Genome assembly, a universal theoretical framework: unifying and generalizing the safe and complete algorithms

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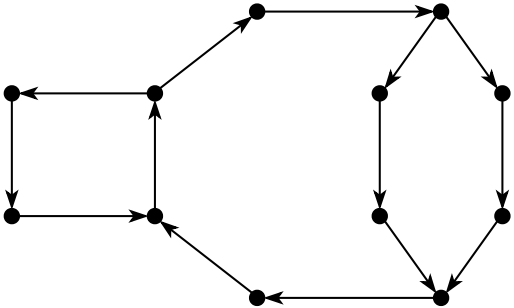
Outline

Genome Assembly & Safety

Models of genome assembly

Genome graph:

- Used by almost all modern assemblers
- Each edge is part of the genome
- The genome is a walk



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Additional information:

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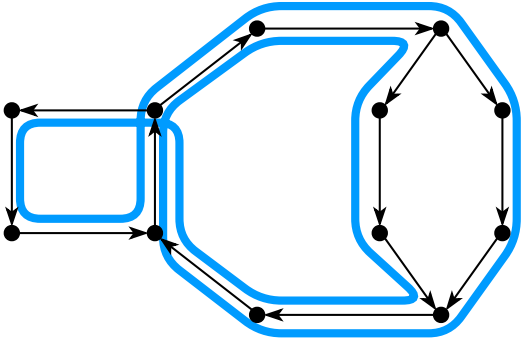

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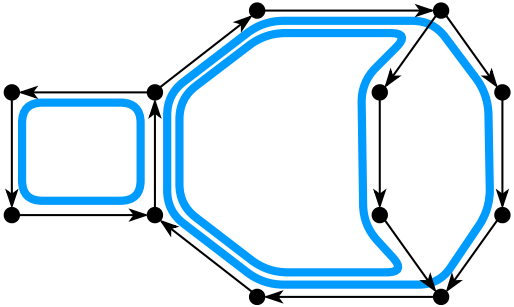
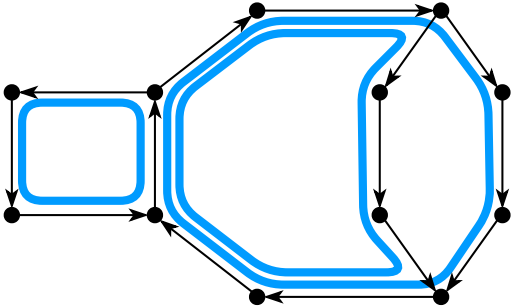


Finding the true genome

Challenge:

- Infinitely many possible solutions
  What is the correct one?



Finding the true genome

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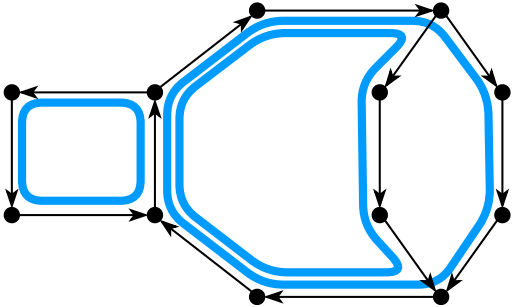
Solution:

- Find only safe subwalks
  of the true genome
- But be as complete as possible



Accounting for practical issues

Father: AATGCAGTATGCAGTCATGCAGTTACGACGT
Mother: AATGCAGTATGCAGTCATGCAGTGACGACGT

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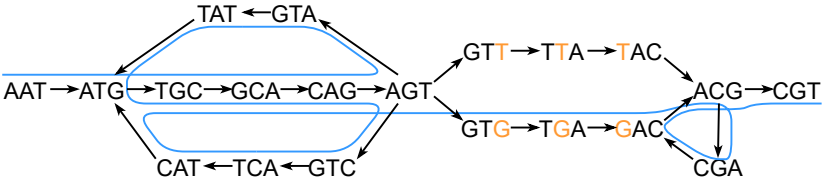

