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On Sorting Genomes with DCJ and Indels

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AG Genome Informatics - Bielefeld University

RECOMB-CG 2010

This work is an extension of **Genomic Distance with DCJ and Indels**
(M. D. V. Braga, E. Willing and J. Stoye), presented at *WABI*, 2010.

Overview

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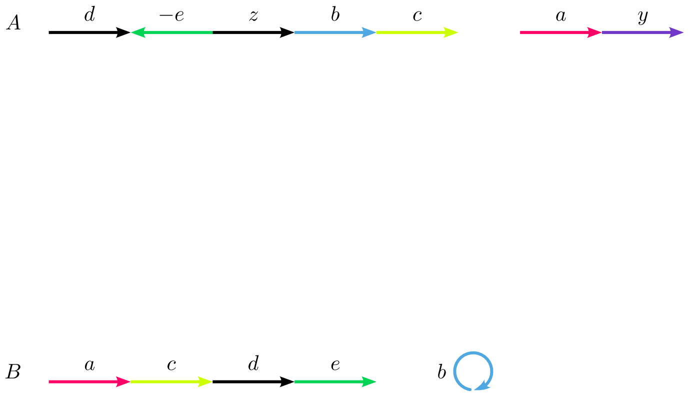
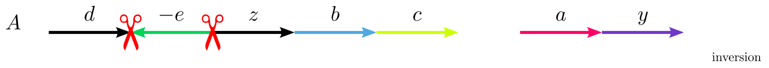
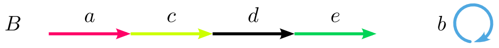
Overview

DCJ, Adjacency Graph, Indels

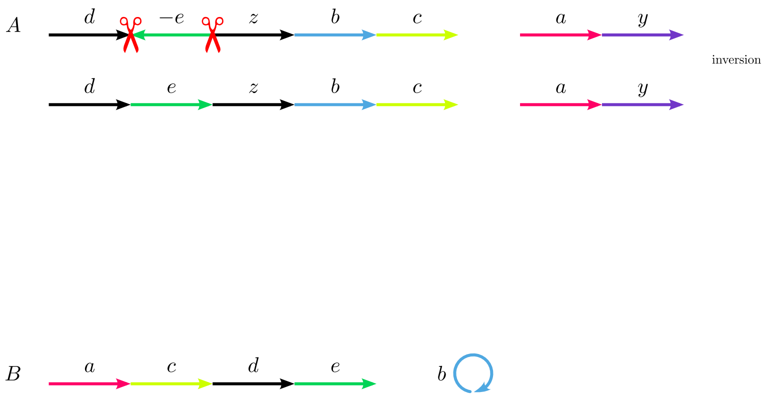


DCJ, Adjacency Graph, Indels





DCJ, Adjacency Graph, Indels



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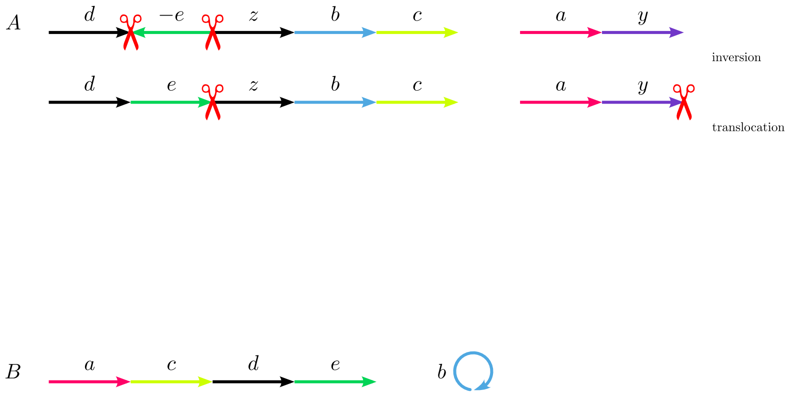

