Fast scaffolding with small independent mixed integer programs

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DNA fragment assembly workflow

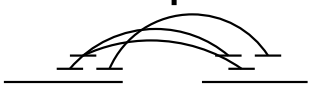
Reads

Error Correction

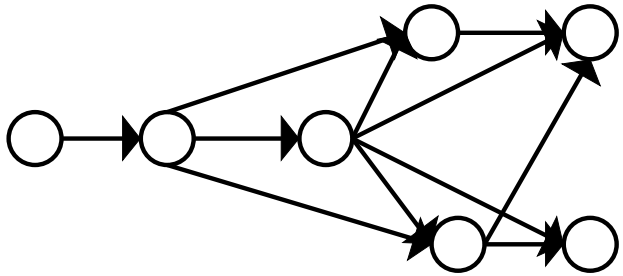
Overlap Computation

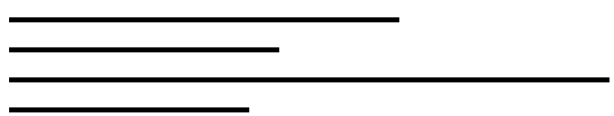
Contig Assembly:
paths → contigs

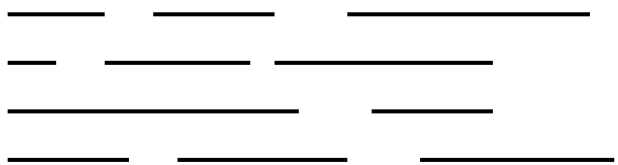
Scaffolding:
remove minimum number of mate pairs so that the remaining ones are consistent



Mate pairs

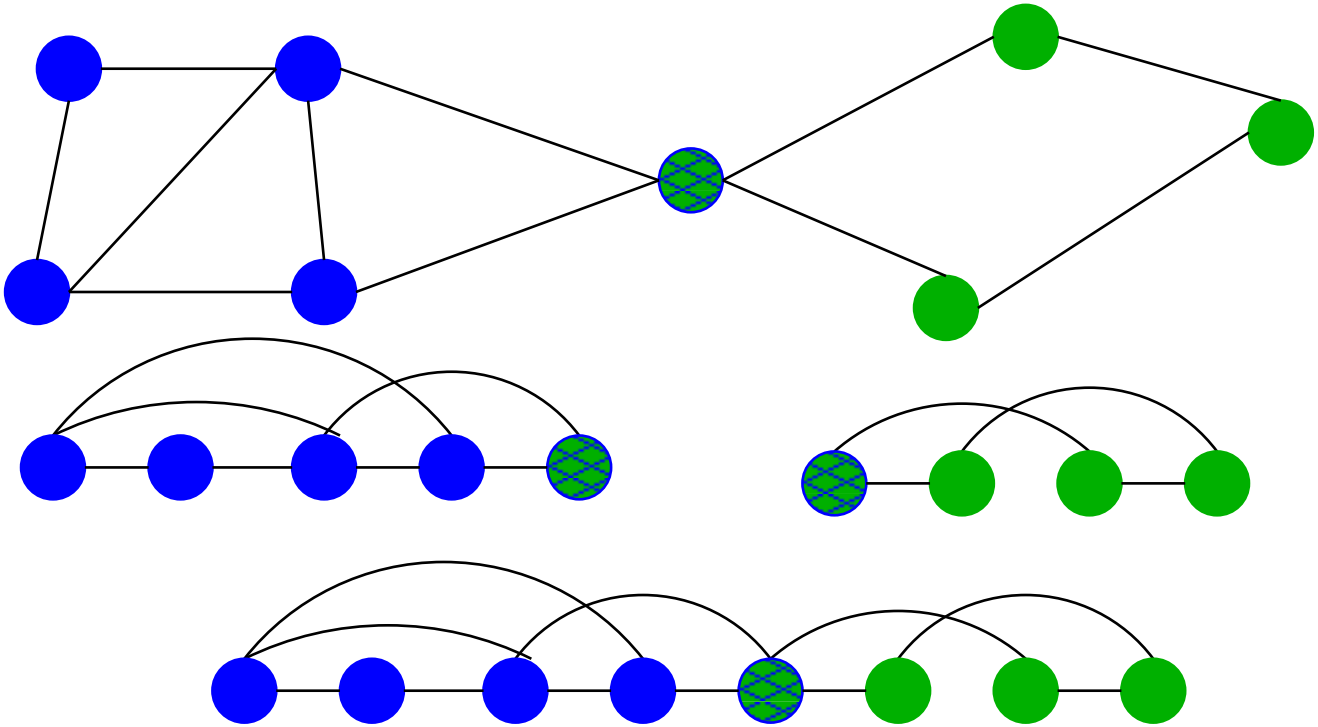






Previous work

- Even determining the orientation of contigs is NP-complete:
  $\Rightarrow$ All approaches use heuristics
- Biconnected components of the scaffolding graph can be solved independently (Dayarian et al. 2010)



