Reference-Based Transcriptome Assembly

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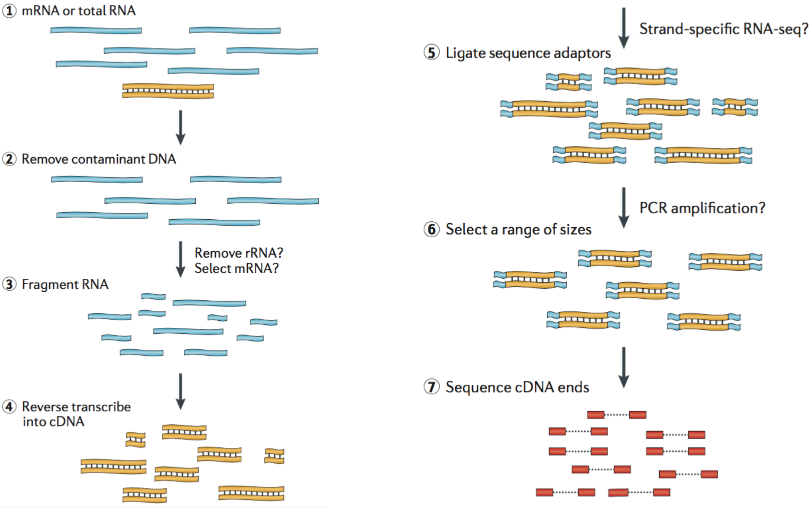
RNA-seq Experiments



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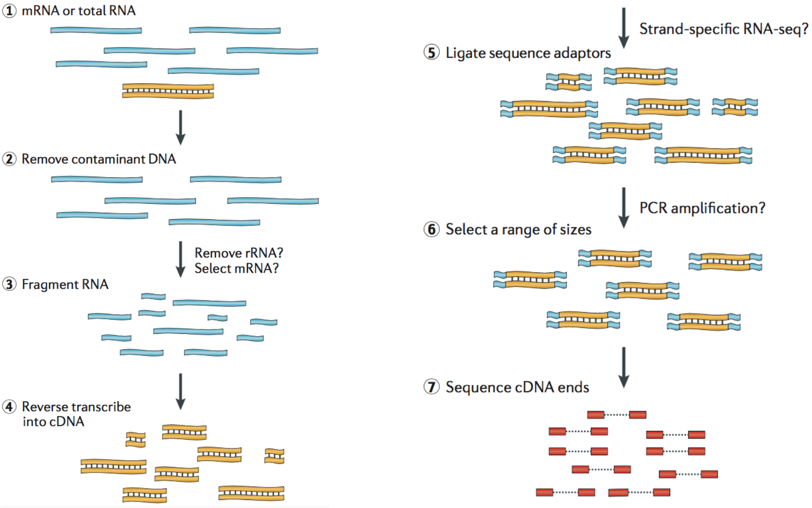

Transcriptome Assembly: To determine the transcripts and their abundance from the (paired-end) reads.

Existing Softwares/Methods

- **Reference-based** methods:
  - Cufflinks (Trapnell *et al.*, 2010)
  - Scripture (Guttman *et al.*, 2010)
  - IsoLasso (Li *et al.*, 2011)
  - SLIDE (Li *et al.*, 2011)
  - CLIIQ (Lin *et al.*, 2012)
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- ***De novo*** methods:
  - Trans-ABySS (Robertson *et al.*, 2010)
  - Trinity (Grabherr *et al.*, 2011)
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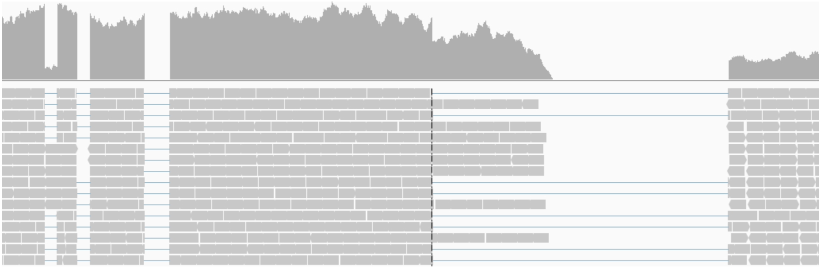

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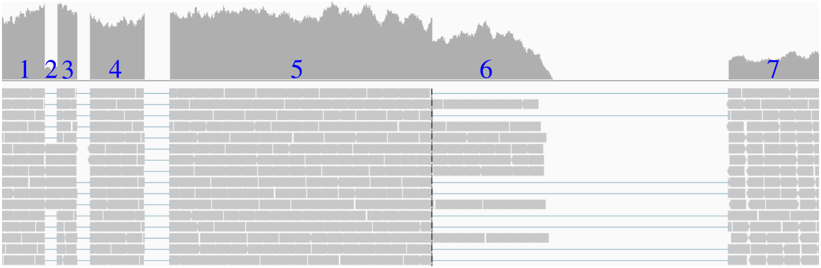