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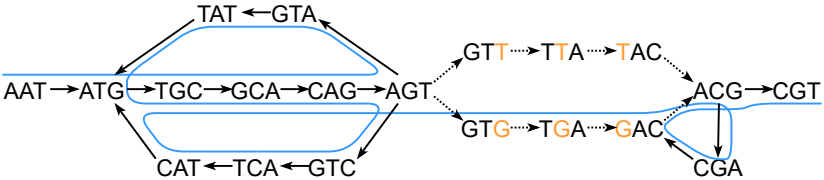

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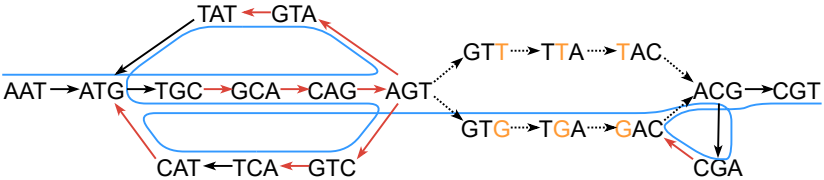

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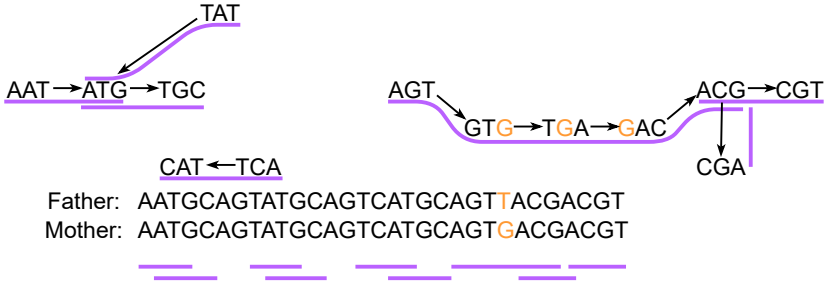

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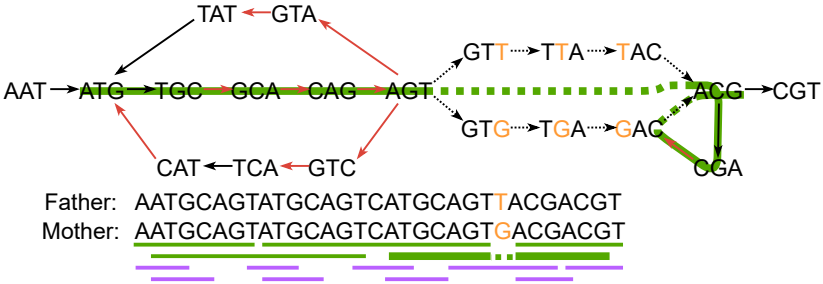
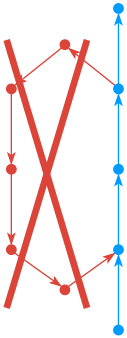


Current Safe and Complete Algorithms

Properties of current safe and complete algorithms

Single circular, Omnitigs:
characterisation (Tomescu and Medvedev, 2017)
optimal $O(mn)$ (Cairo et al., 2019)
output optimal $O(m + n + o)$ (Cairo et al., 2020b)

Multi circular:
$O(m^2 n)$ (Acosta, Mäkinen, and Tomescu, 2018)



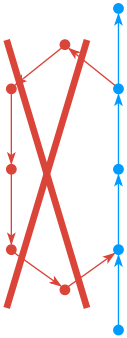
Properties of current safe and complete algorithms

Single circular: $O(mn)$, $O(m+n+o)$
Multi circular: $O(m^2 n)$

But many other models are relevant:

- k solution walks
- linear models
- partial coverage
- partial visibility

Unified theory for all combinations of these?



Unifying the Theory: the Hydrostructure (Cairo et al., 2020a)

Unification: the hydrostructure of a walk W

- Defined on a strongly connected graph $G := V \cup E$ and a walk $W \subseteq G$

