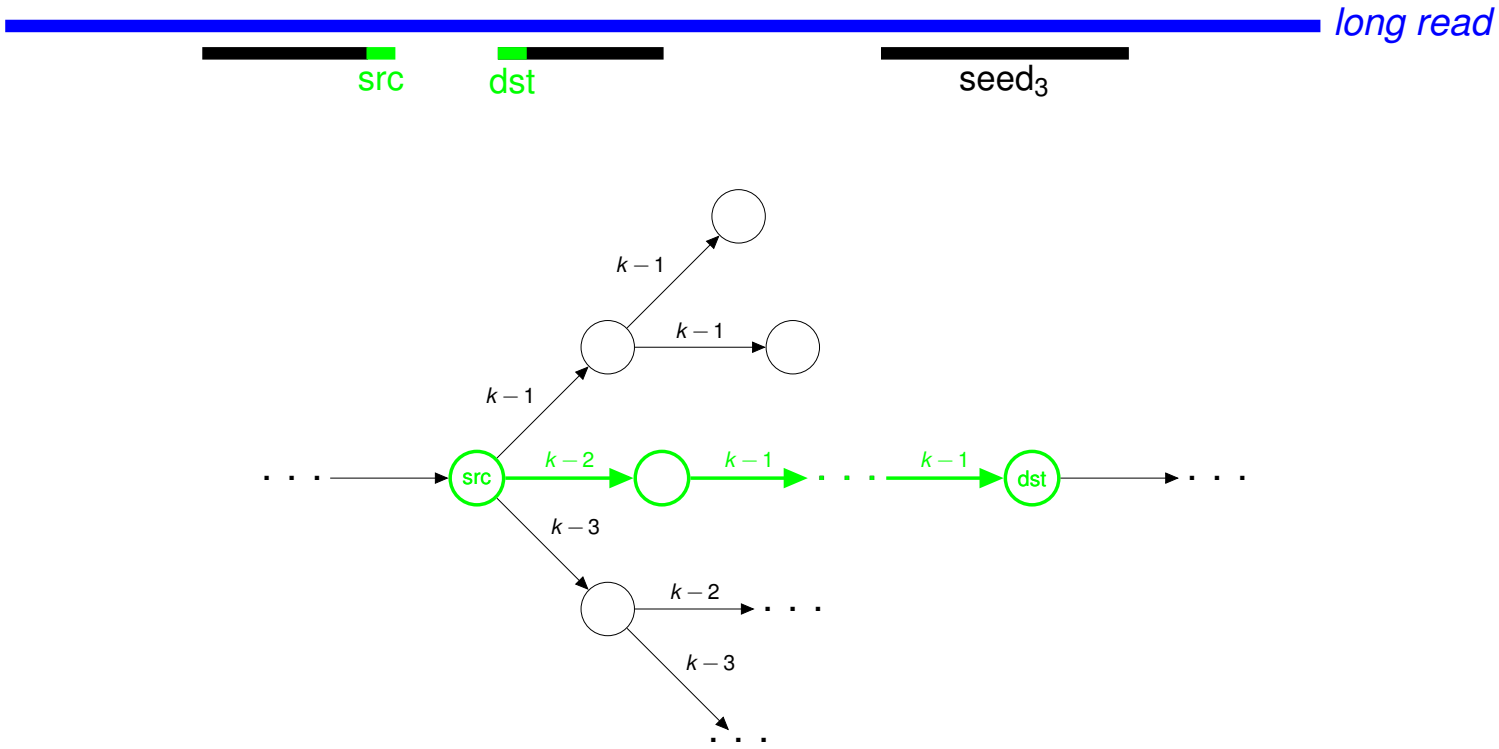

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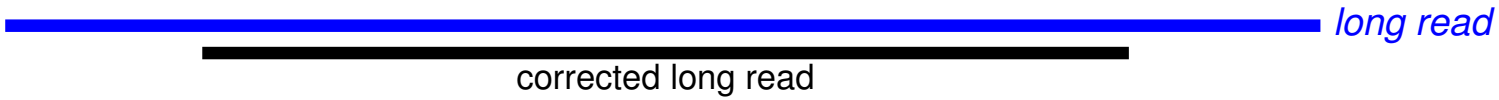

Step 5: Tips extension

- Seeds don't always map right at the beginning and at the end of the long read
- Once all the seeds have been linked, HG-CoLoR keeps on traversing the graph
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- Some seeds might be impossible to link together
- $\Rightarrow$ Fill in the uncorrected part of the long reads with original bases
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Comparison to the state-of-the-art

We compared HG-CoLoR to the following state-of-the-art error correction tools:

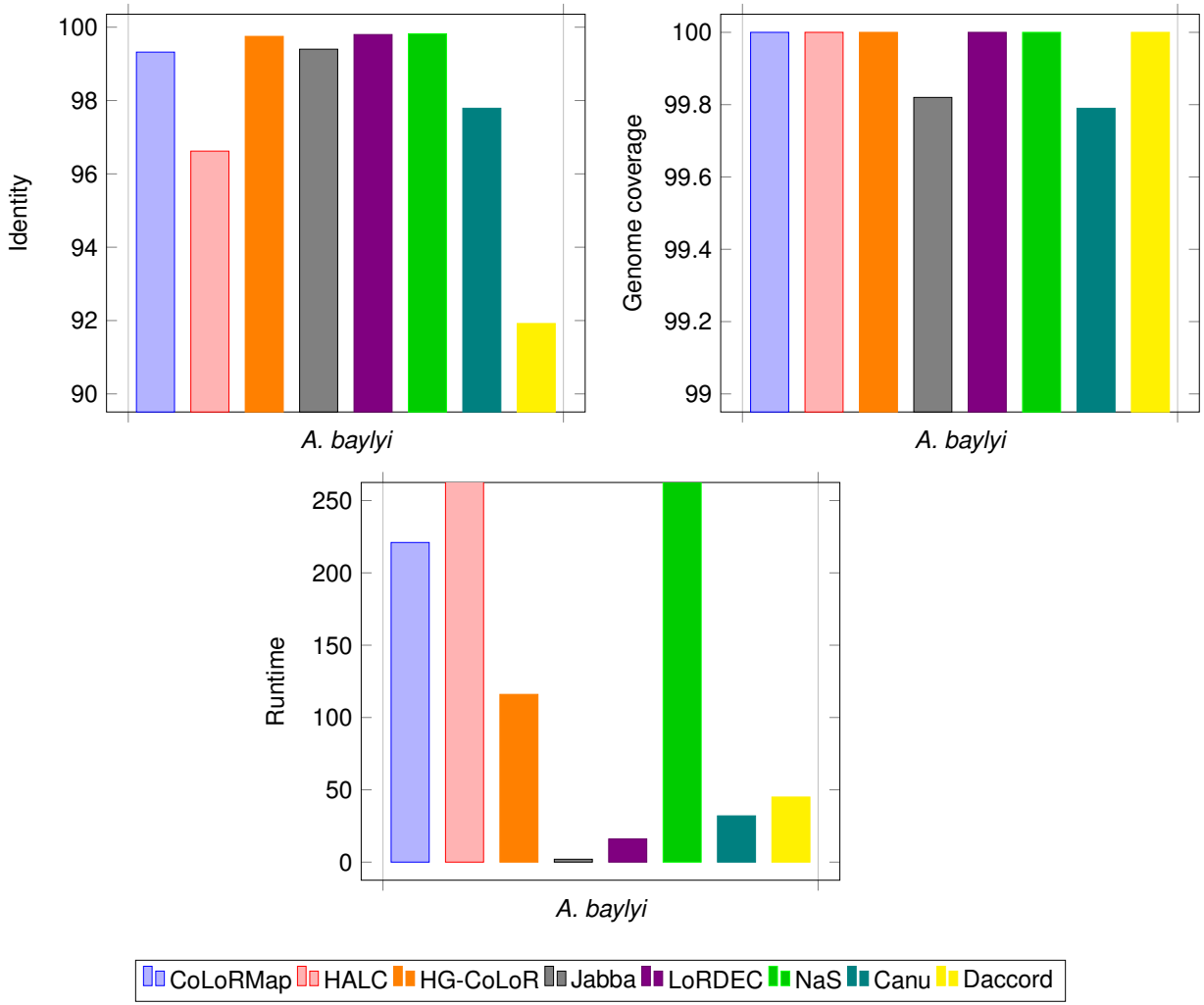
- CoLoRMap [Haghshenas et al., 2016]
- HALC [Bao and Lan, 2017]
- Jabba [Miclotte et al., 2016]
- LoRDEC [Salmela and Rivals, 2014]
- NaS [Madoui et al., 2015]
- Canu [Koren et al., 2017]
- Daccord [Tischler and Myers, 2017]

Datasets

The different tools were compared on the following datasets:

Dataset	*A. baylyi*	*E. coli*	*S. cerevisiae*	*C. elegans*
Reference organism				
Strain	ADP1	K-12 substr. MG1655	W303	Bristol N2
Reference sequence	CR543861	NC_000913	scf7180000000{084-13}	GCA_000002985.3
Genome size	3.6 Mbp	4.6 Mbp	12.2 Mbp	100 Mbp
Real Oxford Nanopore data				
Coverage	106x	29x	95x	20x
Error rate	30%	20%	44%	29%
Illumina data				
Coverage	50x	50x	50x	50x
Read length	250	300	250	250

