Genomic distance under gene substitutions

Marília Braga, Raphael Machado,
Leonardo Ribeiro and Jens Stoye

(Inmetro - Brazil / Bielefeld University - Germany)

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Universität Bielefeld

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Overview

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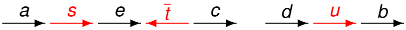
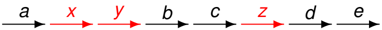
Motivation and Background



Sorting genomes with unequal contents, but without duplicated markers:

. rearrangements that change number of chromosomes, order and orientation of markers (modify the genome **organization**)

.insertions and deletions (modify the genome **content**)



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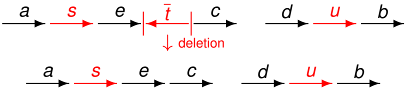

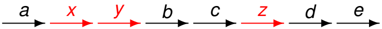

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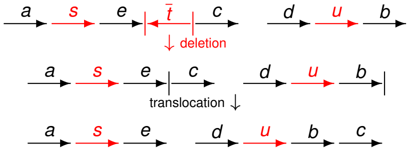

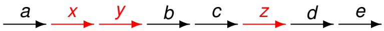

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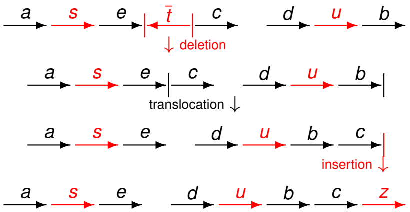

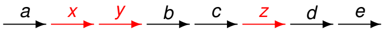

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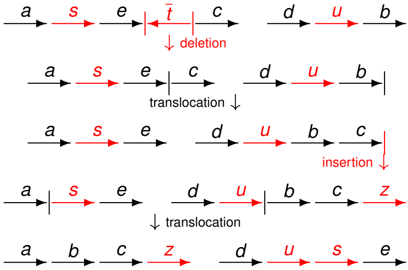

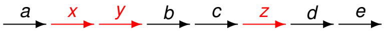

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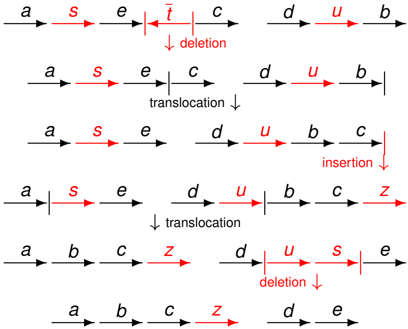

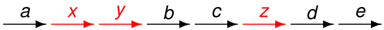

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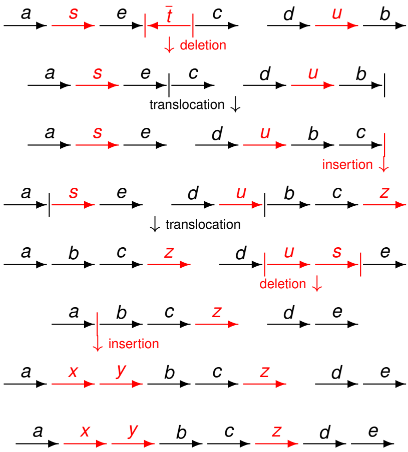

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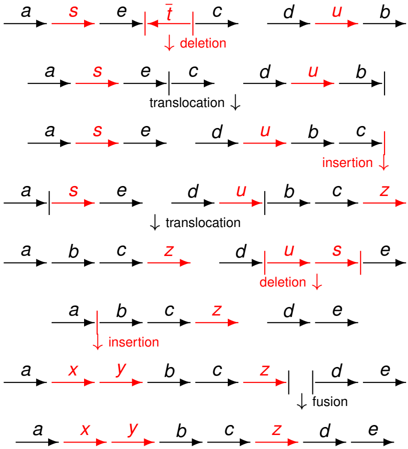

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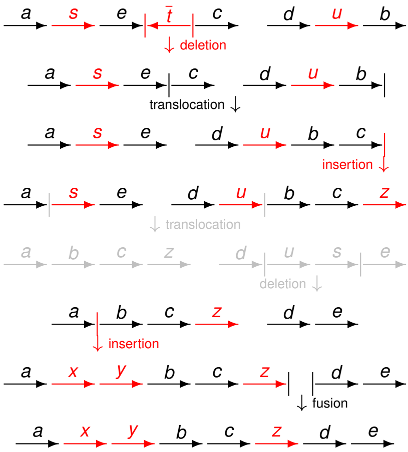

