Combinatorial Optimization in Bioinfo

Lecture 6 – Comparative genomics

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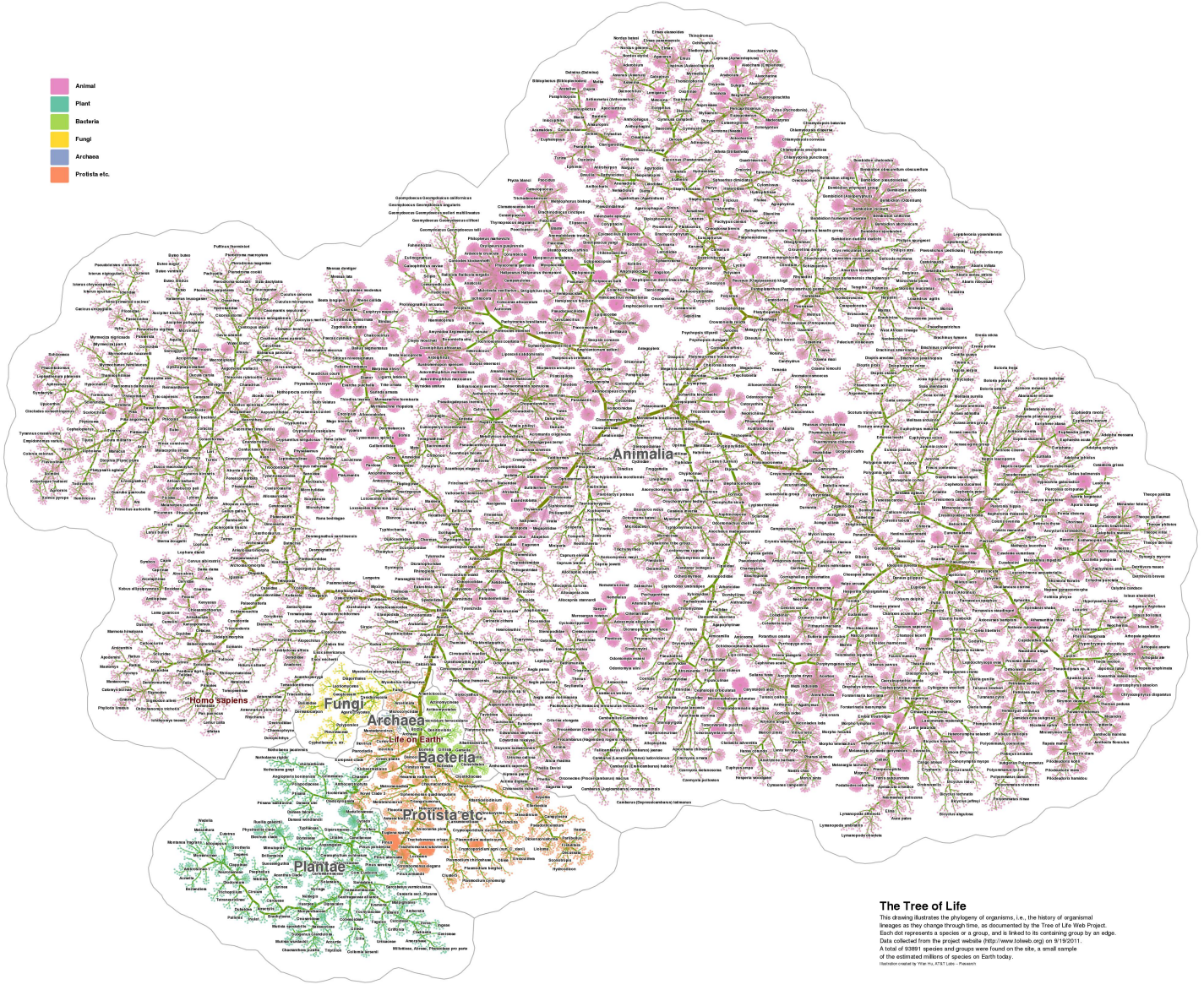
The tree of life



Cool story bro. What next?

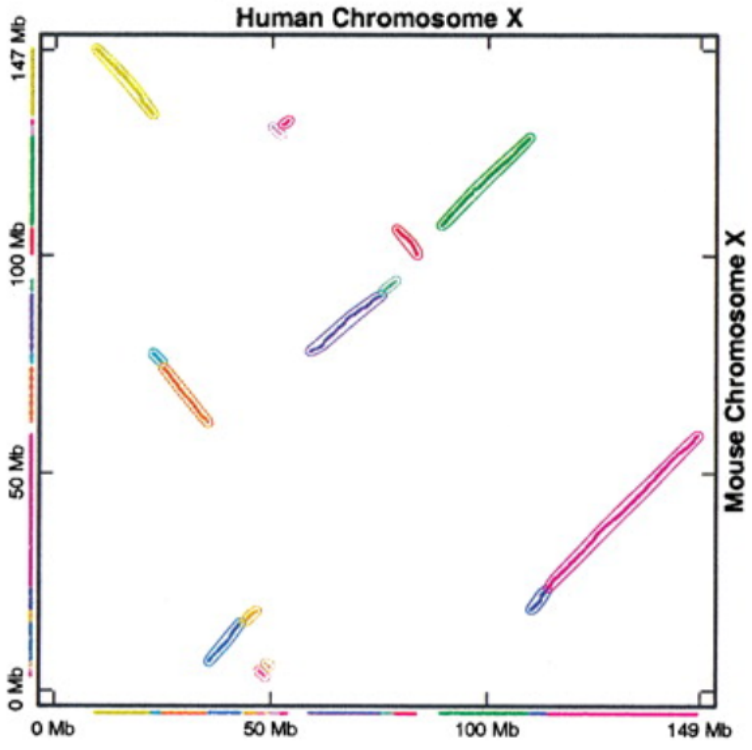
Comparative genomics studies (epi)genomics features of current (extant) species, to gain insight into their evolution and ancestral traits.

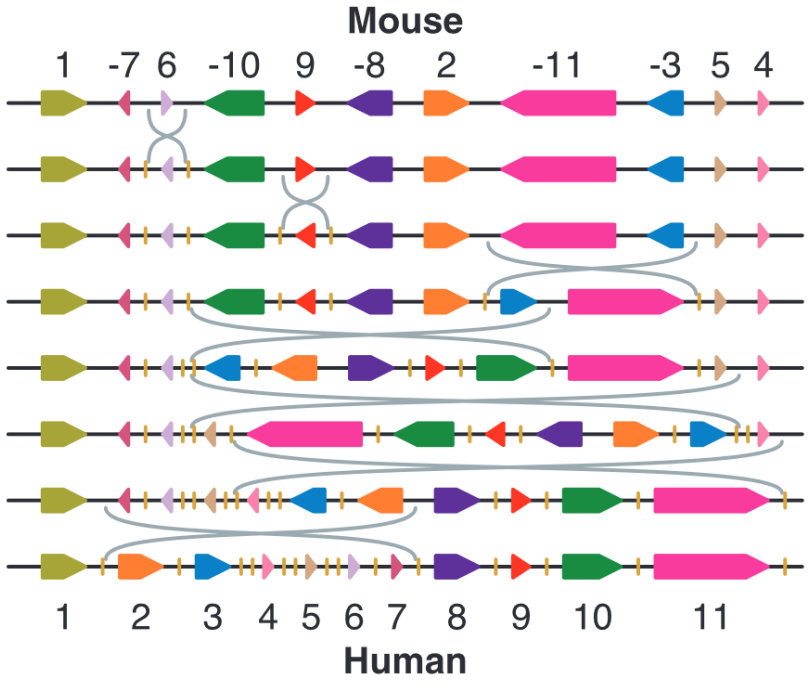
Some examples:

- Accurate inter-species distances by integrating genome-scale organization (genome rearrangements);
- Inference of ancestral features (genomic adjacencies);
- Reconciliations of species and gene trees. . .

Parsimony as a common framework (but not exclusively!)

At **genomic scale** + **longer periods of time**, classic sequence homology becomes insufficient to infer elapsed time and precise correspondences.





[Pevzner and Tesler, Genome Research 2003]

How many **inversions** required to turn a Mouse into a Human?
sort a signed permutation by reversals?

SORTING BY REVERSALS **problem**

Input: *Signed* permutation π

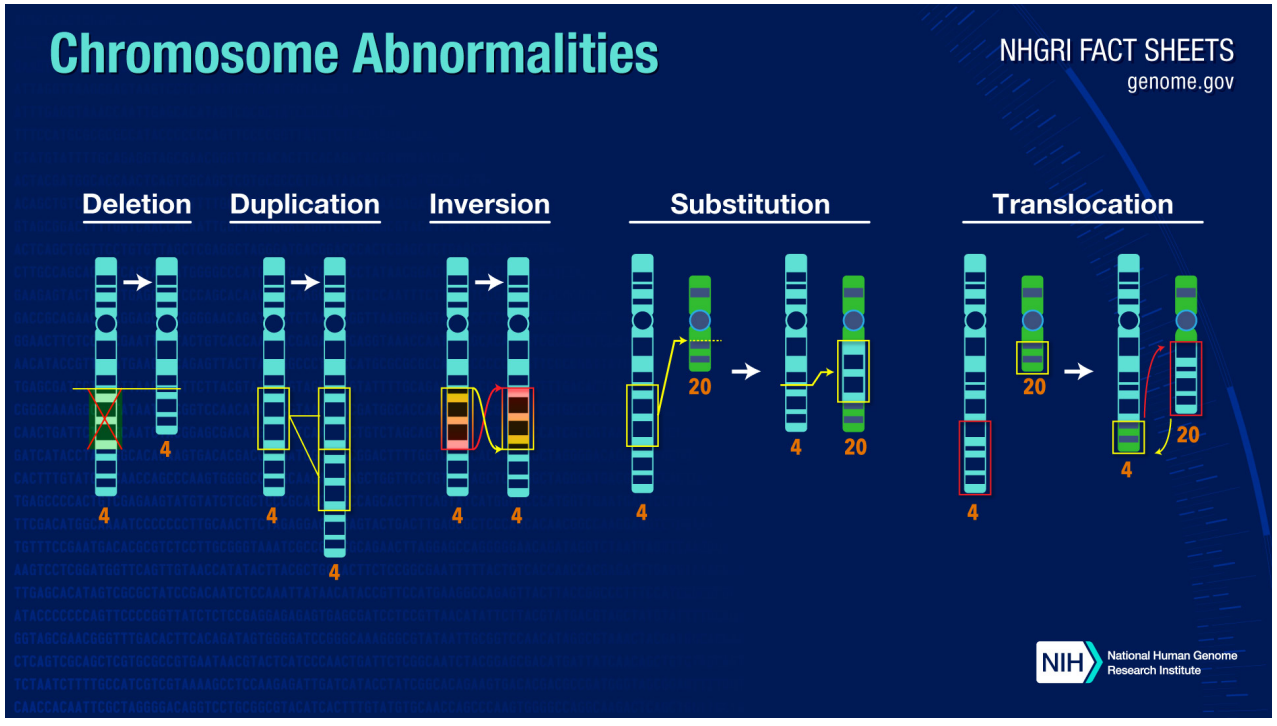
Output: Shortest sequence of reversals turning π into $1, 2, 3 \cdots |\pi|$

Surprisingly, can be solved in polynomial-time [Hannenhalli–Pevzner, JACM 1999]
Distance can even be obtained in linear time! [Baden-Moret-Yan, JCB 2004]
At the origin of multiple works on sorting (structured/signed) permutations.