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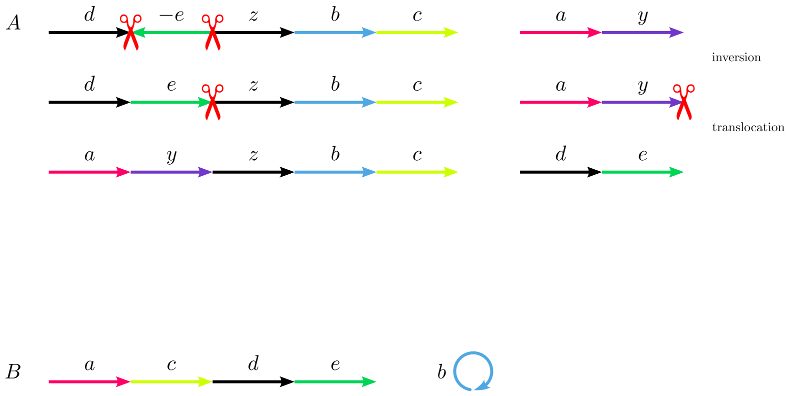

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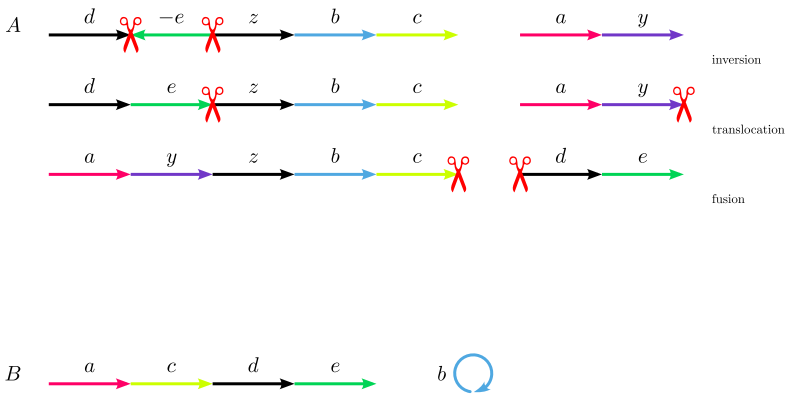

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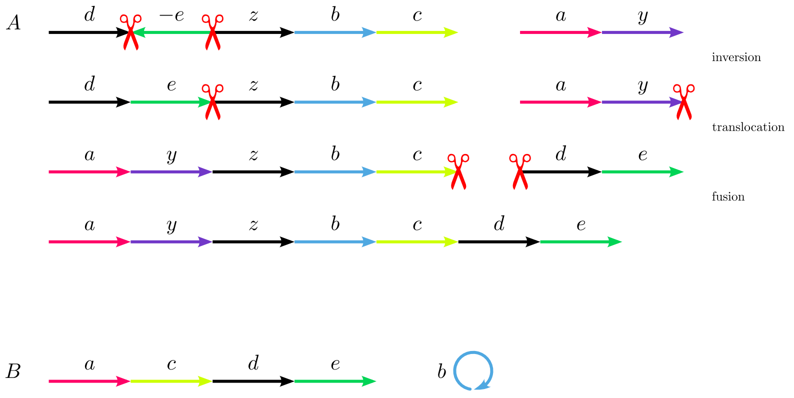

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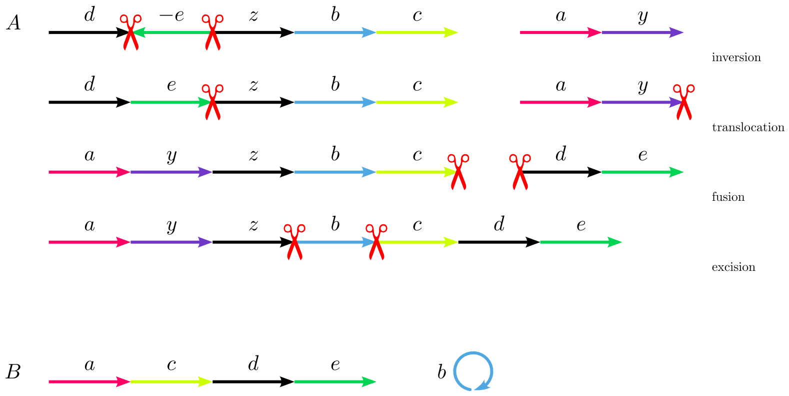
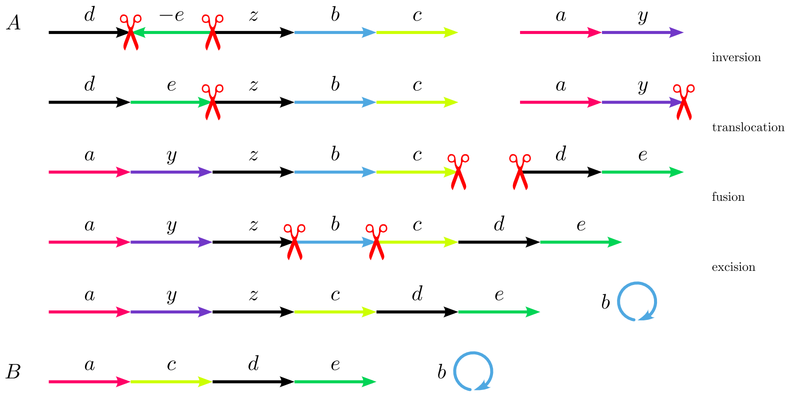


