Quiz 1

1 Which of the following statements about the inversion model are true?

A The inversion distance depends only on the number of cycles in the relational diagram.

B Every bad component in the diagram is a hurdle.

C A good component can always be sorted with (safe) split inversions.

D A super hurdle can be optimally sorted with a neutral inversion.

E A diagram with an even number of bad components can be a fortress.

Topics of today:

Canonical inversion distance and sorting:

1. Component tree
2. Circularizing linear chromosomes

Singular DCJ-indel distance and sorting:

1. Indels: insertions and deletions
2. Relational graph of singular genomes
3. Runs

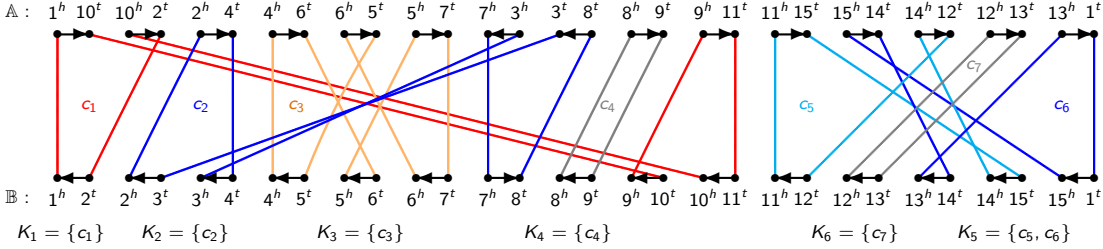
Chained and nested components on the relational diagram

Alternative to component separation: **chaining** and **nesting** relationships between components

Chain: $\begin{cases} \text{sequence of components } K_1, K_2, ..., K_\ell \\ \\ \text{the rightmost adjacency-edge of } K_i \text{ is succeeded by} \\ \text{the leftmost adjacency-edge of } K_{i+1}, \text{ for } 1 \leq i \leq \ell \end{cases}$

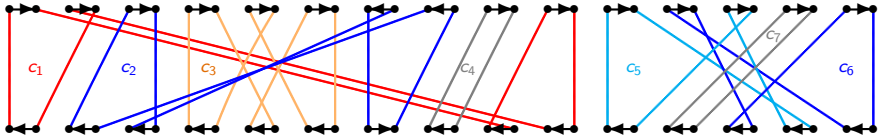
Maximal chain: cannot be extended to the left nor to the right.

A maximal chain H is **nested** in a component K when the leftmost adjacency-edge of H is preceded by an adjacency-edge of K and the rightmost adjacency-edge of H is succeeded by an adjacency-edge of K.



Maximal chains: $\begin{cases} H_1 = K_1 \bowtie K_5\ , \\ H_2 = K_2 \bowtie K_4 \text{ (nested in component } K_1)\ , \\ H_3 = K_3 \text{ (nested in component } K_2)\ , \\ H_4 = K_6 \text{ (nested in component } K_5) \end{cases}$

Chained component tree $\Upsilon_{\blacksquare}$ (rooted)

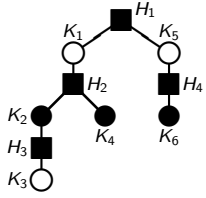


$K_1 = \{c_1\}$ $K_2 = \{c_2\}$ $K_3 = \{c_3\}$ $K_4 = \{c_4\}$ $K_6 = \{c_7\}$ $K_5 = \{c_5, c_6\}$

Maximal chains: $\begin{cases} H_1 = K_1 \bowtie K_5\ , \\ H_2 = K_2 \bowtie K_4 \text{ (nested in component } K_1)\ , \\ H_3 = K_3 \text{ (nested in component } K_2)\ , \\ H_4 = K_6 \text{ (nested in component } K_5) \end{cases}$

1. One round node per component K_i: $\begin{cases} \text{bad node } (\circ)\text{: } K_i \text{ is a bad component;} \\ \text{good node } (\bullet)\text{: } K_i \text{ is a trivial or a good component.} \end{cases}$
2. One square ($\blacksquare$) node per maximal chain H_i, whose children are the round nodes corresponding to the components of H_i. A square node is either the root or a child of the component in which H_1 is nested.