A simple(?) algorithm: [Hannenhalli–Pevzner 1999] + [Bergeron 2005]

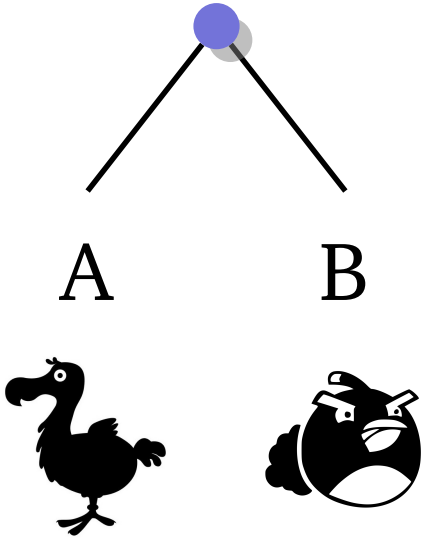
1. Mixed sign (+/-) $\pi \rightarrow$ Greedy reversals inducing max. #oriented pairs
2. Positive sign $\pi \rightarrow$ Elimination (cut/merge $\rightarrow$ reversals) of hurdle(s)

More details to come (lab assignment)

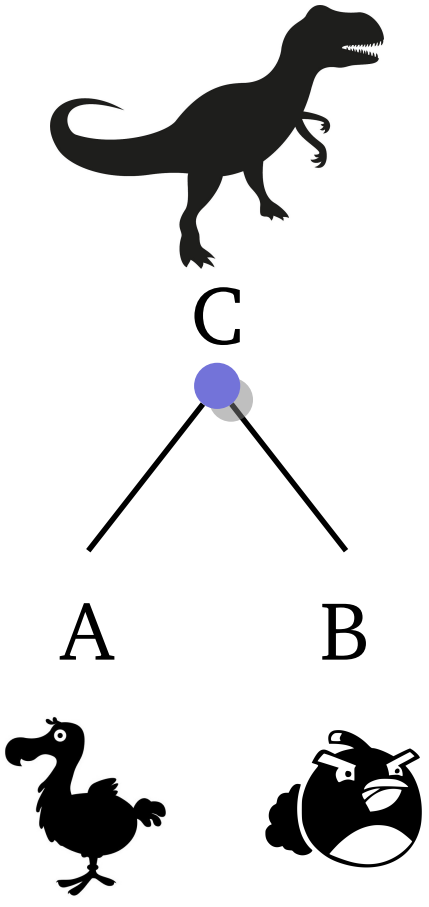


- Fancy operations:
  - Translocations: Exchange ends of chromosomes → Linear time
  - Transpositions: Exchange two consecutive sequences of genes → NP-hard
  - Double Cut and Join...
- Gain/loss of genetic material/syntenic blocks
  → Handle multiple copies of genes
- Extension to unsigned permutations → NP-hard.

Strong connection to graph theory and (enumerative) combinatorics
→ Very clever/elegant, but **headache** to extrapolate!



Goal: To infer features of ancestral genomes



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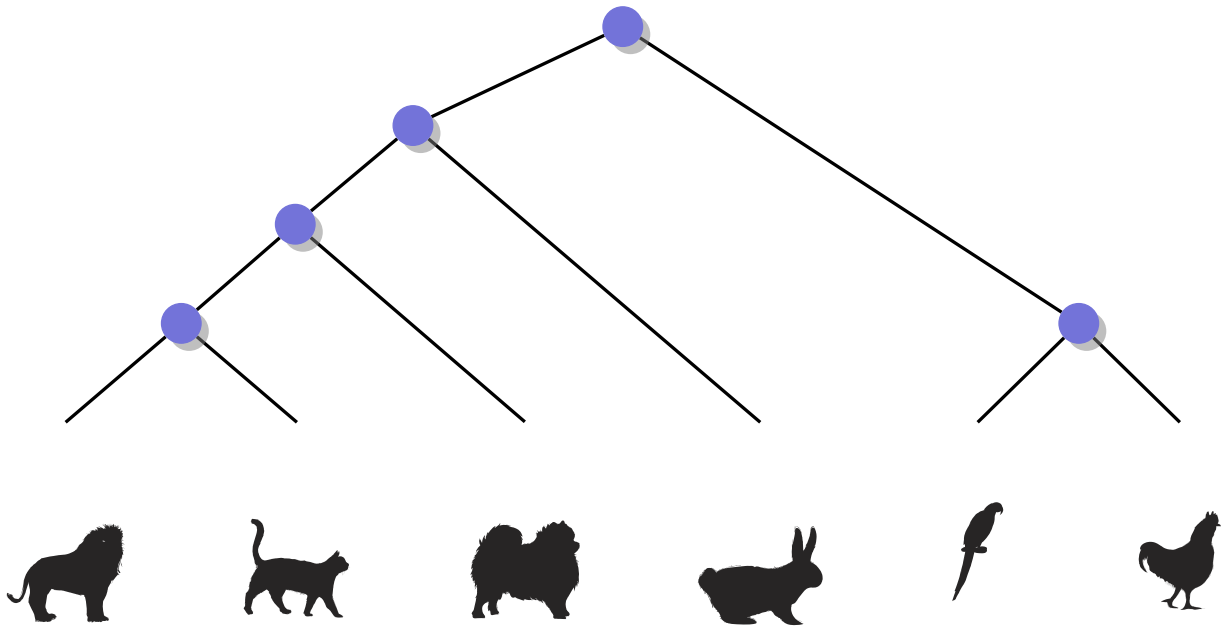
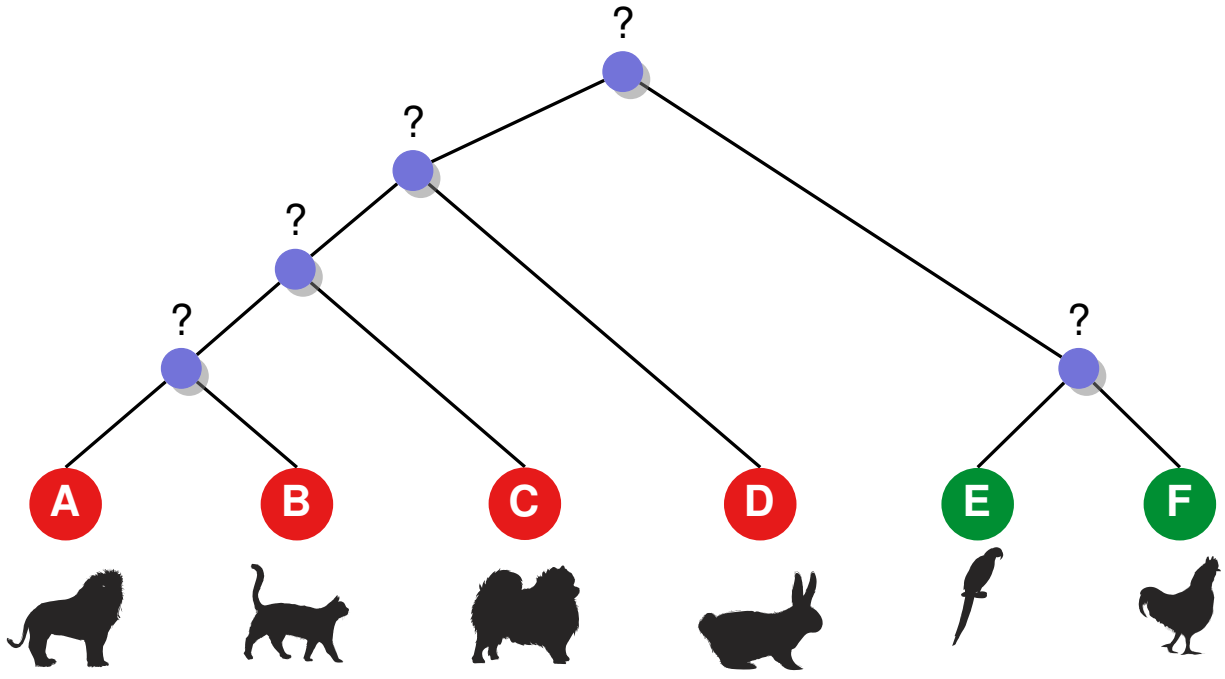


Phylogenetic tree $\mathcal{T} = (V, E)$ + Present/Absent **traits** for extant species
What are the **most likely** features of ancestral species?

Parsimony: Find ancestors labeling $\xi : V \to \{\mathrm{P}, \mathrm{A}\}$ minimizing total change:

$$f(\xi) = \sum_{(u,v)\in\mathcal{T}} d(\xi(u), \xi(v))$$

Example: Min. #event $\to d(\xi(u), \xi(v)) = 1$ if $\xi(u) \neq \xi(v)$; 0 otherwise



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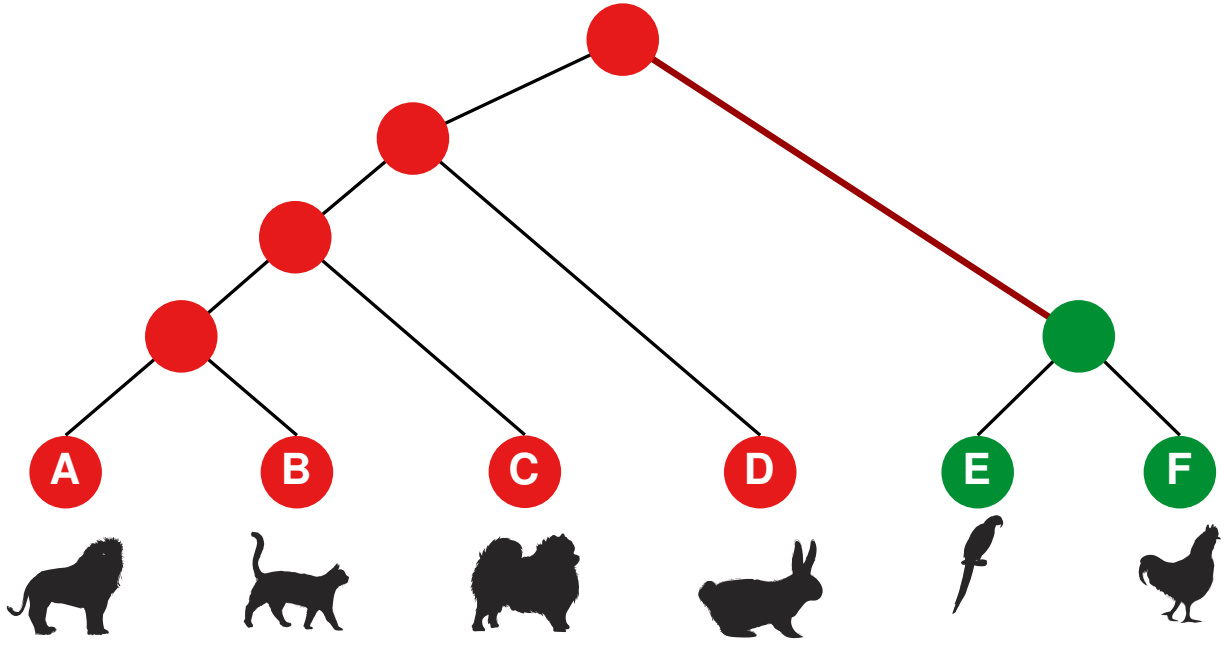

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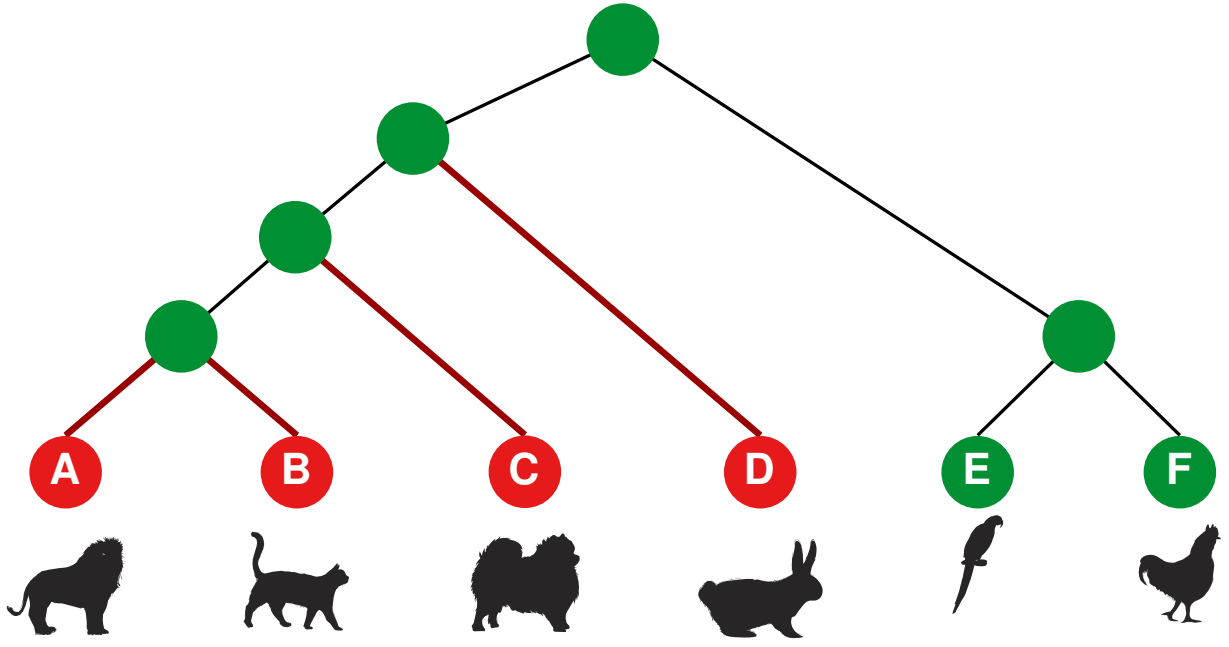

