Popping Superbubbles and Discovering Clumps

Recent Developments in Biological Sequence Analysis

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Outline

Outline

Introduction

Computational genomics can be divided into two complex and major stages, each of which presents many problems:

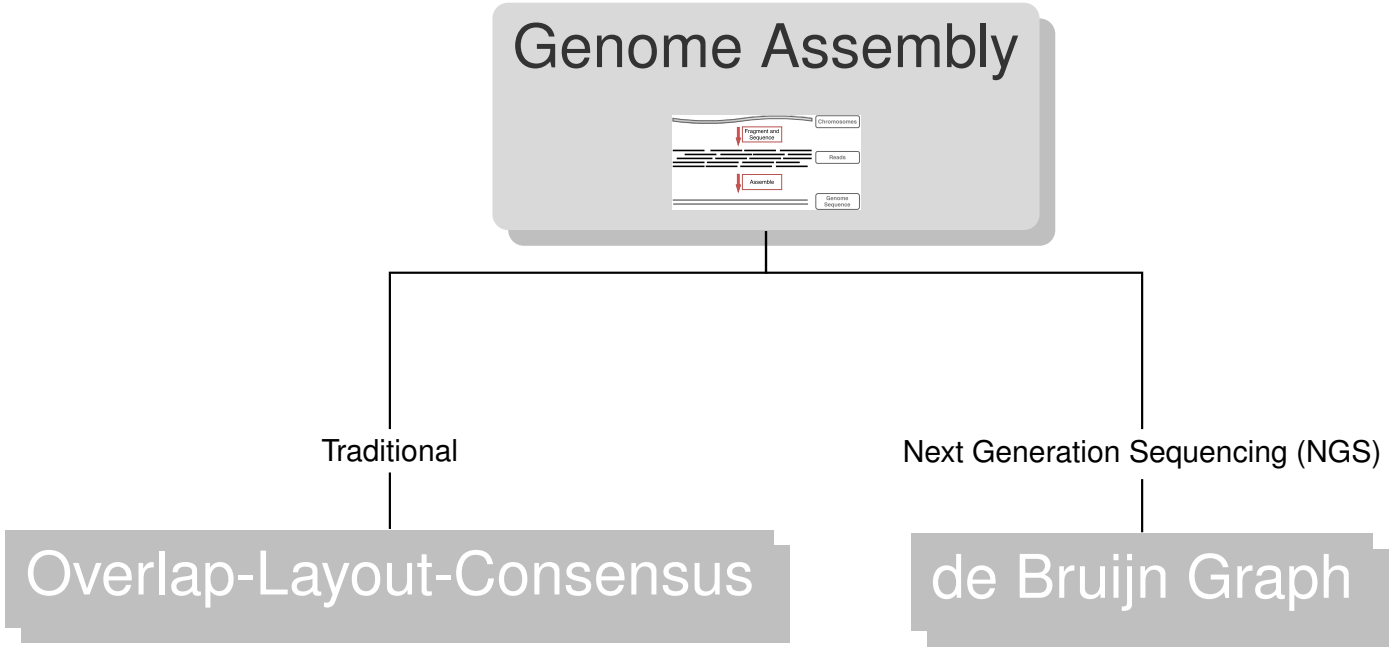
1. Assembly (error correction)
2. Annotation (motif discovery, gene prediction)

We focus on one problem from each stage:

1. *Superbubble* detection during genome assembly
2. Finding *clumps* for genome annotation

Outline

Motivation


Genome Assembly
Chromosomes
Fragment and Sequence
Reads
Assemble
Genome Sequence
Traditional
Next Generation Sequencing (NGS)
Overlap-Layout-Consensus
de Bruijn Graph