Comparison of the error correction



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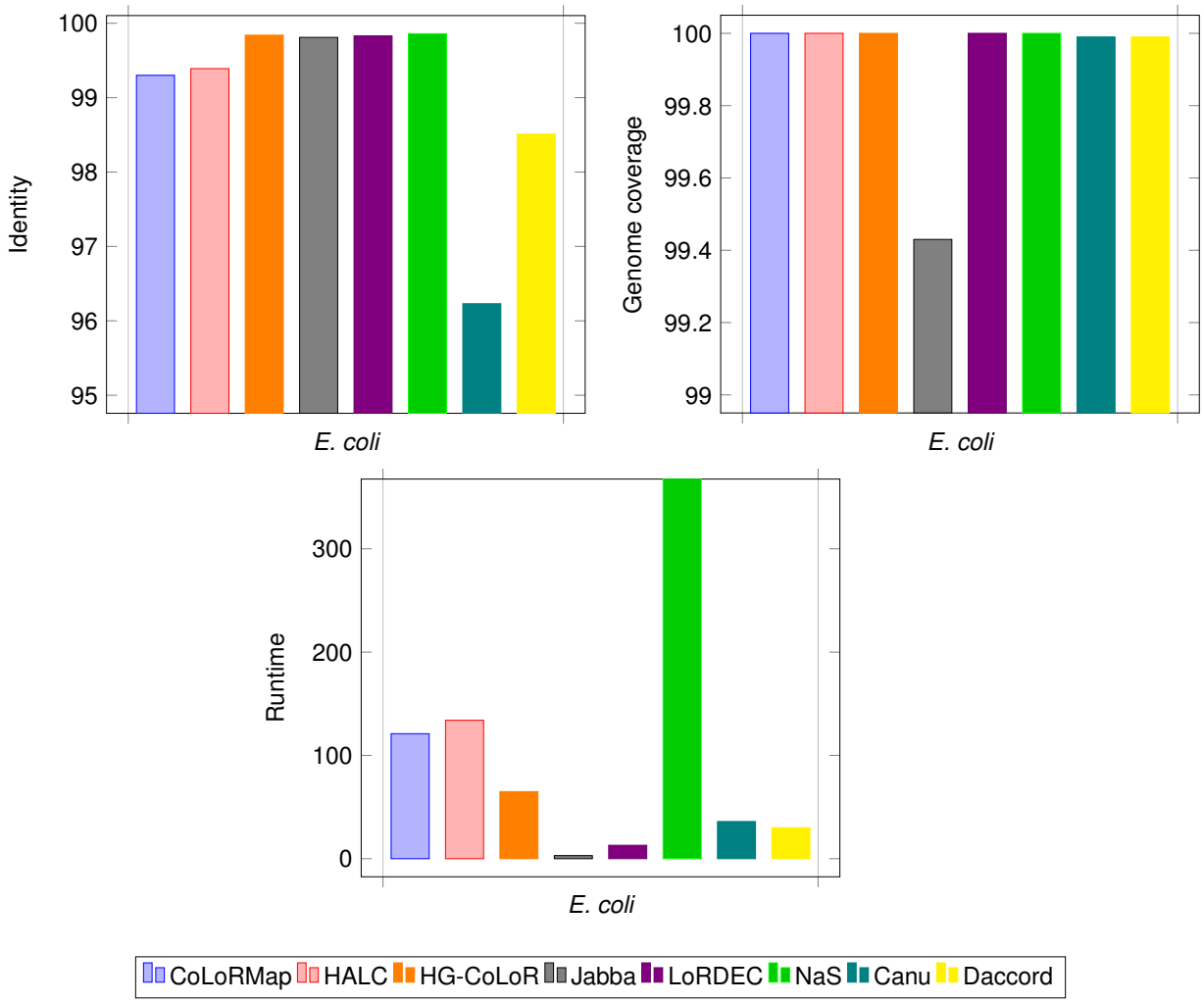