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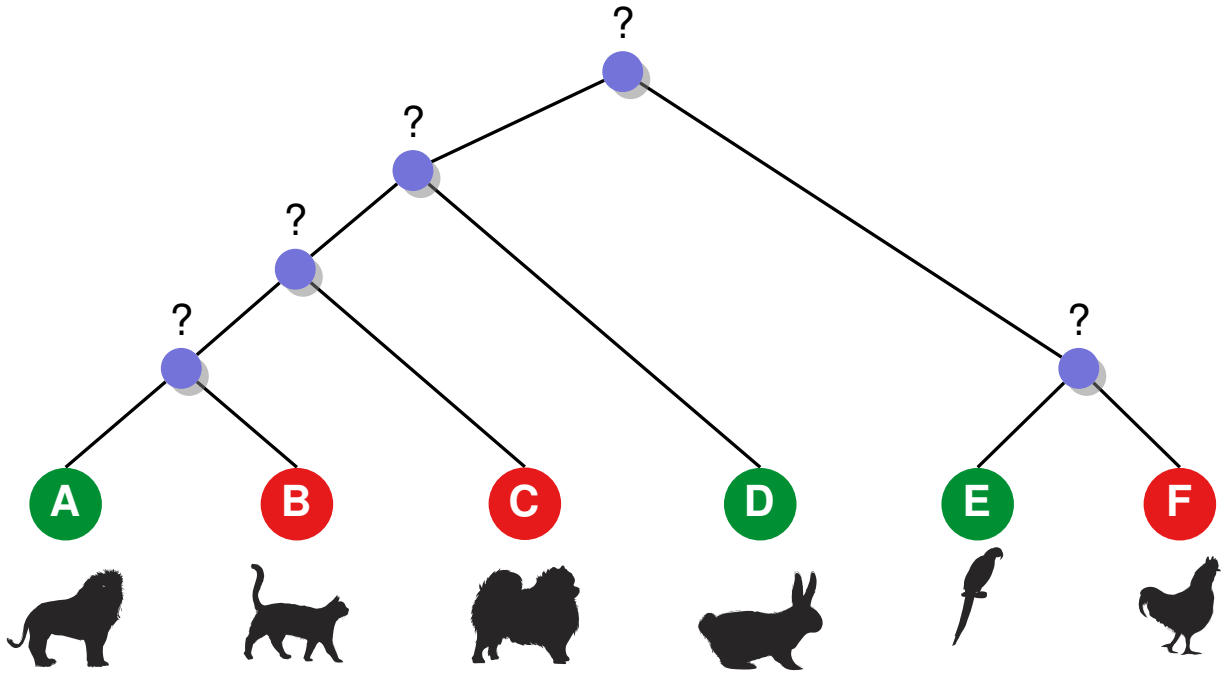

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Example: Min. #event $\to d(\xi(u), \xi(v)) = 1$ if $\xi(u) \neq \xi(v)$; 0 otherwise

A labeling ξ is said to **extend** ξ' iff their labels coincide on extant species

PARSIMONY LABELING **problem**

Input: Species tree $\mathcal{T}$; Labeling $\xi' : V \to \{\mathrm{P}, \mathrm{A}\}$ of extant species

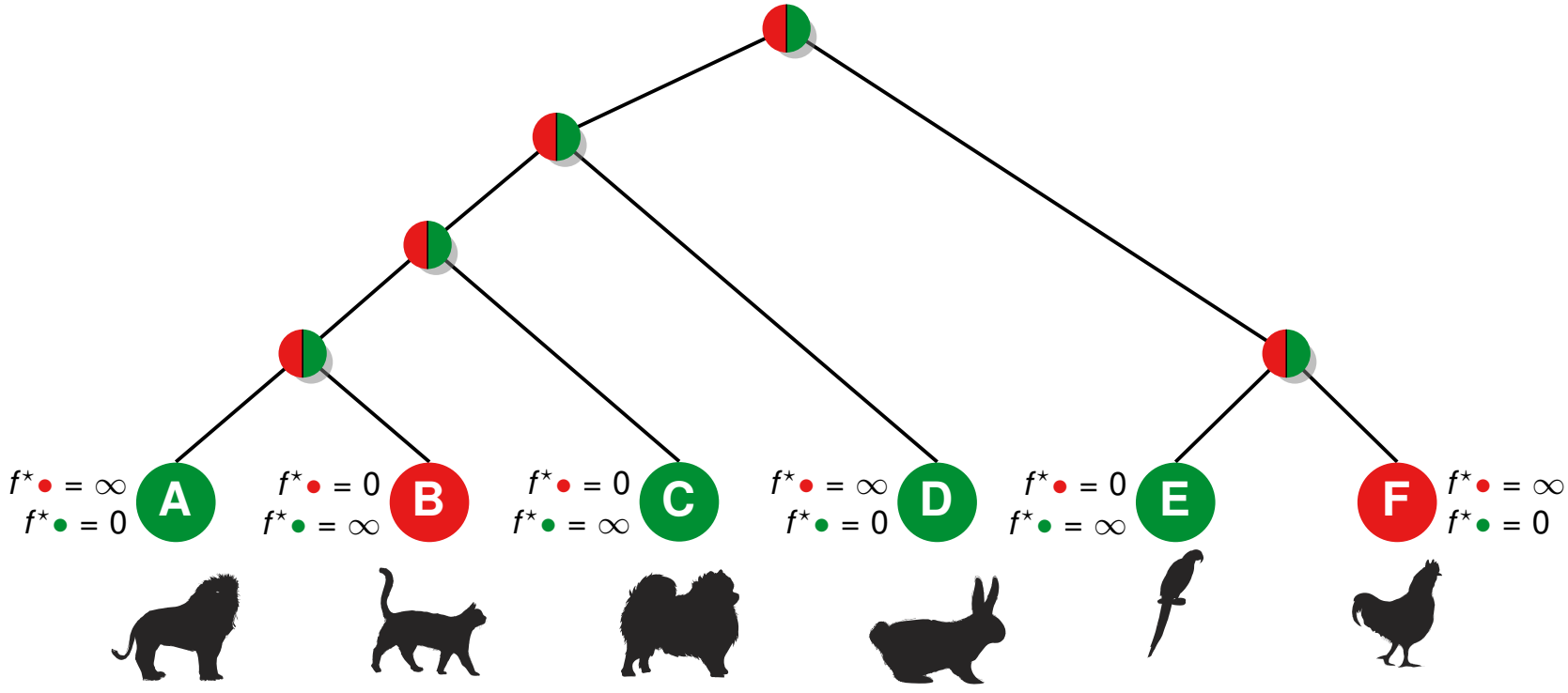
Output: Complete labeling $\xi^\star$ extending ξ' which minimizes total change

$$\xi^\star = \operatorname*{argmin}_{\xi \text{ ext. } \xi'} \sum_{(u,v)\in\mathcal{T}} d(\xi(u), \xi(v))$$

Solved by **dynamic programming** (hey, it's been a while!) [Sankoff/Rousseau 1975]
based on a *hypothetical game*, *played* at any ancestral/internal node u:

- What if ancestral node u had a given label $x \in \{\mathrm{P}, \mathrm{A}\}$?
- Then min change from u with $\xi(u) = x$ is obtained by minimizing over possible labels y, y' for children v, v' of u, and summing:
  - Direct contribution to change: $d(x, y) + d(x, y')$
  - Min change of a labeling of subtrees v, v', independent of (u, x) (rec.)

$$\to \underset{u \text{ ancestral}}{f_x^\star(u)} = \sum_{uv\in\mathcal{T}} \min_{y\in\{\mathrm{P},\mathrm{A}\}} d(x, y) + f_y^\star(v) \qquad \underset{u \text{ extant/leaf}}{f_x^\star(u)} = \begin{cases} 0 & \text{if } x = \xi'(u) \\ +\infty & \text{otherwise} \end{cases}$$



Toy model: Min. #event $\rightarrow d(\xi(u), \xi(v)) = 1$ if $\xi(u) \neq \xi(v)$; 0 otherwise

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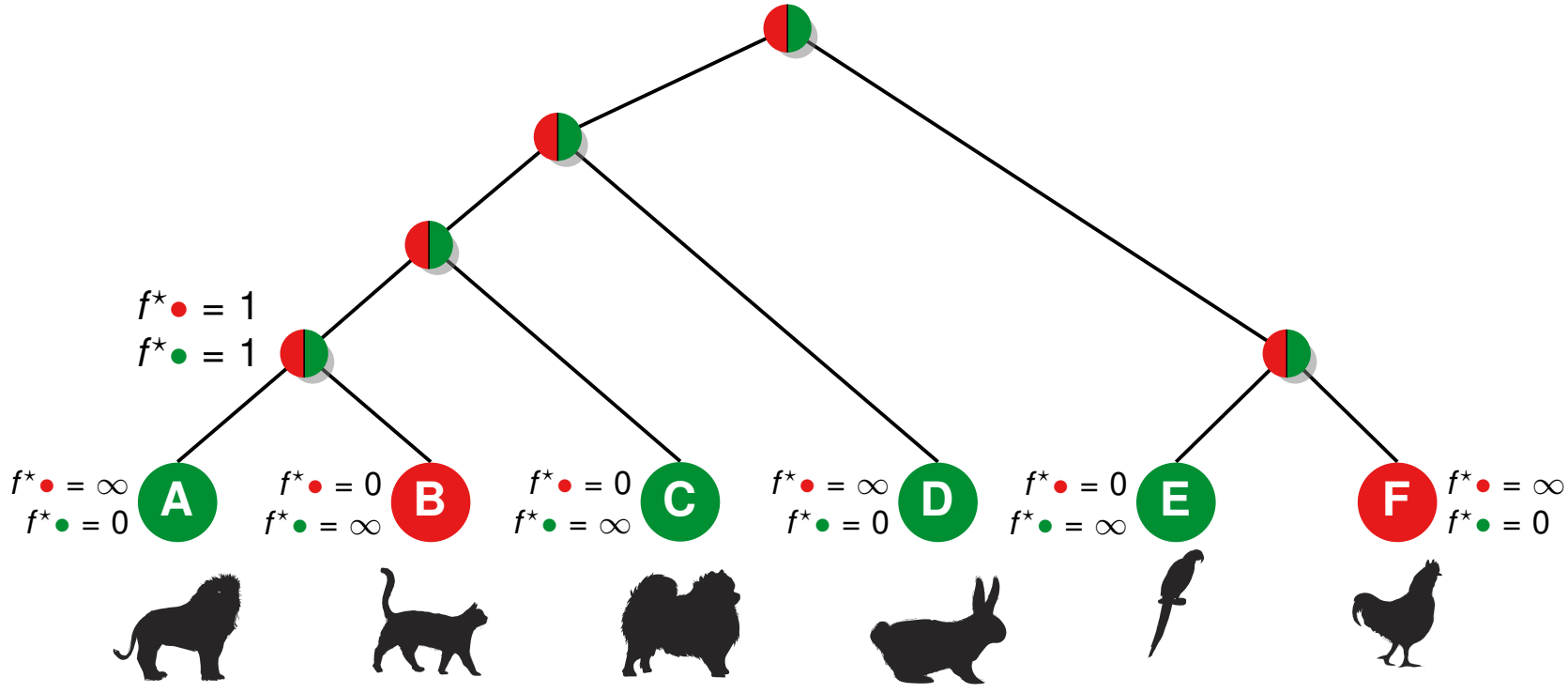

