Gap Filling as Exact Path Length Problem

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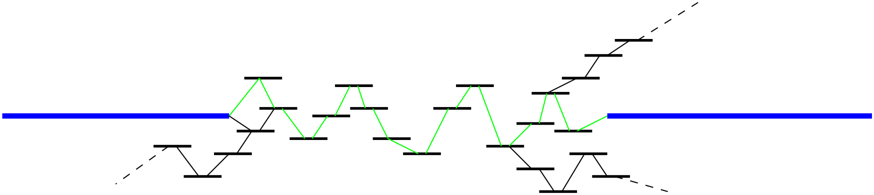
Gap filling

- Gap filling is the last phase in genome assembly
- Input: Scaffolds (=linearly ordered contigs) and reads
- Output: Scaffolds where gaps between contigs have been filled



Previous work

- Gap filling module in many popular assemblers:
    - Allpaths-LG
    - ABySS
    - EULER
    - ...
- Standalone gap filling tools:
    - SOAPdenovo's GapCloser
    - GapFiller (Boetzer & Pirovano 2012)
- General idea:
    - Identify reads potentially filling the gap
    - Local assembly

Our contribution

- Problem formulation as Exact Path Length problem
- Gap Filling is NP-complete
- Pseudopolynomial algorithm for Gap Filling
- Implementation of the algorithm in a tool called Gap2Seq

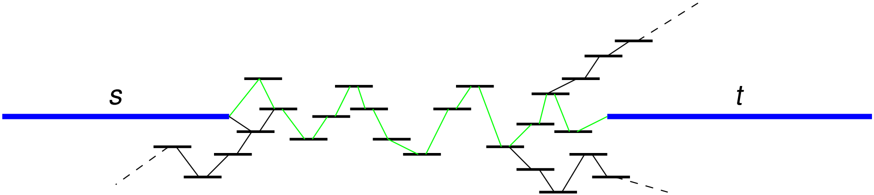
Gap filling: Problem definition

Given

- an (overlap or de Bruijn) graph $G = (V, E)$ of the whole read set
- a cost function $c : E \mapsto \mathbb{Z}_+$
- two vertices s and t representing the flanks of the contigs
- estimate of the gap length $[d', d]$

find for all $x \in [d', d]$ the number of paths $P = v_1, v_2, \ldots, v_k$ such that

$$cost(P) = \sum_{i=1}^{k-1} c(v_i, v_{i+1}) = x.$$



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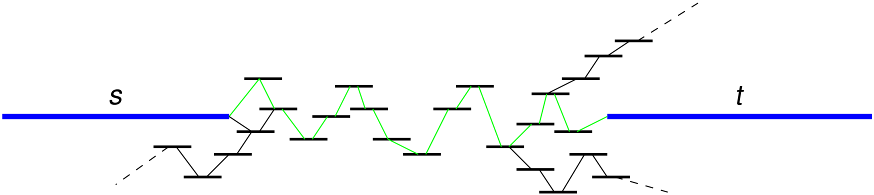
NP-complete

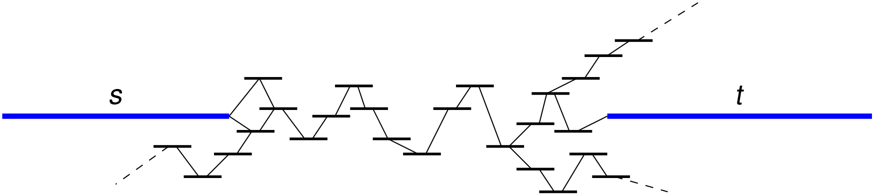
$$\sum_{i=1}$$



Dynamic programming algorithm

- For each $v \in V(G)$ and $\ell \in [0, d]$ define:

$$a(v,\ell) = \text{number of } s - v \text{ paths of cost } \ell$$



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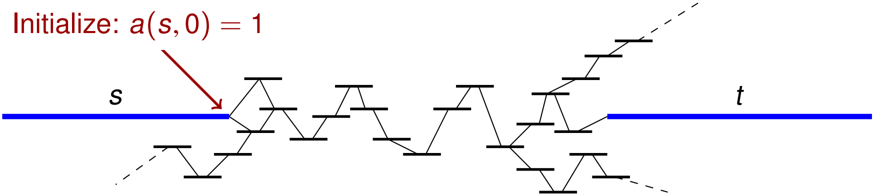