$\Upsilon_{\blacksquare}$:



P: path connecting two distinct round nodes u_1 and u_2 in $\Upsilon_{\blacksquare}(\mathbb{A}, \mathbb{B})$

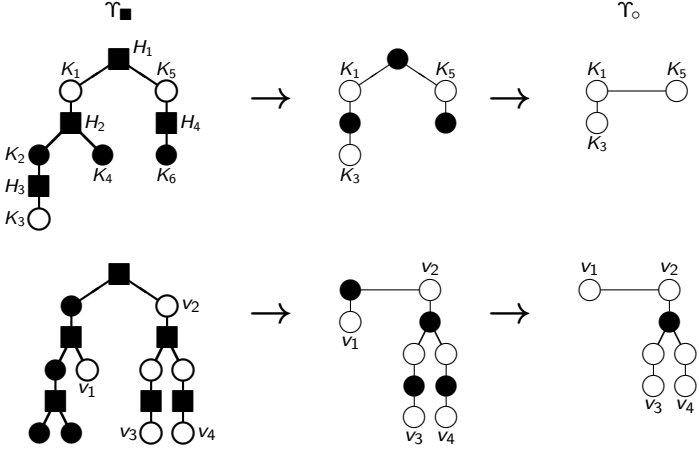
round nodes in $P \backslash \{u_1, u_2\}$: components that separate u_1 and u_2 in $RG(\mathbb{A}, \mathbb{B})$.

Component tree $\Upsilon_\circ$ (unrooted)

Max-flower: maximal connected subgraph composed of good and/or square nodes only.

Contraction of $\Upsilon_\blacksquare$ into unrooted $\Upsilon_\circ$: for each max-flower F of $\Upsilon_\blacksquare$:

1. Replace F by a single good round node g, such that g is connected to all bad nodes connected to F
2. $\begin{cases} \text{If } g \text{ has exactly two neighbors } b_1 \text{ and } b_2\text{: remove } g \text{ from the tree and connect } b_1 \text{ to } b_2\text{;} \\ \text{If } g \text{ is a leaf: simply remove } g \text{ from the tree (all leaves in } \Upsilon_\circ \text{ are bad).} \end{cases}$



Cost of covering the component tree $\Upsilon_\circ$

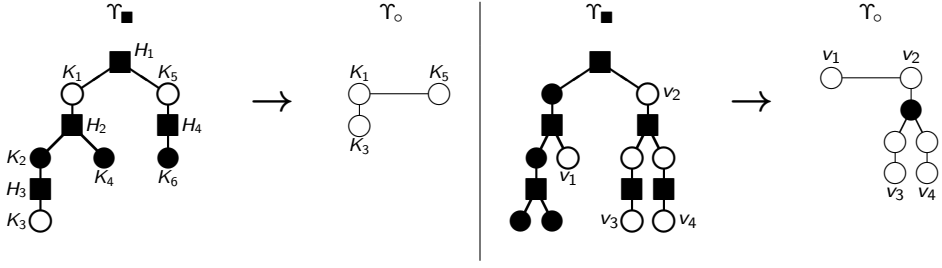
path P in $\Upsilon_\circ$: $\begin{cases} \textbf{short:} \text{ contains a single bad node} \\ \textbf{long:} \text{ contains at least two bad nodes} \end{cases}$

cost of path P: $\tau(P)$ $\begin{cases} P \text{ is short} : \tau(P) = 1 \text{ (cut a bad component)} \\ P \text{ is long} : \tau(P) = 2 \text{ (merge two or more components)} \end{cases}$

Cover of $\Upsilon_\circ$**:** set of paths $\widehat{\mathcal{P}}$ such that each bad node of $\Upsilon_\circ$ is contained in at least one path $P \in \widehat{\mathcal{P}}$

Cost of cover $\widehat{\mathcal{P}}$**:** $\tau(\widehat{\mathcal{P}}) = \sum_{P \in \widehat{\mathcal{P}}} \tau(P)$

Cost of an optimal cover of $\Upsilon_\circ$**:** $\tau(\Upsilon_\circ) = \min_{\widehat{\mathcal{P}} \text{ is a cover of } \Upsilon_\circ} \tau(\widehat{\mathcal{P}})$



$$\tau(\Upsilon_\blacksquare) = \tau(\Upsilon_\circ)$$

Covering the component tree $\Upsilon_\circ$

$\mathcal{L}$: # of leaves in $\Upsilon_\circ$; **Branching node** of $\Upsilon_\circ$: any node whose degree is ≥ 3