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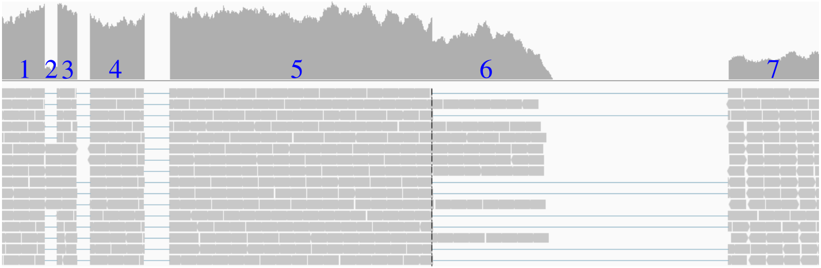

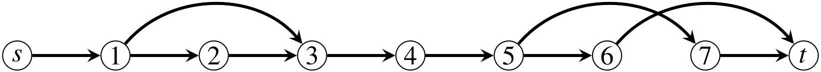

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- **Edges:** adjacent regions or connected by spliced reads

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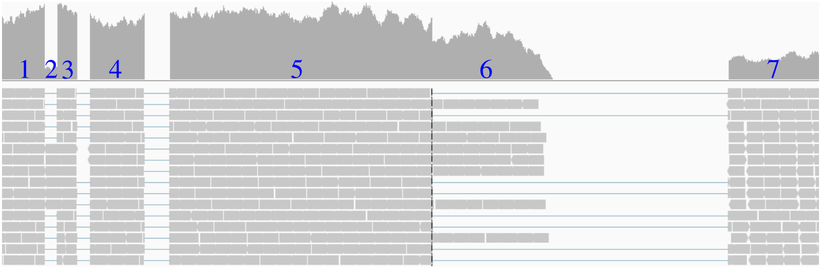
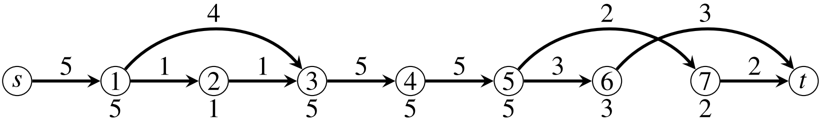
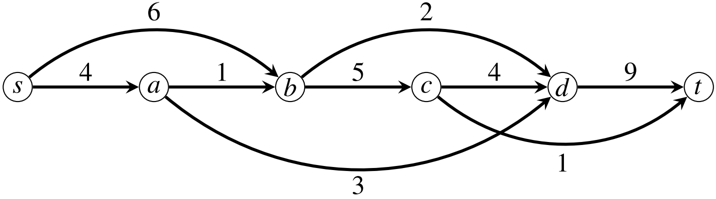




- **Nodes:** continuous regions not seperated by spliced reads
- **Edges:** adjacent regions or connected by spliced reads
- **Weight of nodes:** estimated from the average coverage
- **Weight of edges:** estimated from number of spanning reads

Optimization Problem

- **Input:** Directed acyclic graph (DAG) $G = (V, E)$ with a single source s and a single sink t; weight $w(e)$ for $e \in E$.



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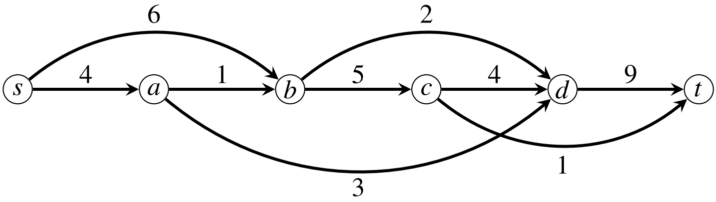
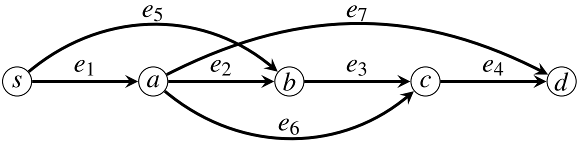


- **Output:** A set of s-t paths $\mathscr{P}$ and abundance $a(P)$ for $P \in \mathscr{P}$, such that
  1. each $e \in E$ is covered by at least one path $P \in \mathscr{P}$, and that
  2. $|\mathscr{P}|$ is as small as possible, and that
  3. $\sum_{e \in E} \|w(e) - \sum_{P: e \in P} a(P)\|$ is as small as possible.

Minimize the Number of Paths

Problem: Given DAG $G = (V, E)$ with source s and sink t, to compute minimum number of paths that can cover all edges.



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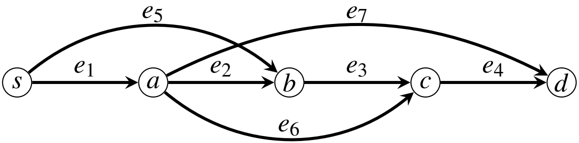

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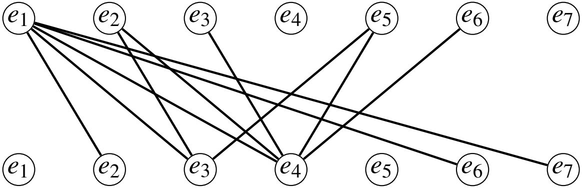

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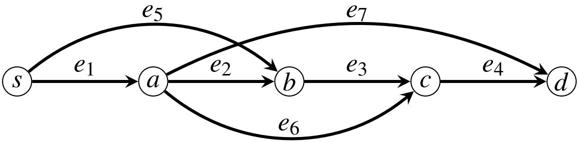