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- For each $v \in V(G)$ and $\ell \in [0, d]$ define:

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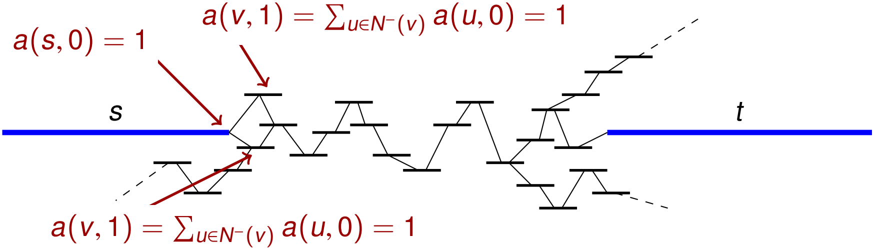
- Recurrence: $a(v, \ell) = \sum_{u \in N^-(v)} a(u, \ell - c(u, v))$
  where $N^-(v)$ is the set of in-neighbors of v



$a(s, 0) = 1$

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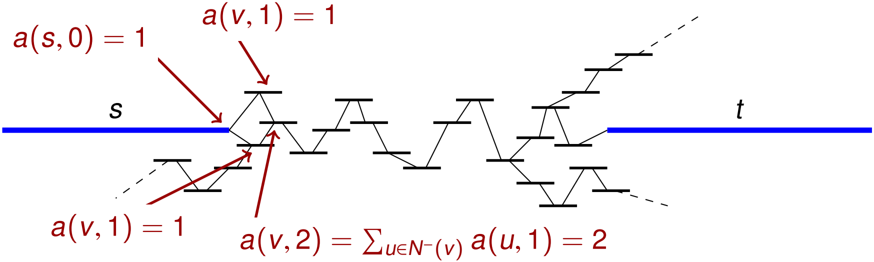

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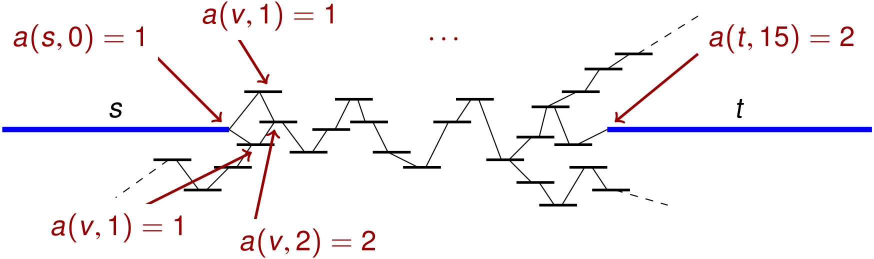

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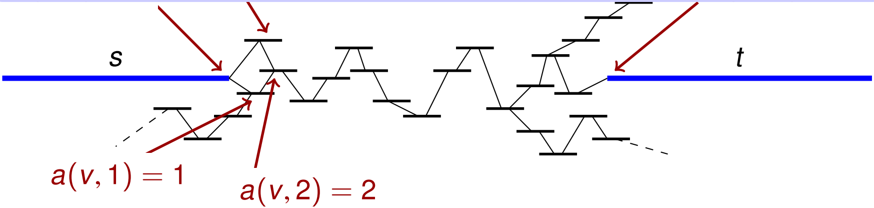
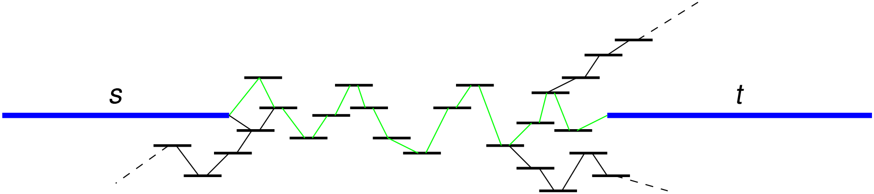
Pseudopolynomial algorithm running in $O(dm)$ time
(d: length of gap, m: number of arcs)