Leaf-branch of $\Upsilon_\circ$:
- if $\mathcal{L} \leq 2$: the complete tree $\Upsilon_\circ$
- if $\mathcal{L} \geq 3$: maximal path $u_1, u_2, ..., u_k$, such that u_1 is a leaf of $\Upsilon_\circ$ and, for $i = 2, ..., k$, the degree of internal node u_i in $\Upsilon_\circ$ is two

A leaf-branch may be a path of length 1 (a leaf directly connected to a branching node of $\Upsilon_\circ$)

Traversal: path connecting two leaves of $\Upsilon_\circ$

Suppose $\mathcal{L} = 2, 4, 6, ...$:

$\widehat{\mathcal{P}}_\Upsilon(\Upsilon_\circ)$: smallest set of traversals covering all nodes of $\Upsilon_\circ$: $|\widehat{\mathcal{P}}_\Upsilon(\Upsilon_\circ)| = \frac{\mathcal{L}}{2}$

CoverTreeWithTraversals
Input: unrooted tree $\Upsilon_\circ$ with $\mathcal{L} = 2n$ leaves
Output: set $\widehat{\mathcal{P}}_\Upsilon$ of n traversals covering all nodes of $\Upsilon_\circ$

Based on any planar view of $\Upsilon_\circ$, enumerate the leaves from 1 to $2n$ in circular order;
$\widehat{\mathcal{P}}_\Upsilon = \emptyset$;
for $i = 1$ **to** n **do**
    $\widehat{\mathcal{P}}_\Upsilon = \widehat{\mathcal{P}}_\Upsilon \cup \{$traversal connecting leaves i and $i + n\}$;
Return $\widehat{\mathcal{P}}_\Upsilon$;

Computing $\tau(\Upsilon_\circ)$

Lower bound for the cost of an optimal cover of $\Upsilon_\circ$: $\quad \tau(\Upsilon_\circ) \geq \mathcal{L}$

Each traversal T has cost $\tau(T) = 2$

If $\mathcal{L}$ is even, $\widehat{\mathcal{P}}_{\mathrm{T}}(\Upsilon_\circ)$ is an optimal cover:

$$\Rightarrow \tau(\Upsilon_\circ) = \tau\left(\widehat{\mathcal{P}}_{\mathrm{T}}(\Upsilon_\circ)\right) = 2\tfrac{\mathcal{L}}{2} = \mathcal{L}$$

If $\mathcal{L}$ is odd and $\Upsilon_\circ$ has a short leaf-branch s $(\tau(s) = 1)$:

$$\Rightarrow \tau(\Upsilon_\circ) = \tau\left(\widehat{\mathcal{P}}_{\mathrm{T}}(\Upsilon_\circ \setminus s)\right) + \tau(s) = 2\tfrac{\mathcal{L}-1}{2} + 1 = \mathcal{L}$$

If $\mathcal{L}$ is odd and $\Upsilon_\circ$ has no short leaf-branch ("fortress"); let ℓ be any long leaf-branch of $\Upsilon_\circ$ $(\tau(\ell) = 2)$:

$$\Rightarrow \tau(\Upsilon_\circ) = \tau\left(\widehat{\mathcal{P}}_{\mathrm{T}}(\Upsilon_\circ \setminus \ell)\right) + \tau(\ell) = 2\tfrac{\mathcal{L}-1}{2} + 2 = \mathcal{L} + 1$$

The cost of any optimal cover of $\Upsilon_\circ$ is:

$$\tau(\Upsilon_\circ) = \begin{cases} \mathcal{L}+1 & \text{if } \mathcal{L} \text{ is odd and all leaf-branches are long ("fortress"),} \\ \mathcal{L} & \text{otherwise.} \end{cases}$$

Canonical inversion distance

$$\mathsf{d}_{\mathrm{INV}}(\mathbb{A}, \mathbb{B}) = n - |\mathcal{C}| + \tau_*$$

where

$$\tau_* = \tau(\Upsilon_\circ(\mathbb{A}, \mathbb{B})) = h + f$$

Components are framed conserved intervals

Assuming that $\mathbb{B} = (1\ \ 2\ \ 3\ \ \ldots\ \ 16)$, let us identify its **framed conserved intervals** with respect to

$$\mathbb{A} = (1\ \ \overline{4}\ \ 2\ \ 3\ \ 5\ \ 7\ \ 6\ \ 8\ \ \overline{16}\ \ \overline{14}\ \ \overline{15}\ \ \overline{13}\ \ \overline{11}\ \ \overline{12}\ \ \overline{10}\ \ 9)$$

For given $i \geq 1$ and $j \geq 1$ such that $i+j \leq n+1$:

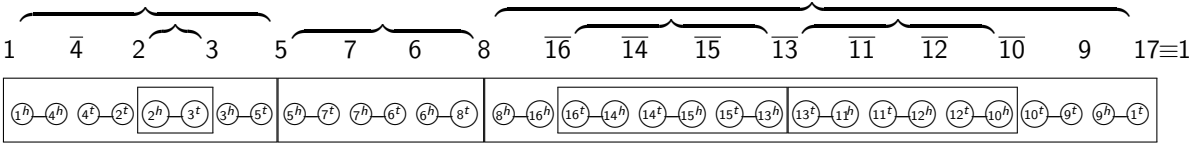
Conserved interval: interval of $\mathbb{A}$ composed of values $i, i+1, \ldots, i+j$ (assuming $n+1 \equiv 1$)

Framed conserved interval
- **direct:** first element is i and last element is $i+j$; or
- **reverse:** first element is $\overline{i+j}$ and last element is $\overline{i}$

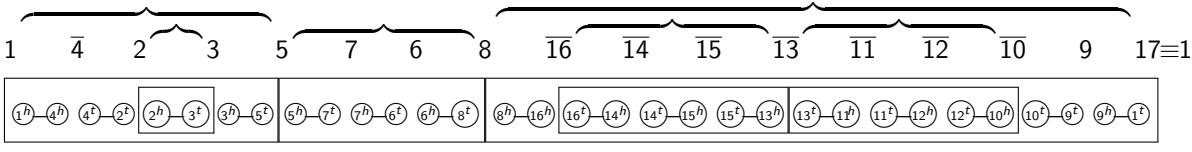
Direct: [1..5]; [2..3]; [5..8]; [8..17] Reverse: $[\overline{16}..\overline{13}]$; $[\overline{13}..\overline{10}]$, $[\overline{16}..\overline{10}]$

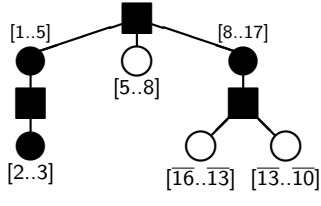
Component: framed conserved interval that is not a union of framed conserved intervals

Direct: [1..5]; [2..3]; [5..8]; [8..17] Reverse: $[\overline{16}..\overline{13}]$; $[\overline{13}..\overline{10}]$



Components are framed conserved intervals





The inversion distance can be computed in linear time, by efficiently identifying chains of framed conserved intervals (Bergeron *et al.*, 2002: Common intervals and sorting by reversals: a marriage of necessity)

An optimal inversion sorting scenario can be computed in subquadratic time.
(Tannier and Sagot, 2004: Sorting by reversals in subquadratic time)

Canonical inversion distance of linear chromosomes

Given canonical linear chromosomes $\mathbb{A}$ and $\mathbb{B}$:

Add one new family (e.g. 0) and circularize chromosome $\mathbb{B}$ into $\mathbb{B}' = (0\ \mathbb{B})$

$$\mathsf{d}_{\text{INV}}(\mathbb{A}, \mathbb{B}) = \min \begin{cases} \mathsf{d}_{\text{INV}}((0\ \mathbb{A}), \mathbb{B}') \\ \mathsf{d}_{\text{INV}}((\bar{0}\ \mathbb{A}), \mathbb{B}') \end{cases}$$

Example:

$$\mathbb{A} = [\bar{5}\ 1\ 2\ \bar{3}\ 4] \quad \text{and} \quad \mathbb{B} = [1\ 2\ 3\ 4\ 5]$$

$$\mathbb{B}' = (0\ 1\ 2\ 3\ 4\ 5)$$

$$\mathsf{d}_{\text{INV}}((0\ \bar{5}\ 1\ 2\ \bar{3}\ 4), \mathbb{B}') = 3$$

$$\mathsf{d}_{\text{INV}}((\bar{0}\ \bar{5}\ 1\ 2\ \bar{3}\ 4), \mathbb{B}') = 2$$

$$\mathsf{d}_{\text{INV}}(\mathbb{A}, \mathbb{B}) = 2$$

Quiz 2

1 What is the bottleneck of the running time of inversion sorting?

A Finding inversions that fix bad components.

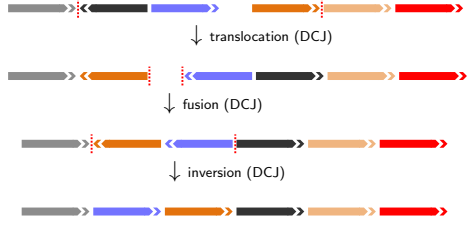
B Finding split inversions.