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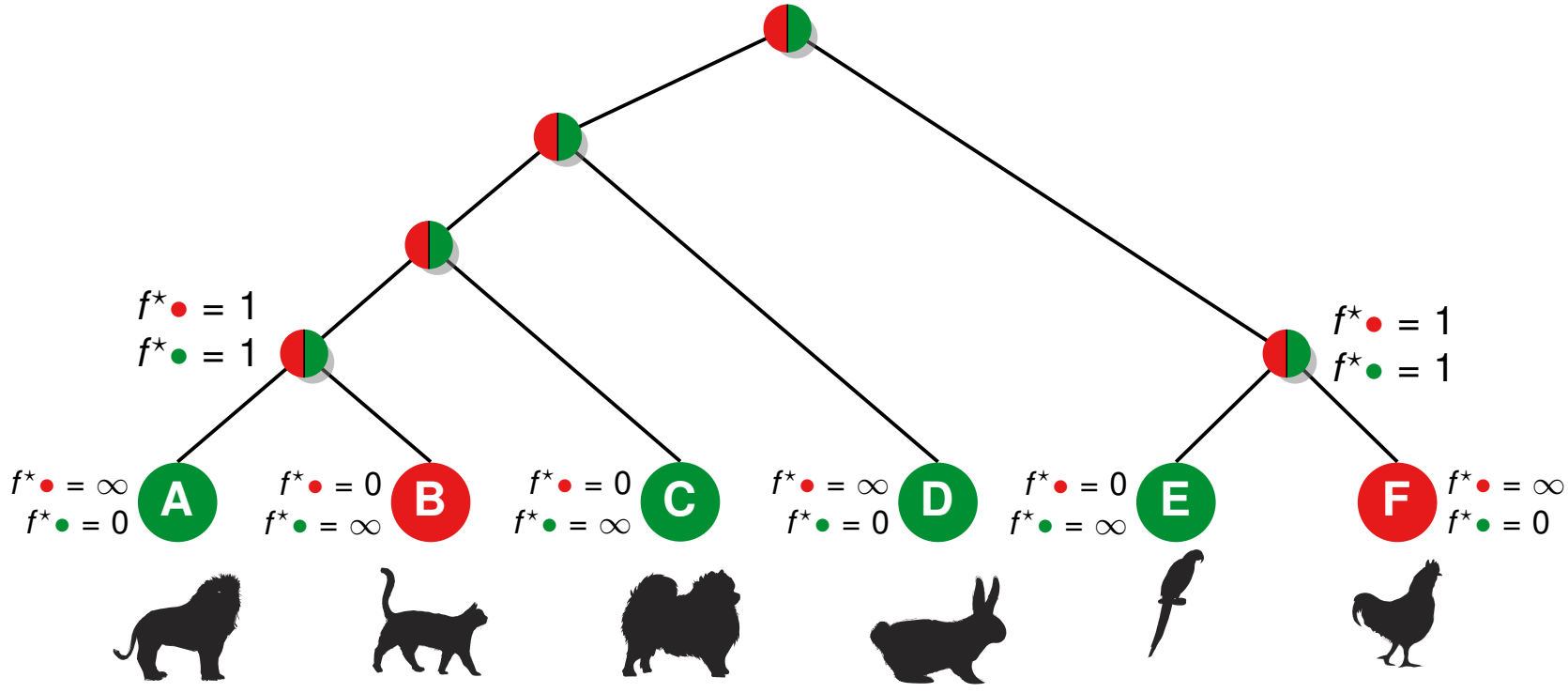

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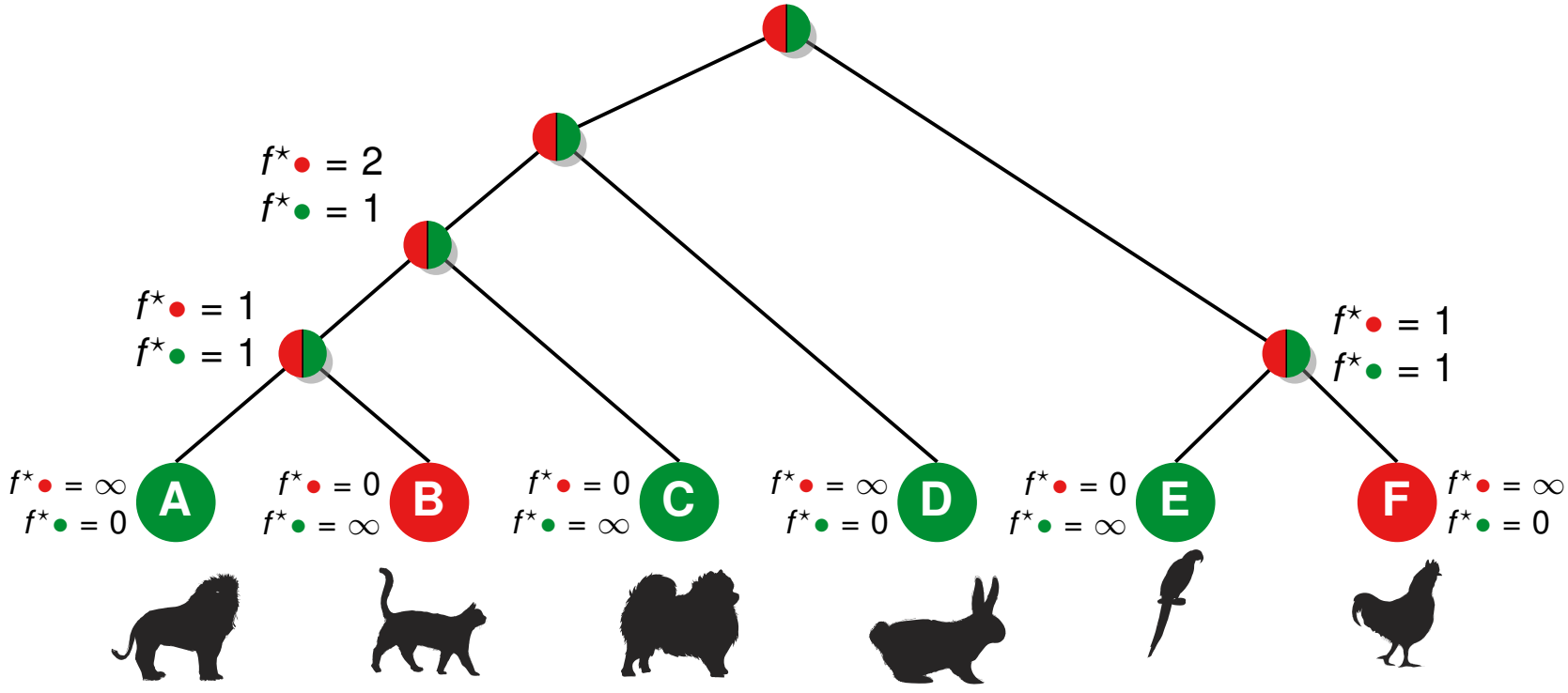

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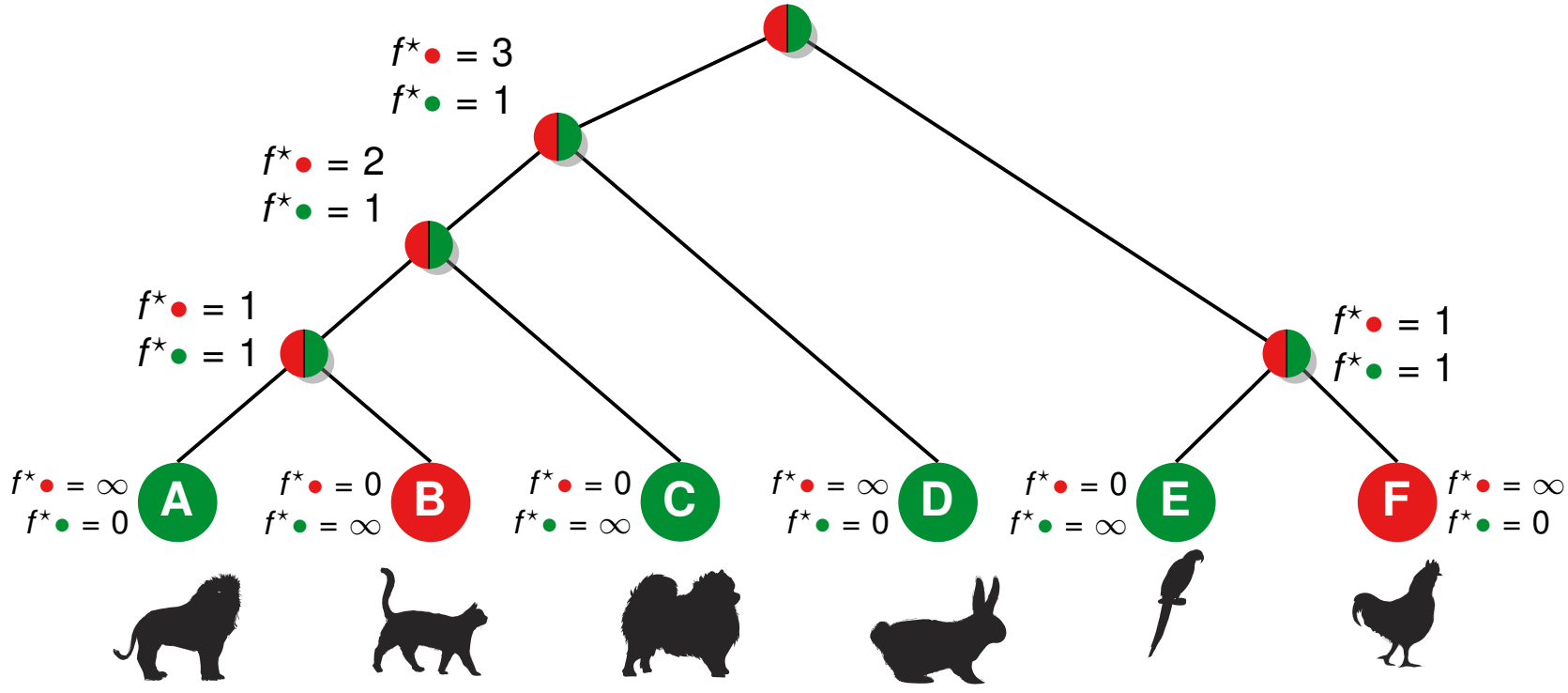

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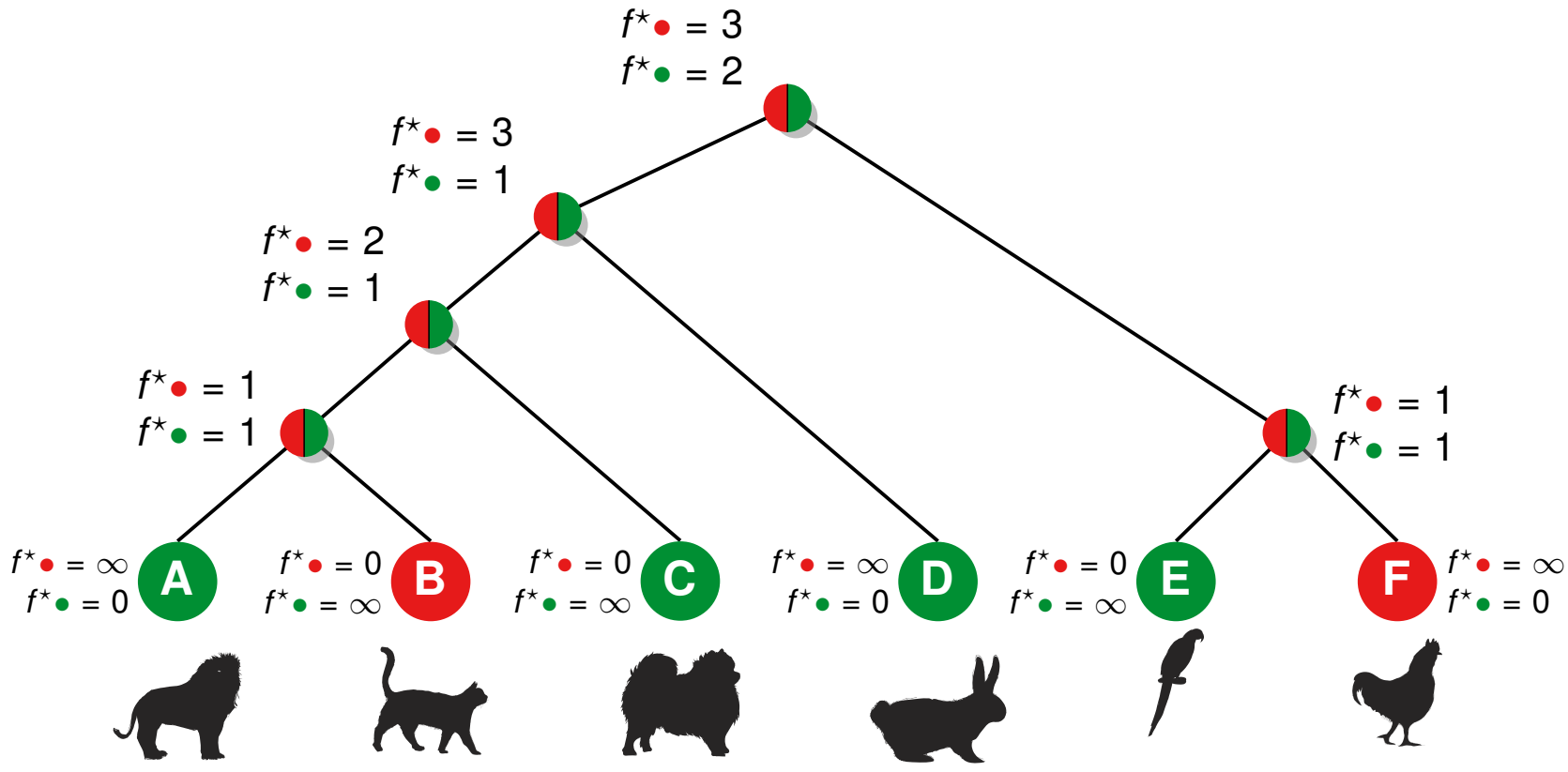