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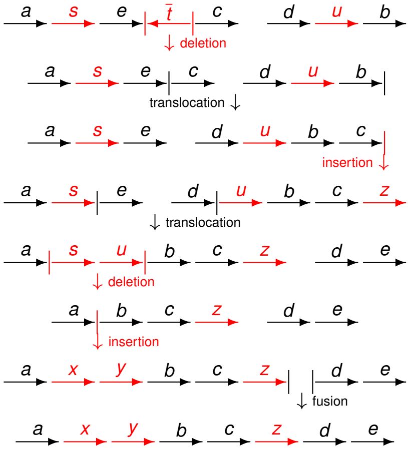

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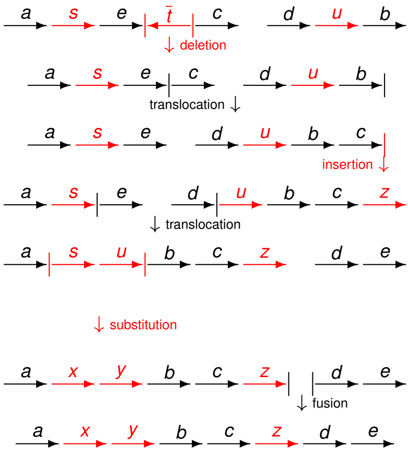

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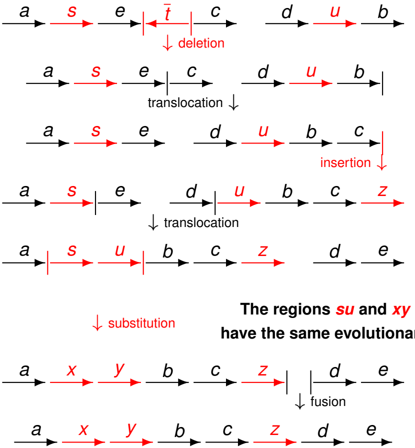

The regions *su* and *xy* could have the same evolutionary origin

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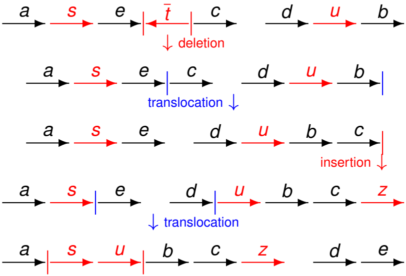

(translocations and fusions are **double-cut-and-join** operations)

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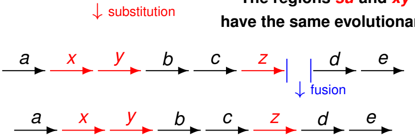

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- genomes with **unequal contents**
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- A **block of markers** can be inserted or deleted **at once**
- **DCJ-indel distance** can be computed in **linear time** [WABI 2010]

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DCJ with substitutions:

- genomes with **unequal contents**
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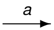
- DCJ-substitution distance can be **exactly computed in linear time**

Overview

Definitions

- *marker:* piece of DNA that has an orientation



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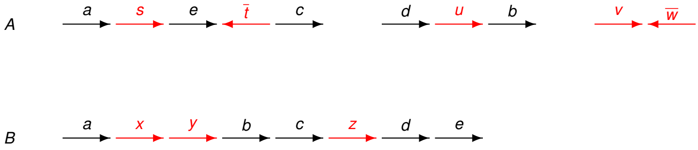

![INMETRO / Universität Bielefeld]

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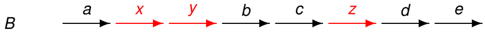
- $\mathcal{G}$*:* set of markers that occur once in A and once in B

$$\mathcal{G} = \{a, b, c, d, e\}$$



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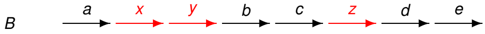
$\mathcal{A} = \{s, t, u, v, w\}$

$\mathcal{G} = \{a, b, c, d, e\}$

$\mathcal{B} = \{x, y, z\}$



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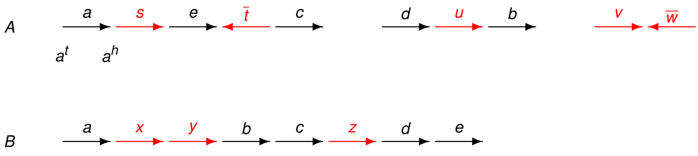

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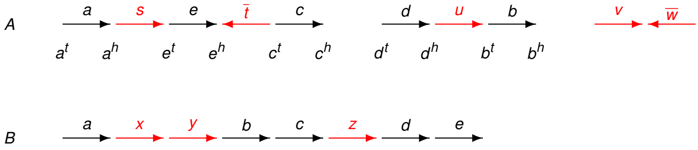