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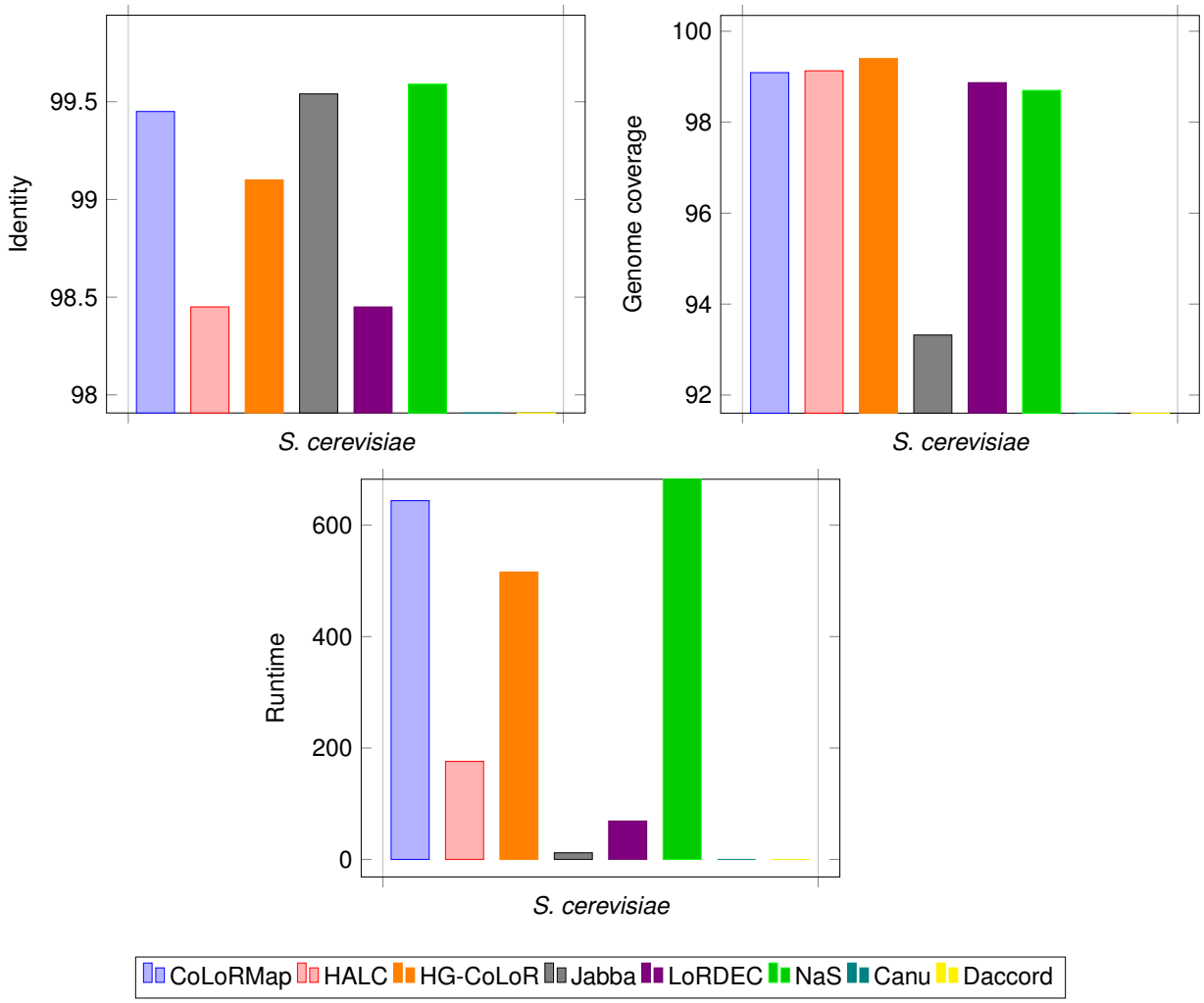