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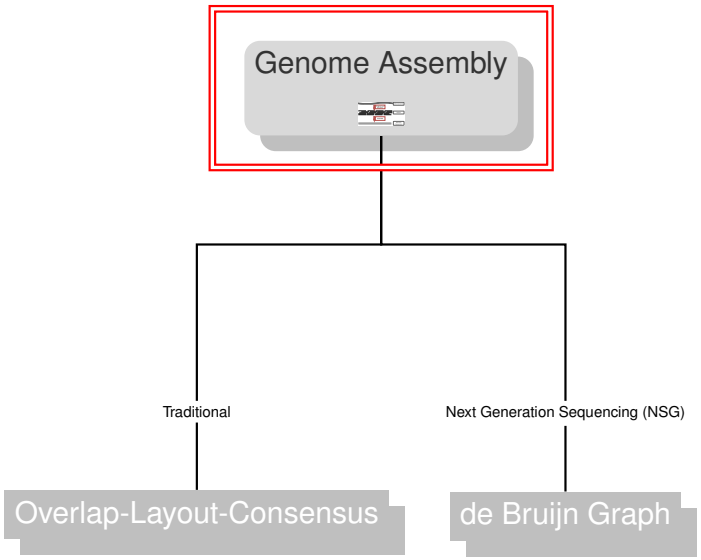
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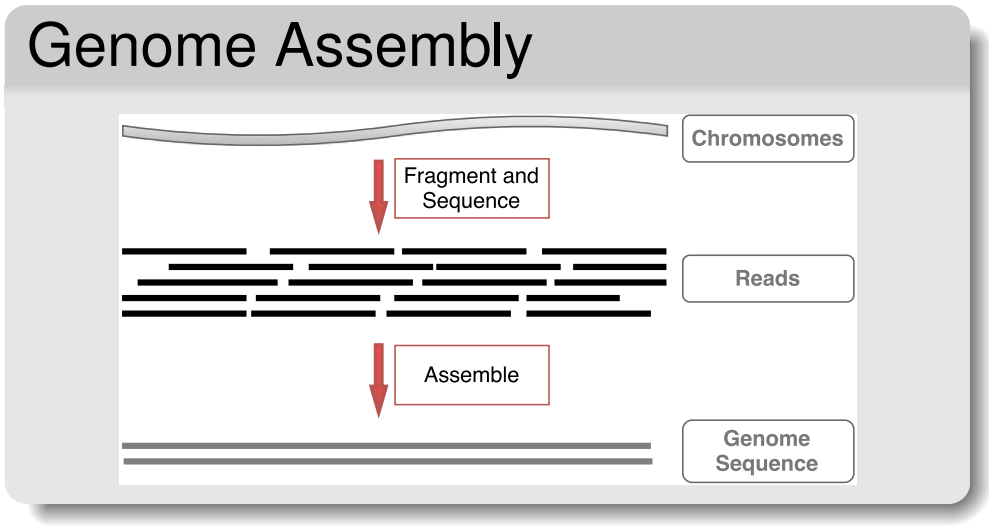
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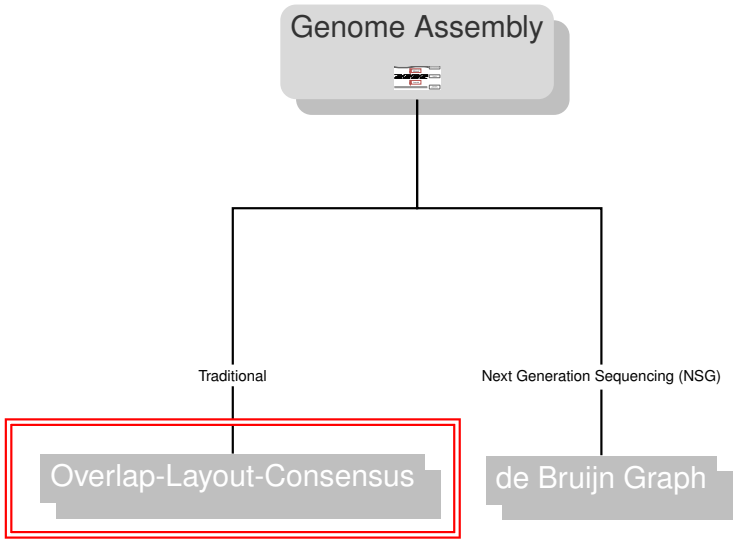
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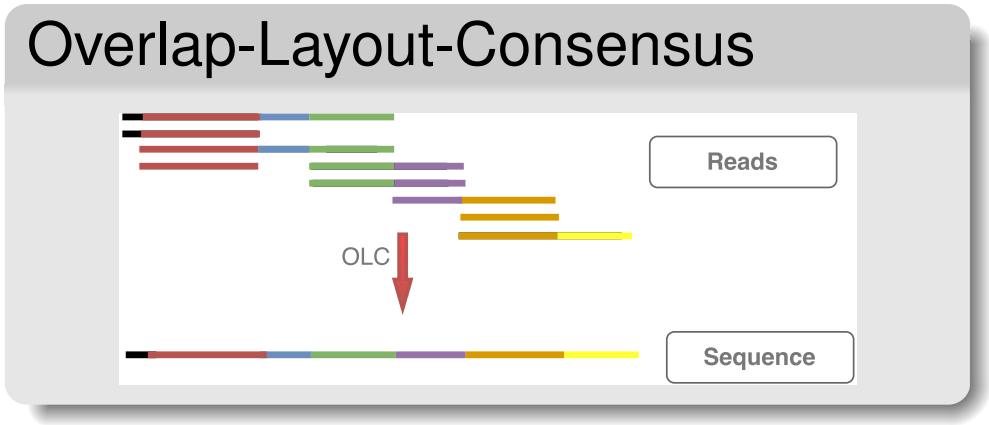
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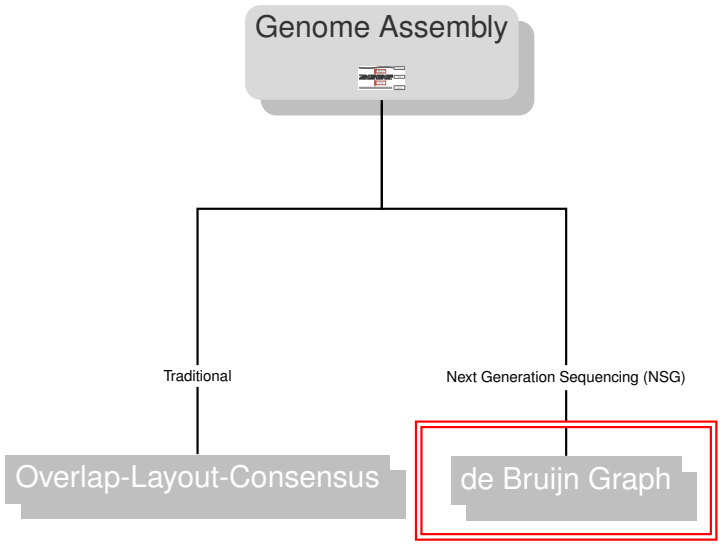