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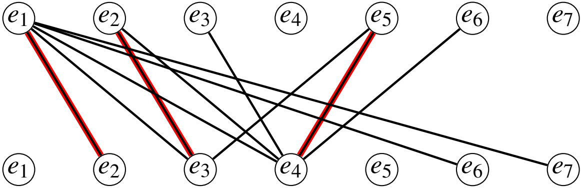

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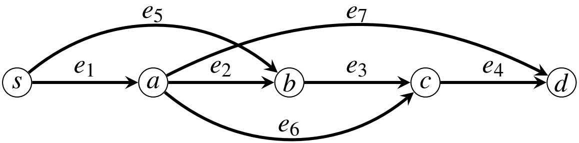

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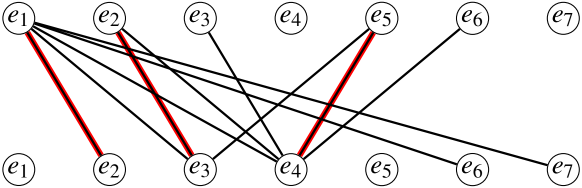

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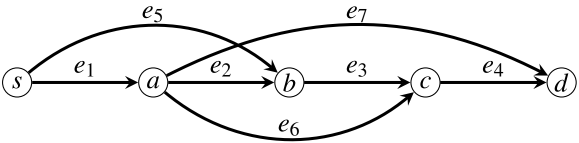

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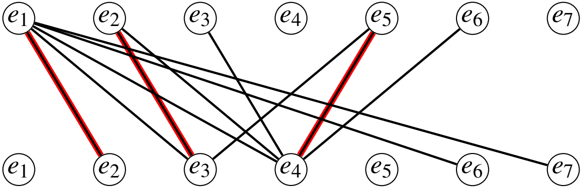

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Existing Software: Cufflinks (Trapnell *et al.*, 2010)

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Problem: Given DAG $G = (V, E)$ with source s, sink t, and weight $w(e)$ for $e \in E$, to compute a set of s-t paths $\mathscr{P}$ so that all edges are covered and that $\sum_{e \in E} |w(e) - \sum_{P: e \in P} a(P)|$ is minimized.

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Fact: There exists a set of paths satisfying $x(e) = \sum_{P \in \mathscr{P} : e \in P} a(P)$ for all $e \in E$ if and only if $x(e)$ forms a flow of G.

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Existing Software: Traph (Tomescu *et al.*, 2013)

Minimize Abundance Error with k Paths

Problem: Given DAG $G=(V,E)$ with source s, sink t, weight $w(e)$ for $e \in E$, to compute a set of at most k s-t paths $\mathscr{P}$ such that $\sum_{e\in E} \|w(e) - \sum_{P:e\in P} a(P)\|$ is minimized.

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4. Polynomial-time algorithm for G with constant treewidth.

Regularization Methods

Optimization Formulation:

$$\min \sum_{e \in E} \|w(e) - \sum_{P: e \in P} a(P)\| + \lambda \sum_{P \in \mathscr{P}} \|a(P)\|^q$$

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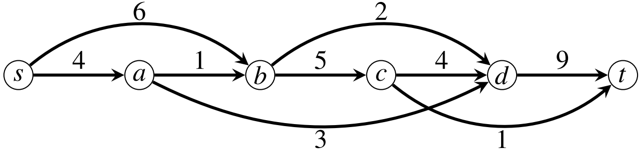

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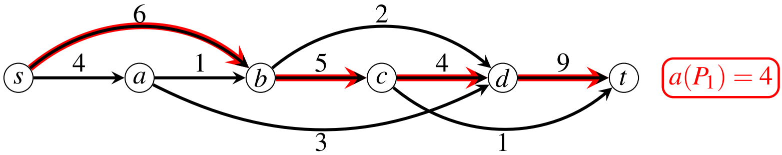

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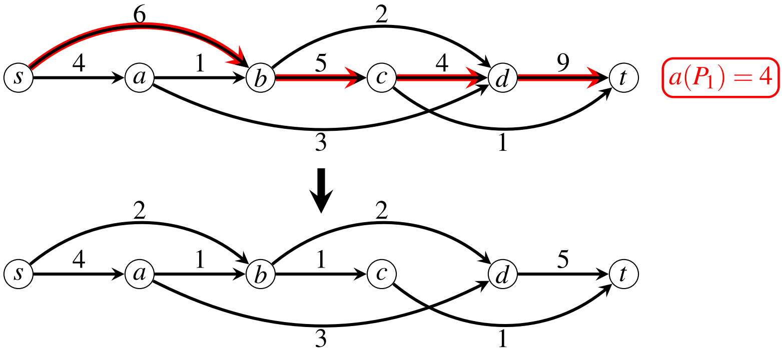