C Finding safe split inversions.

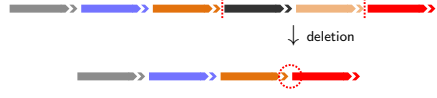
D Finding inversions that merge bad components.

DCJ and indels

- DCJ: structural rearrangements



- Modifying the content: insertions and deletions (**indels**)



Singular DCJ-indel model

Recall that $\mathcal{G}_\star = \mathcal{G}(\mathbb{A}) \cap \mathcal{G}(\mathbb{B})$

Let $\begin{cases} \mathcal{A} = \mathcal{G}(\mathbb{A}) \setminus \mathcal{G}_\star \text{ (set of genes exclusive to genome } \mathbb{A}) \\ \mathcal{B} = \mathcal{G}(\mathbb{B}) \setminus \mathcal{G}_\star \text{ (set of genes exclusive to genome } \mathbb{B}) \end{cases}$

Restrictions for indel operations:

- At most one chromosome can be deleted or inserted at once
- Only genes of set $\mathcal{A}$ can be deleted
- Only genes of set $\mathcal{B}$ can be inserted

Singular DCJ-indel model

Given two singular genomes $\mathbb{A}$ and $\mathbb{B}$,...

Singular DCJ-indel Distance Problem: Compute the minimum number of DCJ and indel operations required to transform $\mathbb{A}$ into $\mathbb{B}$.

Denote by $\mathsf{d}_{\mathrm{DCJ}}^{\mathrm{ID}}(\mathbb{A}, \mathbb{B})$ the DCJ-indel distance of $\mathbb{A}$ and $\mathbb{B}$.

Singular DCJ-indel Sorting Problem: Find a sequence of $\mathsf{d}_{\mathrm{DCJ}}^{\mathrm{ID}}(\mathbb{A}, \mathbb{B})$ DCJ and indel operations that transform $\mathbb{A}$ into $\mathbb{B}$.

First upper bound:

$$\mathsf{d}_{\mathrm{DCJ}}^{\mathrm{ID}}(\mathbb{A}, \mathbb{B}) \leq \mathsf{d}_{\mathrm{DCJ}}(\mathbb{A}_{\mathsf{c}}, \mathbb{B}_{\mathsf{c}}) + |\mathcal{A}| + |\mathcal{B}|$$

where $\begin{cases} \mathbb{A}_{\mathsf{c}} \text{ is the genome obtained from } \mathbb{A} \text{ by simply removing the genes of } \mathcal{A} \\ \mathbb{B}_{\mathsf{c}} \text{ is the genome obtained from } \mathbb{B} \text{ by simply removing the genes of } \mathcal{B} \end{cases}$

Relational graph of singular genomes

Given two singular genomes $\mathbb{A}$ and $\mathbb{B}$, their **relational graph** $RG(\mathbb{A}, \mathbb{B}) = (V, E)$ is described as follows:

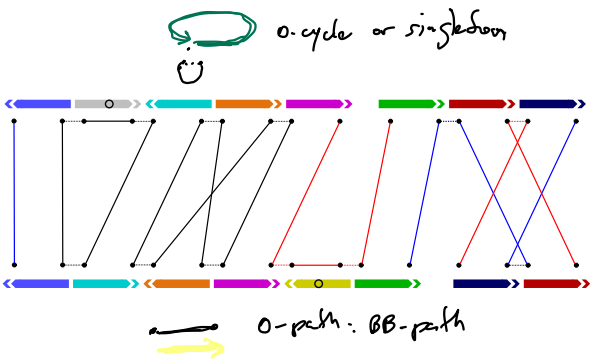
1. $V = V(\xi(\mathbb{A})) \cup V(\xi(\mathbb{B}))$: there is a vertex for each extremity of each gene in $\mathbb{A}$ and a vertex for each extremity of each gene in $\mathbb{B}$

   Each vertex v has a label $\ell(v)$, that corresponds to the extremity it represents.