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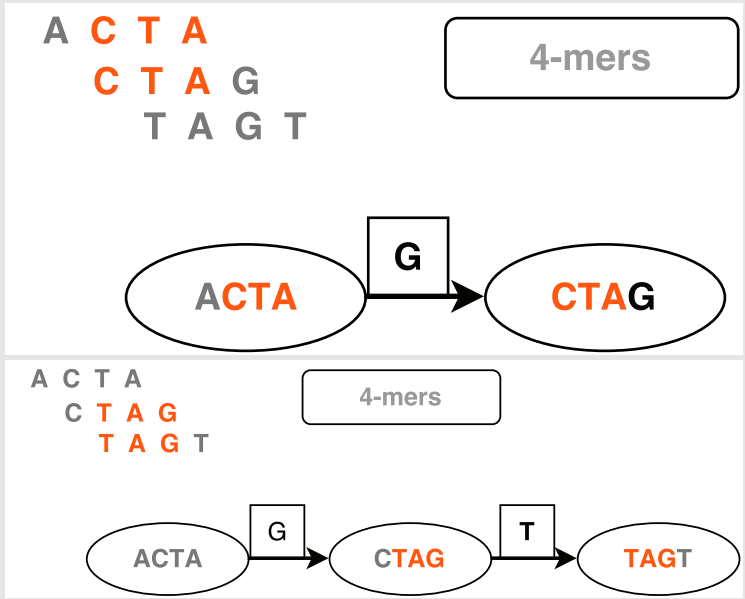

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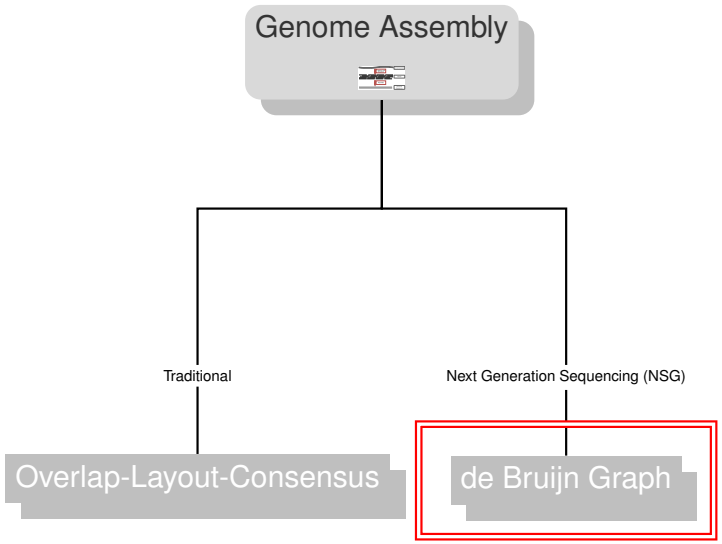
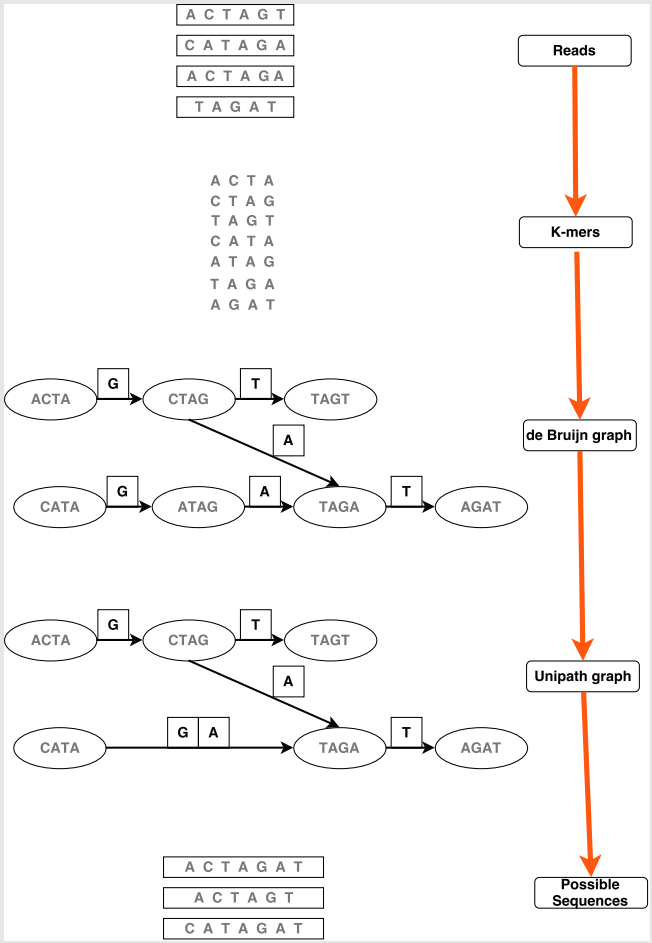


NSG



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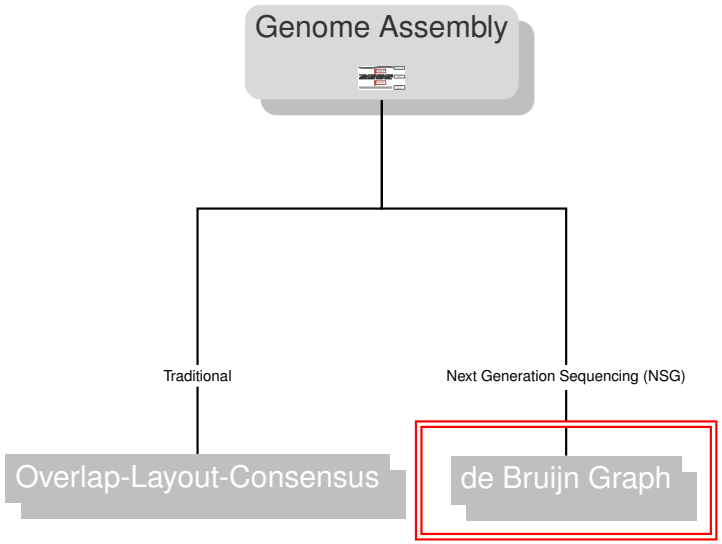