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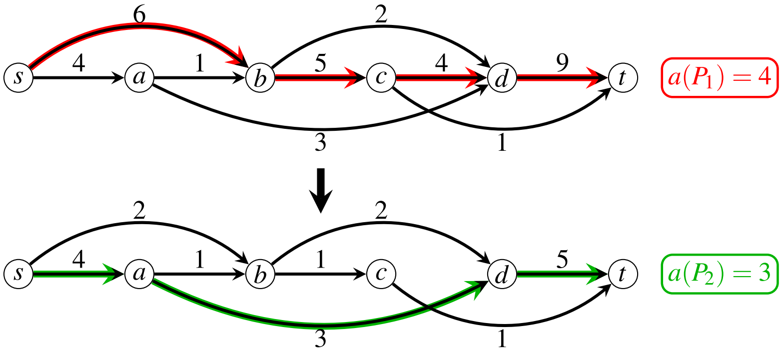

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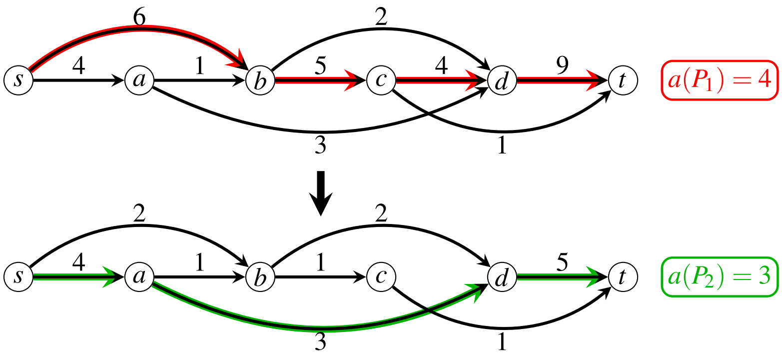

Existing Softwares: Traph (Tomescu *et al.*, 2013), StringTie (Pertea *et al.*, 2015)

Our Method—Framework

1. Initialize a set of paths $\mathscr{P}$ (in polynomial size).
2. Use LP to compute $a(P)$ for $P \in \mathscr{P}$ so as to minimize the estimation error.
3. Reduce the number of paths in $\mathscr{P}$:
   - For two paths with (almost) identical abundance, try to merge them into one path;
   - Discard paths with very small abundance.
4. Iterate between step 2 and step 3.

Example for Greedy Algorithm

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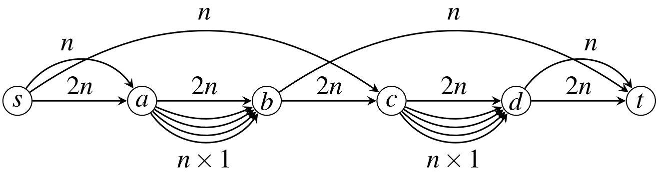

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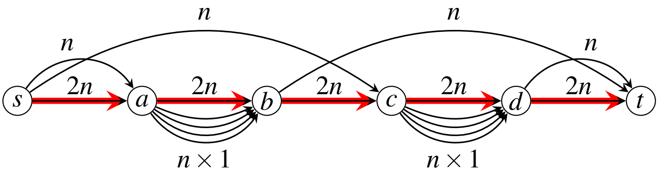

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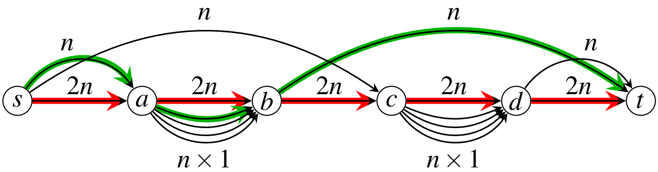

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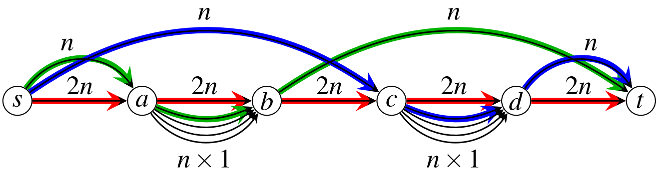

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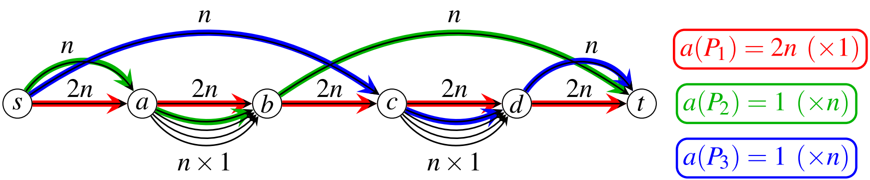

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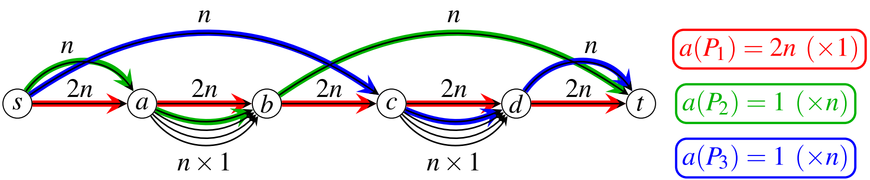

