

DCJ-indel distance of natural genomes

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Types of genomes

Given a pair of genomes \mathbb{A}, \mathbb{B} . Let $\Phi_G(m)$ be the copy number of family m in genome $G \in \{\mathbb{A}, \mathbb{B}\}$.

	Non-Singular $\Phi_G(m)$ arbitrary	Singular $\Phi_G(m) \leq 1$
Unbalanced $ \Phi_{\mathbb{A}}(m) - \Phi_{\mathbb{B}}(m) $ arbitrary	Natural genomes	Singular Genomes
Balanced $ \Phi_{\mathbb{A}}(m) - \Phi_{\mathbb{B}}(m) = 0$	Balanced Genomes	Canonical Genomes

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NP-Hard

Natural Genomes and indels

There is no way to sort $(1\ 2\ 2\ \bar{3}\ 4)$ into $(1\ 2\ 3\ 2\ 2\ 4)$ by DCJs alone.

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Natural Genomes and indels

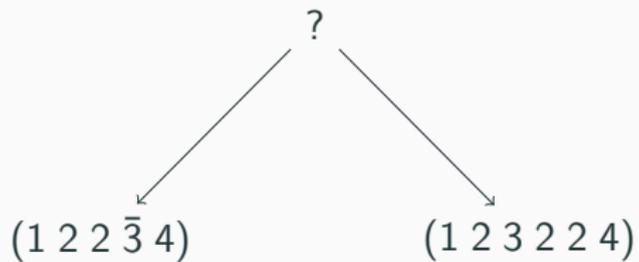
There is no way to sort $(1\ 2\ 2\ \bar{3}\ 4)$ into $(1\ 2\ 3\ 2\ 2\ 4)$ by DCJs alone.

We need indel operations

→ But how many 2s to delete/insert?

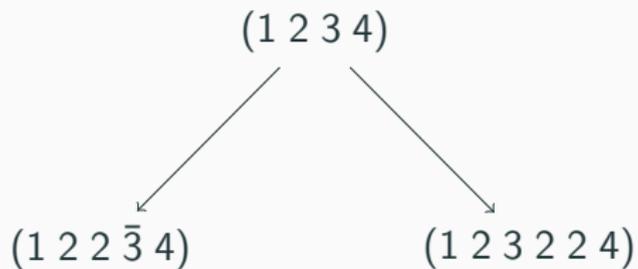
Excursus: Matching models

This depends on the assumed phylogeny!



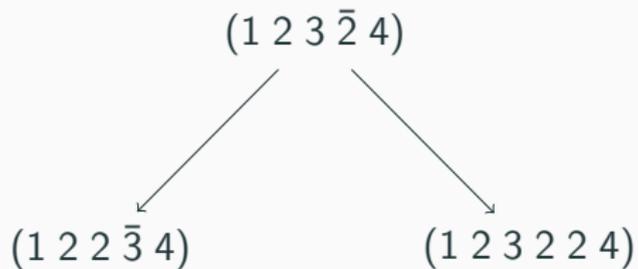
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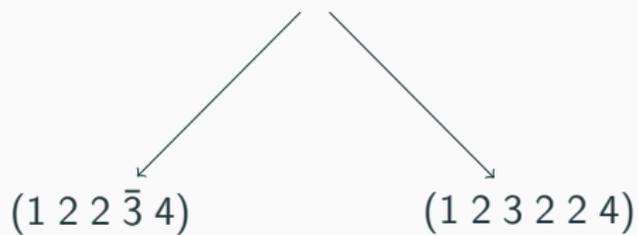
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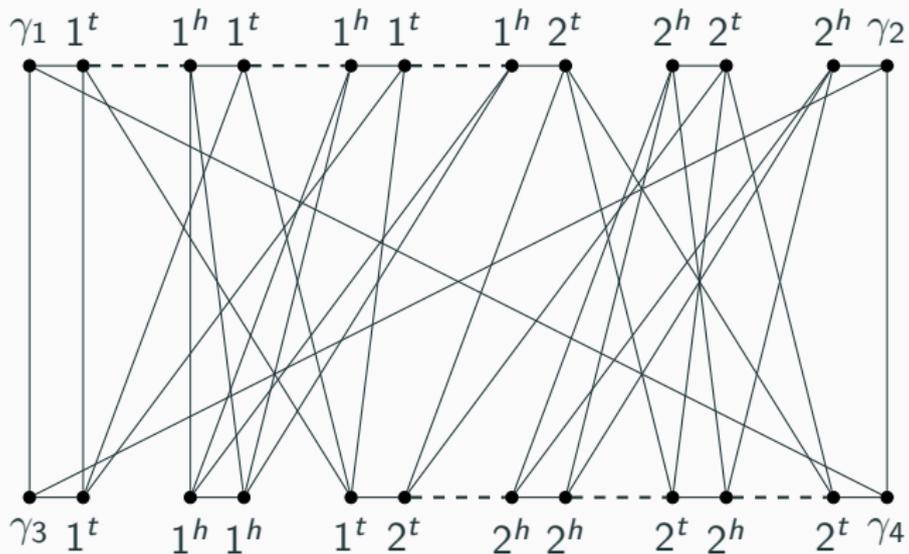


Excursus: Matching models

How to handle a shared family m with $\Phi_A(m) \neq \Phi_B(m)$

Exemplary Matching (EM)	Intermediate Matching (IM)	Maximal Matching (MM)
Exactly one occurrence matched	At least one occurrence matched	As many occurrences as possible matched
$n_m = 1$ genes of family m matched	$1 \leq n_m \leq \min(\Phi_A(m), \Phi_B(m))$ genes of family m matched	$n_m = \min(\Phi_A(m), \Phi_B(m))$ genes of family m matched
Lowest common ancestor: Each shared marker occurs once		Lowest common ancestor: Each shared marker occurs at least as often as in the genome with fewer occurrences

Enforcing MM in the capped MRG



The capped MRG for MM Natural Genomes

Given two natural genomes \mathbb{A} , \mathbb{B} their *capped multi-relational graph* $CMRG(\mathbb{A}, \mathbb{B})$ is described as follows

1. $V = V(\xi(\mathbb{A})) \cup V(\xi(\mathbb{B})) \cup \Gamma$: There is a vertex for each extremity/cap in each genome.

