MindTheGap: integrated detection and assembly of short and long insertions

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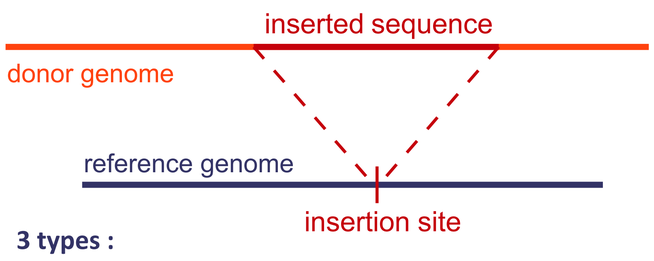
Motivations

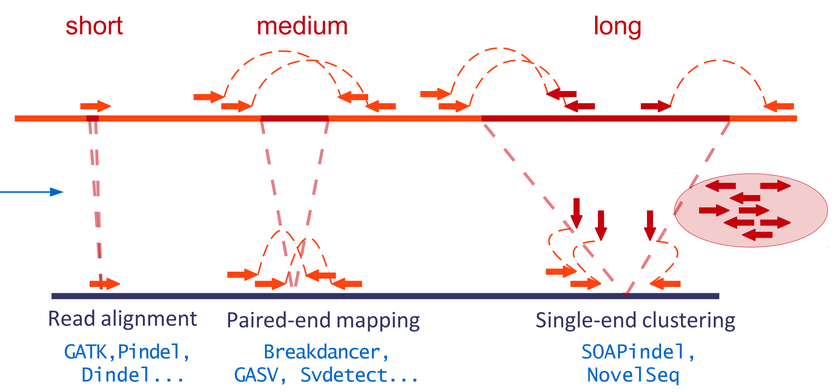
Insertion Variants – definition



3 types :
- *novel* insertion
- *duplicative* insertion
- *transposition*

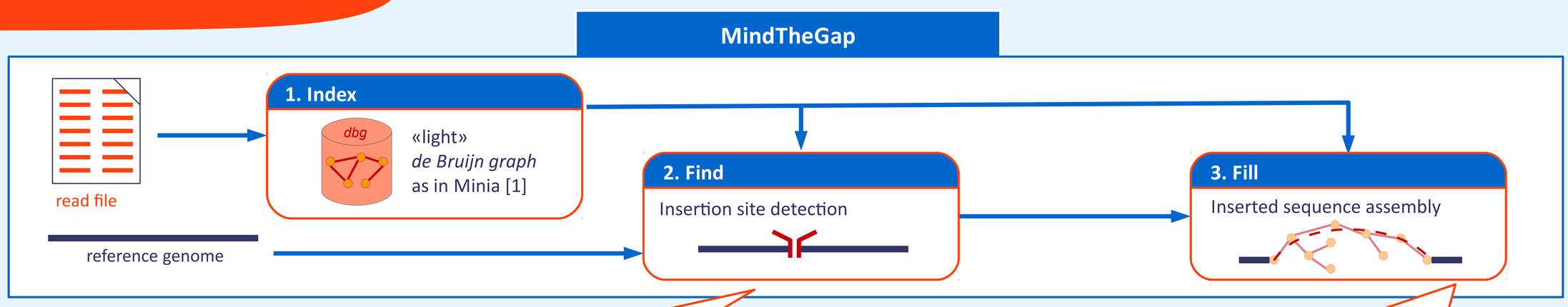
Insertion Variants – detection in short read data

1. Mapping the reads to the reference genome
2. Insertion site detection
   Several methods depending on the insertion size
3. Assembly of the inserted sequence
   Few methods for medium/large insertions
   Local assembly of mate reads → limited size
   Assembly of unmapped reads → only novel insertions

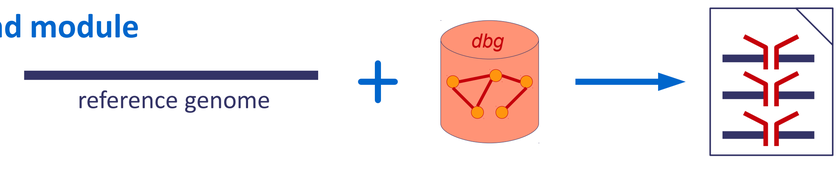


No tool for **all types** and **all sizes** insertions
Especially strong need for tools for long insertions (> insert-size)

Methods

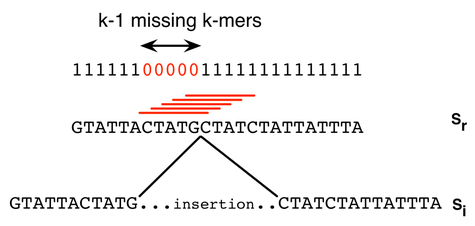


Find module



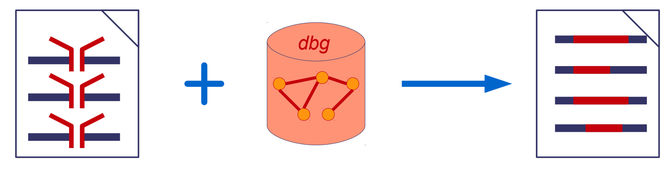
Scanning the reference genome and testing existence of kmers in the donor *dbg*