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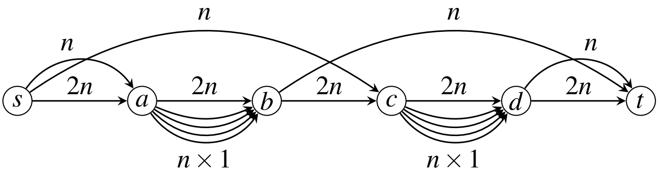
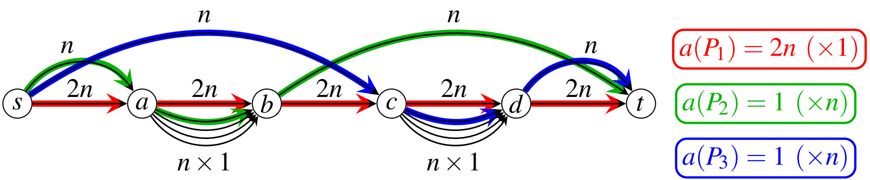


Example for Greedy Algorithm



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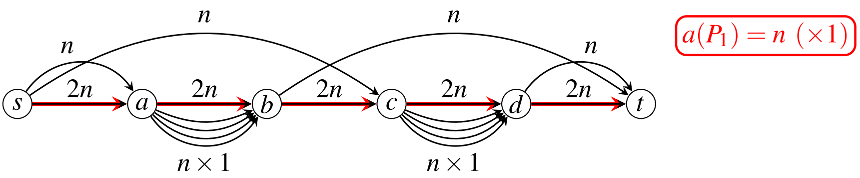
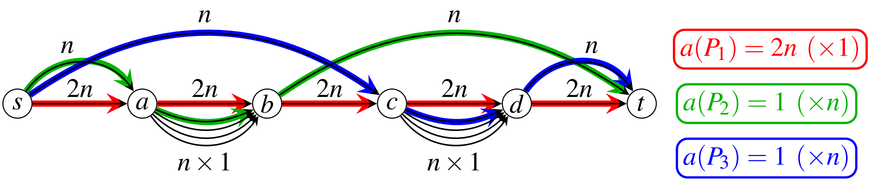
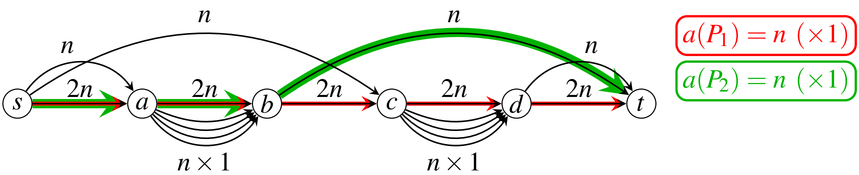


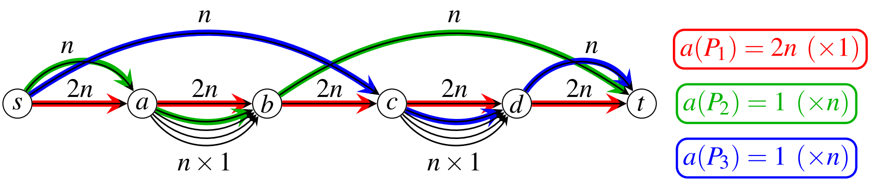
Example for Greedy Algorithm



Solution by greedy algorithm: $2n + 1$ paths.



Example for Greedy Algorithm



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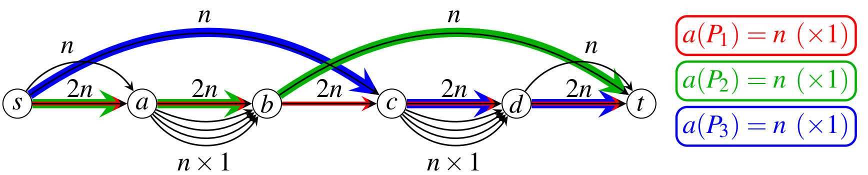
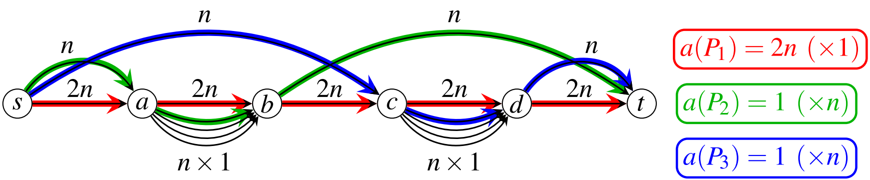


Example for Greedy Algorithm



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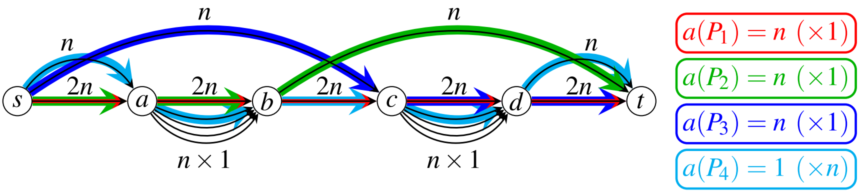
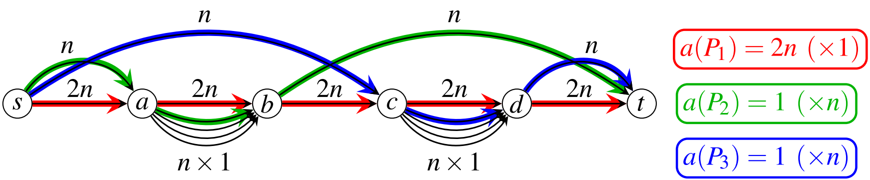