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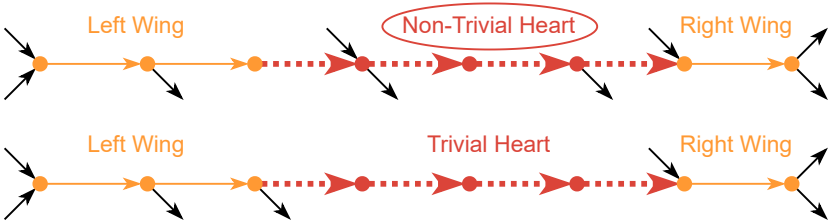
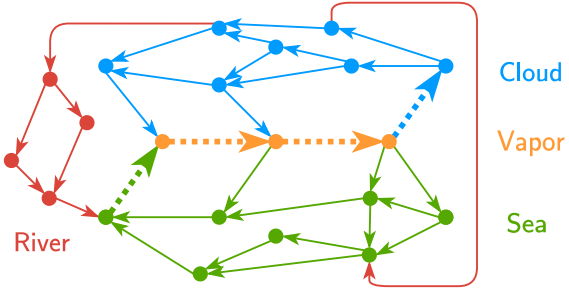
- In this talk: only non-trivial hearts of paths (without repetitions of nodes/edges)



Unification: the hydrostructure of a walk W

- Decomposes the graph into four regions



Unification: the hydrostructure of a walk W

- Decomposes the graph into four regions
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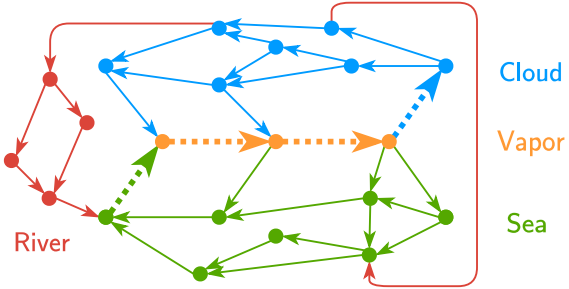

Unification: the hydrostructure of a walk W

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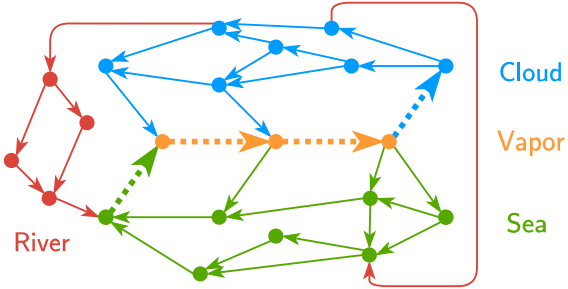
- If Vapor is a path, then W is a Sea-Cloud bottleneck



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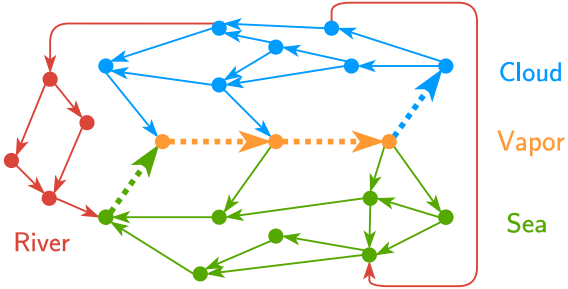
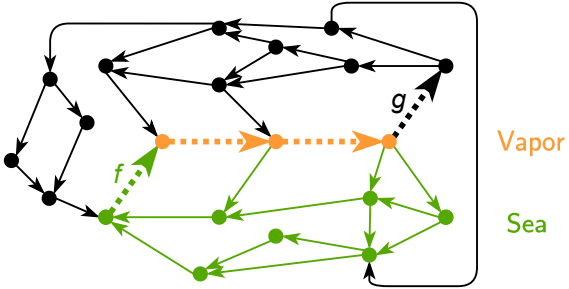
- For any model: if each solution walk goes from Sea to Cloud, then W is safe



Definition of the hydrostructure

- W is a walk from edge f to edge g
- $R^+(W)$ is everything reachable from f in $G \setminus g$



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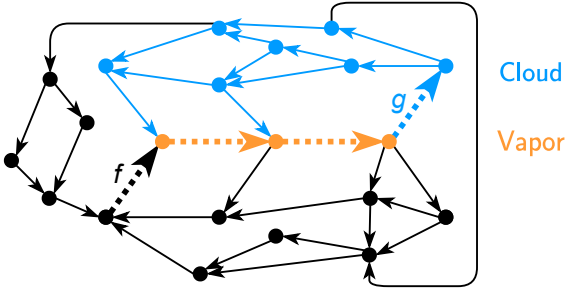