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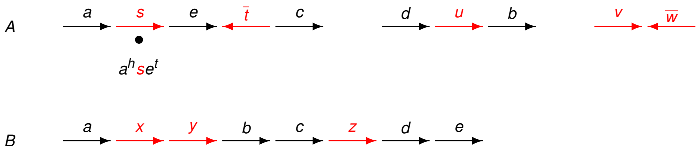

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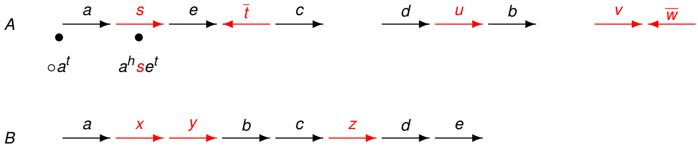

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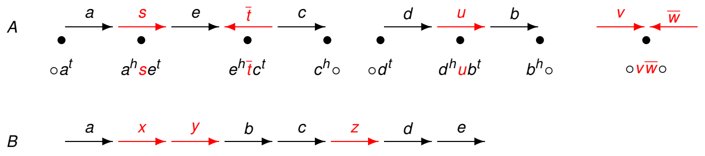
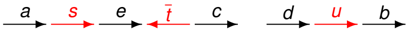


DCJ operation



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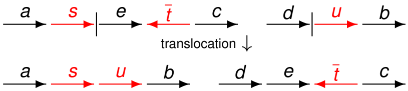

DCJ: $a^h s | e^t \ , \ d^h | u b^t \ \rightarrow \ a^h s | u b^t \ , \ d^h | e^t$

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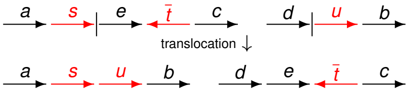

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(a DCJ operation rearranges two adjacencies)

Adjacency graph and DCJ-distance

[Bergeron *et al.* 2006]

A $\circ a^t$ $a^h s e^t$ $e^h \bar{t} c^t$ $c^h \circ$ $\circ d^t$ $d^h u b^t$ $b^h \circ$

B $\circ a^t$ $a^h xy b^t$ $b^h c^t$ $c^h z d^t$ $d^h e^t$ $e^h \circ$

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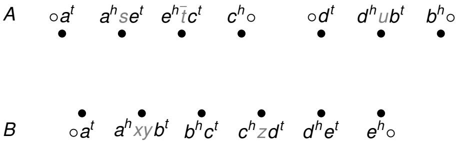

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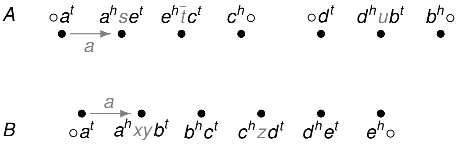

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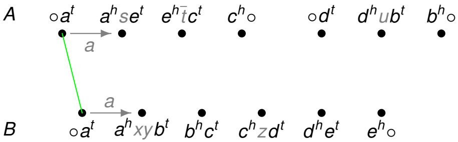

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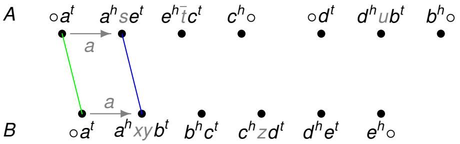

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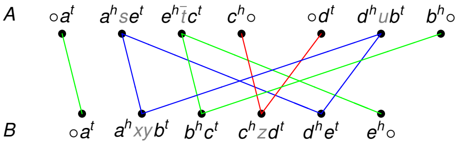

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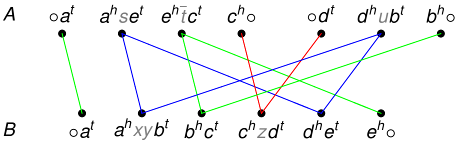

Components of AG(A, B): 1 cycle, 2 *AB*-paths and 1 *AA*-path

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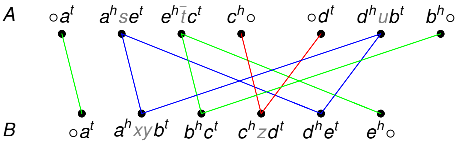

Components of AG(A, B): 1 cycle, 2 AB-paths and 1 AA-path

Minimum number of DCJs necessary to sort A into B (ignoring labels):

$$d_{\text{DCJ}}(A, B) = |\mathcal{G}| - (c + \frac{b}{2}),$$

where $c = \#$ cycles, $b = \#$ AB-paths

Types of DCJ operation

c: number of cycles in AG(A, B)

b: number of AB-paths in AG(A, B)

DCJ	effect on AG(A, B)	weight
optimal	increase c or b	0
neutral	c and b unchanged	+1
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An **optimal DCJ** either **creates** one cycle or two AB-paths.