Example for Greedy Algorithm



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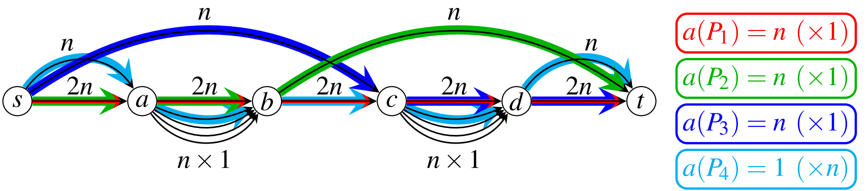
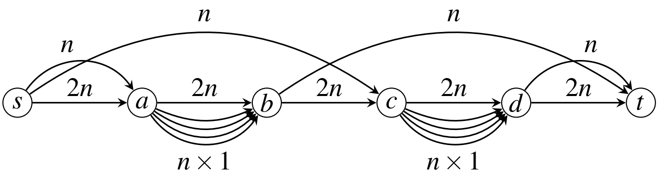


Optimal solution: $n + 3$ paths.

Use the Residual Graph

Use the Residual Graph



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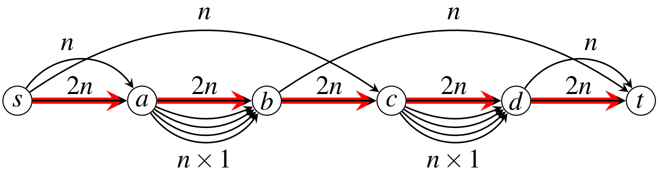
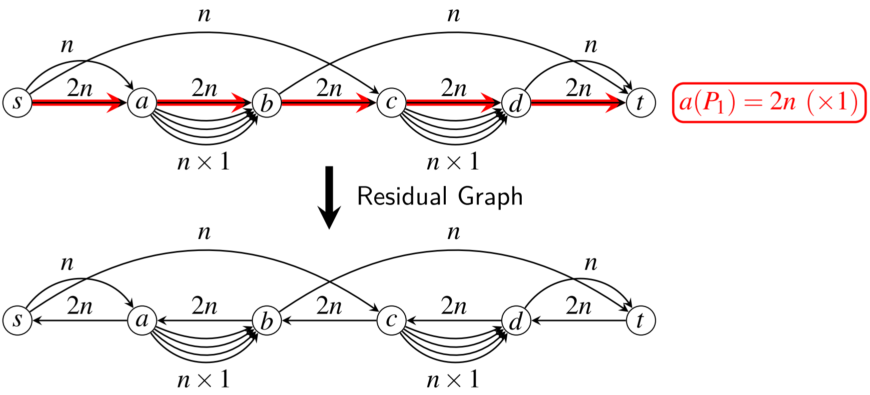


$\boxed{a(P_1) = 2n \ (\times 1)}$

Use the Residual Graph



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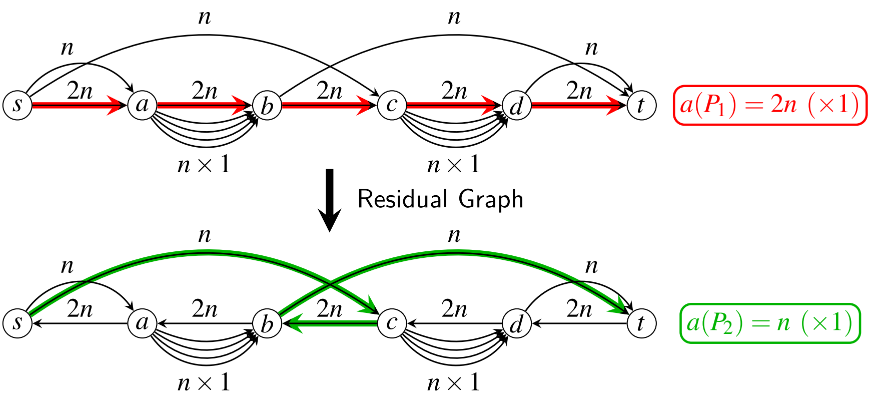

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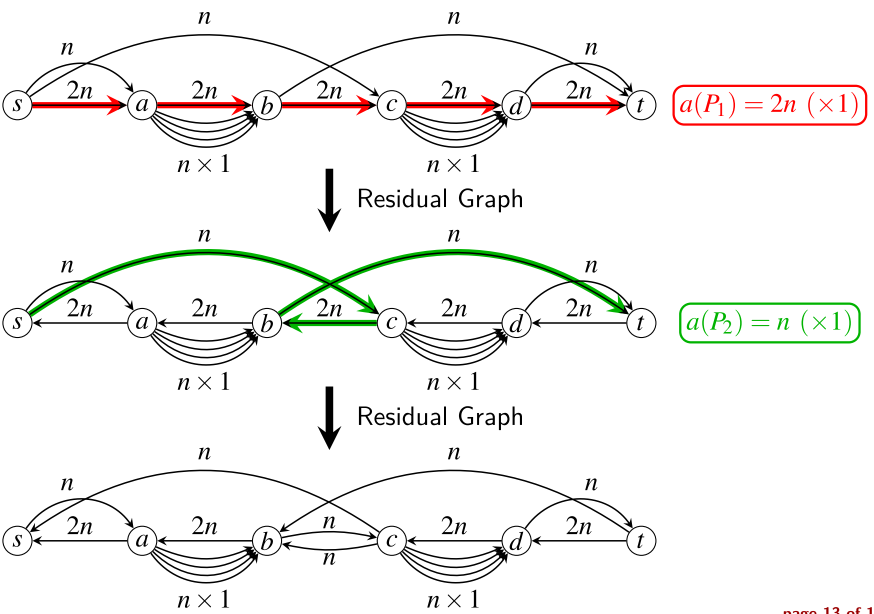