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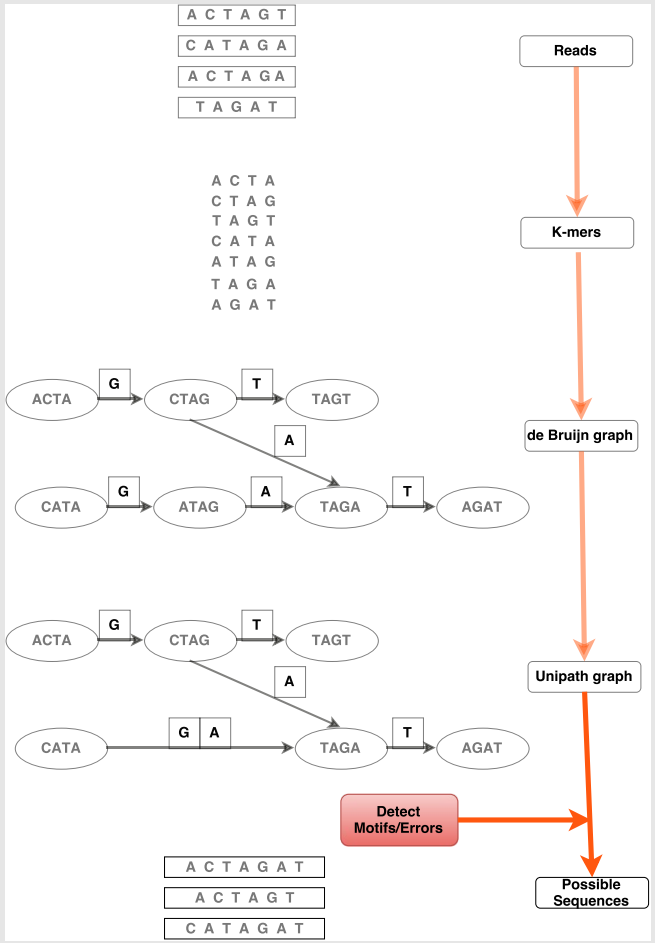
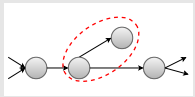
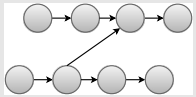


Motifs

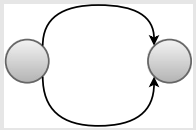
- Tips
  - A low-frequency edge whose end (or start) vertex has no outgoing (resp. incoming) edges, which goes out from (resp. comes into) a high-frequency vertex.
  - Often appears in case there are some error(s) around the end of a read.



- Cross-links
  - It is a low-frequency edge that lies between high-frequency vertices.
  - Appears when a substring of a read accidentally becomes (by error) the same substring that appears in a different region.



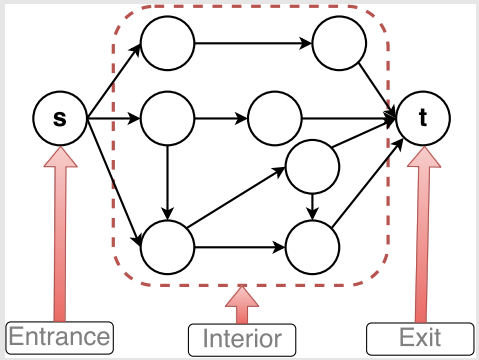
- Bubbles
  - It consists of multiple edges (with the same direction) between a pair of vertices.
  - Often caused by error(s) somewhere in the middle of a read.