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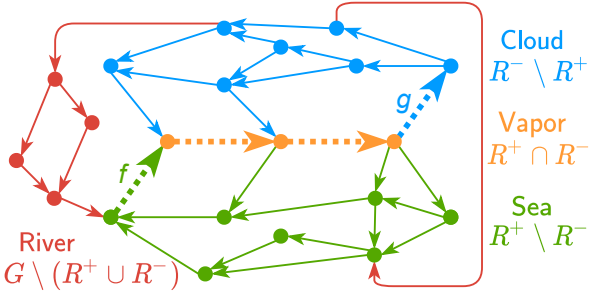

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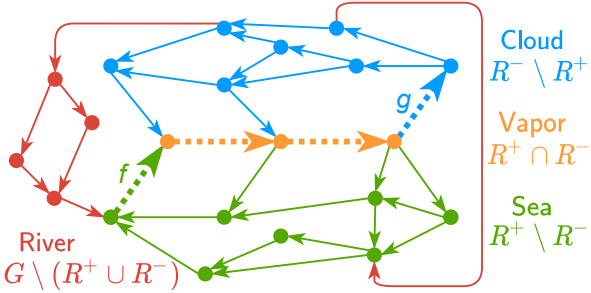
- W is a Sea-Cloud bottleneck if and only if **Vapor is a path**

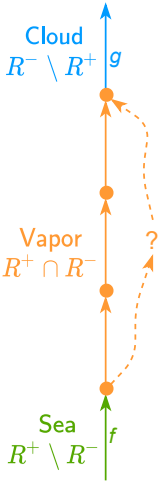


The bottleneck property

Definition 1: $R^+(W) := \{x \in G \mid f \to x \in G \setminus g\}$
Definition 2: $R^-(W) := \{x \in G \mid x \to g \in G \setminus f\}$
Definition 3: W is a Sea-Cloud bottleneck if each walk from Sea to Cloud has W as subwalk

Lemma: W is a Sea-Cloud bottleneck $\iff$ Vapor is a path

- f is the only way to enter $R^-(W)$ (by Def. 2)



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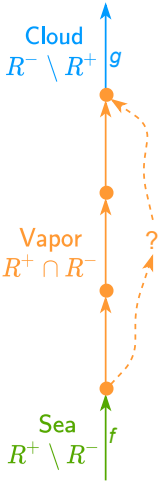

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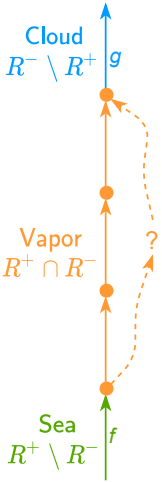
- $\Rightarrow$ Sea-Cloud walks have a head(f)-tail(g) subwalk X



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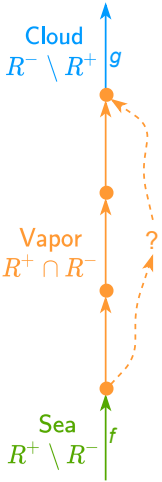

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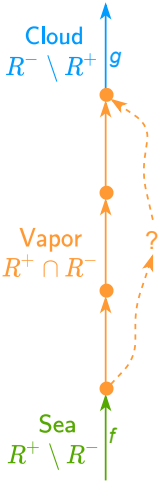
$\Rightarrow$ If W Sea-Cloud bottleneck, then $fXg = W$, so Vapor is a path



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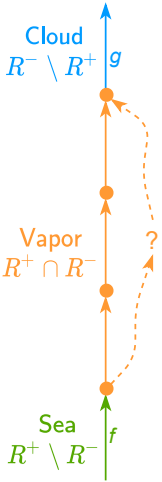
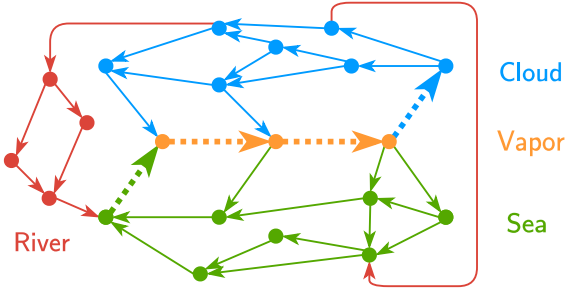