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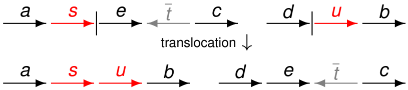
Using DCJs to save substitutions

DCJs x Substitutions



DCJ: $a^h s|e^t \,,\; d^h|ub^t \;\to\; a^h s|ub^t \,,\; d^h|e^t$

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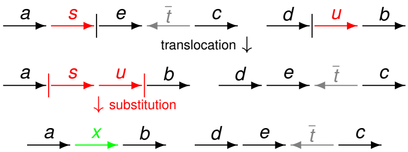

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Substitution: $a^h|su|b^t \;\rightarrow\; a^h|x|b^t$

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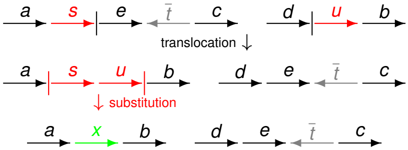

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Substitution: $a^h | s u | b^t \;\rightarrow\; a^h | x | b^t$

(a substitution affects the label of a single adjacency)

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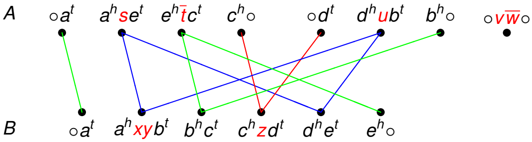
Representing a single component in $AG(A, B)$



Using DCJs to save substitutions

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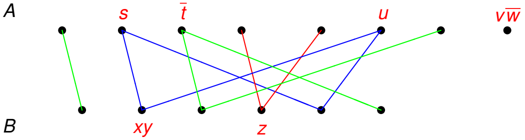

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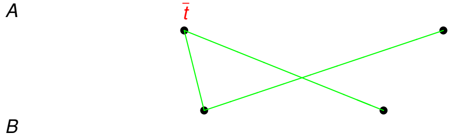

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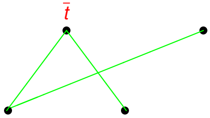

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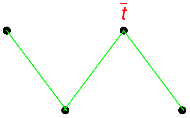

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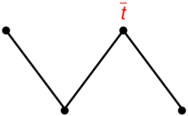

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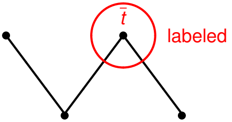

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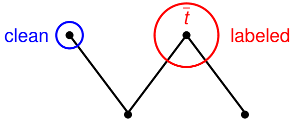

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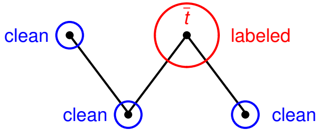

Using DCJs to save substitutions

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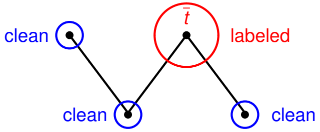

Ignoring substitutions (labels), it is possible to
sort a component individually with **optimal DCJs only**:

$d_{\text{DCJ}}(C) =$ number of optimal DCJs required to sort the component C

Using DCJs to save substitutions

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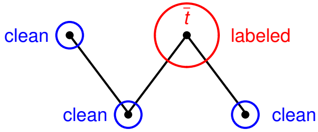

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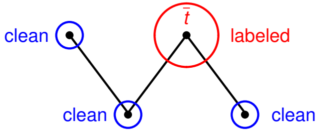
Using DCJs to save substitutions

Representing a single component in $\mathrm{AG}(A, B)$



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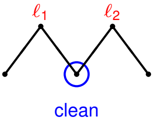
Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

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



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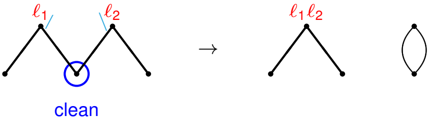

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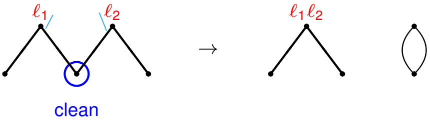
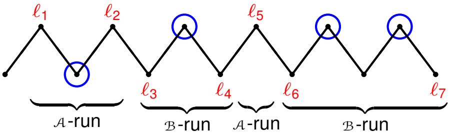


Runs of a component C:



Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

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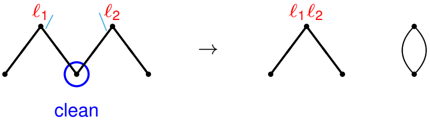
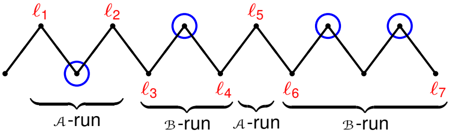


Runs of a component C:
$\Lambda(C) = 4$



Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

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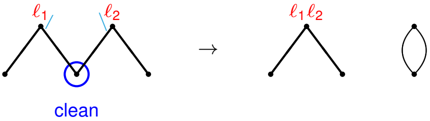

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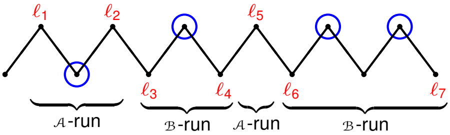
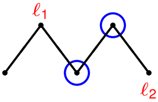


Each *run* can be entirely *accumulated* in the label of a single adjacency with optimal DCJs.