- More Complex Structures? **Superbubble**

Superbubble

Superbubble: $\langle s,\ t \rangle$

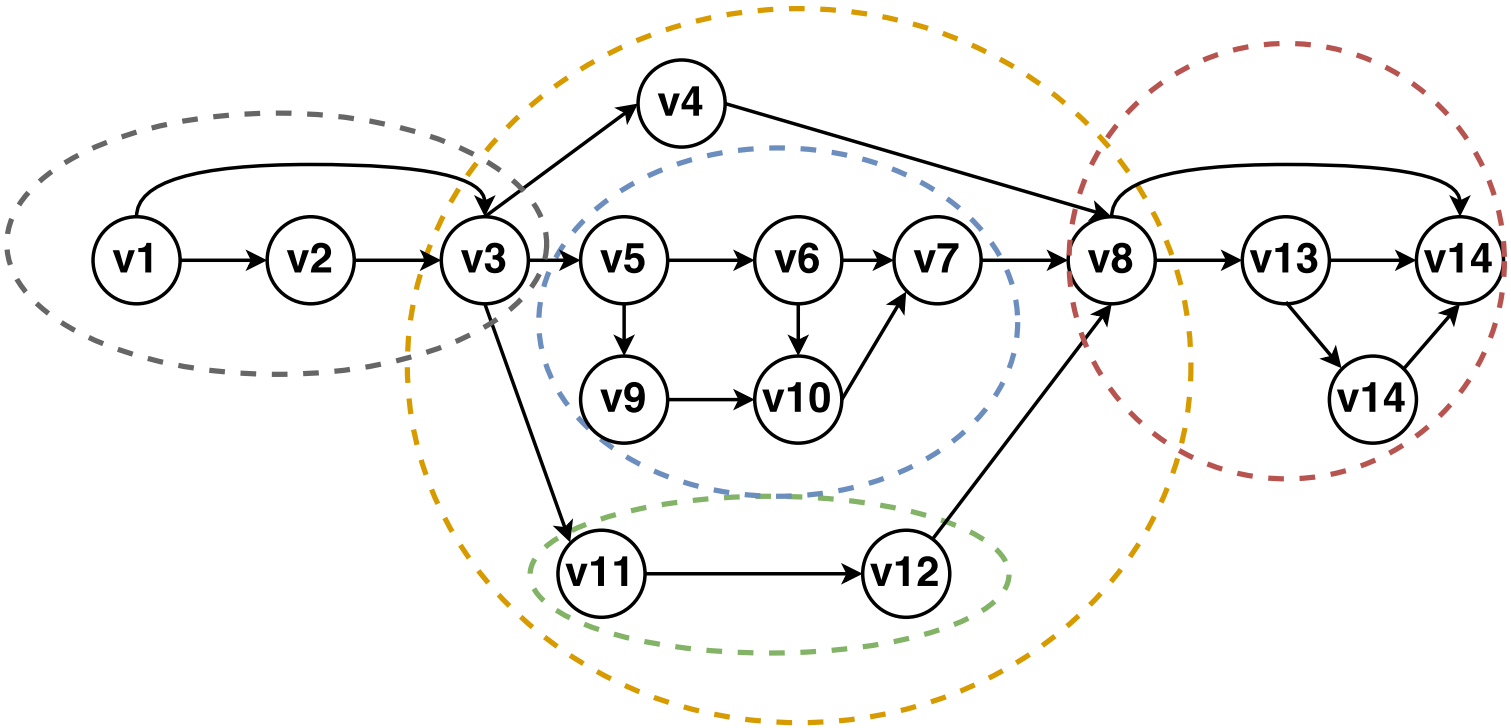


Definition [Onodera et al., 2013]

Let $G = (V, E)$ be a directed graph. For any ordered pair of distinct nodes s and t, $\langle s, t \rangle$ is called a *superbubble* if it satisfies the following:

- **reachability:** t is reachable from s;
- **matching:** the set of nodes reachable from s without passing through t is equal to the set of nodes from which t is reachable without passing through s;
- **acyclicity:** the subgraph induced by U is acyclic, where U is the set of nodes satisfying the matching criterion;
- **minimality:** no node in U other than t forms a pair with s that satisfies the conditions above;

Example



Properties of superbubbles

Lemma ([Onodera et al., 2013])

Any node can be the entrance (respectively exit) of at most one superbubble.

Lemma ([Sung et al., 2015])

Let G be a directed acyclic graph. We have the following two observations.
1) Suppose (p, c) is an edge in G, where p has one child and c has one parent, then $\langle p, c\rangle$ is a superbubble in G.
2) For any superbubble $\langle s, t\rangle$ in G, there must exist some parent p of t such that p has exactly one child t.

Lemma ([Brankovic et al., 2015])

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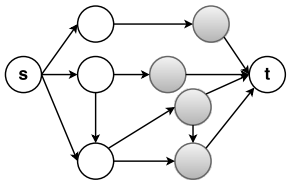

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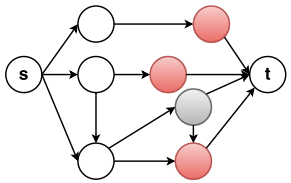

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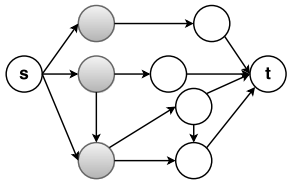

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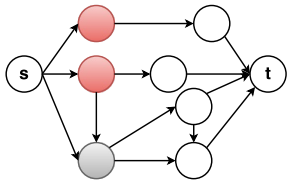

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Problem : Report All Superbubbles

Input

A directed graph $G = (V, E)$.

Output

All ordered pairs of distinct nodes s and t, such that $\langle s, t \rangle$ is a *superbubble.*

Solutions

- **Solution 1:** $\mathcal{O}(nm)$**-time algorithm [Onodera et al., 2013]**
- **Solution 2:** $\mathcal{O}(m \log m)$**-time algorithm [Sung et al., 2015]**
- **Solution 3:** $\mathcal{O}(n + m)$**-time algorithm [Brankovic et al., 2015]**

Solution 1

- Visit nodes in an order that follows the standard topological sorting, starting from a given node s in the given directed graph $G = (V, E)$, to eventually report a node t such that $\langle s, t \rangle$ is a *superbubble* (if any).
  - Abort every time either a tip or a cycle is encountered.
- Iterate for all $s \in V$.

Solution 2

- Partition graphs into a set of sub-graphs -
  - subgraphs corresponding to each non-singleton strongly connected component
  - a subgraph corresponding to the set of all the nodes involved in singleton strongly connected components.
- Convert each subgraph into acyclic if it is cyclic.
- Find superbubbles in each of the subgraph.

Solution 2

- Partition graphs into a set of sub-graphs - → linear
  - subgraphs corresponding to each non-singleton strongly connected component
  - a subgraph corresponding to the set of all the nodes involved in singleton strongly connected components.
- Convert each subgraph into acyclic if it is cyclic. → linear
- Find superbubbles in each of the subgraph. → $\mathcal{O}(m \log m)$

Solution 3

- Topologically order the vertices
- Identify possible entrance and exit candidates: *Candidate-list*
- Traverse candidate-list (in reverse topological order) to find superbubbles using subroutines:
  - *Report*
  - *Validate*

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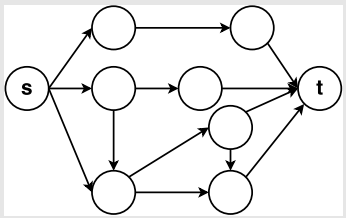
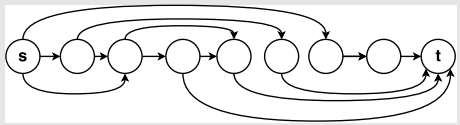
Example





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Candidate

A node v is an

- **exit candidate:** if it has at least one parent with exactly one child (out-degree 1)
- **entrance candidate:** if it has at least one child with exactly one parent (in-degree 1)

(From Lemmas 2 and 3)

Identifying Candidates

Check each node in V, in topological order, to identify whether it is an exit or an entrance candidate (or both).

- If both, add twice (first as entrance and then as exit).