Homozyguous insertions
generate *gaps* of size < k



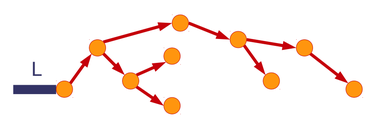
Heterozyguous insertions
generate overlapping *branching* kmers

Fill module

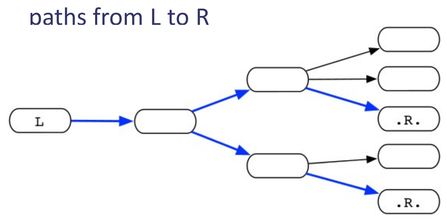


De novo assembly starting from *Left* kmer, searching for *Right* kmer in the contig graph

dbg traversal and building of contigs



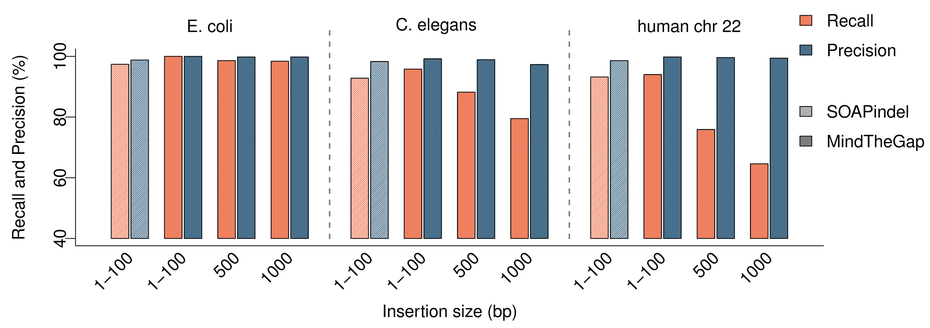
In the graph of contigs, finding all paths from L to R



Results

Simulated data:
- Insertions : random deletions in real genomes (ref)
- Donor reads:
  - wgsim (2x100 bp, 40x) on initial genome
  - real *C. elegans* SRX026594 (70x)

Comparison with SOAPindel [2] (limited to 1-100 bp insertions).

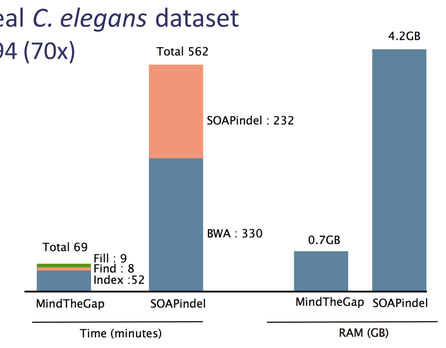


1 Kb insertions	Recall (%)	Precision (%)	N sim.	Find module TP	Find module FP	Fill module TP	Fill module FP
E. Coli simulated dataset	98.4	99.8	500	499	0	492	1
C. elegans simulated dataset	79.5	97.3	1000	992	0	795	22
C. elegans real reads, simulated insertions	81.1	–	1000	980	–	811	–
Human chromosme 22 simulated dataset	64.6	99.4	1000	1000	0	646	4
Heterozyguous insertions							
C. elegans simulated dataset	59.9	93.4	1000	807	11	599	42
Human chromosome 22 simulated dataset	35.5	89.0	1000	816	28	355	44

Real «big» data :
- Human NA12878, 2.8 G reads ~100x
- Real insertions detected in fosmid data [3]
- 11/23 detected insertion sites
- 2 insertions of 4,137 and 6,729 pb correctly assembled

Faster and with little memory

On the real *C. elegans* dataset SRX026594 (70x)



On the human «big» dataset (280 Gbp): <14 GB memory and 45 hours

MindTheGap:
- ★ The only tool to assemble large insertions (>1Kb)
- ★ Integrated and unified method for all types and all sizes insertions
- ★ Independent of mapper and insert-size
- ★ Time/memory scalable on big datasets
- ★ Can be used as a gap-filler in assembly pipelines

References:
[1] R. Chikhi & G. Rizk. Space-efficient and exact de Bruijn graph representation based on a Bloom filter. *Algorithms Mol Biol*, 2013, 8: 22.
[2] S Li, R. Li, H. Li, J. Lu, Y. Li, L. Bolund, M. H. Schierup & J. Wang. SOAPindel: efficient identification of indels from short paired reads. Genome Res, 2013, 23: 195-200.
[3] S. Kim, P. Medvedev, T. A. Paton & V. Bafna. Reprever: resolving low-copy duplicated sequences using template driven assembly. *Nucleic Acids Res*, 2013, 41: e128.

Download and use MindTheGap

http://mindthegap.genouest.org

C++, Open Source, released under A-GPL license

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