Using DCJs to save substitutions

Sorting the components of $\mathrm{AG}(A, B)$ individually

Optimal DCJs
eliminate gaps
between runs:



Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

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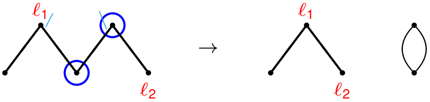

Using DCJs to save substitutions

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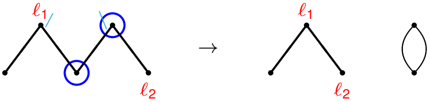
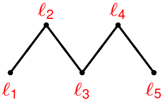


A DCJ can *merge* at most two $\mathcal{A}$-runs and two $\mathcal{B}$-runs:



Λ : 5 *runs*

Sorting the components of AG(A, B) individually

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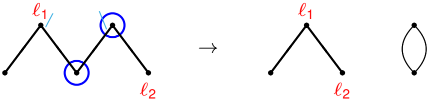

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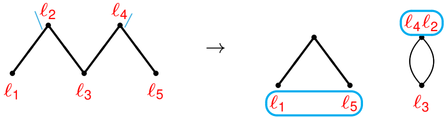

Λ : 5 *runs* 1 + 2 *runs* ($\Delta\Lambda = -2$)

Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

Using DCJs to save substitutions

Sorting the components of $AG(A, B)$ individually

$d_{\text{DCJ}}(C) =$ number of optimal DCJs required to sort a component C

Using DCJs to save substitutions

Sorting the components of $\mathrm{AG}(A, B)$ individually

$d_{\mathrm{DCJ}}(C) =$ number of optimal DCJs required to sort a component C

Substitution-potential of a component C

Minimum number of substitutions (pairs of consecutive runs) obtained by sorting C with $d_{\mathrm{DCJ}}(C)$ **optimal** DCJs:

$$\sigma(C) = \left\lceil \frac{\Lambda(C) + 1}{4} \right\rceil \qquad (\textit{for } \Lambda(C) \geq 1)$$

Using DCJs to save substitutions

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$\Lambda(C)$	$\sigma(C)$
0	0
1	1
2	1
3	1
4	2
5	2
6	2
7	2
⋮	⋮

Using DCJs to save substitutions

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6	2
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(We cannot do better with neutral or counter-optimal DCJs.)

Using DCJs to save substitutions

Sorting the components of $\text{AG}(A, B)$ individually

(Proving the potential formula by induction...)

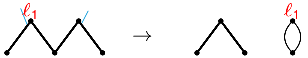
$$T(i) = \left\lceil \frac{i+1}{4} \right\rceil \quad (\textit{for} \;\; i \geq 1)$$

i	$T(i)$
0	0

Sorting the components of AG(A, B) individually

(Proving the potential formula by induction. . .)

$$T(i) = \left\lceil \frac{i+1}{4} \right\rceil \quad (\textit{for} \;\; i \geq 1)$$



$i = 1$ 0 1 ($\Delta\Lambda = 0$)

$T(1) = 1$

i	$T(i)$
0	0
1	1

Using DCJs to save substitutions

Sorting the components of $\mathrm{AG}(A, B)$ individually

(Proving the potential formula by induction...)

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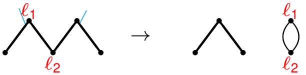

$i = 2$ → 0, 2 $(\Delta\Lambda = 0)$

$T(2) = 1$

i	$T(i)$
0	0
1	1
2	1

Using DCJs to save substitutions

Sorting the components of $\mathrm{AG}(A, B)$ individually

(Proving the potential formula by induction. . .)

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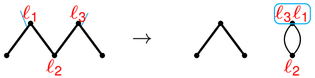

$i = 3$ 0   2 $(\Delta\Lambda = -1)$

$T(3) = T(2) = 1$

i	$T(i)$
0	0
1	1
2	1
3	1

Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

(Proving the potential formula by induction. . .)