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- Reports all the possible superbubbles (including nested ones) between given *start* and *exit*
- Called for each exit candidate in decreasing order either by *main* routine or through a recursive call to identify a nested superbubble.

Solution 3

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  - *Report*
  - *Validate*

- Valid: For a valid superbubble $\langle s, t \rangle$, every $x \in U \backslash \{s, t\}$ has
  - t as its *topologically furthest* child
  - s as its *topologically furthest* parent
- Maintain arrays of topological furthest child and parent resp., for each vertex and using RMQ to verify the conditions for validity.

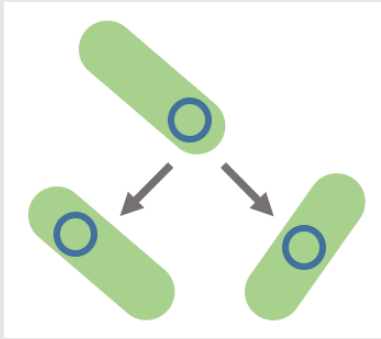
Discussion

- A critical step of assembly algorithms utilizing de Bruijn graphs is to detect typical motif structures in the graph caused by sequencing errors and genome repeats, and filter them out; one such complex subgraph class is a so-called *superbubble*.
- A superbubble $\langle s, t \rangle$ is equivalent to a single source, single sink, acyclic directed subgraph of G with source s and sink t, which does not have any cut nodes and preserves all in-degrees and out-degrees of nodes in $U \backslash \{s, t\}$, as well as the out-degree of s and in-degree of t.
- Given a directed acyclic graph $G = (V, E)$, where $n = |V|$ and $m = |E|$, all superbubbles in G can be identified in $\mathcal{O}(n + m)$-time.
- What's next? More complex motifs.

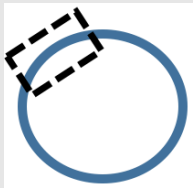
Outline

Motivation

DNA replication occurs during bacterial proliferation.



The Origin of Replication (OriC) is the region where DNA replication begins in a circular bacterial genome.



OriC can be identified by the occurrence of specific patterns in a region.

Motivating Example

E. coli

OriC in *E. coli* is 245 base pairs long. It contains:

- Three `AT`-rich 13-mers
- Three 6-mers (`AGATCT`) called DnaA boxes
- Seven 4-mers (`GATC`) which are enzyme recognition sites

Adjacent to this region, five 9-mers occur (`TTWTNCACA`).

Note

`W` $= \{$`T,A`$\}$ and `N` $= \{$`A,G,C,T`$\}$. Thus, degenerate symbols must be allowed.

Preliminary Definitions

Degenerate Symbol

A *degenerate* (or *non-solid*) symbol $\tilde{\sigma}$ over an alphabet Σ is a non-empty subset of Σ. For example, for the English alphabet, $\tilde{\sigma} = \{a, b, d, f\}$ is a degenerate symbol.

Degenerate String

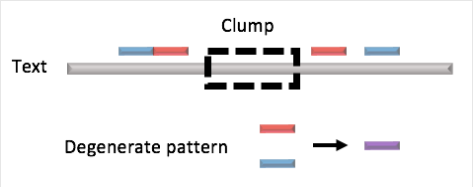
A *degenerate string* is built over the potential $2^{|\Sigma|} - 1$ non-empty sets of letters belonging to Σ. In other words, a degenerate string $\tilde{X} = \tilde{X}[1..n]$, such that every $\tilde{X}[i]$ is a degenerate symbol, $1 \leq i \leq n$. For example, $\tilde{X} = \{a, b\}\{a\}\{c\}\{b, c\}\{a\}\{a, b, c\}$ is a degenerate string of length 6 over $\Sigma = \{a, b, c\}$.

Conservative Degenerate String

A *conservative degenerate string* is a degenerate string where its number of degenerate symbols is upper-bounded by a fixed positive constant k.

Clumps

Clump



Definition

For a given text T, an (ℓ, k)-clump in T is defined as a factor $T[i..i+\ell]$, which contains a conservative degenerate pattern $\tilde{P}$, such that $|\tilde{P}| = m$ and

$$Occ_{T[i..i+\ell]}(\tilde{P}) \geq k,$$

where $Occ_T(\tilde{P})$ is the number of occurrences of pattern $\tilde{P}$ in T, and the number of degenerate symbols in $\tilde{P} \leq d$.

Problem: Finding Clumps

Input

A text T of length n, and integers $\ell < n$, $k < \ell/2$, $m < \ell$ and $d < m$.

Output

All (ℓ, k)-clumps in T, that is, all factors $T[i..i + \ell]$, which contain a conservative degenerate pattern $\tilde{P}$.

Solution

- Construct the suffix array SA of the string T.
- Construct the longest common prefix array LCP of the string T.
- Assign a rank for each prefix (of length m) of each suffix, based on the order of the suffix array. Use these ranks to construct a new string T'.
- Construct and maintain a *Parikh vector* $\mathcal{V}(T')$, where each component of $\mathcal{V}(T')$ denotes the number of occurrences of the corresponding rank.
- At step i, when the window is shifted one position to the right, to position $i+1$, we have to update $\mathcal{V}(T')$.
- Compute the number of occurrences of every possible conservative degenerate pattern $\tilde{P}$.

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i	1	2	3	4	5	6	7	8	9	10	11	12
$T[i]$	A	G	C	T	T	G	C	T	A	G	C	T
SA$[i]$	9	1	11	7	3	10	6	2	12	8	5	4

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LCP$[i]$	0	4	0	2	2	0	3	3	0	1	1	1

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LCP$[i]$	0	4	0	2	2	0	3	3	0	1	1	1
$T'[i]$	0	3	2	6	5	3	1	4	0	3		

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- The vector $\mathcal{V}(T')$ is initialised with the numbers of occurrences of all ranks in the prefix of T' of length $\ell' = \ell + m - 1$.
- After the initialisation, we proceed using a sliding window of length ℓ' to maintain the Parikh vector $\mathcal{V}(T')$.