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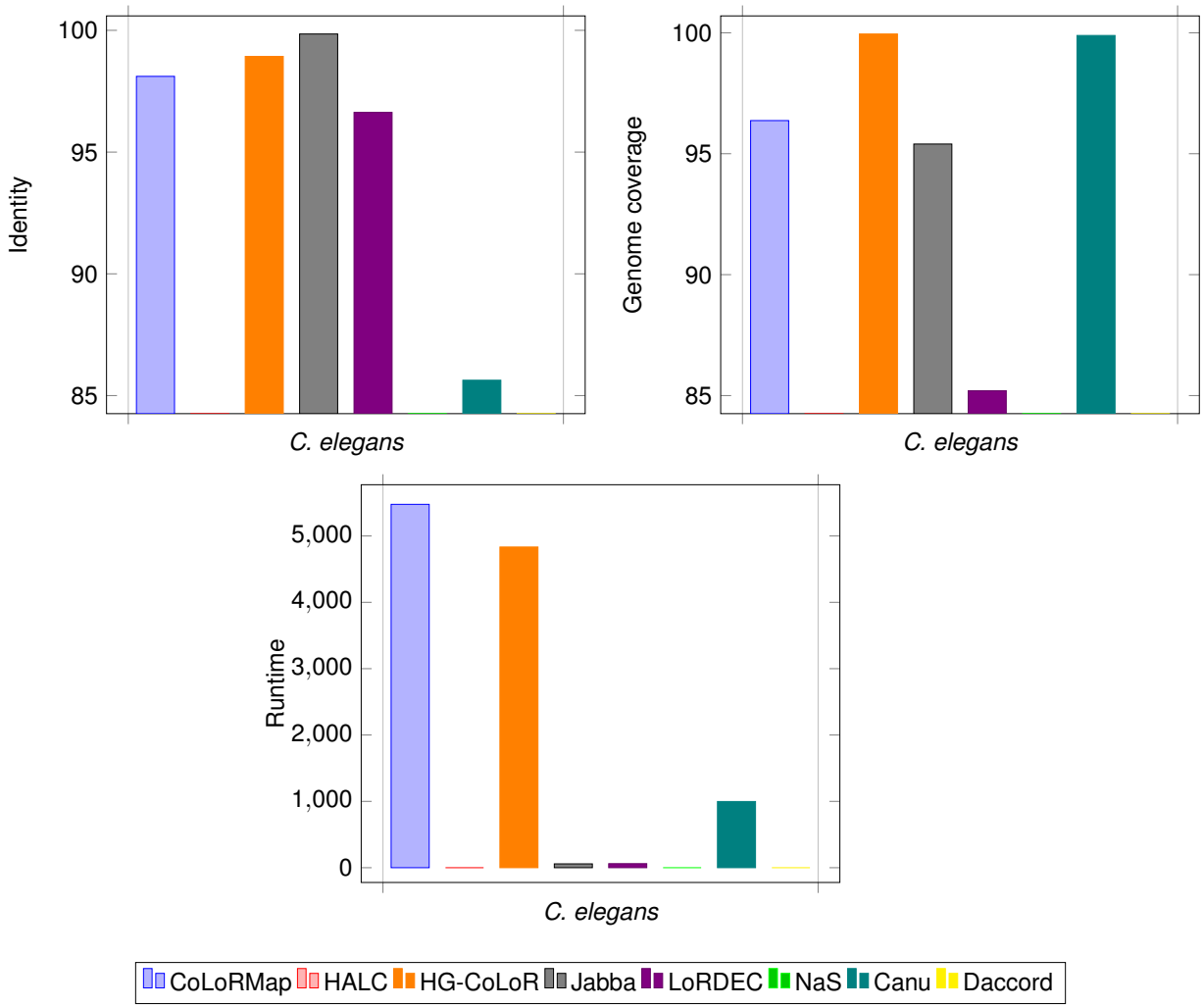

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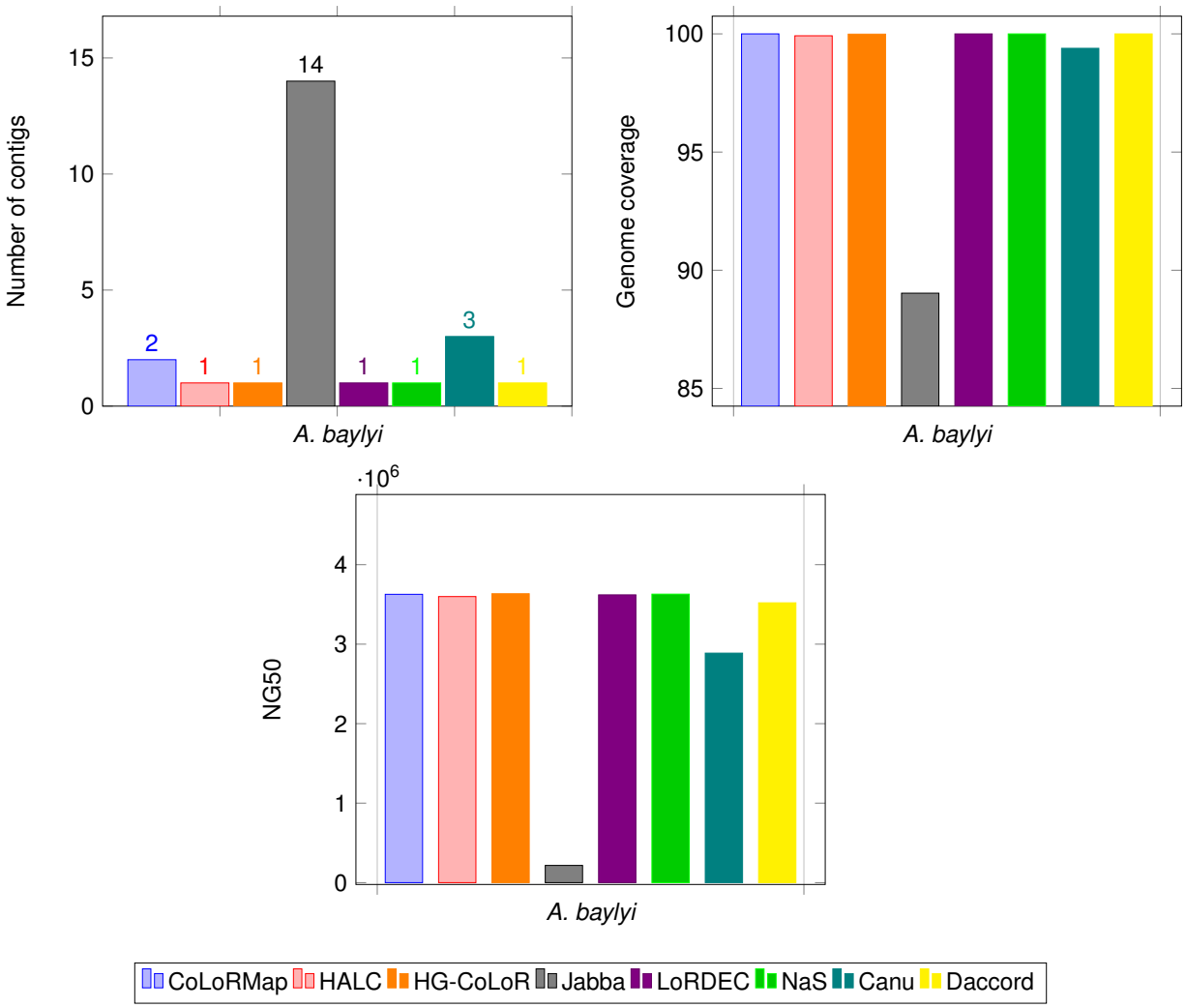