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

2. $E = E_\alpha(\mathbb{A}) \cup E_\alpha(\mathbb{B}) \cup E_\xi \cup E_{\xi'} \cup E_{ID}(\mathbb{A}) \cup E_{ID}(\mathbb{B})$

- $E_\alpha(\mathbb{G}) = \{uv : u, v \in V(\xi(\mathbb{G})) \text{ and } \ell(u)\ell(v) \in \alpha(\mathbb{G})\}$
- $E_\xi = \{uv : u \in V(\xi(\mathbb{A})) \text{ and } v \in V(\xi(\mathbb{B})) \text{ and } \ell(u) = \ell(v)\}$
- $E_{\xi'}$... edges connecting caps
-

$E_{ID}(\mathbb{G}) = \{uv : u, v \in V(\xi(\mathbb{G})) \text{ and } u, v \text{ are extremities of the same gene of family } m$

with $\Phi_{\mathbb{G}}(m) > \min(\Phi_{\mathbb{A}}(m), \Phi_{\mathbb{B}}(m))\}$

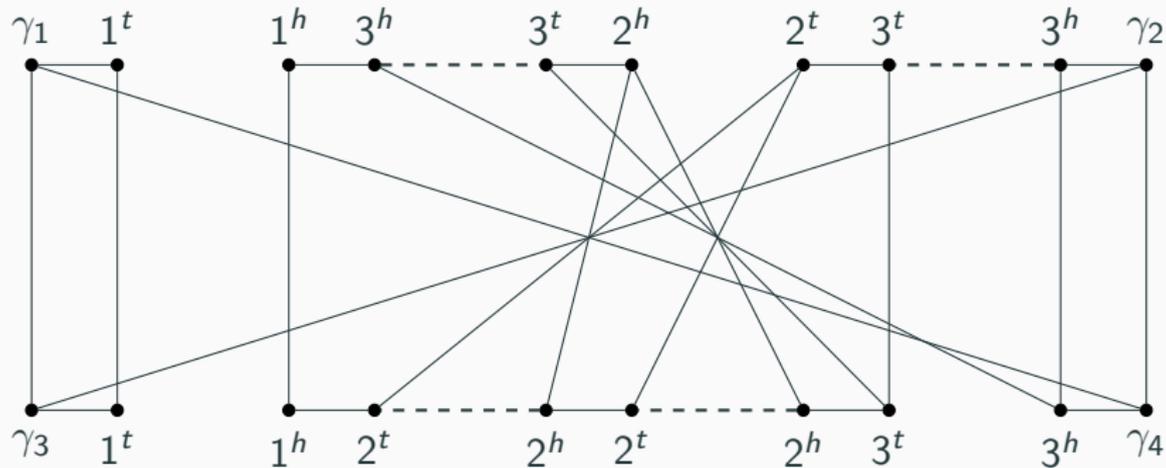
Consistent decompositions in the CMRG

Capped consistent

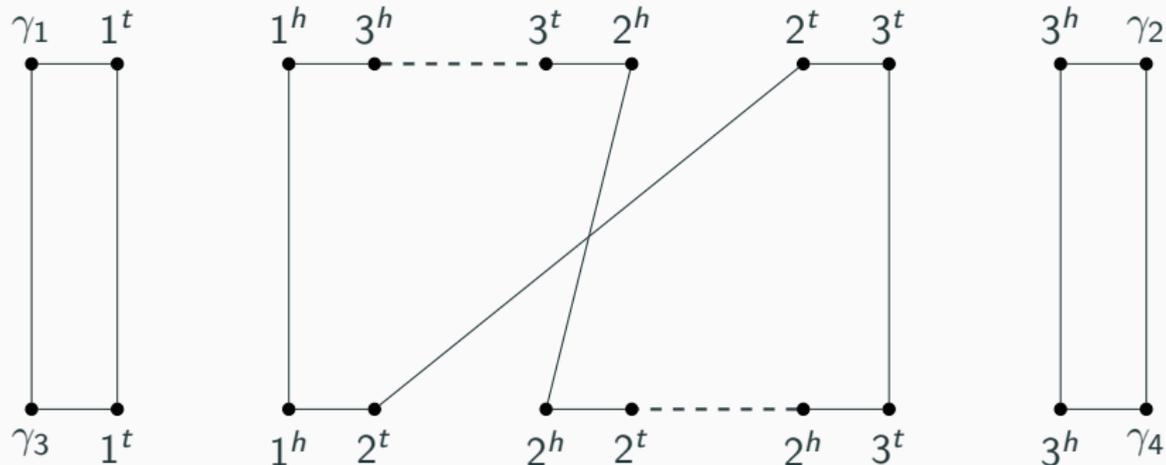
decomposition $Q[S, P]$

- is **induced** by a maximal sibling-set S and a maximal capping-set P
- is the union of S with P with all adjacency edges and indel edges of genes not matched in S
- covers all vertices of $CMRG(\mathbb{A}, \mathbb{B})$
- is composed of cycles only