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- Construct the suffix array SA of the string T.
- Construct the longest common prefix array LCP of the string T.
- Assign a rank for each prefix (of length m) of each suffix, based on the order of the suffix array. Use these ranks to construct a new string T'.
- Construct and maintain a *Parikh vector* $\mathcal{V}(T')$, where each component of $\mathcal{V}(T')$ denotes the number of occurrences of the corresponding rank.
- At step i, when the window is shifted one position to the right, to position $i+1$, we have to update $\mathcal{V}(T')$.
- Compute the number of occurrences of every possible conservative degenerate pattern $\tilde{P}$.

If $\mathcal{V}_{T'[i+\ell']}(T')$ is at least k; then the factor $T[i..i+\ell-1]$ is a (ℓ, k)-clump with at least k occurrences of a some solid pattern P of length m.

Solution

- Construct the suffix array SA of the string T.
- Construct the longest common prefix array LCP of the string T.
- Assign a rank for each prefix (of length m) of each suffix, based on the order of the suffix array. Use these ranks to construct a new string T'.
- Construct and maintain a *Parikh vector* $\mathcal{V}(T')$, where each component of $\mathcal{V}(T')$ denotes the number of occurrences of the corresponding rank.
- At step i, when the window is shifted one position to the right, to position $i+1$, we have to update $\mathcal{V}(T')$.
- Compute the number of occurrences of every possible conservative degenerate pattern $\tilde{P}$.

Each such pattern $\tilde{P}$ is formed by merging components of $\mathcal{V}(T')$ which have at most d mismatches with the factor of rank $T'[i+\ell']$. We calculate the number of occurrences of $\tilde{P}$ by adding the appropriate components of $\mathcal{V}(T')$.

Example

i	1	2	3	4	5	6	7	8	9	10	11	12
$T[i]$	A	G	C	T	T	G	C	T	A	G	C	T
SA$[i]$	9	1	11	7	3	10	6	2	12	8	5	4
LCP$[i]$	0	4	0	2	2	0	3	3	0	1	1	1
$T'[i]$	0	3	2	6	5	3	1	4	0	3		

Here, rank 0 represents AGC and occurs twice in T'; rank 1 represents CTA; rank 2 represents CTT; rank 3 represents GCT and occurs three times in T'; rank 4 represents TAG; rank 5 represents TGC; and rank 6 represents TTG .

Example

Supposing $\ell = 7$, the tables below represent $\mathcal{V}(T')$ when it is initialised (Step 0) and after each of the first 5 steps of the computation.

Step 0

0	1
1	0
2	1
3	1
4	0
5	1
6	1

$\Rightarrow$

Step 1

0	0
1	0
2	1
3	2
4	0
5	1
6	1

$\Rightarrow$

Step 2

0	0
1	1
2	1
3	1
4	0
5	1
6	1

$\Rightarrow$

Step 3

0	0
1	1
2	0
3	1
4	1
5	1
6	1

$\Rightarrow$

Step 4

0	1
1	1
2	0
3	1
4	1
5	1
6	0

$\Rightarrow$

Step 5

0	1
1	1
2	0
3	2
4	1
5	0
6	0

- Suppose $d = 0$, two $(7, 2)$-clumps are reported at Step 1 & Step 5 both associated with the solid pattern `GCT` of rank 3.
- Suppose $d = 1$, then three more $(7, 2)$-clumps are reported at Step 0, 2 & 3 associated with {A, T}GC, CT{A, T}, and T{A, T}G.

Discussion

Algorithm complexity

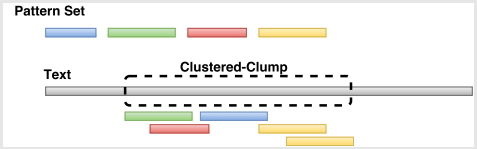
Reporting all possible (ℓ, k)-clumps in a given text T can be achieved in $\mathcal{O}(nm^d)$ time.

Future work

Compare the efficiency and accuracy of our approach with OriFinder [Gao and Zhang, 2008], a tool which uses statistical analysis.

Clustered-Clumps

Clustered-clump



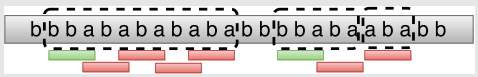
Definition [Bassino et al., 2008]

For a given set of patterns $\mathcal{P} = \{P_1, \cdots, P_{|\mathcal{P}|}\}$, a *clustered-clump* is a maximal set of occurrences of patterns of $\mathcal{P}$ such that

- any consecutive letters of the clustered-clump is a *f*actor of at least one occurrence of a pattern from $\mathcal{P}$.
- either the clustered-clump is composed of a *s*ingle occurrence that overlaps no other occurrence, or each occurrence *o*verlaps at least one other occurrence.

Example

If $\mathcal{P} = \{\texttt{aba}, \texttt{bba}\}$ and the text $T = \texttt{bbbabababababbbbabaabababb}$,



Motivation

The locations of genes can be predicted by the occurrences of regulatory sequences adjacent to them.

- Gene promoters
- Start/stop codons
- Protein-binding sites

Problem: Finding Clustered-Clumps

Input

A text T of length n, a set of conserved degenerate patterns $\tilde{\mathcal{P}} = \{\tilde{P}_1, \cdots, \tilde{P}_{|\tilde{\mathcal{P}}|}\}$, and integers d and m.

Output

All clustered-clumps in T, where the total number of non-solid symbols in $\tilde{\mathcal{P}} \leq d$ and $m = \sum_{1 \leq i \leq |\tilde{\mathcal{P}}|} |\tilde{P}_i|$.