Safety problems as Sea-Cloud connectivity problems

- For any model: if each solution walk goes from Sea to Cloud, then W is safe



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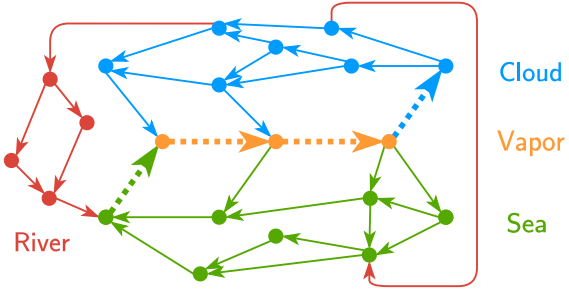

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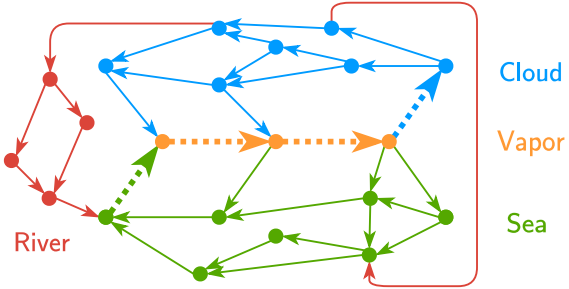

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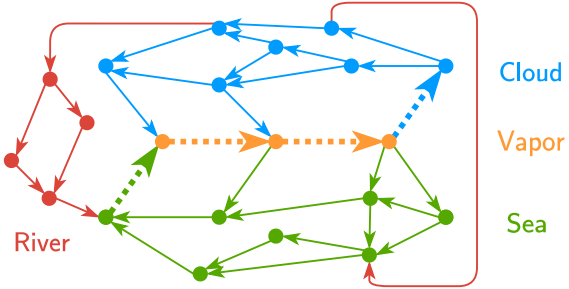
- Simplifies single/multi linear



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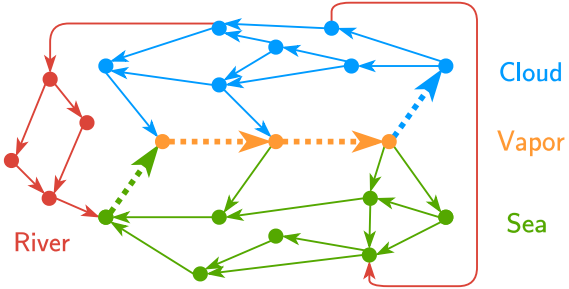

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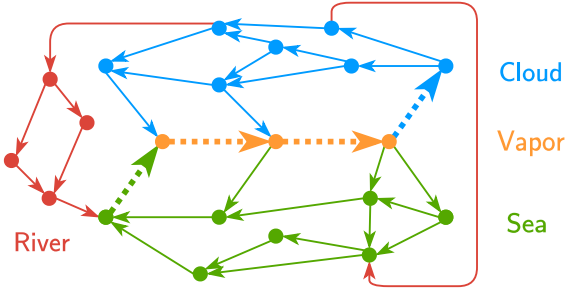
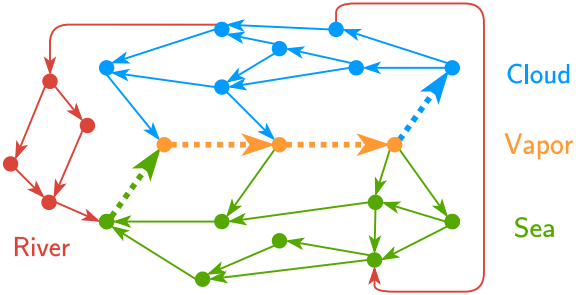