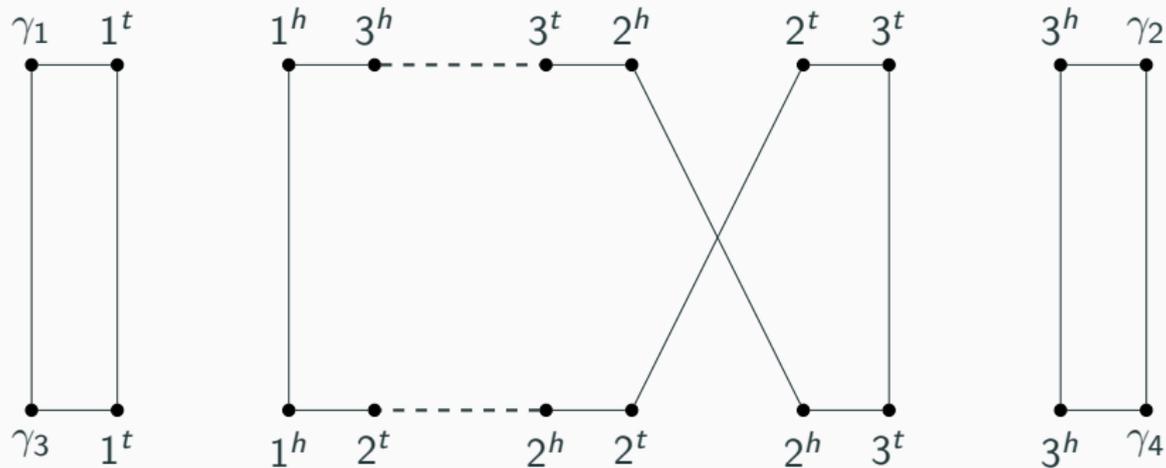
Consistent Decompositions \equiv Matchings



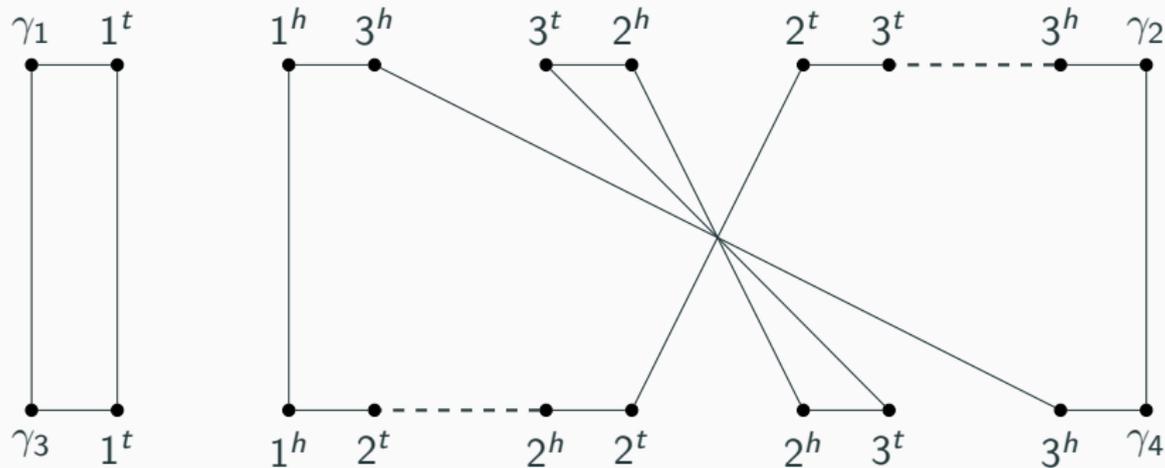
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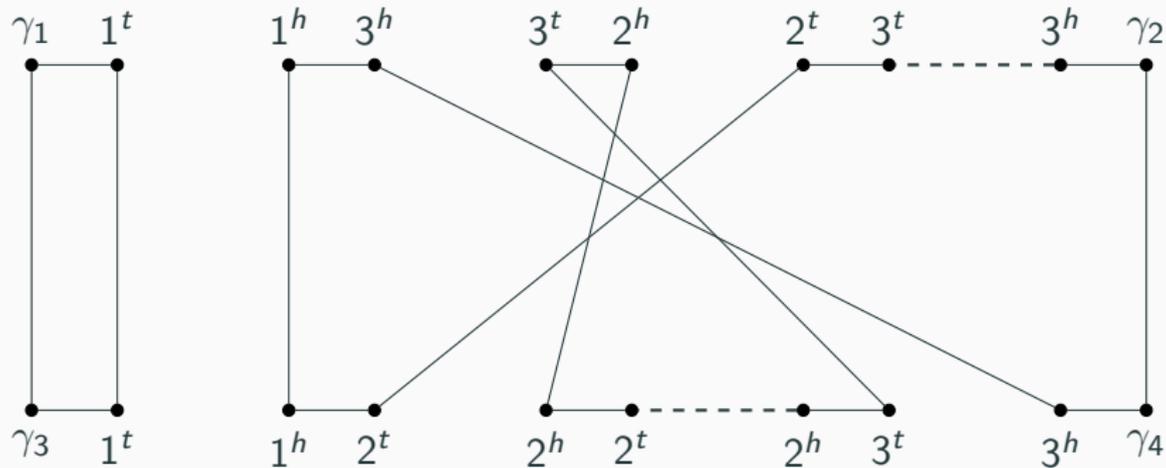
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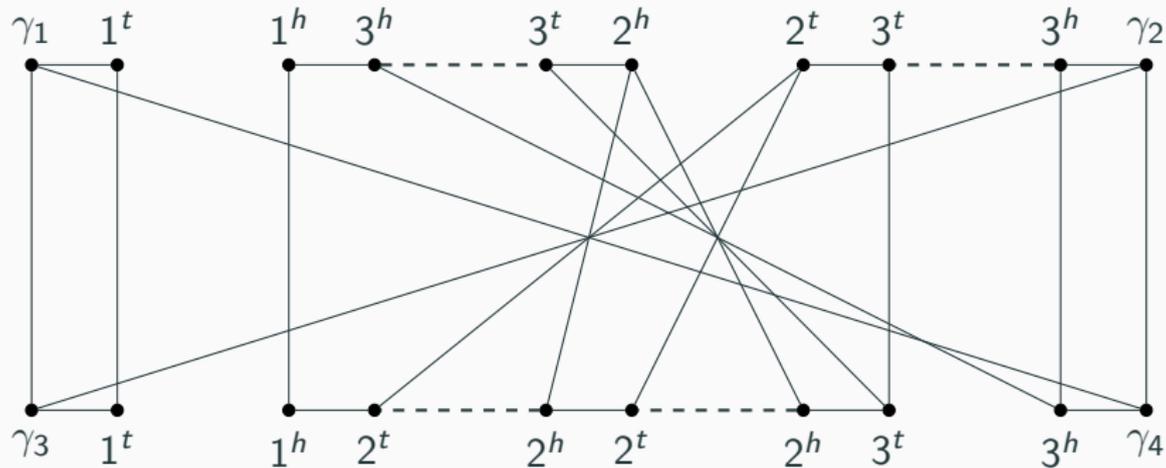
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Finding the best decomposition