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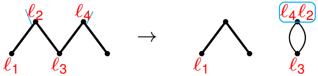


$i = 4$ 1   2 $(\Delta\Lambda = -1)$

$T(4) = T(1) + T(2) = 1 + 1 = 2$

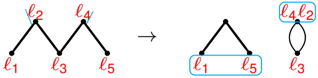
i	$T(i)$
0	0
1	1
2	1
3	1
4	2

Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

(Proving the potential formula by induction...)

$$T(i) = \left\lceil \frac{i+1}{4} \right\rceil \quad (\textit{for} \;\; i \geq 1)$$



$i \geq 5$ $\quad$ $i-4$ $\quad$ 2 $\quad$ $(\Delta\Lambda = -2)$

$$T(i) = T(i-4) + T(2) = \lceil \tfrac{(i-4)+1}{4} \rceil + 1 = \lceil \tfrac{i-4+1+4}{4} \rceil = \lceil \tfrac{i+1}{4} \rceil$$

i	$T(i)$
0	0
1	1
2	1
3	1
4	2
5	2
6	2
7	2
⋮	⋮
i	$\lceil (i+1)/4 \rceil$

Using DCJs to save substitutions

Sorting the components of $\mathrm{AG}(A, B)$ individually

A component C can be sorted with $\boldsymbol{d_{\mathrm{DCJ}}(C) + \sigma(C)}$ operations

Using DCJs to save substitutions

Sorting the components of AG(A, B) individually

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An **upper bound** to the **DCJ-substitution distance** is given by:

$$d_{\mathrm{DCJ}}^{sb}(A, B) \leq \sum_{C \in \mathrm{AG}(A,B)} (d_{\mathrm{DCJ}}(C) + \sigma(C))$$

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Using DCJs to save substitutions

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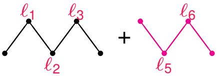
$$\downarrow$$

$$\boldsymbol{d_{\mathrm{DCJ}}^{sb}(A, B) \leq d_{\mathrm{DCJ}}(A, B) + \sum_{C \in \mathrm{AG}(A,B)} \sigma(C)}$$

Using DCJs to save substitutions

Recombinations of two paths

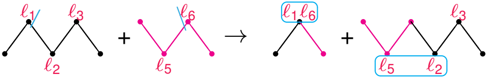


Λ:	3	+	2	
σ:	1	+	1	

$\Lambda(C)$	$\sigma(C)$
0	0
1	1
2	1
3	1
4	2
5	2
6	2
7	2
$\vdots$	$\vdots$

Using DCJs to save substitutions

Recombinations of two paths



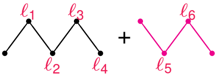
Λ: 3 + 2 → 1 + 2 ($\Delta\Lambda = -2$)

σ: 1 + 1 → 1 + 1 ($\Delta\sigma = 0$)

$\Lambda(C)$	$\sigma(C)$
0	0
1	1
2	1
3	1
4	2
5	2
6	2
7	2
⋮	⋮

Using DCJs to save substitutions

Recombinations of two paths



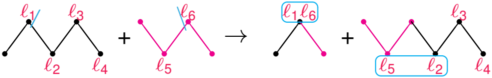
Λ: 4 + 2

σ: 2 + 1

$\Lambda(C)$	$\sigma(C)$
0	0
1	1
2	1
3	1
4	2
5	2
6	2
7	2
⋮	⋮

Using DCJs to save substitutions

Recombinations of two paths

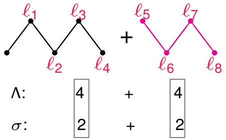


Λ: 4 + 2 → 1 + 3 ($\Delta\Lambda = -2$)

σ: 2 + 1 → 1 + 1 ($\Delta\sigma = -1$)

$\Lambda(C)$	$\sigma(C)$
0	0
1	1
2	1
3	1
4	2
5	2
6	2
7	2
⋮	⋮

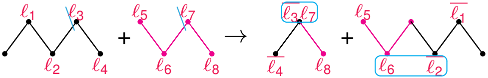
Recombinations of two paths



$\Lambda(C)$	$\sigma(C)$	
0	0	
1	1	
2	1	
3	1	
4	2	(x2)
5	2	
6	2	
7	2	
⋮	⋮	

Using DCJs to save substitutions

Recombinations of two paths



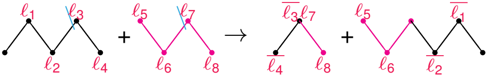
Λ: 4 + 4 → 3 + 3 ($\Delta\Lambda = -2$)

σ: 2 + 2 → 1 + 1 ($\Delta\sigma = -2$)