Solution

- Split every pattern, $\tilde{P}_i$, into subpatterns, $P_{i,j}$, by chopping out the parts containing non-solid symbols so that each of the subpatterns is solid: this new set of solid subpatterns is $\mathcal{P}$.
  - Let *sub*(i) denote the number of subpatterns obtained from a pattern $\tilde{P}_i$.
- Build the Aho-Corasick Automaton, $\mathcal{S}(\mathcal{P})$, of the set $\mathcal{P}$.
  - $\mathcal{S}(\mathcal{P})$ is the minimal deterministic finite automaton whose language is the set of suffixes of subpatterns in $\mathcal{P}$.
- Process the occurrences of each of the subpatterns such that an occurrence of $P_{i,sub(i)}$ corresponds to an occurrence of a non-solid pattern $\tilde{P}_i$ in T.
- Populate an array of size n that stores the length of the longest pattern occurring at each position of the text.

Solution

- Split every pattern, $\tilde{P}_i$, into subpatterns, $P_{i,j}$, by chopping out the parts containing non-solid symbols so that each of the subpatterns is solid: this new set of solid subpatterns is $\mathcal{P}$.
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- Populate an array of size n that stores the length of the longest pattern occurring at each position of the text.

Example

Suppose $\tilde{\mathcal{P}}$= {AC{TG}AA{CG}TAA, AT{C,G}TT{A,G}C}. Then $\mathcal{P}$ = {AC, AA, TAA, AT, TT, C}, and $sub(1) = sub(2) = 3$.

Solution

- Split every pattern, $\tilde{P}_i$, into subpatterns, $P_{i,j}$, by chopping out the parts containing non-solid symbols so that each of the subpatterns is solid: this new set of solid subpatterns is $\mathcal{P}$.
  - Let $sub(i)$ denote the number of subpatterns obtained from a pattern $\tilde{P}_i$.
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- Process the occurrences of each of the subpatterns such that an occurrence of $P_{i,sub(i)}$ corresponds to an occurrence of a non-solid pattern $\tilde{P}_i$ in T.
- Populate an array of size n that stores the length of the longest pattern occurring at each position of the text.

Compute all the occurrences of the solid subpatterns in the text T (linear time).

Solution

- Split every pattern, $\tilde{P}_i$, into subpatterns, $P_{i,j}$, by chopping out the parts containing non-solid symbols so that each of the subpatterns is solid: this new set of solid subpatterns is $\mathcal{P}$.
  - Let $sub(i)$ denote the number of subpatterns obtained from a pattern $\tilde{P}_i$.
- Build the Aho-Corasick Automaton, $\mathcal{S}(\mathcal{P})$, of the set $\mathcal{P}$.
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- Process the occurrences of each of the subpatterns such that an occurrence of $P_{i,sub(i)}$ corresponds to an occurrence of a non-solid pattern $\tilde{P}_i$ in T.
- Populate an array of size n that stores the length of the longest pattern occurring at each position of the text.

If an occurrence of $P_{i,j}$ for $j > 1$ is found, then we need to check:

- Whether the non-solid symbol in $\tilde{P}_i$ preceding $P_{i,j}$ matches the corresponding position in T.
- Whether $P_{i,j-1}$ occurs in the corresponding position in T.

Solution

- Split every pattern, $\tilde{P}_i$, into subpatterns, $P_{i,j}$, by chopping out the parts containing non-solid symbols so that each of the subpatterns is solid: this new set of solid subpatterns is $\mathcal{P}$.
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- Process the occurrences of each of the subpatterns such that an occurrence of $P_{i,sub(i)}$ corresponds to an occurrence of a non-solid pattern $\tilde{P}_i$ in T.
- Populate an array of size n that stores the length of the longest pattern occurring at each position of the text.

A single scan of this array can report the indices of all clustered-clumps in T.

Discussion

Algorithm complexity

The solution finds all the clustered-clumps in the text in time equal to $\mathcal{O}(n+m)$ (for constant d)

- Computing both $\mathcal{P}$ and $\mathcal{S}(\mathcal{P})$ takes $\mathcal{O}(m)$.
- $\mathcal{O}(dn)$ time is required for finding the occurrences of all solid subpatterns (to fill the matrix) and the occurrences of non-solid patterns subsequently.
- Scanning of the array in the last step can be done in $\mathcal{O}(n)$ time.

Future work

Extension of our solutions for finding clustered-clumps in texts with non-solid symbols.

Outline

Summary

Two research problems:

1. Error correction during genome assembly
   - Linear-time superbubble identification algorithm.
2. Genome annotation given complex parameters
   - Different types of clumps.
   - Full results published soon.

References I


Bassino, F., Clément, J., Fayolle, J., and Nicodème, P. (2008).
Constructions for clumps statistics.
CoRR, abs/0804.3671.


Brankovic, L., Iliopoulos, C. S., Kundu, R., Mohamed, M., Pissis, S. P., and Vayani, F. (2015).
Linear-time superbubble identification algorithm for genome assembly.
Theoretical Computer Science.


Gao, F. and Zhang, C.-T. (2008).
Ori-finder: a web-based system for finding orics in unannotated bacterial genomes.
BMC bioinformatics, 9(1):79.

References II

Onodera, T., Sadakane, K., and Shibuya, T. (2013).
Detecting superbubbles in assembly graphs.
In *WABI*, pages 338–348.

Sung, W., Sadakane, K., Shibuya, T., Belorkar, A., and Pyrogova, I. (2015).
An O(m log m)-time algorithm for detecting superbubbles.
IEEE/ACM Trans. Comput. Biology Bioinform., 12(4):770–777.

Thank You!