$$d_{DCJ}^{ID}(A, B) = \min_{S \in \mathfrak{S}_{MAX}, P \in \mathfrak{P}_{MAX}} \{d_{DCJ}^{ID}(Q[S, P])\} = n_* + p_* - \max_{S \in \mathfrak{S}_{MAX}, P \in \mathfrak{P}_{MAX}} \{w(Q[S, P])\},$$

$$\text{where } \begin{cases} \mathfrak{S}_{MAX} \text{ is the set of all maximal sibling-sets of } CMRG(\mathbb{A}, \mathbb{B}) \\ \mathfrak{P}_{MAX} \text{ is the set of all maximal capping-sets of } CMRG(\mathbb{A}, \mathbb{B}) \\ n_* \text{ and } p_* \text{ are constant for any capped consistent decomposition} \end{cases}$$

$$\text{with } w(Q[S, P]) = |\mathcal{C}^Q| - \sum_{C \in \mathcal{C}^Q \cup \mathcal{S}^Q} (\lambda(C))$$

where

\mathcal{C}^Q are cycles containing extremity edges

\mathcal{S}^Q are circular singletons

Recap: Shao-Lin-Moret

Match the parts of the ILP to their function!

A $\ell_i \leq \ell_j + i(1 - x_{\{v_i, v_j\}}) \quad \forall \{v_i, v_j\} \in E$

B $\sum_{\{u, v\} \in E} x_{\{u, v\}} = 2 \quad \forall u \in V$

C $i \cdot z_i \leq \ell_i \quad \forall 1 \leq i \leq |V|$

D $x_e = 1 \quad \forall e \in E_\alpha(\mathbb{A}) \cup E_\alpha(\mathbb{B})$

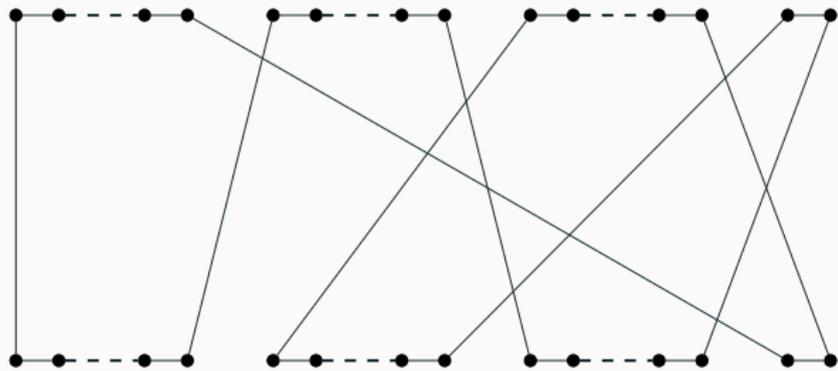
E $x_e = x_d$
 e and d are siblings $\quad \forall e, d \in E_\xi$ such that

- 1 Each adjacency edge is in the decomposition
- 2 Sibling edges are only selected together
- 3 A cycle is only counted at the vertex with the smallest label
- 4 A decomposition consists only of simple cycles
- 5 Cycle labels of adjacent vertices are the same