$\Lambda(C)$	$\sigma(C)$	
0	0	
1	1	
2	1	
3	1	(x2)
4	2	(x2)
5	2	
6	2	
7	2	
⋮	⋮	

Using DCJs to save substitutions

Recombinations of two paths



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

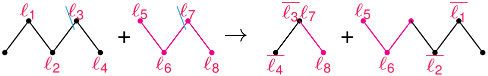
σ: 2 + 2 → 1 + 1 ($\Delta\sigma = -2$)

$$\boldsymbol{\Delta\sigma \geq -2}$$

$\Lambda(C)$	$\sigma(C)$	
0	0	
1	1	
2	1	
3	1	(x2)
4	2	(x2)
5	2	
6	2	
7	2	
⋮	⋮	

Using DCJs to save substitutions

Recombinations of two paths



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

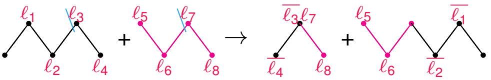
σ: 2 + 2 → 1 + 1 ($\Delta\sigma = -2$)

$$\boldsymbol{\Delta\sigma \geq -2}$$

$\Lambda(C)$	$\sigma(C)$
0	0
1	1
2	1
3	1
4	2
5	2
6	2
7	2
⋮	⋮
$4i$	$i+1$
$4i+1$	$i+1$
$4i+2$	$i+1$
$4i+3$	$i+1$

Using DCJs to save substitutions

Recombinations of two paths

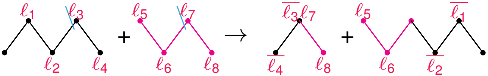


σ: 2 + 2 → 1 + 1 ($\Delta\sigma = -2$)

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

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

Recombinations of two paths



$BB \quad + \quad AB \quad \longrightarrow \quad BB \quad + \quad AB \quad (\Delta d_{\mathrm{DCJ}} = +1)$

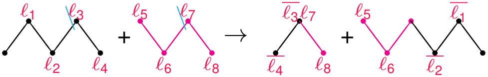
$\sigma: \quad 2 \quad + \quad 2 \quad \longrightarrow \quad 1 \quad + \quad 1 \quad (\Delta\sigma = -2)$

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

Change in the DCJ-substitution distance: $\Delta d = \Delta d_{\mathrm{DCJ}} + \Delta\sigma$

Using DCJs to save substitutions

Recombinations of two paths



BB + AB $\longrightarrow$ BB + AB $(\Delta d_{\text{DCJ}} = +1)$

σ: 2 + 2 $\longrightarrow$ 1 + 1 $(\Delta\sigma = -2)$

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

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

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

Using DCJs to save substitutions

The DCJ-substitution distance

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

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

The DCJ-substitution distance

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	Δd_{DCJ}	$\Delta \sigma$		Δd
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Considering all labeled paths of AG(A, B), find a shortest sequence of recombinations $\boldsymbol{S}$

such that the **weight** $\boldsymbol{w(S)} = \sum_{\rho \in S} \Delta d(\rho)$ is minimum: **can be solved in linear time**

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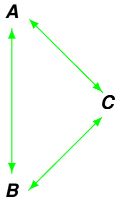
DCJ-substitution distance formula

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

Establishing the triangular inequality

Triangular inequality:



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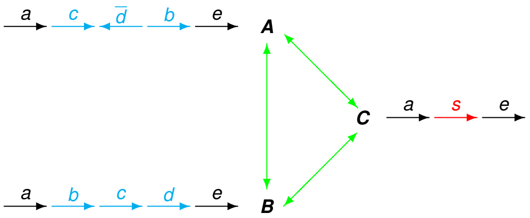

Using DCJs to save substitutions

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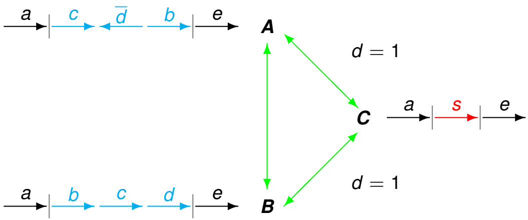

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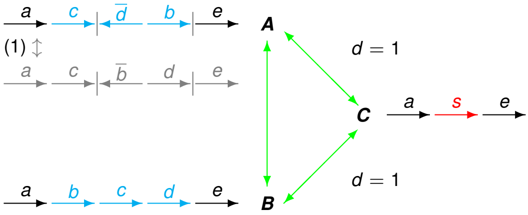

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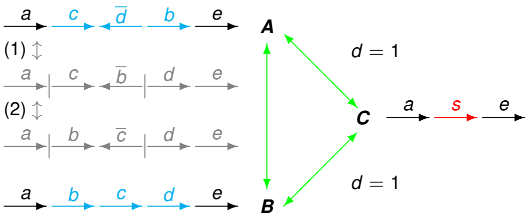