A
d $-e$ z b c a y
inversion
d e z b c a y
translocation
a y z b c d e
fusion
a y z b c d e
excision
B
a c d e
b

DCJ, Adjacency Graph, Indels



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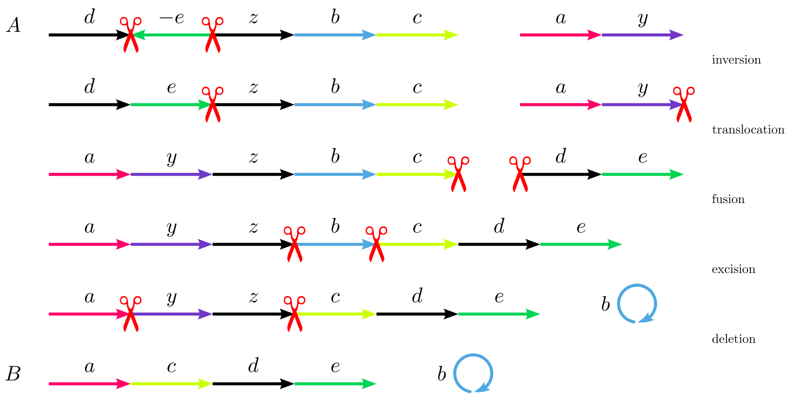

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d e z b c a y
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a y z c d e b
deletion
B
a c d e b

DCJ, Adjacency Graph, Indels

The double cut and join model

(Traditional) DCJ [Yancopoulos *et al.* 2005, Bergeron *et al.* 2006]:

- cuts the genome twice and rejoins loose ends
- represents most genome rearrangement operations (same gene content, no duplications)

DCJ with indels [Yancopoulos *et al.* 2008]:

- allows DCJ operations, insertions and deletions (indels)
- DCJ-indel distance can be computed in linear time [WABI 2010]

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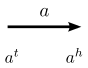
DCJ, Adjacency Graph, Indels

Definitions:

- *marker:* piece of DNA that has an orientation
- *$\mathcal{G}$ = small genome of A and B*: set of markers that occur once in *A* and once in *B* (no duplications)
- a marker $g \in \mathcal{G}$ has two extremities: head (g^h) and tail (g^t)
- $\mathcal{A}$ and $\mathcal{B}$: sets of *unique markers* of *A* resp. *B*
- *$\mathcal{G}$-adjacency:* adjacency of markers from $\mathcal{G}$ (with *labels* from $\mathcal{A}$ or $\mathcal{B}$)



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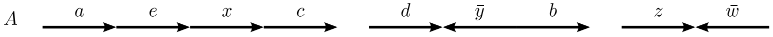

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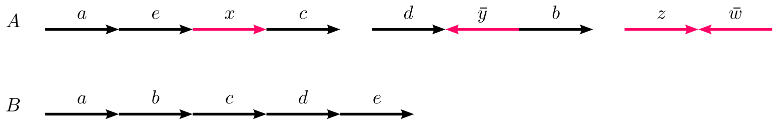

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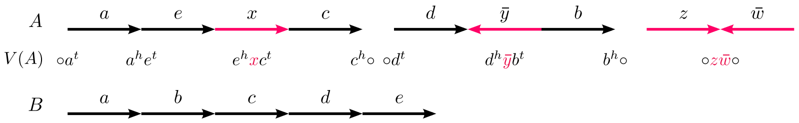

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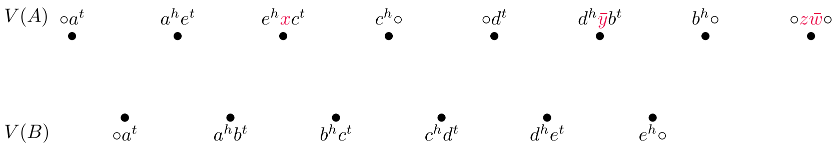
DCJ, Adjacency Graph, Indels

The adjacency graph with $\mathcal{G}$-adjacencies

The adjacency graph AG(*A*, *B*) for genomes *A* and *B*:



Genome *A* has four unique markers (*w*, *x*, *y* and *z*).