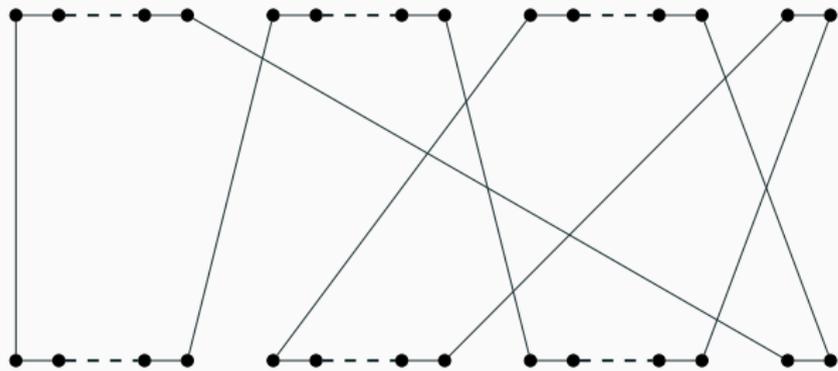
Recap: Capping and indels

id	sources	linking AB-cycle	T	Δn	Δc	$\Delta(2i)$	$\Delta\lambda$	Δd
\mathcal{P} WM	$AA_{AB} + BB_{AB}$	(AA_{AB}, BB_{BA})		+1	+1	0	-2	-2
\mathcal{Q} WWMM	$2 \times AA_{AB} + BB_A + BB_B$	$(AA_{AB}, BB_B, AA_{BA}, BB_A)$		+2	+1	0	-4	-3
MMWW	$2 \times BB_{AB} + AA_A + AA_B$	$(BB_{AB}, AA_B, BB_{BA}, AA_A)$		+2	+1	0	-4	-3
\mathcal{J} WZM	$AA_{AB} + BB_A + AB_{AB}$	(AB_{AB}, AA_{BA}, BB_A)		+1.5	+1	-0.5	-3	-2
WWM	$2 \times AA_{AB} + BB_A$	$(AA_{BA}, BB_A, AA_{AB}, BB_\varepsilon \prec \Gamma_B)$	\cup	+2	+1	0	-3	-2
WNM	$AA_{AB} + BB_B + AB_{BA}$	(AB_{BA}, AA_{AB}, BB_B)		+1.5	+1	-0.5	-3	-2
WWM	$2 \times AA_{AB} + BB_B$	$(AA_{AB}, BB_A, AA_{AB}, BB_\varepsilon \prec \Gamma_B)$	\cup	+2	+1	0	-3	-2
MNW	$BB_{AB} + AA_A + AB_{BA}$	(AB_{BA}, AA_A, BB_{AB})		+1.5	+1	-0.5	-3	-2
MMW	$2 \times BB_{AB} + AA_A$	$(BB_{BA}, AA_A, BB_{AB}, AA_\varepsilon \prec \Gamma_A)$	\cap	+2	+1	0	-3	-2
MZW	$BB_{AB} + AA_B + AB_{AB}$	(AB_{AB}, AA_B, BB_{BA})		+1.5	+1	-0.5	-3	-2
MMW	$2 \times BB_{AB} + AA_B$	$(BB_{AB}, AA_B, BB_{BA}, AA_\varepsilon \prec \Gamma_A)$	\cap	+2	+1	0	-3	-2
\mathcal{S} ZN	$AB_{AB} + AB_{BA}$	(AB_{AB}, AB_{BA})		+1	+1	-1	-2	-1
WM	$AA_A + BB_A$	(AA_A, BB_A)		+1	+1	0	-1	-1
WM	$AA_B + BB_B$	(AA_B, BB_B)		+1	+1	0	-1	-1
WM	$AA_{AB} + BB_A$	(AA_{BA}, BB_A)		+1	+1	0	-1	-1
WM	$AA_{AB} + BB_B$	(AA_{AB}, BB_B)		+1	+1	0	-1	-1
WZ	$AA_{AB} + AB_{AB}$	$(AA_{BA}, BB_\varepsilon \prec \Gamma_B, AB_{AB})$	\cup	+1.5	+1	-0.5	-2	-1
WN	$AA_{AB} + AB_{BA}$	$(AA_{AB}, BB_\varepsilon \prec \Gamma_B, AB_{BA})$	\cup	+1.5	+1	-0.5	-2	-1
WW	$AA_{AB} + AA_{AB}$	$(AA_{AB}, BB_\varepsilon \prec \Gamma_B, AA_{BA}, BB_\varepsilon \prec \Gamma_B)$	\cup	+2	+1	0	-2	-1
MW	$BB_{AB} + AA_A$	(AA_A, BB_{AB})		+1	+1	0	-1	-1
MW	$BB_{AB} + AA_B$	(AA_B, BB_{BA})		+1	+1	0	-1	-1
MZ	$BB_{AB} + AB_{AB}$	$(BB_{BA}, AB_{AB}, AA_\varepsilon \prec \Gamma_A)$	\cap	+1.5	+1	-0.5	-2	-1
MN	$BB_{AB} + AB_{BA}$	$(BB_{AB}, AB_{BA}, AA_\varepsilon \prec \Gamma_A)$	\cap	+1.5	+1	-0.5	-2	-1
MM	$BB_{AB} + BB_{AB}$	$(BB_{AB}, AA_\varepsilon \prec \Gamma_A, BB_{BA}, AA_\varepsilon \prec \Gamma_A)$	\cap	+2	+1	0	-2	-1
\mathcal{M} ZZWM	$2 \times AB_{AB} + AA_B + BB_A$	$(AB_{AB}, AA_B, BA_{BA}, BB_A)$		+2	+1	-1	-4	-2
NNWM	$2 \times AB_{BA} + AA_A + BB_B$	$(AB_{BA}, AA_A, BA_{AB}, BB_B)$		+2	+1	-1	-4	-2

Recap: Indels via Transitions



Recap: Indels via Transitions



$$\lambda(C) = \frac{N(C)}{2} + r(C)$$

$$\text{with } r(C) = \begin{cases} 1 & \text{if } C \text{ is indel-enclosing} \\ 0 & \text{otherwise} \end{cases}$$

Transition counting in the ILP

Set label to 0 on active indel-edge in \mathbb{A}

$$r_v \leq 1 - x_{\{u,v\}}$$

$$\forall \{u, v\} \in E_{ID}(\mathbb{A}),$$

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Set label to 1 on active indel-edge in \mathbb{B}

$$r_{v'} \geq x_{\{u',v'\}}$$

$$\forall \{u', v'\} \in E_{ID}(\mathbb{B})$$

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Set label to 1 on active indel-edge in \mathbb{B}

$$r_{v'} \geq x_{\{u',v'\}}$$

$$\forall \{u', v'\} \in E_{ID}(\mathbb{B})$$

Record the transition in variable

$$t_{\{u,v\}} \geq r_v - r_u$$

$$\forall \{u, v\} \in E$$

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$$r_{v'} \geq x_{\{u',v'\}}$$

$$\forall \{u', v'\} \in E_{ID}(\mathbb{B})$$

Record the transition in variable

$$t_{\{u,v\}} \geq r_v - r_u - (1 - x_{\{u,v\}})$$

$$\forall \{u, v\} \in E$$

What about $r(C)$?

$$\begin{aligned}w(Q[S, P]) &= |C^Q| - \sum_{C \in \mathcal{C}^Q \cup S^Q} \left(\frac{\aleph(C)}{2} + r(C) \right) = |C^Q| - \frac{\aleph(Q)}{2} - \sum_{C \in \mathcal{C}^Q \cup S^Q} r(C) \\&= |C^Q| - \frac{\aleph(Q)}{2} - |\{C \in \mathcal{C}^Q : C \text{ is indel-enclosing}\}| - |S^Q| \\&= |\{C \in \mathcal{C}^Q : C \text{ is not indel-enclosing}\}| - \frac{\aleph(Q)}{2} - |S^Q|\end{aligned}$$

where S^Q are circular singletons in the decomposition,

$$r(C) = \begin{cases} 1 & \text{if } C \text{ is indel-enclosing} \\ 0 & \text{otherwise} \end{cases}$$

Removing indel-enclosing cycles from the count

Idea: Set the cycle label to 0.

$$\ell_i \leq i(1 - x_{\{v_i, v_j\}}) \quad \forall \{v_i, v_j\} \in E_{ID}(\mathbb{A}) \cup E_{ID}(\mathbb{B})$$