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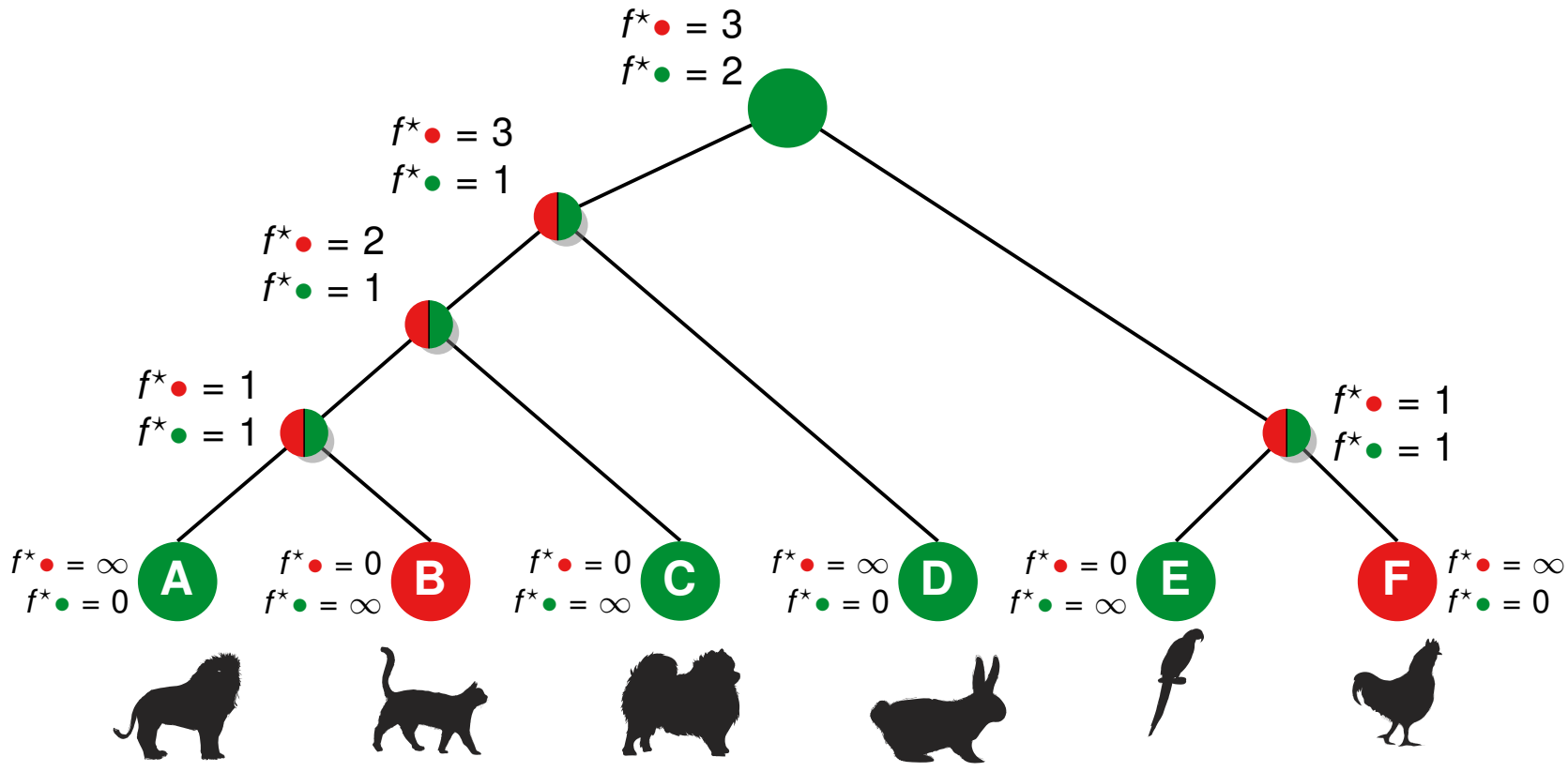

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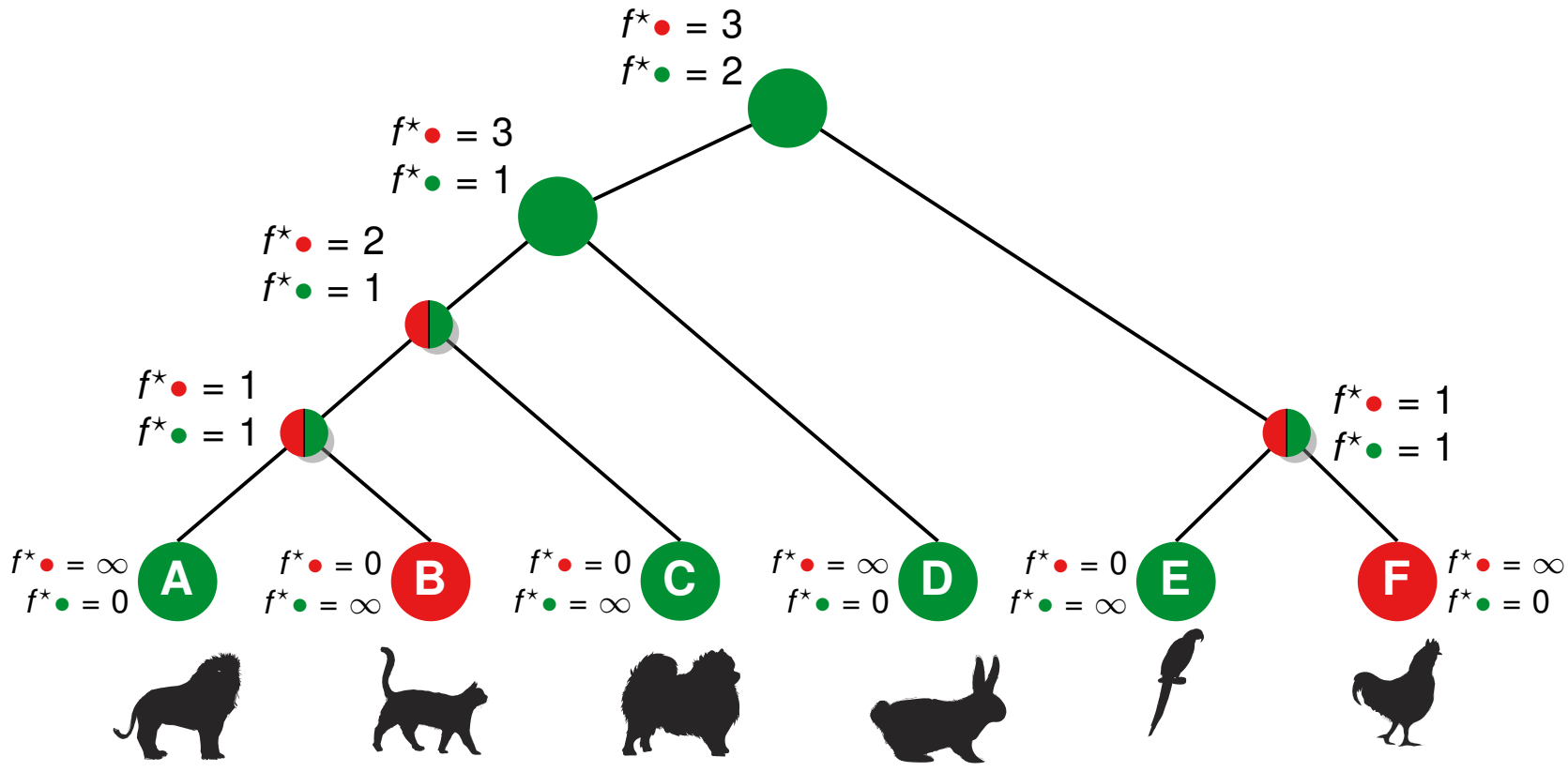

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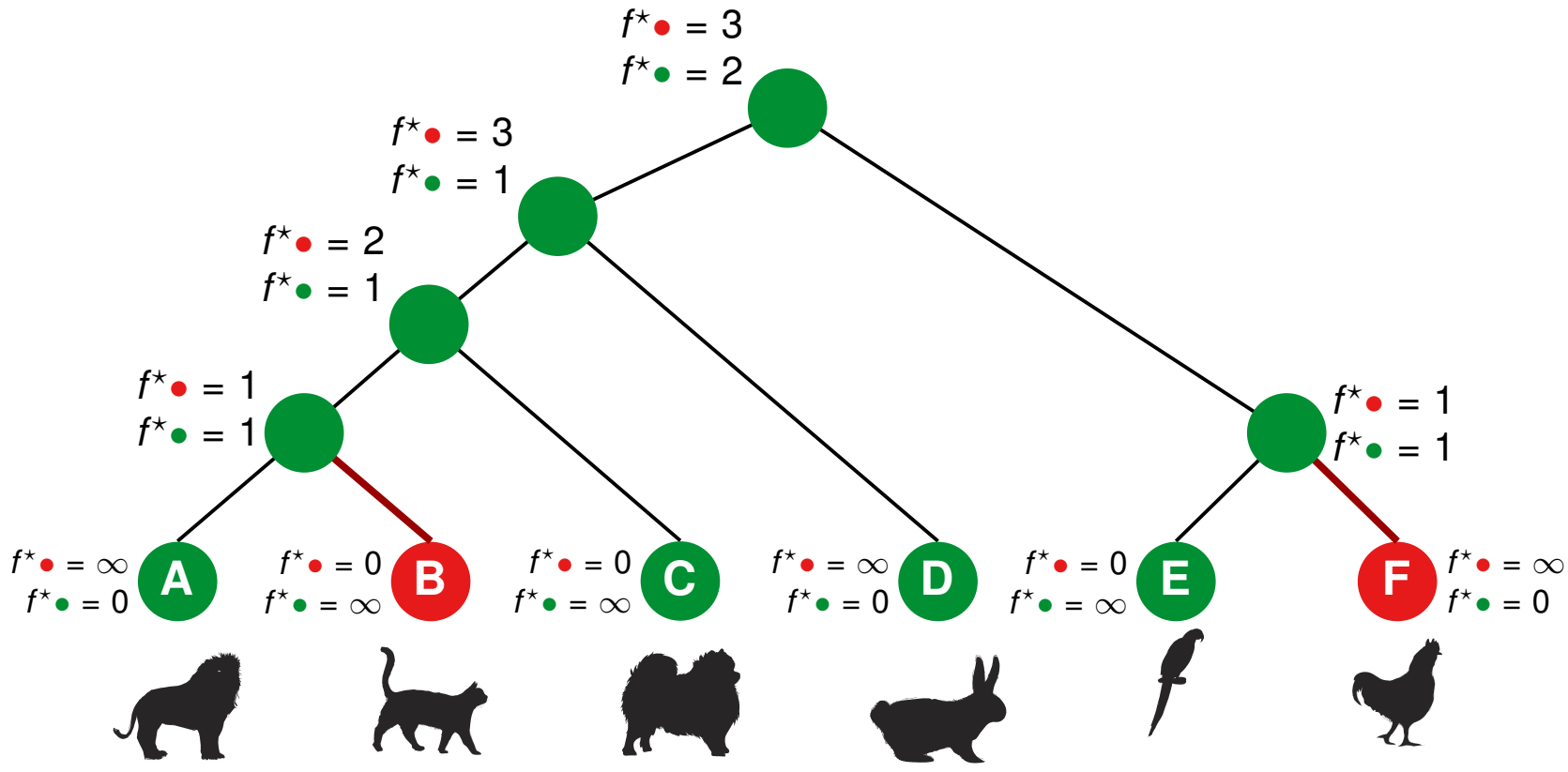