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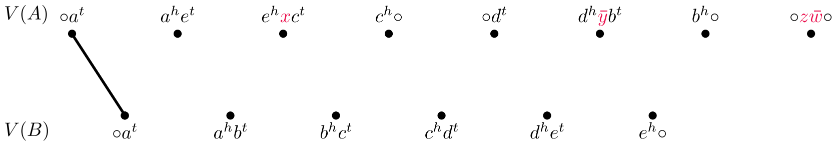

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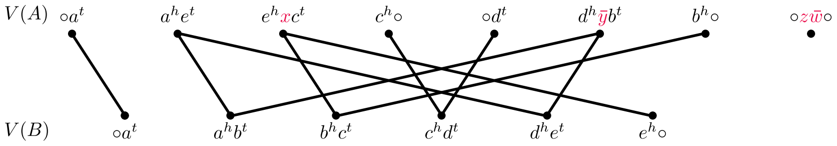

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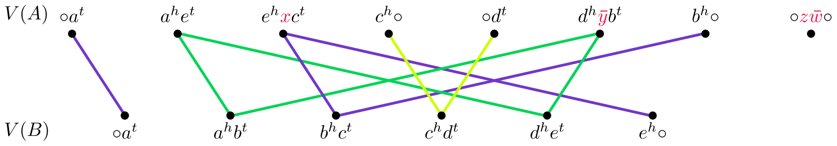

Components of AG(*A*, *B*): 1 cycle, 2 *AB*-paths and 2 *AA*-paths

DCJ, Adjacency Graph, Indels

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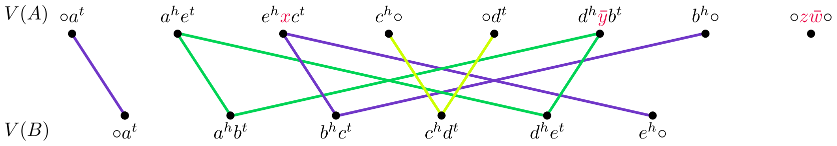


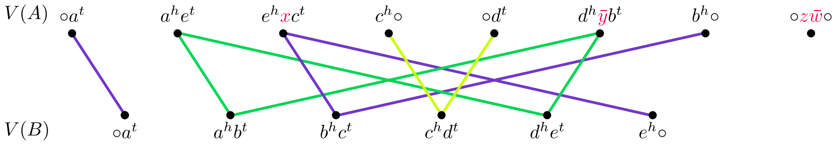
Components of AG(*A*, *B*): 1 cycle, 2 *AB*-paths and 2 *AA*-paths

Minimum number of DCJs necessary to sort *A* into *B* (ignoring indels):
$\boldsymbol{d_{\mathrm{DCJ}}(A, B) = |\mathcal{G}| - (c + \frac{b}{2})}$, where $c =$ # cycles, $b =$ # *AB*-paths [Bergeron *et al.* 2006]

DCJ, Adjacency Graph, Indels

The adjacency graph with $\mathcal{G}$-adjacencies

The adjacency graph AG(A, B) for genomes A and B:



Components of AG(A, B): 1 cycle, 2 AB-paths and 2 AA-paths ; $\boldsymbol{d_{\mathrm{DCJ}} = 5 - 1 - 2/2 = 3}$

Minimum number of DCJs necessary to sort A into B (ignoring indels):
$\boldsymbol{d_{\mathrm{DCJ}}(A, B) = |\mathcal{G}| - (c + \frac{b}{2})}$, where $c = \#$ cycles, $b = \#$ AB-paths [Bergeron *et al.* 2006]

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Sorting with DCJs and indels