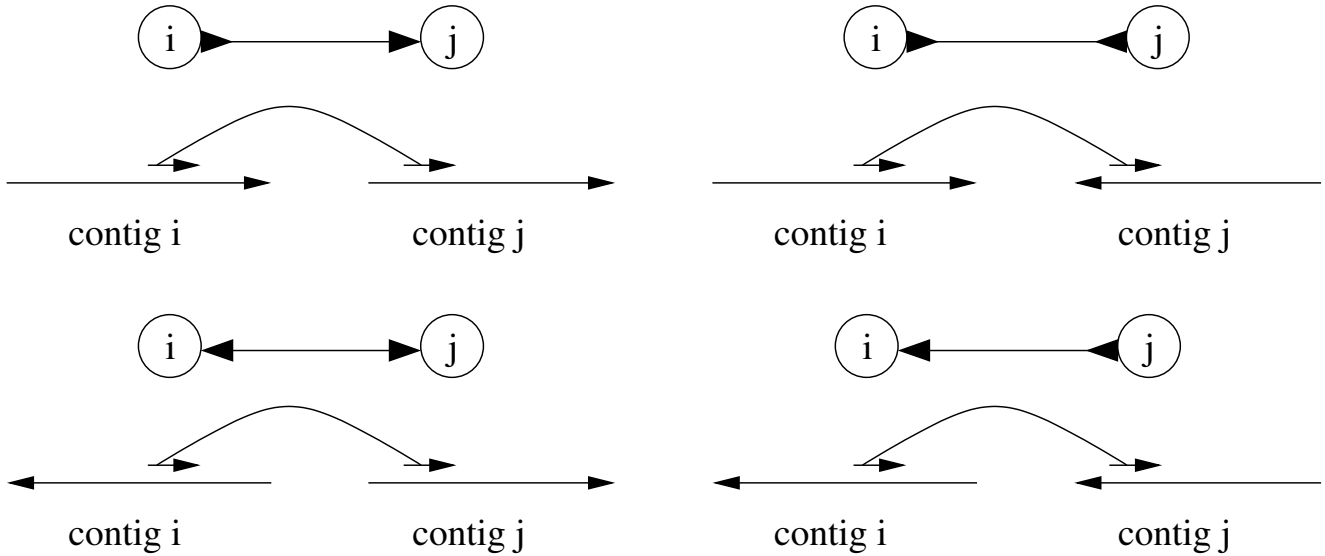
- Several tools developed: SOPRA, Bambus, SSPACE, OPERA...

Overview of our work

- Cleaning input:
  - Keeping only more reliable mate pairs
  - Bundling mate pairs that connect the same contigs together
  - Estimating the distance between contigs based on the mate pairs
- Partitioning the problem into smaller subproblems of restricted size
- Solving each subproblem as a mixed integer program (MIP)