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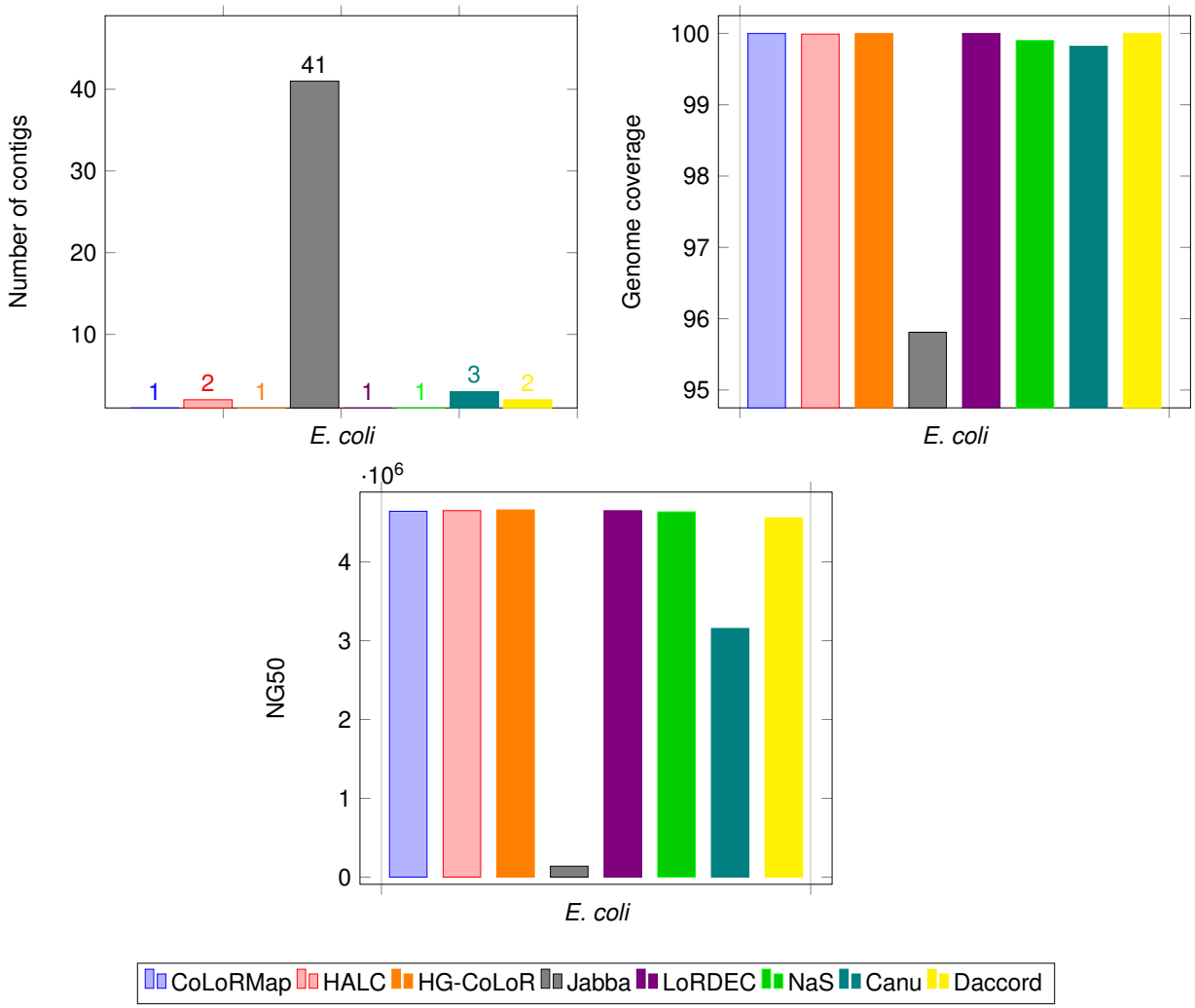