Overview

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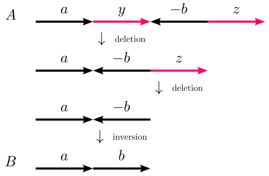
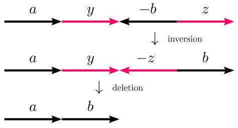
Sorting with DCJs and indels

Saving indel operations



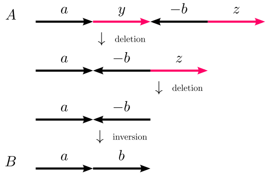
3 steps (trivial)



2 steps

Sorting with DCJs and indels

Saving indel operations



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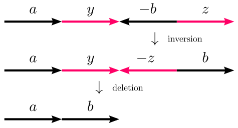


2 steps

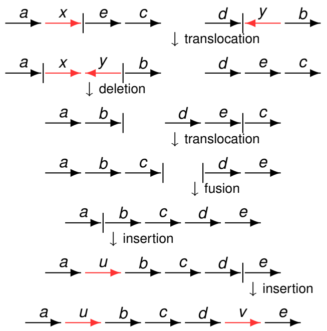
Types of DCJ operation:

DCJ	effect on AG(A, B)	weight
optimal	increase c or b	0
neutral	c and b unchanged	+1
counter-optimal	decrease c or b	+2

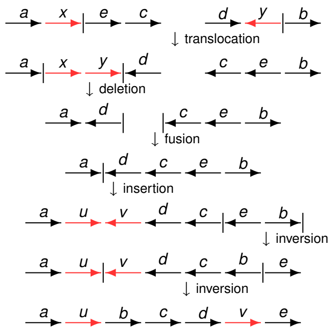
Sorting with DCJs and indels

The optimal sorting scenarios can have different compositions with respect to the number of DCJ and indel operations.

3 DCJs + 3 indels



4 DCJs + 2 indels



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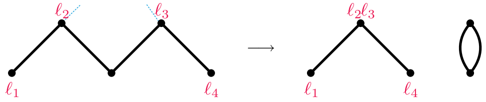
Sorting with DCJs and indels

Accumulating runs

An optimal DCJ *accumulates* labels in a single vertex:



Sorting with DCJs and indels

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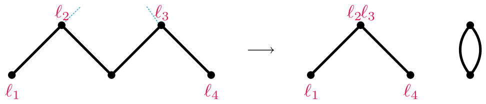
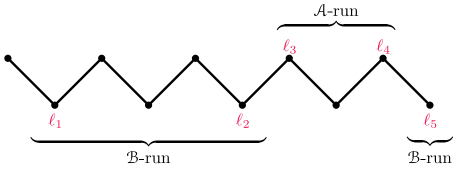


Runs of a component C:



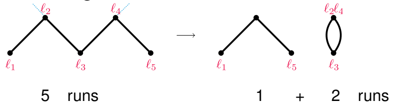
$\Lambda(C) = 3$

Optimal DCJs accumulate the labels of one run in a single $\mathcal{G}$-adjacency
$\Rightarrow$ **only 1 indel per run is necessary**

Sorting with DCJs and indels

Sorting one component individually

A DCJ can merge at most two $\mathcal{A}$-runs and two $\mathcal{B}$-runs:



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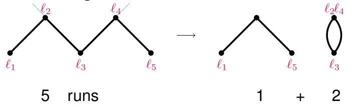

Ignoring indels (labels), it is possible to sort a component individually with optimal DCJs only: $d(C) =$ number of DCJs required to sort C

Indel-potential of a component C [WABI 2010]

Minimum number of runs obtained by sorting C with **optimal** DCJs:

$$\lambda(C) = \left\lceil \frac{\Lambda(C) + 1}{2} \right\rceil$$

Sorting with DCJs and indels

Sorting one component individually

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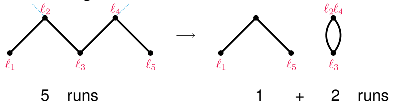

Ignoring indels (labels), it is possible to sort a component individually with optimal DCJs only: $d(C) =$ number of DCJs required to sort C

$\Lambda(C)$	$\lambda(C)$
0	0
1	1
2	2
3	2
4	3
5	3
$\vdots$	$\vdots$

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Minimum number of runs obtained by sorting C with **optimal** DCJs:

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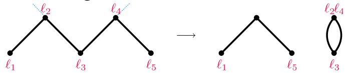

5 runs 1 + 2 runs

Ignoring indels (labels), it is possible to sort a component individually with optimal DCJs only: $d(C) =$ number of DCJs required to sort C

Indel-potential of a component C [WABI 2010]

Minimum number of runs obtained by sorting C with **optimal** DCJs:

$$\lambda(C) = \left\lceil \frac{\Lambda(C)+1}{2} \right\rceil$$

A component C can be sorted with $\boldsymbol{d(C)}$ **DCJs** $+\boldsymbol{\lambda(C)}$ **indels**.