Counting circular singletons

Idea: Each circular chromosome $k \in K$ is a potential circular singleton.

$$\sum_{e \in E_D(k)} x_e - |k| + 1 \leq s_k \quad \forall k \in K$$

Final Objective Function

$$w(Q[S, P]) = |\{C \in \mathcal{C}^Q : C \text{ is not indel-enclosing}\}| - \frac{N(Q)}{2} - |S^Q|$$

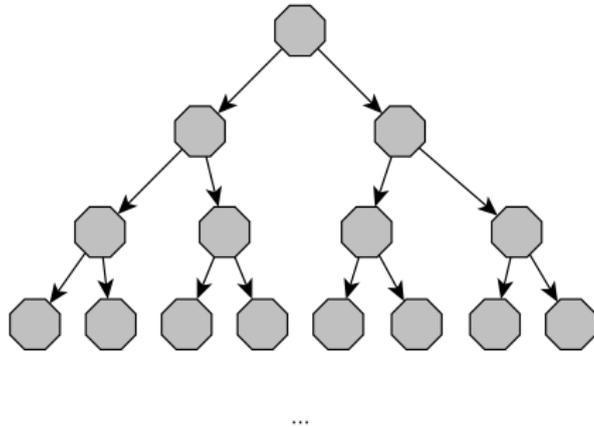
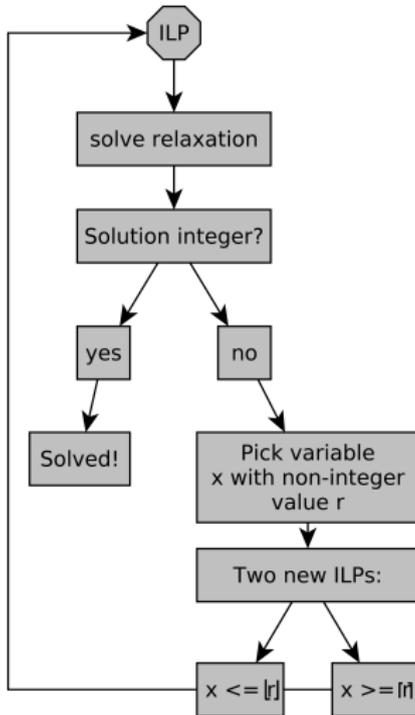
Objective:

$$\text{Maximize } \sum_{1 \leq i \leq |V|} z_i - \frac{1}{2} \sum_{e \in E} t_e - \sum_{k \in K} s_k$$

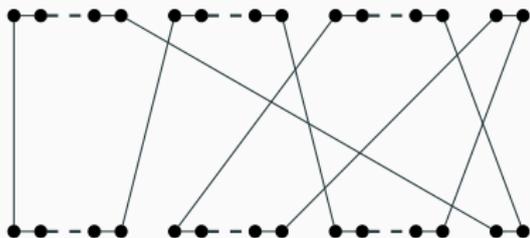
Match the following parts of the ILP to their function!

- | | | | |
|---|---|---|---|
| A | $\ell_i \leq i(1 - x_{\{v_i, v_j\}})$ | $\forall \{v_i, v_j\} \in E_{ID}(\mathbb{A}) \cup E_{ID}(\mathbb{B})$ | 1 Setting run-variable
(preparing to find transitions) |
| B | $r_v \leq 1 - x_{\{u, v\}}$
$r_{v'} \geq x_{\{u', v'\}}$ | $\forall \{u, v\} \in E_{ID}(\mathbb{A}),$
$\forall \{u', v'\} \in E_{ID}(\mathbb{B})$ | 2 Removal of indel-
enclosing cycles |
| C | $t_{\{u, v\}} \geq r_v - r_u - (1 - x_{\{u, v\}})$ | $\forall \{u, v\} \in E$ | 3 Recording transitions |
| D | $\sum_{e \in E_{id}^k} x_e - k + 1 \leq s_k$ | $\forall k \in K$ | 4 Flagging circular sin-
gletons |

Excursus: ILP solvers



Refinement - Restricting where transitions occur



Only permit transitions in adjacencies in \mathbb{A}

$$t_e = 0$$

$$\forall e \in E \setminus E_\alpha(\mathbb{A})$$

Only permit transitions next to indels

$$\sum_{\substack{d \in E_{ID}(\mathbb{A}), \\ d \cap e \neq \emptyset}} x_d - t_e \geq 0$$

$$\forall e \in E_\alpha(\mathbb{A})$$

Full ILP Solution

Objective:

$$\text{Maximize } \sum_{1 \leq i \leq |V|} z_i - \frac{1}{2} \sum_{e \in E} t_e - \sum_{k \in K} s_k$$

Constraints:

$$(C.01) \quad x_e = 1 \quad \forall e \in E_\alpha(\mathbb{A}) \cup E_\alpha(\mathbb{B})$$

$$(C.02) \quad \sum_{\{u,v\} \in E} x_{\{u,v\}} = 2 \quad \forall u \in V$$

$$(C.03) \quad x_e = x_d \quad \forall e, d \in E_\xi \text{ such that } e \text{ and } d \text{ are siblings}$$

$$(C.04) \quad \ell_i \leq \ell_j + i(1 - x_{\{v_i, v_j\}}) \quad \forall \{v_i, v_j\} \in E,$$

$$(C.06) \quad i \cdot z_i \leq \ell_i \quad \forall 1 \leq i \leq |V|$$

$$(C.05) \quad \ell_i \leq i(1 - x_{\{v_i, v_j\}}) \quad \forall \{v_i, v_j\} \in E_{ID}(\mathbb{A}) \cup E_{ID}(\mathbb{B})$$

$$(C.07) \quad r_v \leq 1 - x_{\{u,v\}} \quad \forall \{u,v\} \in E_{ID}(\mathbb{A}),$$

$$r_{v'} \geq x_{\{u',v'\}} \quad \forall \{u',v'\} \in E_{ID}(\mathbb{B})$$

$$(C.08) \quad t_{\{u,v\}} \geq r_v - r_u - (1 - x_{\{u,v\}}) \quad \forall \{u,v\} \in E$$

$$(C.09) \quad \sum_{\substack{d \in E_{ID}(\mathbb{A}), \\ d \cap e \neq \emptyset}} x_d - t_e \geq 0 \quad \forall e \in E_\alpha(\mathbb{A})$$

$$(C.10) \quad t_e = 0 \quad \forall e \in E \setminus E_\alpha(\mathbb{A})$$

$$(C.11) \quad \sum_{e \in E_{id}^k} x_e - |k| + 1 \leq s_k \quad \forall k \in K$$