Hydrostructure Algorithms

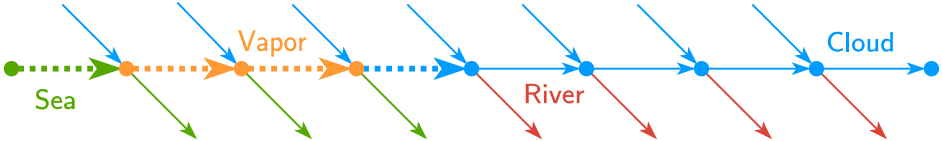
Algorithmic properties: verification



$O(m)$ construction:

- $O(m)$ verification algorithms
  ($O(mn)$ for linear $2 \leq k \leq O(n)$, subset visibility)

Algorithmic properties: enumeration



$O(m)$ incremental construction:

- $O(m + o)$ enumeration of safe subwalks of a given bottleneck walk ($O(mn)$ for linear $2 \leq k \leq O(n)$, subset visibility)

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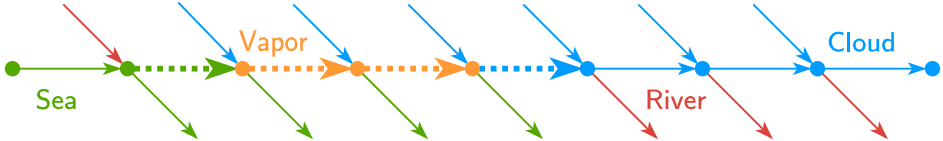

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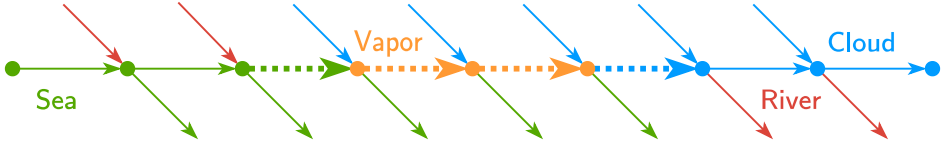

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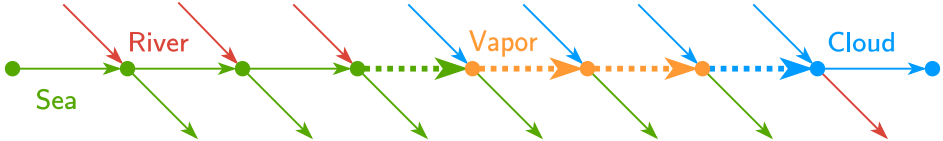

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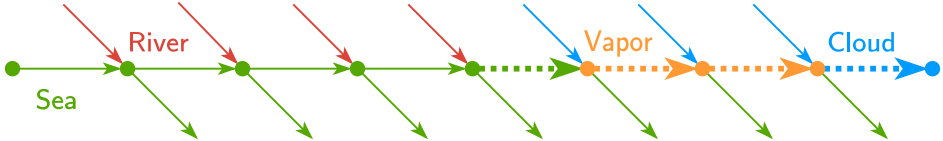

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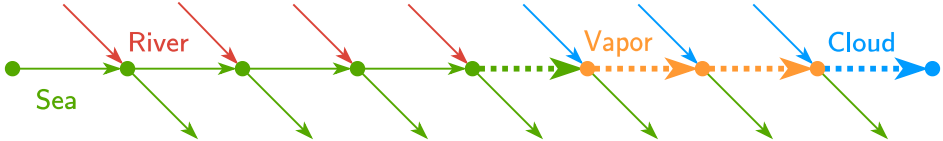


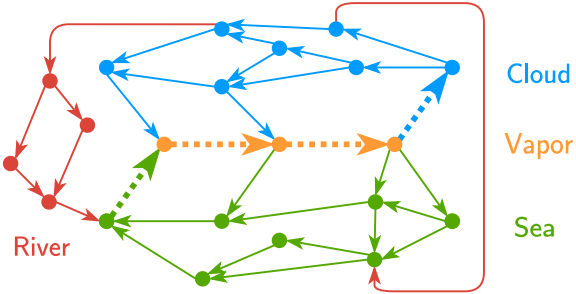
$O(m)$ incremental construction:

- $O(m + o)$ enumeration of safe subwalks of a given bottleneck walk ($O(mn)$ for linear $2 \leq k \leq O(n)$, subset visibility)

Safe walks are subwalks of omnitigs:

- Omnitig enumeration takes $O(mn)$ time and only $O(n)$ of them are bottlenecks
- Optimal $O(mn + o)$ enumeration of all maximal safe walks ($O(m^2 n)$ for linear $2 \leq k \leq O(n)$)

Recap/Conclusion



- The hydrostructure unifies the theory of safe and complete genome assembly
- The hydrostructure yields optimal algorithms for most model combinations

References I

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References II

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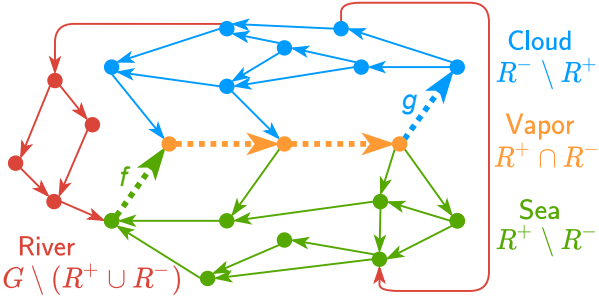
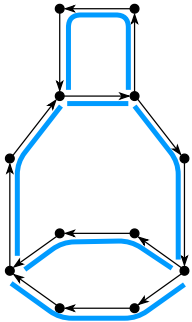
- Tomescu, Alexandru I. and Paul Medvedev (2017). “Safe and complete contig assembly through omnitigs”. In: *Journal of Computational Biology* 24.6. Preliminary version appeared in RECOMB 2016., pp. 590–602.

Thank you for attending! Questions?



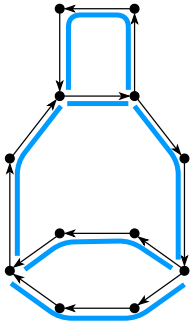
- The hydrostructure unifies the theory of safe and complete genome assembly
- The hydrostructure yields optimal algorithms for most model combinations

Safety in the single circular model

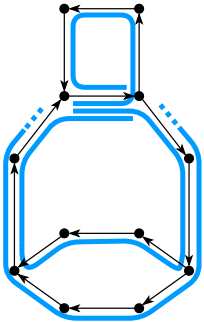


Unitigs

Safety in the single circular model

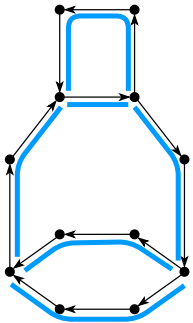


Unitigs

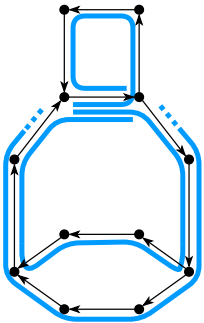


Y-to-V Unitigs
(excerpt)

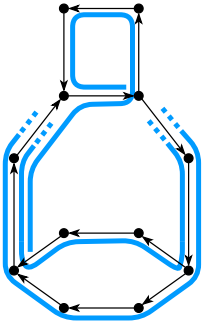
Safety in the single circular model



Unitigs



Y-to-V Unitigs (excerpt)

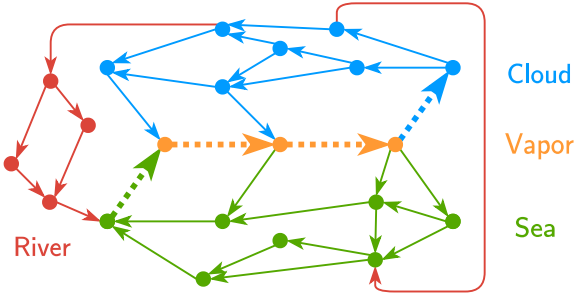


Omnitigs (excerpt) (Tomescu and Medvedev, 2017)

Algorithmic Properties

Verification:

- $O(m)$ verification algorithms ($O(mn)$ for linear $2 \leq k \leq O(n)$ subset visibility)



Algorithmic Properties

Verification:

- $O(m)$ verification algorithms ($O(mn)$ for linear $2 \leq k \leq O(n)$ subset visibility)

Enumeration:

- Optimal $O(mn + o)$ enumeration of all maximal safe walks ($O(m^2 n)$ for linear $2 \leq k \leq O(n)$)