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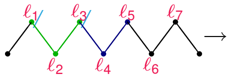
Sorting with DCJs and indels

Sorting one component individually

Neutral DCJs in components with $\lambda \geq 3$ save one indel:

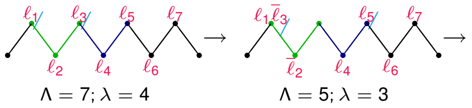


$\Lambda = 7; \lambda = 4$

Sorting with DCJs and indels

Sorting one component individually

Neutral DCJs in components with $\lambda \geq 3$ save one indel:



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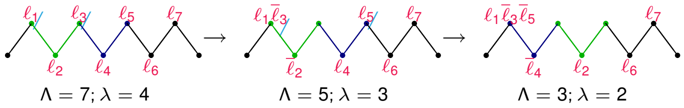
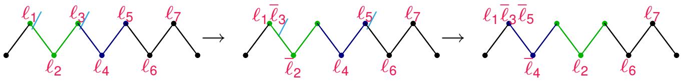


ℓ_1 ℓ_3 ℓ_5 ℓ_7
ℓ_2 ℓ_4 ℓ_6
$\Lambda = 7; \lambda = 4$
$\longrightarrow$
$\ell_1\overline{\ell}_3$ ℓ_5 ℓ_7
$\overline{\ell}_2$ ℓ_4 ℓ_6
$\Lambda = 5; \lambda = 3$
$\longrightarrow$
$\ell_1\overline{\ell}_3\overline{\ell}_5$ ℓ_7
$\overline{\ell}_4$ ℓ_2 ℓ_6
$\Lambda = 3; \lambda = 2$

Sorting with DCJs and indels

Sorting one component individually

Neutral DCJs in components with $\lambda \geq 3$ save one indel:



$\Lambda = 7; \lambda = 4$ $\Lambda = 5; \lambda = 3$ $\Lambda = 3; \lambda = 2$

$\Lambda(C)$	$\lambda(C)$
0	0
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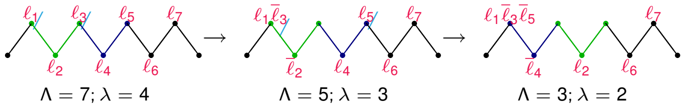
⋮	⋮

Sorting with DCJs and indels

Sorting one component individually

Neutral DCJs in components with $\lambda \geq 3$ save one indel:



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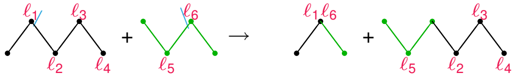
$\overline{\ell}_4$ ℓ_2 ℓ_6
$\Lambda = 3; \lambda = 2$

A component C can be sorted with $\boldsymbol{d(C) + \lambda(C)}$ **operations**:

DCJs	**indels**	
$d(C)$	$\lambda(C)$	(min DCJs)
$d(C) + 1$	$\lambda(C) - 1$	
$d(C) + 2$	$\lambda(C) - 2$	
$\vdots$	$\vdots$	
$d(C) + \lambda(C) - 2$	2	(min indels)

Sorting with DCJs and indels

Recombination of two components



Λ:	4	+	2	$\longrightarrow$	1	+	3	$(\Delta\Lambda = -2)$
λ:	3	+	2	$\longrightarrow$	1	+	2	$(\Delta\lambda = -2)$

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Sorting with DCJs and indels

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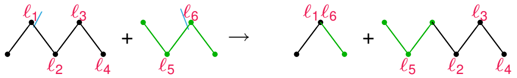

Λ: 4 + 2 $\longrightarrow$ 1 + 3 $(\Delta\Lambda = -2)$

λ: 3 + 2 $\longrightarrow$ 1 + 2 $(\Delta\lambda = -2)$

$\Lambda(C)$	$\lambda(C)$
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⋮	⋮