2. $E = E_\alpha(\mathbb{A}) \cup E_\alpha(\mathbb{B}) \cup E_\xi \cup E_{\text{ID}}(\mathbb{A}) \cup E_{\text{ID}}(\mathbb{B})$, where:

   - **Adjacency edges:** $\begin{cases} E_\alpha(\mathbb{A}) = \{uv : u, v \in V(\xi(\mathbb{A})) \text{ and } \ell(u)\ell(v) \in \alpha(\mathbb{A})\} \\ E_\alpha(\mathbb{B}) = \{uv : u, v \in V(\xi(\mathbb{B})) \text{ and } \ell(u)\ell(v) \in \alpha(\mathbb{B})\} \end{cases}$
   - **Extremity edges:** $E_\xi = \{uv : u \in V(\xi(\mathbb{A})) \text{ and } v \in V(\xi(\mathbb{B})) \text{ and } \ell(u) = \ell(v)\}$
   - **Indel edges:** $\begin{cases} E_{\text{ID}}(\mathbb{A}) = \{uv : \ell(u) = g^t \text{ and } \ell(v) = g^h \text{ and } g \in \mathcal{A}\} \\ E_{\text{ID}}(\mathbb{B}) = \{uv : \ell(u) = g^t \text{ and } \ell(v) = g^h \text{ and } g \in \mathcal{B}\} \end{cases}$

Relational graph of singular genomes



components can be **indel-inclosing** or **indel-free**

$n = |G_*|$

If $\mathbb{A}_c = \mathbb{B}_c$,
$RG(\mathbb{A}, \mathbb{B})$ has only 2-cycles and 1-paths:

$$2n = 2|\mathcal{C}| + |\mathcal{P}_{\mathbb{AB}}| \quad \Rightarrow \quad n = |\mathcal{C}| + \frac{|\mathcal{P}_{\mathbb{AB}}|}{2}$$

Every vertex has degree one or two:
$RG(\mathbb{A}, \mathbb{B})$ is a collection of paths and cycles

cycle with k edges in E_ξ: k-cycle or c_k
path with k edges n E_ξ: k-path or p_k

if $k = 0$ the component is a **singleton**

$\mathcal{C} = \{c_k : k \geq 2\}$: set of cycles (k is even)

$\mathcal{S} = \{c_k : k = 0\}$: set of circular singletons

$\mathcal{P}_{\mathbb{AA}} = \{p_k$: starts and ends in $\mathbb{A}\}$:
set of $\mathbb{AA}$-paths (k is even)

$\mathcal{P}_{\mathbb{BB}} = \{p_k$: starts and ends in $\mathbb{B}\}$:
set of $\mathbb{BB}$-paths (k is even)

$\mathcal{P}_{\mathbb{AB}} = \{p_k$: starts in $\mathbb{A}$ and ends in $\mathbb{B}\}$:
set of $\mathbb{AB}$-paths (k is odd)

$|\mathcal{P}_{\mathbb{AB}}|$ is even (E_ξ has $2n$ edges)

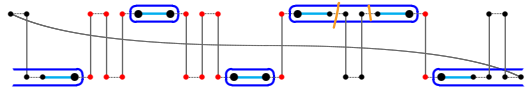
$|\mathcal{P}_{\mathbb{AA}}| + |\mathcal{P}_{\mathbb{BB}}| + |\mathcal{P}_{\mathbb{AB}}| = \kappa(\mathbb{A}) + \kappa(\mathbb{B})$

Otherwise, if $\mathbb{A}_c \neq \mathbb{B}_c$:

$$n > |\mathcal{C}| + \frac{|\mathcal{P}_{\mathbb{AB}}|}{2}$$

Runs of indel-edges

One indel-enclosing cycle:



indel edges , runs

$\Lambda = 4$

$\Lambda(C)$ is the number of **runs** in component C

Λ	
0	cycles or paths
1	cycles, paths and singletons
2	cycles, paths
3	paths
4	cycles, paths
5	paths
6	cycles, paths
⋮	⋮

indel-free

indel-enclosing

Each **run** can be inserted/deleted at once

$\Rightarrow$ Second upper bound:

$$\mathrm{d}_{\mathrm{DCJ}}^{\mathrm{ID}}(\mathbb{A},\mathbb{B}) \leq n - |\mathcal{C}| - \frac{|\mathcal{P}_{\mathbb{AB}}|}{2} + \sum_{C \in RG} \Lambda(C)$$

References

The Inversion Distance Problem

(Anne Bergeron, Julia Mixtacki and Jens Stoye)

In: Mathematics of Evolution and Phylogeny. Gascuel O (Ed); (2005)

Double Cut and Join with Insertions and Deletions

(Marília D.V. Braga, Eyla Willing and Jens Stoye)

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