Scaffolding graph

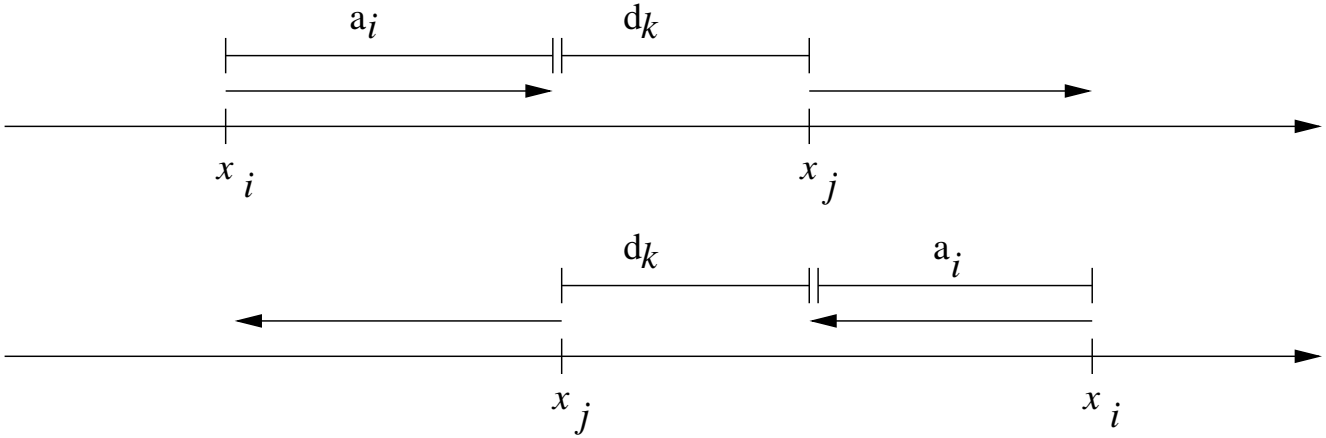
- Nodes: contigs
- Edges: mate pairs connecting contigs
  - Support is the number of mate pairs connecting the contigs
  - Distance is the estimated distance of the contigs based on the mate pairs linking the contigs directly
  - Orientation of the contigs



Partitioning the problem

- Initially: Nodes=contigs, no edges
- Sort the edge candidates according to their support
- Add edges to the graph in descending order of their support but only if the edge does not create a too large biconnected component in the graph.
- Biconnected components of the graph can be maintained under updates efficiently using a data structure by Westbrook and Tarjan (1992)

MIP formulation



- $x_i \in \{1...N\}$: location of contig i
- $o_i \in \{0 = \text{reverse}, 1 = \text{forward}\}$: orientation of contig i
- $l_k \in [0, 1]$: smoothed indicator of edge k
- a_i: length of contig i
- s_k: support of edge k
- d_k: distance of edge k
- C: large constant

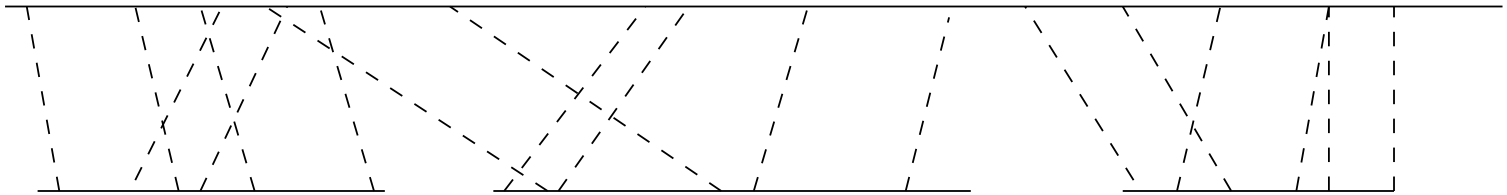
maximize $\sum_k s_k l_k$

such that

$$o_i - o_j - (1 - l_k) \leq 0$$
$$o_i - o_j + (1 - l_k) \geq 0$$
$$x_i + a_i + d_k - C(1 - l_k) - C(1 - o_i) \leq x_j$$
$$x_i + a_i + d_k + C(1 - l_k) + C(1 - o_i) \geq x_j$$
$$x_j + d_k + a_i - C(1 - l_k) - Co_i \leq x_j$$
$$x_j + d_k + a_i + C(1 - l_k) + Co_i \geq x_j$$

Validation

- Align the scaffolds to the reference genome:
  - Find local maximal approximate matches (swift by Rasmussen et al. 2006)



  - Produce maximal colinear chains of the above matches (colinear chaining algorithm by Abouelhoda 2007)
- N50: “length-weighted median”, sequences longer than the N50 value cover half of the combined length of a sequence set
- Normalized N50: we computed the N50 statistic for the aligned parts of the scaffolds

Experimental results: Normalized N50 values

Scaffolder	*E.Coli*	*C.Elegans*	*P.Syringae*	Human
SOPRA	185,227	130,346	72,714	-
SSPACE	-	-	93,850	179,418
MIP Scaffolder	170,796	183,891	84,779	190,008

Thanks!

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- More information:
  L. Salmela, V. Mäkinen, E. Ukkonen, N. Välimäki, and J. Ylinen: Fast scaffolding with small independent mixed integer programs. To appear in *Bioinformatics*.