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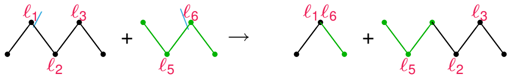
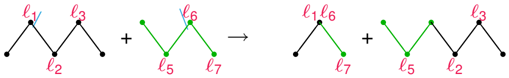


Λ:	3	+	2	$\longrightarrow$	1	+	2	$(\Delta\Lambda = -2)$
λ:	2	+	2	$\longrightarrow$	1	+	2	$(\Delta\lambda = -1)$

$\Lambda(C)$	$\lambda(C)$
0	0
1	1
2	2
3	2
4	3
5	3
$\vdots$	$\vdots$

Sorting with DCJs and indels

Recombination of two components



Λ:	3	+	3	$\longrightarrow$	2	+	2 $(\Delta\Lambda = -2)$
λ:	2	+	2	$\longrightarrow$	2	+	2 $(\Delta\lambda = 0)$

$\Lambda(C)$	$\lambda(C)$
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Sorting with DCJs and indels

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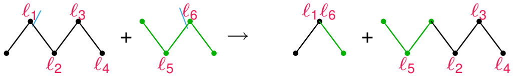

Λ: 4 + 2 $\longrightarrow$ 1 + 3 $(\Delta\Lambda = -2)$

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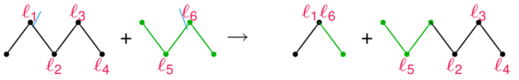
Sorting with DCJs and indels

Recombination of two components

Change in the DCJ-indel distance: $\Delta d = \Delta d_{\text{DCJ}} + \Delta\lambda$



Λ:	4	+	2	$\longrightarrow$	1	+	3	$(\Delta\Lambda = -2)$
λ:	3	+	2	$\longrightarrow$	1	+	2	$(\Delta\lambda = -2)$

DCJ	Δd_{DCJ}
optimal	0
neutral	$+1$
counter-opt	$+2$

Sorting with DCJs and indels

Recombination of two components

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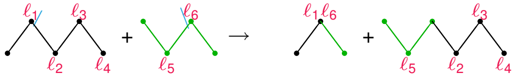

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Sorting with DCJs and indels

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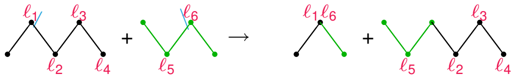

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λ: $3 + 2 \rightarrow 1 + 2$ $(\Delta\lambda = -2)$

$\boldsymbol{\Delta d = +1 - 2 = -1}$

DCJ	Δd_{DCJ}
optimal	0
neutral	$+1$
counter-opt	$+2$

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Sorting with DCJs and indels

A recombination saves
at most 2 indels

Possible ways to achieve $\Delta d \leq -1$:

	Δd_{DCJ}	$\Delta\lambda$		Δd
optimal	0	$-\ 2$	$=$	-2
optimal	0	$-\ 1$	$=$	-1
neutral	$+1$	$-\ 2$	$=$	-1

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Sorting with DCJs and indels

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Considering all components of AG(A, B), find a sequence of recombinations S such that the **weight** $w(S) = \sum_{\rho \in S} \Delta d(\rho)$ is minimum: solved in linear time [WABI 2010]

Sorting with DCJs and indels

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Considering all components of AG(A, B), find a sequence of recombinations S such that the **weight** $w(S) = \sum_{\rho \in S} \Delta d(\rho)$ is minimum: solved in linear time [WABI 2010]

DCJ-indel distance formula [WABI 2010]

$$d^{id}_{\text{DCJ}}(A, B) = d_{\text{DCJ}}(A, B) + \sum_{C \in \text{AG}(A,B)} \lambda(C) - w(S)$$

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Sorting with minimum number of DCJs

Overview

Sorting with minimum number of DCJs

Algorithm 1: Sorting genome *A* into *B* with minimum number of DCJs

1. Apply all recombinations in S.
2. For each component $C \in \text{AG}(A, B)$:
   - 2.1 Split C with **optimal** DCJs (that have $\boldsymbol{\Delta\lambda = 0}$) until only components that have at most 2 runs are obtained and the total number of runs in all new components is equal to $\lambda(C)$.
   - 2.2 Accumulate all runs in the smaller components derived from C with **optimal** DCJ operations (that have $\boldsymbol{\Delta\lambda = 0}$).
   - 2.3 Apply **optimal** DCJ operations (that have $\boldsymbol{\Delta\lambda = 0}$) in the smaller components derived from C until only DCJ-sorted components exist.
   - 2.4 **Delete/insert** all runs in the DCJ-sorted components derived from C.