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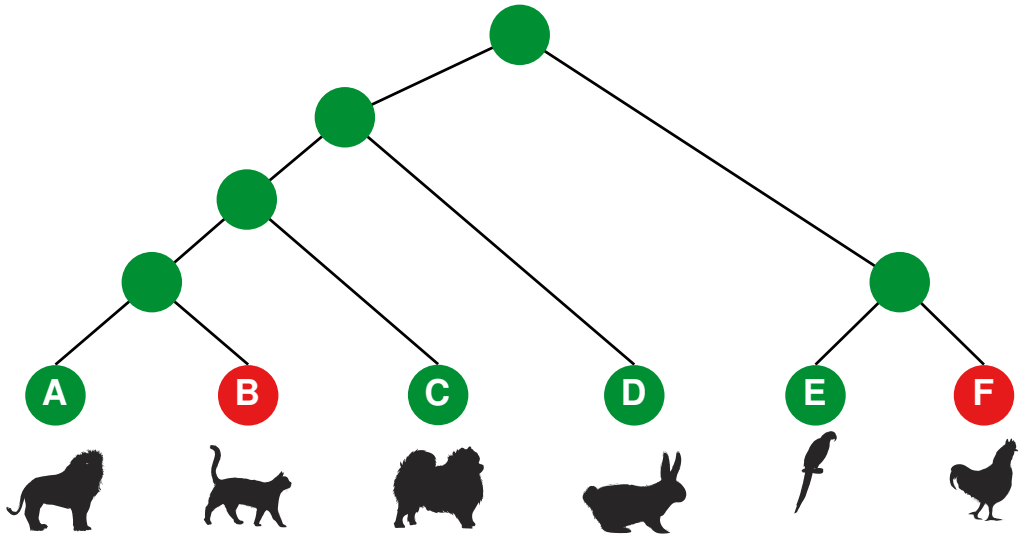
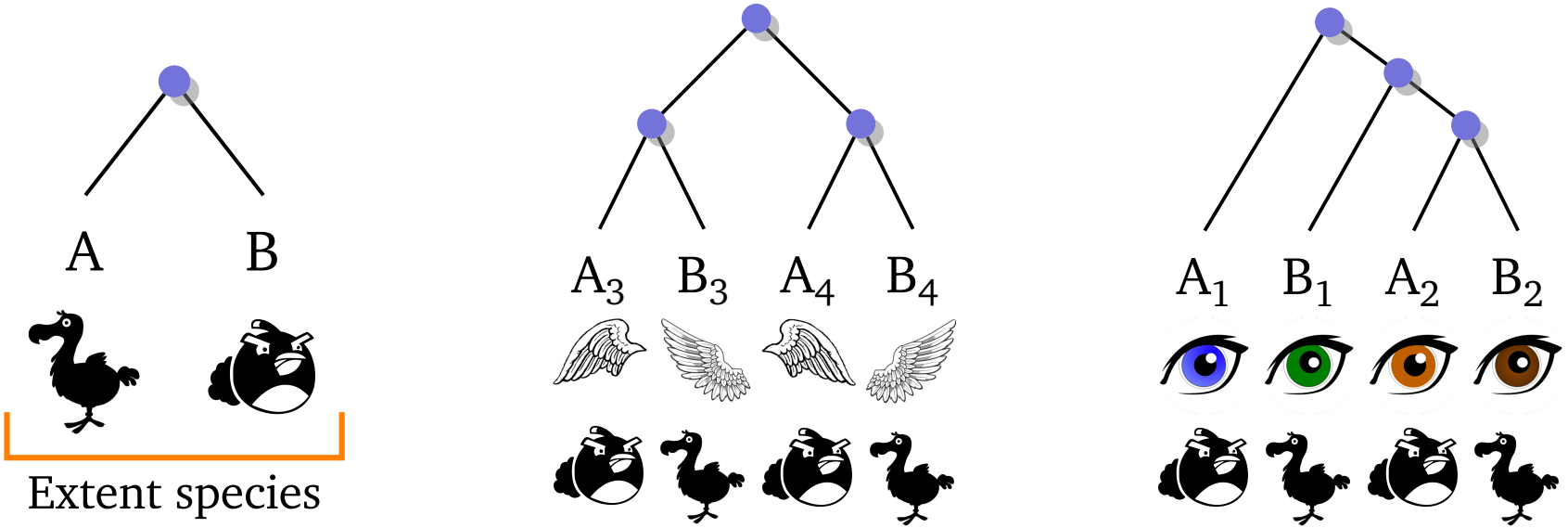


Sankoff/Rousseau parsimony represents a very general framework, which can be used to infer:

- presence/absence of regulatory motifs
- ancestral sequences
- ancestral structures (Sankoff algo. for RNA comparative folding)
- ancestral genome architectures (adjacencies, gene loss/gain)
- ancestral allele frequencies (∞ #labels $\rightarrow$ restriction on d)

Much can be learned from apparent contradictions. . .

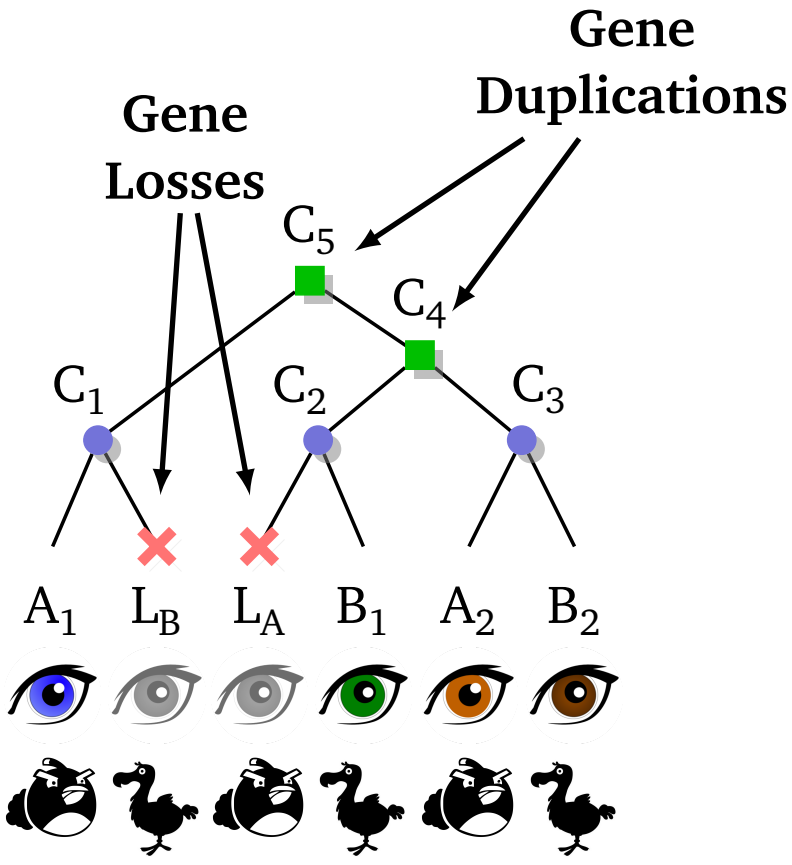


Species tree

Gene trees

How best to **explain** those topological discrepancies?

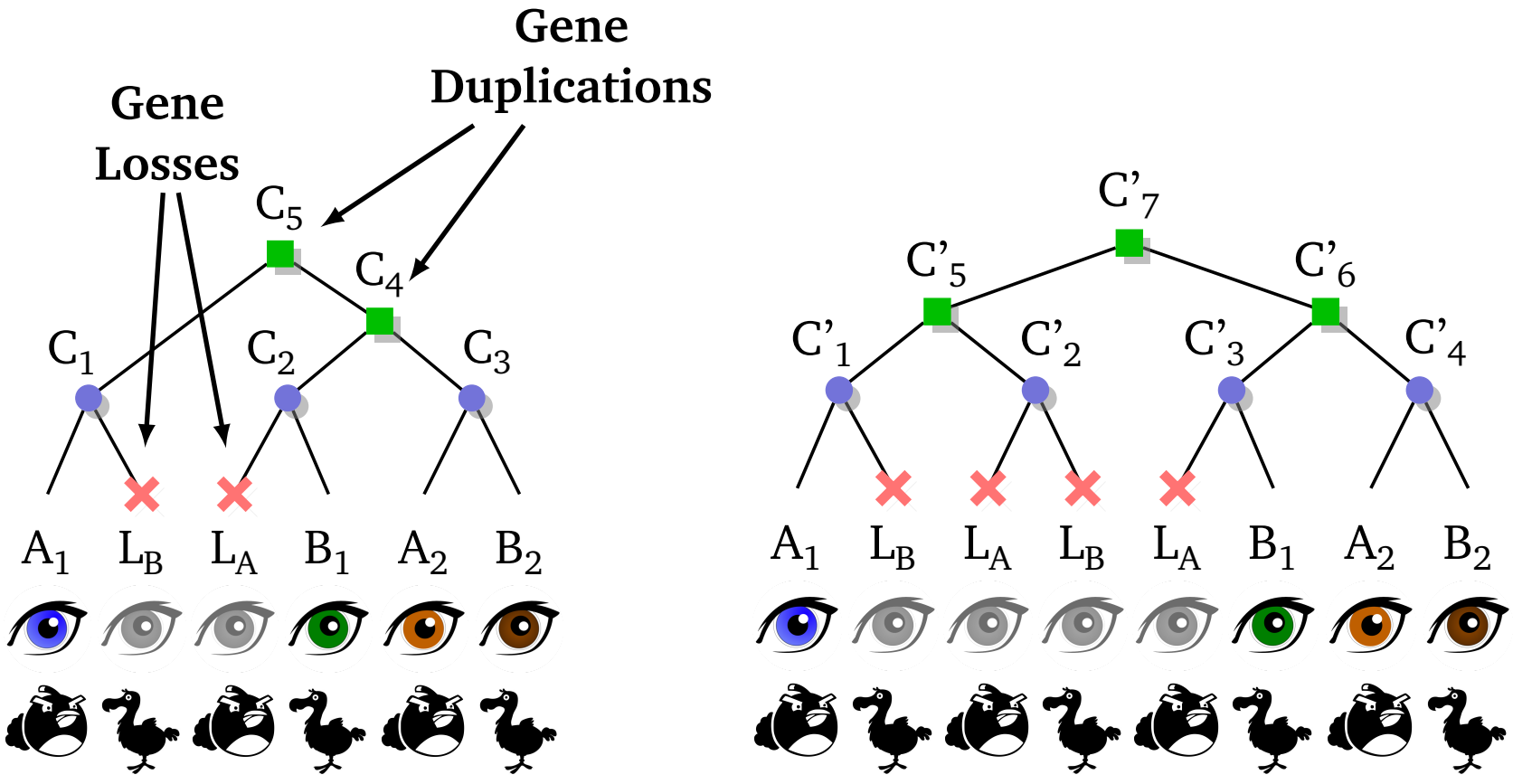
and **learn** something along the way



Ancestral events (duplication/losses/...) induce **apparent** inconsistencies

Reconciliations represent evolutionary scenario that **explain** gene trees by embedding them within species trees **but** some more *reasonable* than others

Goal: Find **parsimonious** reconciliation



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Duplication/Loss reconciliation: Binary tree R such that :

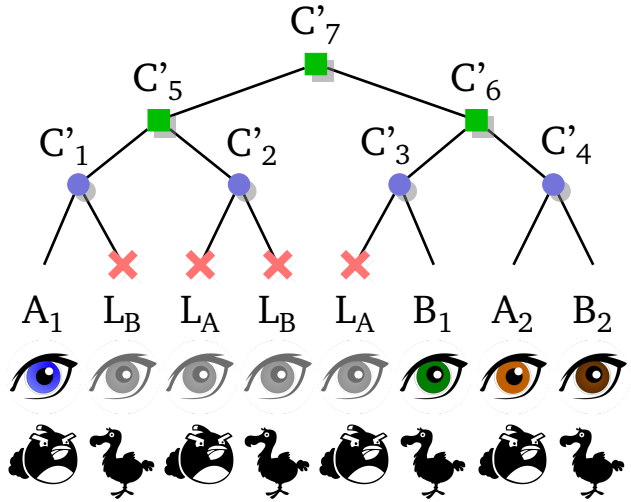
- leaf labeled with extant gene or Loss operation;
- internal node labeled with Dup or Spec event