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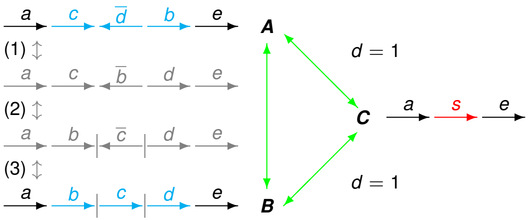

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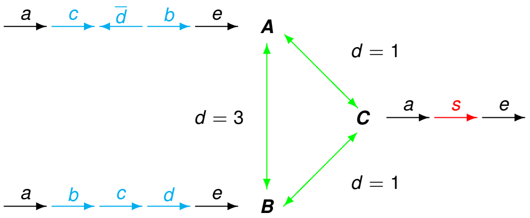
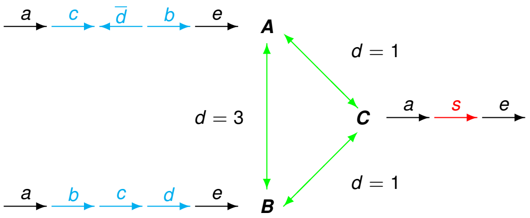


Using DCJs to save substitutions

Establishing the triangular inequality

Triangular inequality: $d(A, B) \leq d(A, C) + d(B, C)$ (!)

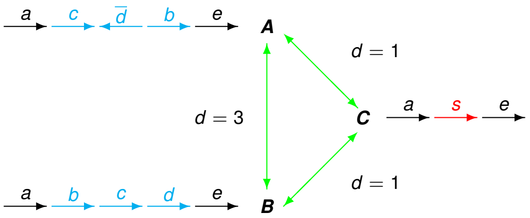
$3 > 1 + 1$ (!)



Establishing the triangular inequality

Triangular inequality: $d(A, B) \leq d(A, C) + d(B, C)$ (!)

- **Correction can be done** *a posteriori* [presented yesterday by Jens Stoye]



Overview

1. Motivation and Background
2. Preliminaries
   - Definitions
   - Adjacency graph and DCJ-distance
3. Using DCJs to save substitutions
   - Substitution potential and distance upper bound
   - Recombinations and the DCJ-substitution distance
4. **Conclusions and Future Work**

Conclusions and Future Work

Conclusions

Genomic distance under DCJs and substitutions:

Conclusions and Future Work

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- Genomes with unequal contents but free of duplicated markers

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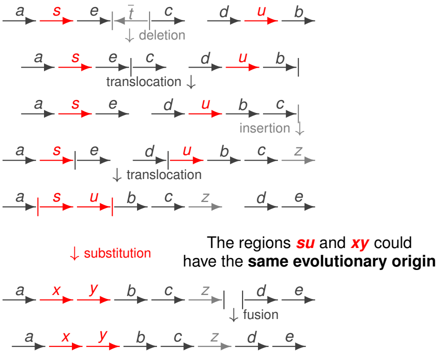
Genomic distance under DCJs and substitutions:

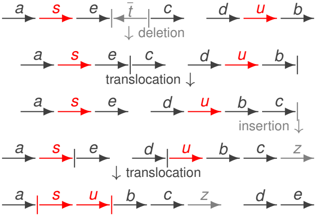
- Genomes with unequal contents but free of duplicated markers
- Substitutions include indels
- Distance can be computed in linear time
- Triangular inequality can be established *a posteriori*

Conclusions and Future Work

Future work

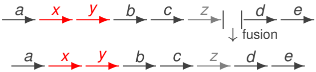


Future work



↓ substitution

The regions ***su*** and ***xy*** could be **homologous**?
(Do they correspond to an **unannotated orthology**?)



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Conclusions and Future Work

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- Explore the solution space of sorting genomes with DCJ operations and substitutions
- Develop a method to **refine orthology assignments**
- Extend the model to handle duplicated markers

Thank you for your attention!

References

- A. Bergeron, J. Mixtacki and J. Stoye. A unifying view of genome rearrangements. In Proceedings of *WABI*, 2006.
- M. D. V. Braga, L. C. Ribeiro, R. Machado and J. Stoye. On the weight of indels in genomic distances. *RECOMB-CG*, 2011.
- M. D. V. Braga and J. Stoye. The solution space of sorting by DCJ. *Journal of Computational Biology*, 2010.
- M. D. V. Braga, E. Willing and J. Stoye. Double cut and join with insertions and deletions. *Journal of Computational Biology*, 2011.
- S. Yancopoulos, O. Attie and R. Friedberg. Efficient sorting of genomic permutations by translocation, inversion and block interchange. *Bioinformatics*, 2005.
- S. Yancopoulos and R. Friedberg. DCJ path formulation for genome transformations which include insertions, deletions, and duplications. *Journal of Computational Biology*, 2009.