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Sorting with minimum number of indels

Overview

Sorting with minimum number of indels

Group runs with recombinations

Neutral operations in components with $\lambda \geq 3$ saves one indel
$\rightarrow$ **Grouping runs in one component first is good!**

Sorting with minimum number of indels

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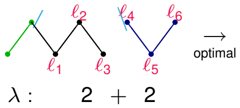

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Sorting with minimum number of indels

Group runs with recombinations

Neutral operations in components with $\lambda \geq 3$ saves one indel
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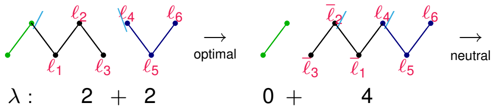

Sorting with minimum number of indels

Group runs with recombinations

Neutral operations in components with $\lambda \geq 3$ saves one indel
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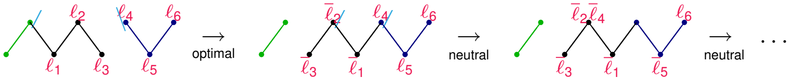


λ : 2 + 2 0 + 4 0 + 3 ...

Sorting with minimum number of indels

Algorithm 2: Sorting genome *A* into *B* with minimum number of indels

1. Apply all recombinations in *S*.
2. (*) Group runs of two components in one component using **counter-optimal** recombinations with $\Delta\lambda = -2$, **neutral** recombinations with $\Delta\lambda = -1$ and **optimal** recombinations with $\Delta\lambda = 0$.
   [After this step, there is at most one component with 2 or more runs; the others have at most one run.]
3. For each component $C \in \text{AG}(A, B)$:
   - 3.1 (*) While $\lambda(C) \geq 3$, apply a **neutral** DCJ on *C* with $\boldsymbol{\Delta\lambda = -1}$.
   - 3.2 If $\Lambda(C) = 3$ (*C* is a path), merge the last and the first runs of *C* extracting a cycle with all runs (**optimal** DCJ with $\boldsymbol{\Delta\lambda = 0}$).
   - 3.3 Accumulate all runs in the smaller components derived from *C* with **optimal** DCJ operations that have $\boldsymbol{\Delta\lambda = 0}$.
   - 3.4 Apply **optimal** DCJ operations in the smaller components derived from *C* until only DCJ-sorted components exist (these DCJs have $\boldsymbol{\Delta\lambda = 0}$).
   - 3.5 **Delete/insert** all runs in the DCJ-sorted components derived from *C*.

Experiment and Discussion

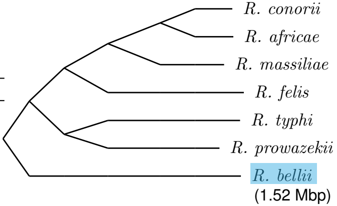
Overview

Experiment and Discussion

Comparing species of *Rickettsia*

Data from Blanc *et al.* PLoS Genet. 2007

species	Mbp	d^{id}_{DCJ}	MIN DCJs DCJs+indels	MIN indels DCJs+indels
R. conorii	1.27	414	261 + 153	313 + 101
R. africae	1.28	426	260 + 166	322 + 104
R. massiliae	1.36	448	276 + 172	340 + 108
R. felis	1.55	493	312 + 181	389 + 104
R. typhi	1.11	309	195 + 114	212 + 97
R. prowazekii	1.11	314	197 + 117	216 + 98
			$\Delta = 67$	$\Delta = 11$



Experiment and Discussion

Summary: Sorting with DCJs and indels

- Minimizing number of DCJs
- Minimizing number of indels

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Experiment and Discussion

Summary: Sorting with DCJs and indels

- Minimizing number of DCJs
- Minimizing number of indels

Future work

- Study the whole space of solutions of the problem
- Incoporporate substitutions in the model?

Acknowledgments

- Eyla Willing
- Jens Stoye
- Sophia Yancopoulos

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Thank you for your attention!

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