Domains:

$$(D.01) \quad x_e \in \{0, 1\} \quad \forall e \in E$$

$$(D.02) \quad 0 \leq \ell_i \leq i \quad \forall 1 \leq i \leq |V|$$

$$(D.03) \quad z_i \in \{0, 1\} \quad \forall 1 \leq i \leq |V|$$

$$(D.04) \quad r_v \in \{0, 1\} \quad \forall v \in V$$

$$(D.05) \quad t_e \in \{0, 1\} \quad \forall e \in E$$

$$(D.06) \quad s_k \in \{0, 1\} \quad \forall k \in K$$

Full ILP Solution

Objective:

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$$(C.05) \quad \ell_i \leq i(1 - x_{\{v_i, v_j\}}) \quad \forall \{v_i, v_j\} \in E_{ID}(\mathbb{A}) \cup E_{ID}(\mathbb{B})$$

$$(C.07) \quad r_v \leq 1 - x_{\{u,v\}} \quad \forall \{u,v\} \in E_{ID}(\mathbb{A}), \\ r_{v'} \geq x_{\{u',v'\}} \quad \forall \{u',v'\} \in E_{ID}(\mathbb{B})$$

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$$(C.09) \quad \sum_{\substack{d \in E_{ID}(\mathbb{A}), \\ d \cap e \neq \emptyset}} x_d - t_e \geq 0 \quad \forall e \in E_\alpha(\mathbb{A})$$

$$(C.10) \quad t_e = 0 \quad \forall e \in E \setminus E_\alpha(\mathbb{A})$$

$$(C.11) \quad \sum_{e \in E_{id}^k} x_e - |k| + 1 \leq s_k \quad \forall k \in K$$

Domains:

$$(D.01) \quad x_e \in \{0, 1\} \quad \forall e \in E$$

$$(D.02) \quad 0 \leq \ell_i \leq i \quad \forall 1 \leq i \leq |V|$$

$$(D.03) \quad z_i \in \{0, 1\} \quad \forall 1 \leq i \leq |V|$$

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Shao et al.

Full ILP Solution

Objective:

$$\text{Maximize } \sum_{1 \leq i \leq |V|} z_i - \frac{1}{2} \sum_{e \in E} t_e - \sum_{k \in K} s_k$$

Constraints:

$$(C.01) \quad x_e = 1 \quad \forall e \in E_\alpha(\mathbb{A}) \cup E_\alpha(\mathbb{B})$$

$$(C.02) \quad \sum_{\{u,v\} \in E} x_{\{u,v\}} = 2 \quad \forall u \in V$$

$$(C.03) \quad x_e = x_d \quad \forall e, d \in E_\xi \text{ such that } e \text{ and } d \text{ are siblings}$$

$$(C.04) \quad \ell_i \leq \ell_j + i(1 - x_{\{v_i, v_j\}}) \quad \forall \{v_i, v_j\} \in E,$$

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DING extension

Full ILP Solution

Objective:

$$\text{Maximize } \sum_{1 \leq i \leq |V|} z_i - \frac{1}{2} \sum_{e \in E} t_e - \sum_{k \in K} s_k$$

Constraints:

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Circ. singleton
handling

Full ILP Solution

Objective:

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Indel enclosing
cycles

Full ILP Solution

Objective:

$$\text{Maximize } \sum_{1 \leq i \leq |V|} z_i - \frac{1}{2} \sum_{e \in E} t_e - \sum_{k \in K} s_k$$

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Transition
counting

Full ILP Solution

Objective:

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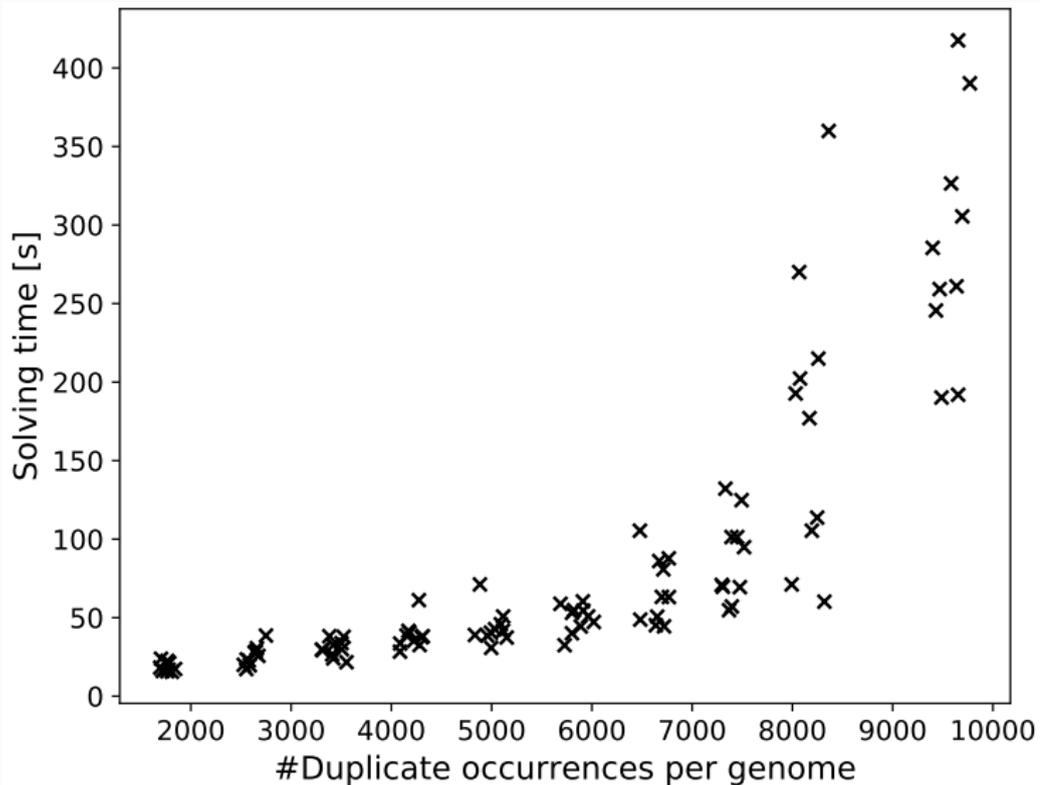
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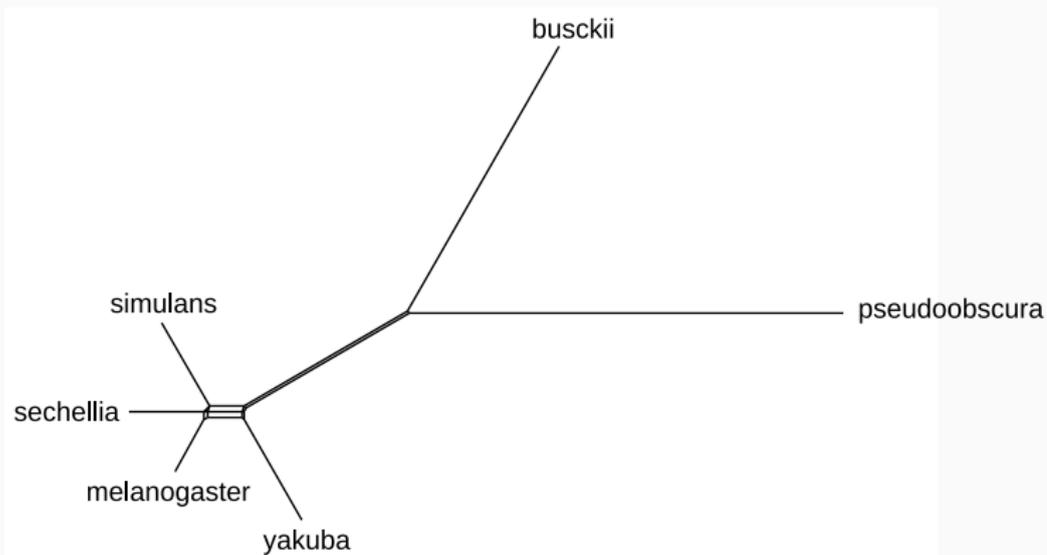
ILPs can be very fast



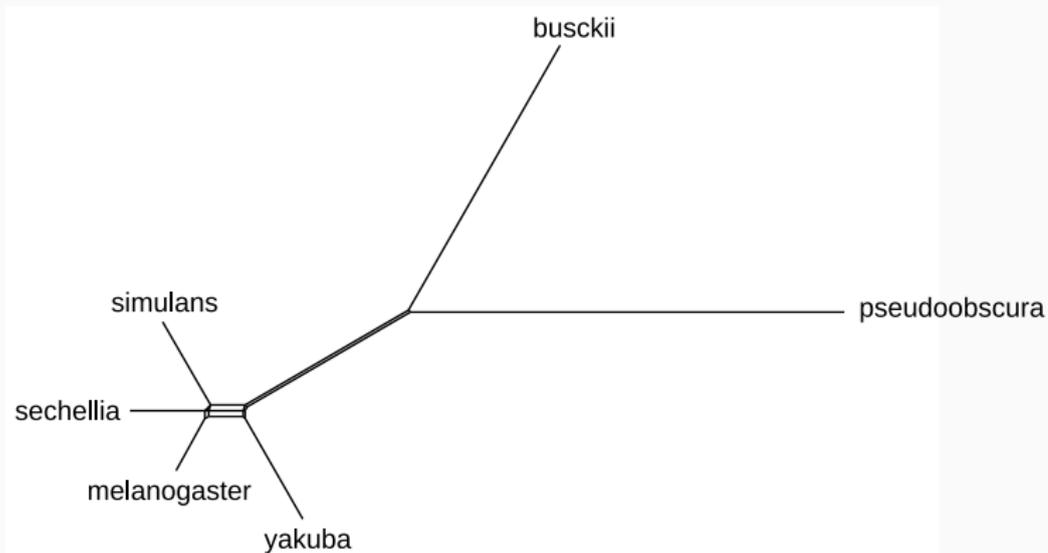
ILPs can be very fast

Genome pair	Max. multiplicity of dupl. marker	#duplicate markers	#duplicate occ.	d_{DCJ}^{id}	solving time [s]
dbus-dmel	23	303	832	4661	6.02
dbus-dpse	17	361	934	4688	5.29
dbus-dsec	15	295	766	4710	5.64
dbus-dsim	13	281	721	4767	5.05
dbus-dyak	19	318	785	4756	5.00
dmel-dpse	23	469	1319	3799	32218.93
dmel-dsec	23	326	902	901	6.78
dmel-dsim	23	322	893	1093	5.73
dmel-dyak	23	362	972	1379	7.22
dpse-dsec	17	464	1227	3866	13.82
dpse-dsim	17	449	1198	3962	6.81
dpse-dyak	19	481	1259	3951	8.96
dsec-dsim	15	314	843	1138	5.67
dsec-dyak	19	354	903	1516	6.56
dsim-dyak	19	347	864	1661	23.07

Resolved Phylogeny



Resolved Phylogeny



Not quite, but for an improved procedure, stay tuned for next lecture :)



Gurobi mip solver introduction.

<https://www.gurobi.com/resource/mip-basics/>.

Accessed: 2021-01-26.



Bohnenkämper, L., Braga, M. D., Doerr, D., and Stoye, J. (0).

Computing the rearrangement distance of natural genomes.

Journal of Computational Biology, 0(0):null.

PMID: 33393848.