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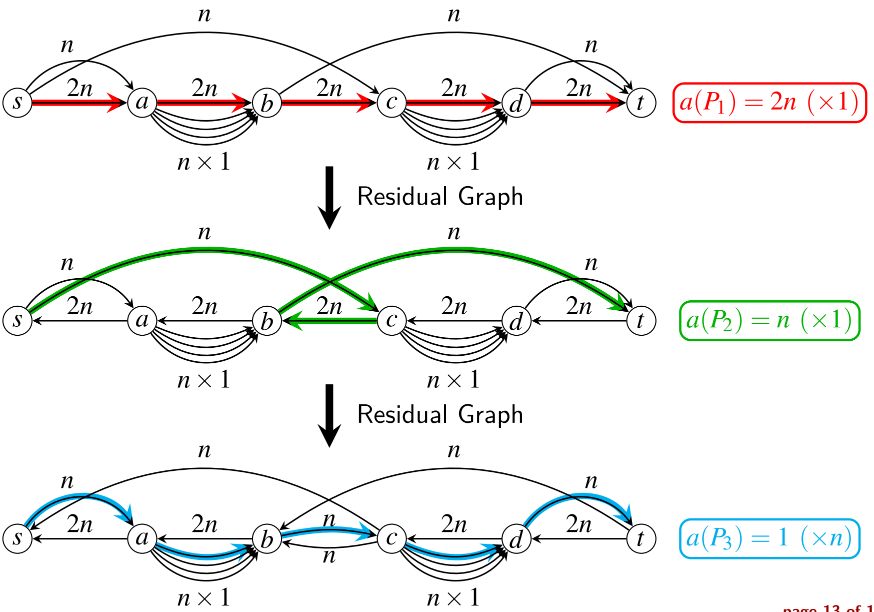

Resolve Path with Backward Edges

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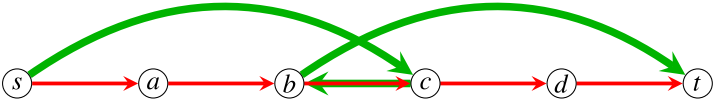
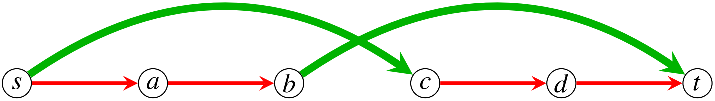
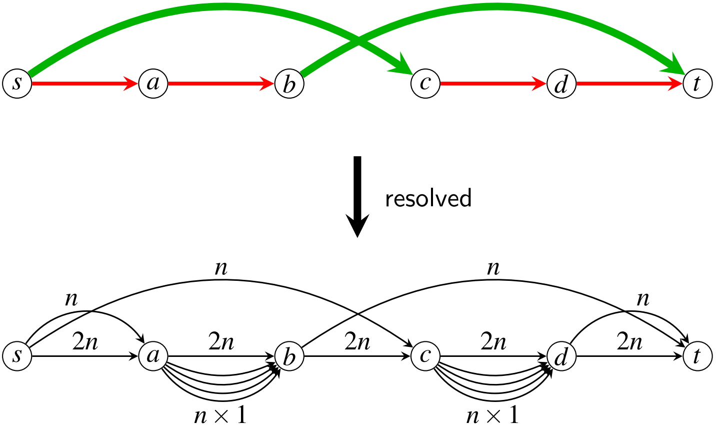