All nodes are mapped through σ to a species

R **congruent** with **gene tree** G if removing Loss from R + contract 1^{ary} branches $\rightarrow G$

R **congruent** with **species tree** S if:

- For each Spec node $u \rightarrow v, w$ in R, we have $\sigma_u \rightarrow \sigma_v, \sigma_w$ in S
- For each Dup node $u \rightarrow v, w$ in R, we have $\sigma_u = \sigma_v = \sigma_w$



DL RECONCILIATION **problem**

Input: Gene tree G, Species tree S

Output: Reconciliation R **congruent** to both G and S, minimizing cost

$$\text{Cost}(R) = \alpha \times \#\text{Loss}(R) + \beta \times \#\text{Dup}(R)$$

Can be solved efficiently using LCA mapping... [Page, Syst. Biol. 1994]

...or using dynamic programming in $\mathcal{O}(|S| \times |G|)$ time/space

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Notations:

$C[g, s]$ Best cost of reconciliation for node/subtrees $g \sqsubseteq G$ and $s \sqsubseteq S$

L_u, R_u Left/right child of node u

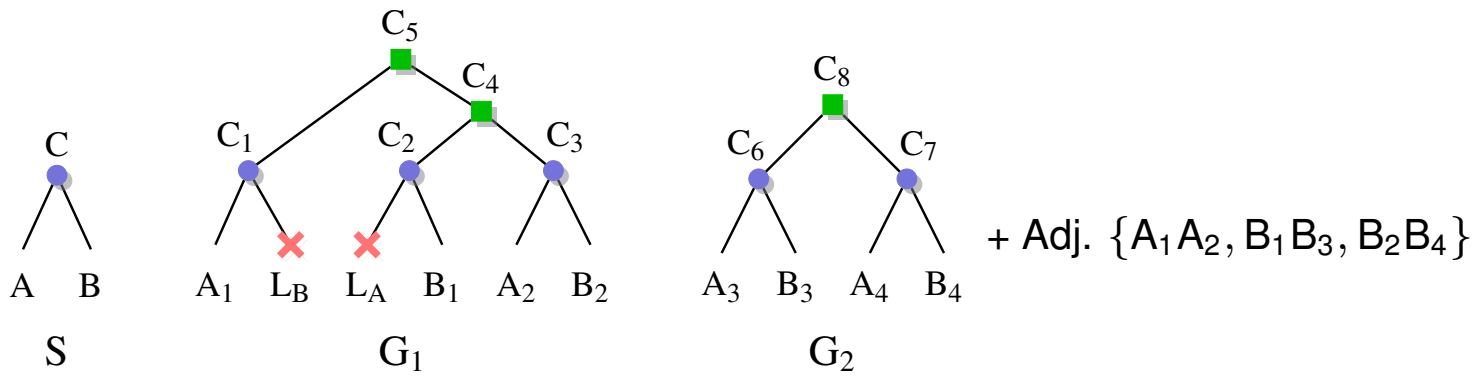
$\sigma(u)$ Species of a leaf u within gene tree (or species tree... duh!)

$$\underset{g,s \text{ leaves}}{C[g, s]} = \begin{cases} 0 & \text{if } \sigma(g) = \sigma(s) \\ +\infty & \text{otherwise} \end{cases} \qquad \underset{g \text{ leaf}, s \text{ internal}}{C[g, s]} = +\infty$$

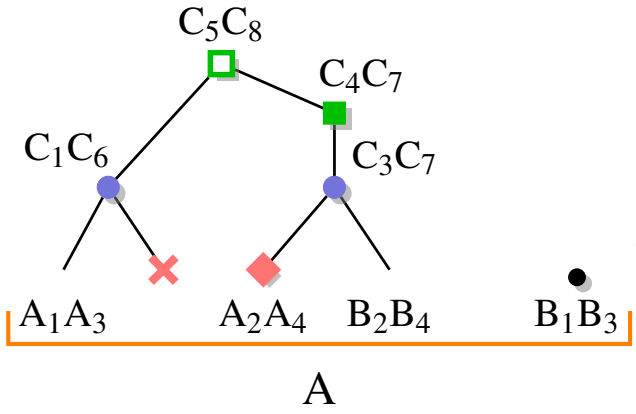
$$C[g, s] = \begin{cases} \beta + C[L_g, s] + C[R_g, s] & \text{Ancestor gene } g \text{ duplicated in species } s \\ C[L_g, L_s] + C[R_g, R_s] & \text{Speciation event, direct mapping} \\ C[L_g, R_s] + C[R_g, L_s] & \text{Speciation event, crossed mapping} \\ \alpha + C[g, L_s] & \text{Loss of gene subtree } g \text{ in right part of species tree} \\ \alpha + C[g, R_s] & \text{Loss of gene subtree } g \text{ in left part of species tree} \end{cases}$$

- Efficient algorithms exist for parsimonious scenarios for genomic characters (genes under DTL, for instance).
- Bérard *et al* (2012) extended methods to gene adjacencies under gene Speciation, Duplication, Loss.
- DeCo considers cost of gains/ breaks due to rearrangements.

Problem: Given two reconciliations (R_1, R_2) + extant adjacencies, construct parsimonious evolutionary scenario



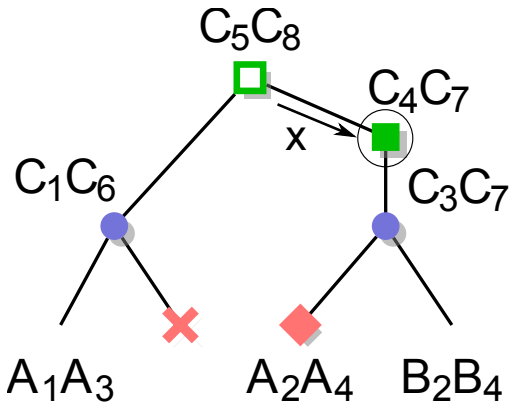
Output: Adjacency forest



→ Ancestral genome architecture

Event costs/parameters

- Adjacency gain: x
- Adjacency break: y



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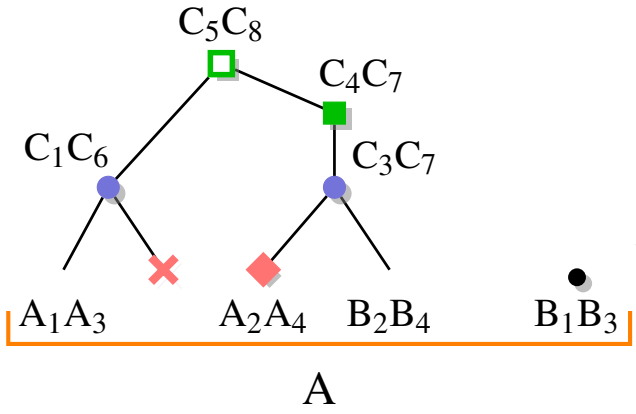

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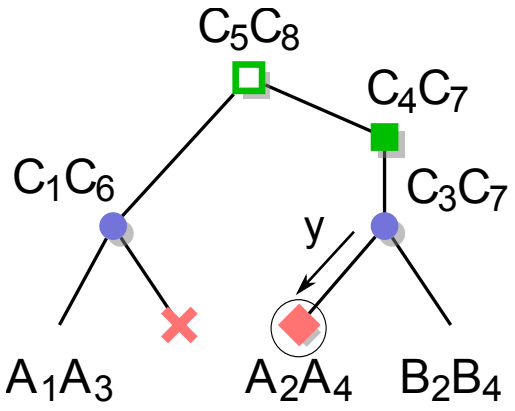
- Adjacency gain: x
- Adjacency break: y



1. $e(g_1) = \text{Extant}$ and $e(g_2) = \text{Extant}$:

$$c_1(g_1, g_2) = \begin{cases} 0 & \text{if } g_1 g_2 \text{ is an adjacency} \\ 0 & \text{otherwise} \end{cases}$$

$$c_0(g_1, g_2) = \begin{cases} 0 & \text{if } g_1 g_2 \text{ is not an adjacency} \\ 0 & \text{otherwise} \end{cases}$$

2. $e(g_1) = \text{GLoss}$ and $e(g_2) \in \{\text{Extant}, \text{Spec}, \text{GDup}\}$:

$$c_1(g_1, g_2) = c_0(g_1, g_2) = 0^{\#\text{NonGDup}(g_2)}$$

3. $e(g_1) \in \{\text{Extant}, \text{Spec}, \text{GDup}\}$ and $e(g_2) = \text{GLoss}$:

$$c_1(g_1, g_2) = c_0(g_1, g_2) = 0^{\#\text{NonGDup}(g_1)}$$

4. $e(g_1) = \text{GLoss}$ and $e(g_2) = \text{GLoss}$:

$$c_1(g_1, g_2) = c_0(g_1, g_2) = 0$$

5. $e(g_1) \in \{\text{Extant}, \text{Spec}\}$ and $e(g_2) = \text{GDup}$:

$$c_1(g_1, g_2) = \min \begin{cases} c_1(g_1, b_{g_2}) + c_0(g_1, a_{g_2}), & c_0(g_1, b_{g_2}) + c_1(g_1, a_{g_2}), \\ c_1(g_1, b_{g_2}) + c_1(g_1, a_{g_2}) + x, & c_0(g_1, b_{g_2}) + c_0(g_1, a_{g_2}) + y \end{cases}$$

$$c_0(g_1, g_2) = \min \begin{cases} c_0(g_1, b_{g_2}) + c_0(g_1, a_{g_2}), & c_0(g_1, b_{g_2}) + c_1(g_1, a_{g_2}) + x, \\ c_1(g_1, b_{g_2}) + c_0(g_1, a_{g_2}) + x, & c_1(g_1, b_{g_2}) + c_1(g_1, a_{g_2}) + 2x \end{cases}$$

6. $e(g_1) = \text{GDup}$ and $e(g_2) \in \{\text{Extant}, \text{Spec}\}$:

$$c_1(g_1, g_2) = \min \begin{cases} c_1(a_{g_1}, g_2) + c_0(b_{g_1}, g_2), & c_0(a_{g_1}, g_2) + c_1(b_{g_1}, g_2), \\ c_1(a_{g_1}, g_2) + c_1(b_{g_1}, g_2) + x, & c_0(a_{g_1}, g_2) + c_0(b_{g_1}, g_2) + y \end{cases}$$

$$c_0(g_1, g_2) = \min \begin{cases} c_0(a_{g_1}, g_2) + c_0(b_{g_1}, g_2), & c_0(a_{g_1}, g_2) + c_1(b_{g_1}, g_2) + x, \\ c_1(a_{g_1}, g_2) + c_0(b_{g_1}, g_2) + x, & c_1(a_{g_1}, g_2) + c_1(b_{g_1}, g_2) + 2x, \end{cases}$$

7. $e(g_1) = \text{Spec}$ and $e(g_2) = \text{Spec}$:

$$c_1(g_1, g_2) = \min \begin{cases} c_1(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + 0, & c_1(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + y + 0, \\ c_0(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + y + 0, & c_0(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + 2y + 0, \\ c_1(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + 0, & c_1(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + y + 0, \\ c_0(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + y + 0, & c_0(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + 2y + 0 \end{cases}$$

$$c_0(g_1, g_2) = \min \begin{cases} c_0(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + 0, & c_1(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + x + 0, \\ c_0(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + x + 0, & c_1(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + 2x + 0, \\ c_0(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + 0, & c_1(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + x + 0, \\ c_0(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + x + 0, & c_1(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + 2x + 0, \end{cases}$$