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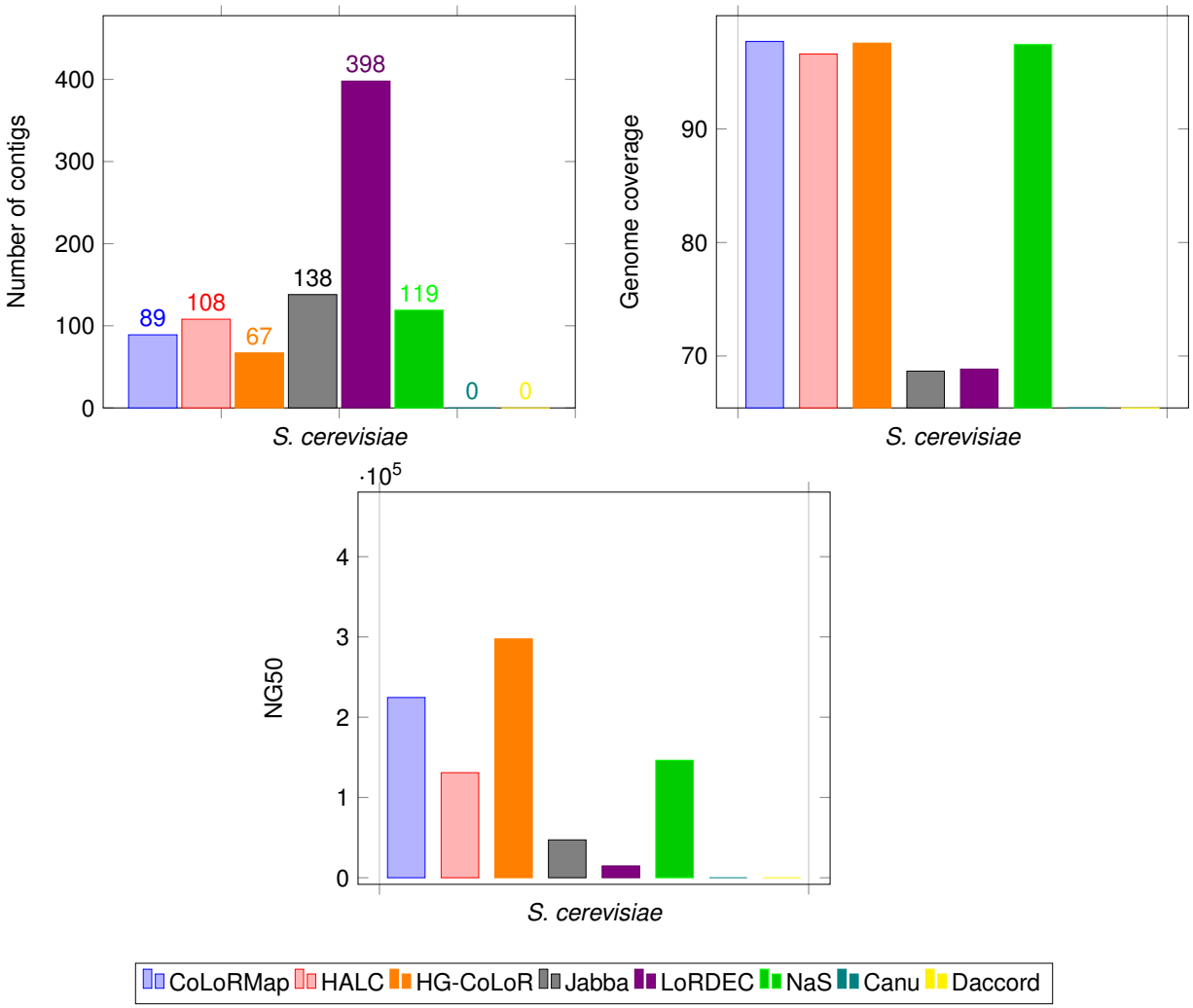