Choosing the path

- If there are several paths:
  1. Choose the one closest to $(d' + d)/2$
  2. If several such paths, choose one at random.
- Backtracing in the DP matrix gives the path



Implementation: Gap2Seq

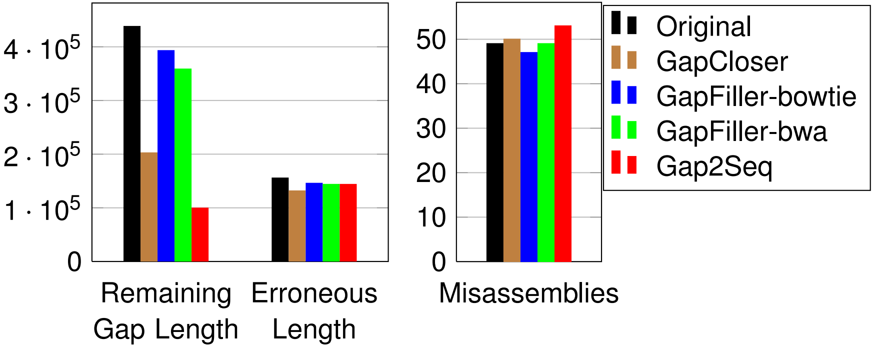
- Build a de Bruijn graph of the reads
  - We use GATB for efficient implementation of the DBG
- Use a hash table to link reachable vertices to their DP table rows
- DP table rows are sparse

  $\Longrightarrow$ List only non-zero entries
- k-mers flanking gaps can have errors

  $\Longrightarrow$ Allow paths to start/end at up to e flanking k-mers
- Parallelisation on the scaffold level
- Limit the memory usage of the DP table

  $\Longrightarrow$ Abandon search on a gap if limit exceeded

Experimental results: *S. aureus* GAGE data



- Experiments run on all 8 GAGE assemblies.
- We show aggregates over all assemblies.

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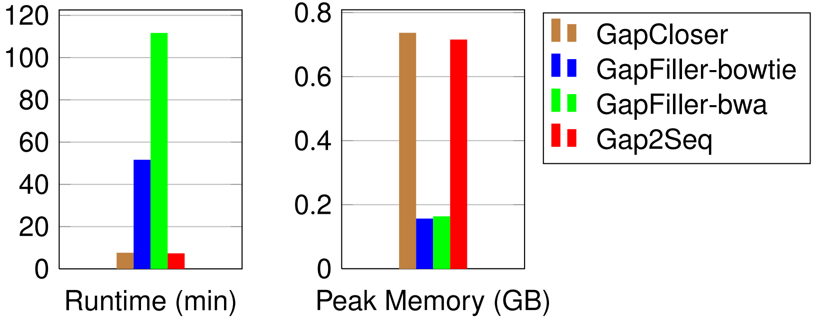

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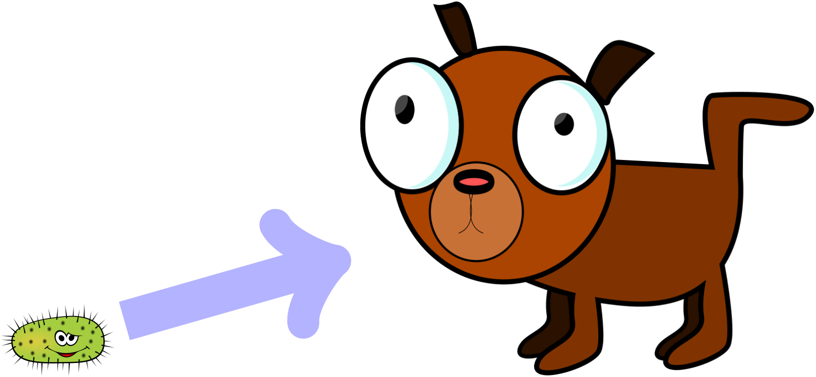
Further work

- Scaling to larger genomes
- Improving runtime and memory usage
    - Meet-in-the-middle: start the search from both flanks of the gap



Thanks!

Questions?

http://www.cs.helsinki.fi/u/lmsalmel/Gap2Seq/