8. $e(g_1) = \text{GDup}$ and $e(g_2) = \text{GDup}$:

$$c_1(g_1, g_2) = \min \begin{cases} c_1(a_{g_1}, g_2) + c_0(b_{g_1}, g_2), & c_0(a_{g_1}, g_2) + c_1(b_{g_1}, g_2), \\ c_1(a_{g_1}, g_2) + c_1(b_{g_1}, g_2) + x, & c_0(a_{g_1}, g_2) + c_0(b_{g_1}, g_2) + y, \\ c_1(g_1, a_{g_2}) + c_0(g_1, b_{g_2}), & c_0(g_1, a_{g_2}) + c_1(g_1, b_{g_2}), \\ c_1(g_1, a_{g_2}) + c_1(g_1, b_{g_2}) + x, & c_0(g_1, a_{g_2}) + c_0(g_1, b_{g_2}) + y, \\ c_1(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}), & \\ c_1(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + x, & \\ c_1(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + x, & \\ c_1(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + 2x, & \\ c_1(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + y, & \\ c_1(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + x + y, & \\ c_1(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + x + y, & \\ c_0(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + y, & \\ c_0(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + x + y, & \\ c_0(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + x + y, & \\ c_0(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}), & \\ c_0(a_{g_1}, a_{g_2}) + c_1(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + x, & \\ c_1(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + x, & \\ c_0(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_1(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + y, & \\ c_0(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_1(b_{g_1}, a_{g_2}) + y, & \\ c_0(a_{g_1}, a_{g_2}) + c_0(b_{g_1}, b_{g_2}) + c_0(a_{g_1}, b_{g_2}) + c_0(b_{g_1}, a_{g_2}) + 2y, & \end{cases}$$

$$c_0(g_1, g_2) = \min \begin{cases} c_0(a_{g_1}, g_2) + c_0(b_{g_1}, g_2), & c_0(a_{g_1}, g_2) + c_1(b_{g_1}, g_2) + x, \\ c_1(a_{g_1}, g_2) + c_0(b_{g_1}, g_2) + x, & c_1(a_{g_1}, g_2) + c_1(b_{g_1}, g_2) + 2x, \\ c_0(g_1, a_{g_2}) + c_0(g_1, b_{g_2}), & c_0(g_1, a_{g_2}) + c_1(g_1, b_{g_2}) + x, \\ c_1(g_1, a_{g_2}) + c_0(g_1, b_{g_2}) + x, & c_1(g_1, a_{g_2}) + c_1(g_1, b_{g_2}) + 2x. \end{cases}$$

Deco algorithm [Berard *et al*, 2012]

Dyn. prog. scheme for most parsimonious adjacency forest in $\mathcal{O}(|R_1||R_2|)$.

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7. If $e(g_1) = \text{Spec}$ and $e(g_2) = \text{Spec}$:

$$c_1(g_1, g_2) = \min \begin{cases} c_1(a(g_1), b(g_2)) + c_1(b(g_1), a(g_2)),\ c_1(a(g_1), b(g_2)) + c_0(b(g_1), a(g_2)) + \text{ABreak}, \\ c_0(a(g_1), b(g_2)) + c_1(b(g_1), a(g_2)) + \text{ABreak}, \\ c_0(a(g_1), b(g_2)) + c_0(b(g_1), a(g_2)) + \text{2ABreak}, \\ c_1(a(g_1), a(g_2)) + c_1(b(g_1), b(g_2)),\ c_1(a(g_1), a(g_2)) + c_0(b(g_1), b(g_2)) + \text{ABreak}, \\ c_0(a(g_1), a(g_2)) + c_1(b(g_1), b(g_2)) + \text{ABreak},\ c_0(a(g_1), a(g_2)) + c_0(b(g_1), b(g_2)) + \text{2ABreak} \end{cases}$$

$$c_0(g_1, g_2) = \min \begin{cases} c_0(a(g_1), b(g_2)) + c_0(b(g_1), a(g_2)),\ c_1(a(g_1), b(g_2)) + c_0(b(g_1), a(g_2)) + \text{AGain}, \\ c_0(a(g_1), b(g_2)) + c_1(b(g_1), a(g_2)) + \text{AGain},\ c_1(a(g_1), b(g_2)) + c_1(b(g_1), a(g_2)) + \text{2AGain}, \\ c_0(a(g_1), a(g_2)) + c_0(b(g_1), b(g_2)),\ c_1(a(g_1), a(g_2)) + c_0(b(g_1), b(g_2)) + \text{AGain}, \\ c_0(a(g_1), a(g_2)) + c_1(b(g_1), b(g_2)) + \text{AGain},\ c_1(a(g_1), a(g_2)) + c_1(b(g_1), b(g_2)) + \text{2AGain} \end{cases}$$

8. If $e(g_1) = \text{GDup}$ and $e(g_2) = \text{GDup}$:

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Deco algorithm [Berard *et al*, 2012]

Dyn. prog. scheme for most parsimonious adjacency forest in $\mathcal{O}(|R_1| \times |R_2|)$

Intuition: Jointly explores both reconciliations in all possible ways, to account for adjacency breaks/gains.

Comparative genomics is a vibrant field with strong **2-ways** links with

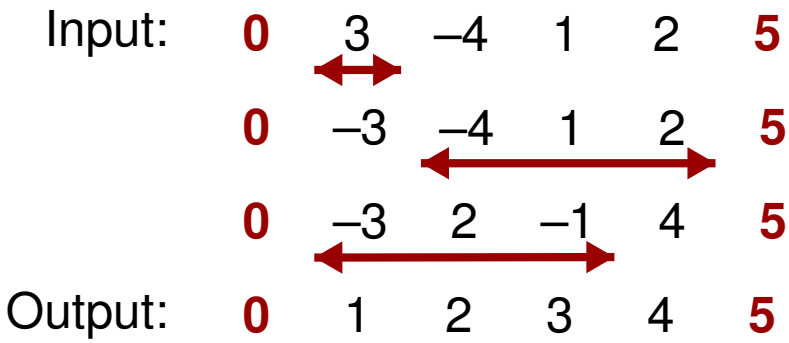
- Phylogenetics, (Epi)genomics, Paleogenomics, Proteomics, Structural biology, Systems Biology . . .
- . . . but also string processing, enumerative combinatorics, discrete algorithms , discrete maths . . .

It predicts the past, but also informs studies of the unobservable present

Some $\pm$ current directions:

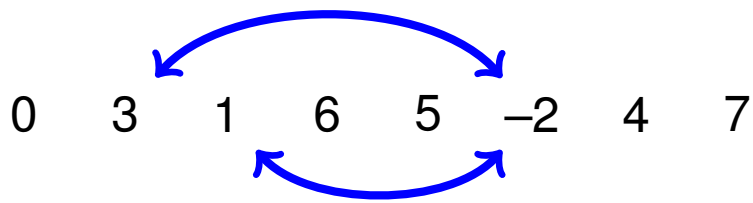
- Beyond parsimony, Bayesian approaches (likelihood maximization) $\rightarrow$ Mainly based on sampling (ABC), but also more direct opt. (DP)
- Distinguishing between erroneous and informative incongruences
- Expressive models for reconciliations: Horizontal gene transfers, polytomies. . .
- Integrating multiple steps of analyses into joint optimizations *e.g.* comparative genome scaffolding
- Advanced algorithms: FPT algo/kernels, guaranteed approximations, exp. time (small exponents), ILP. . . . . for all of the above (+ML)

Goal: Implement **sorting by reversal** for signed permutations [Bergeron 2006]
w.l.o.g. assume that input permutation π **flanked** by **0** and **n+1**



Some **definitions**:

- **Oriented pair:** Two pos. (i, j) with consecutive values of opposite signs



Reversal of oriented pairs (i, j):

$\pi_i + \pi_j = +1 \rightarrow$

$$\cdots \quad \pi_i \quad \pi_{i+1} \quad \cdots \quad \pi_{j-1} \quad \pi_j \quad \cdots$$
$$\cdots \quad -\pi_{j-1} \quad -\pi_{j-2} \quad \cdots \quad -\pi_i \quad \pi_j \quad \cdots$$

$\pi_i + \pi_j = -1 \rightarrow$

$$\cdots \quad \pi_i \quad \pi_{i+1} \quad \cdots \quad \pi_{j-1} \quad \pi_j \quad \cdots$$
$$\cdots \quad \pi_i \quad -\pi_j \quad \cdots \quad -\pi_{i+2} \quad -\pi_{i+1} \quad \cdots$$

Goal: Implement **sorting by reversal** for signed permutations [Bergeron 2006]
w.l.o.g. assume that permutations **flanked** by **0** and **n+1**

Definitions for **positive** permutations:

- **Framed interval:** Interval $[i, j]$ in π of the form

  $$\pi_i\ \pi_{i+1}\ \pi_{i+2} \cdots \pi_j \text{ with } \pi_j = \pi_i + (j - i) \text{ and } \pi_i < \pi_k < \pi_j, \forall i < k < j$$

  or **equivalently** region $[i, j]$ contains a permutation of $[\pi_i, \pi_j]$

  But... one needs to consider **circular** ordering of values

Framed intervals: $[1, 8]$, $[2, 6]$, $[6, \bar{2}]$

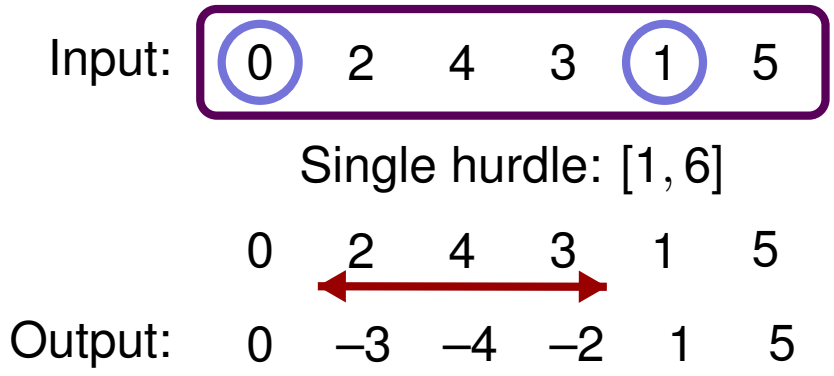
- **Hurdles**: Minimal framed intervals w.r.t. inclusion

Hurdles: $[2, 6]$, $[6, \bar{2}]$

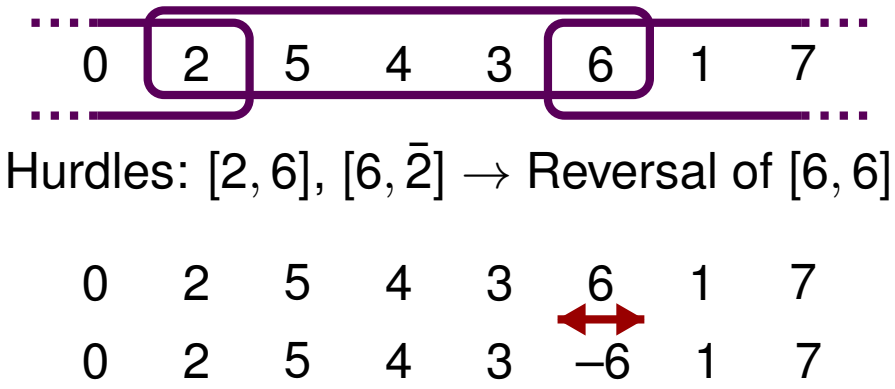
Goal: Implement **sorting by reversal** for signed permutations [Bergeron 2006]
w.l.o.g. assume that permutations **flanked** by **0** and **n+1**

Definitions for **positive** permutations:

- **Splitting a hurdle** $[i, j]$**:** Look for position k such that $\pi_k = \pi_i + 1$, and reverse interval $[i + 1, k - 1]$



- **Merging two hurdles** $[i, j]$ **and** $[k, l]$**,** $j \leq k$**:** Reverse interval $[j, k]$



Goal: Implement **sorting by reversal** for signed permutations [Bergeron 2006]

Final algo. While π not sorted:

- If π negative:
  - Identify Oriented Pair (OP) (i, j) that creates max #OPs
  - Reverse OP (i, j)
  - Iterate until permutation π becomes positive
- If π positive, consider hurdles $\mathcal{H}$ of π:
  - $\mathcal{H} = \{(i, j)\}$
    $\rightarrow$ split (i, j)
  - $\mathcal{H} = \{(i, j), (k, l)\}$
    $\rightarrow$ merge (i, j)
  - $|\mathcal{H}| > 2$, $|\mathcal{H}|$ even
    $\rightarrow$ Merge two non-consecutive hurdles
  - $|\mathcal{H}| > 2$, $|\mathcal{H}|$ odd
    Simple hurdle $h^\star$: Cutting $h^\star$ + reversal of OPs **decreases** #hurdles

    If $\mathcal{H}$ contains simple hurdle $h^\star$
    $\rightarrow$ Cut $h^\star$
    Otherwise
    $\rightarrow$ Merge two non-consecutive hurdles (or consecutive ones if $|\mathcal{H}| = 3$)