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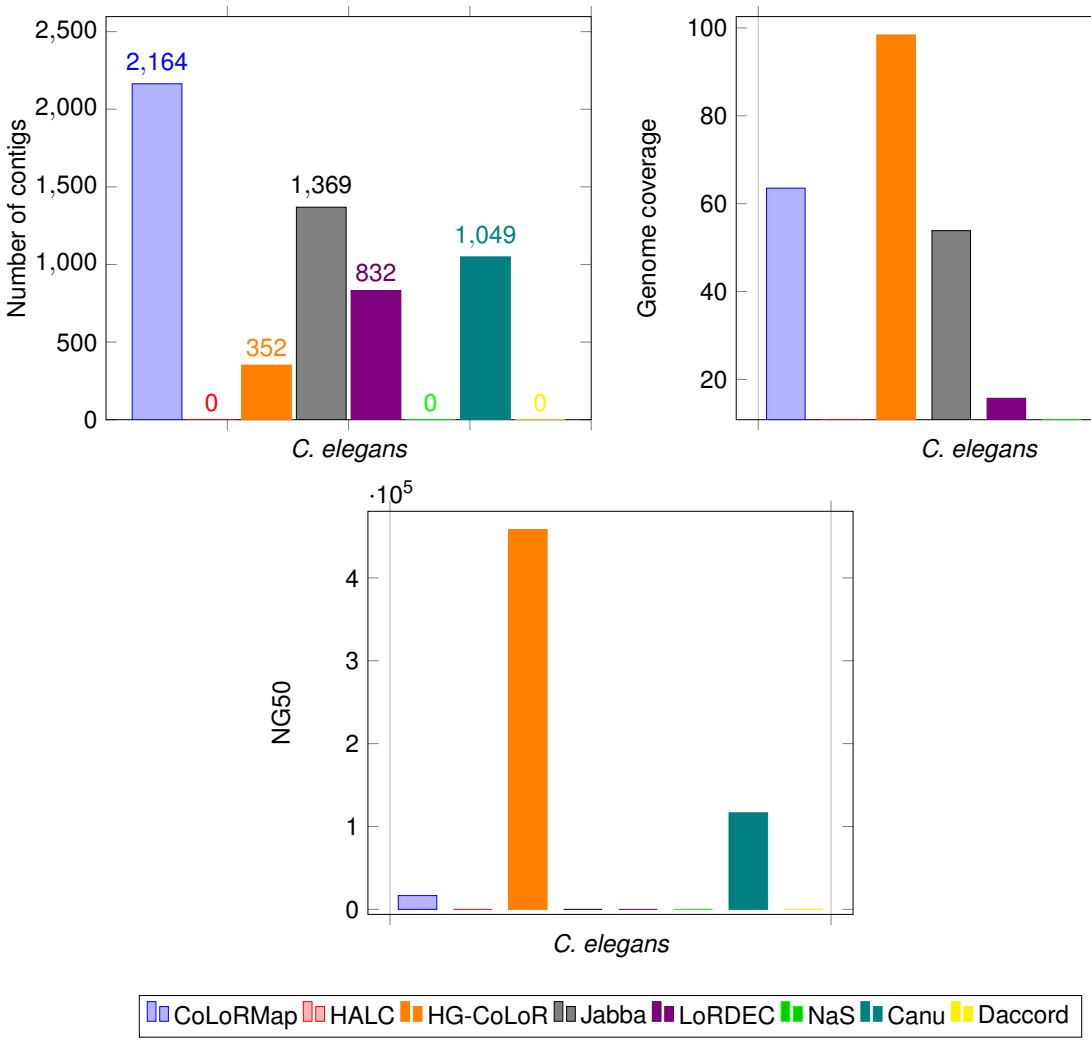

Conclusion

- We introduced a new long read hybrid error correction tool, HG-CoLoR, that:
  - Follows a seed-and-extend approach
  - Exploits the advantages of the variable-order de Bruijn Graph
- Results of our experiments show that HG-CoLoR:
  - Offers a good trade off between runtime and quality, when compared to state-of-the-art methods
  - Efficiently scales to eukaryotic genomes
- Is available from: `https://github.com/morispi/HG-CoLoR`

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Future work

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Thanks for your attention.

Any questions?