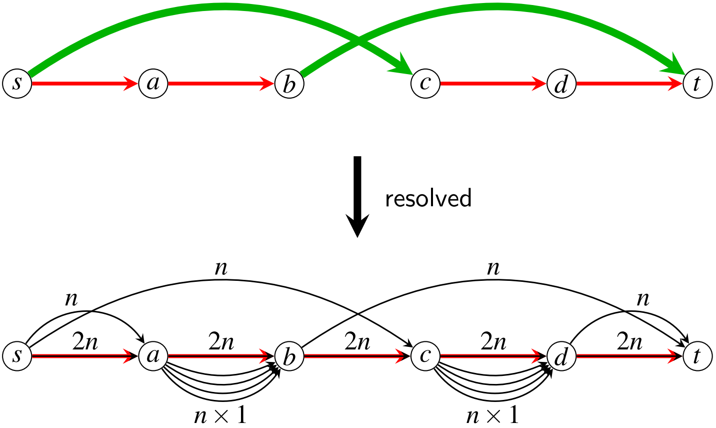
Resolve Path with Backward Edges



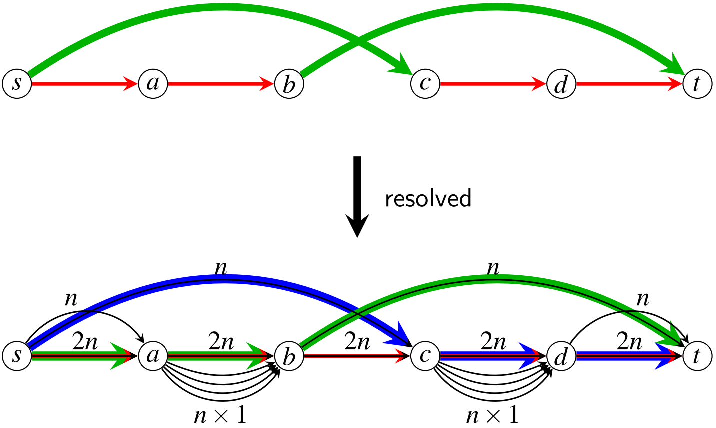
Resolve Path with Backward Edges



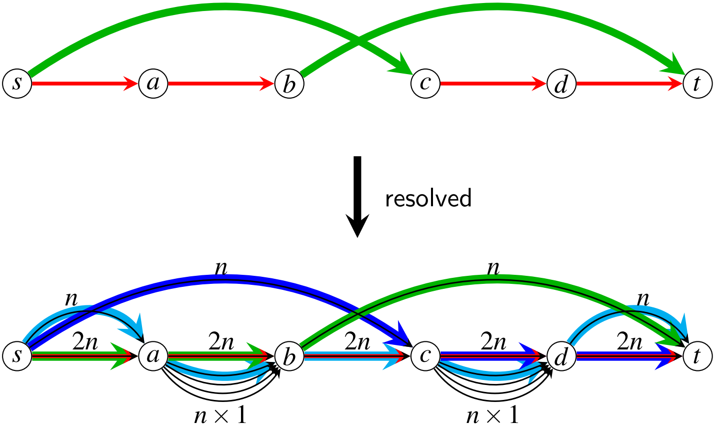
Resolve Path with Backward Edges



Resolve Path with Backward Edges



Resolve Path with Backward Edges



Algorithm to Initialize $\mathscr{P}$

1. Initialize $\mathscr{P} = \emptyset$.
2. Compute a set of paths $\mathscr{P}'$ (paths in $\mathscr{P}'$ may contain backward edges) following the max-flow algorithm.
3. **For** each $P \in \mathscr{P}'$ in its original order:
    1. **If** P does not contain backward edges, let $\mathscr{P} = \mathscr{P} \cup \{P\}$;
    2. **else** resolve P using $\mathscr{P}$ and put all resulting paths into $\mathscr{P}$.
    3. **If** $\mathscr{P}$ becomes a basis, or $|\mathscr{P}| \geq C$, **break**.
4. **Return** $\mathscr{P}$.

Our Method—Framework

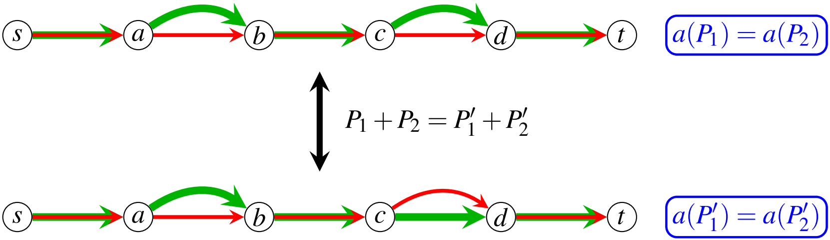
1. Initialize a set of paths $\mathscr{P}$ (in polynomial size).
2. Use LP to compute $a(P)$ for $P \in \mathscr{P}$ so as to minimize the estimation error.
3. Reduce the number of paths in $\mathscr{P}$:
   - For two paths with (almost) identical abundance, try to merge them into one path;
   - Discard paths with very small abundance.
4. Iterate between step 2 and step 3.

Merge Paths: Example

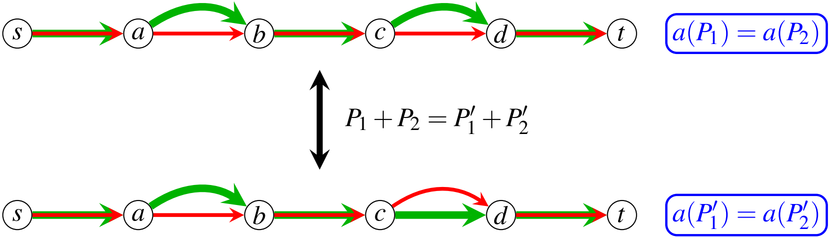
Merge Paths: Example

$\boxed{a(P_1) = a(P_2)}$

Merge Paths: Example



Merge Paths: Example



$$\mathscr{P} = \begin{cases} P_1: & a(P_1) = p \\ P_2: & a(P_2) = p \\ P_1': & a(P_1') = q \\ \dots & \end{cases} \Longrightarrow \mathscr{P}' = \begin{cases} P_1': & a(P_1') = q + p \\ P_2': & a(P_2') = p \\ \dots & \end{cases}$$