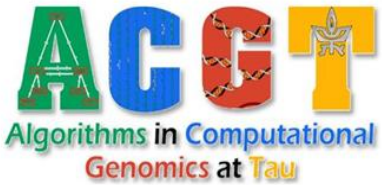


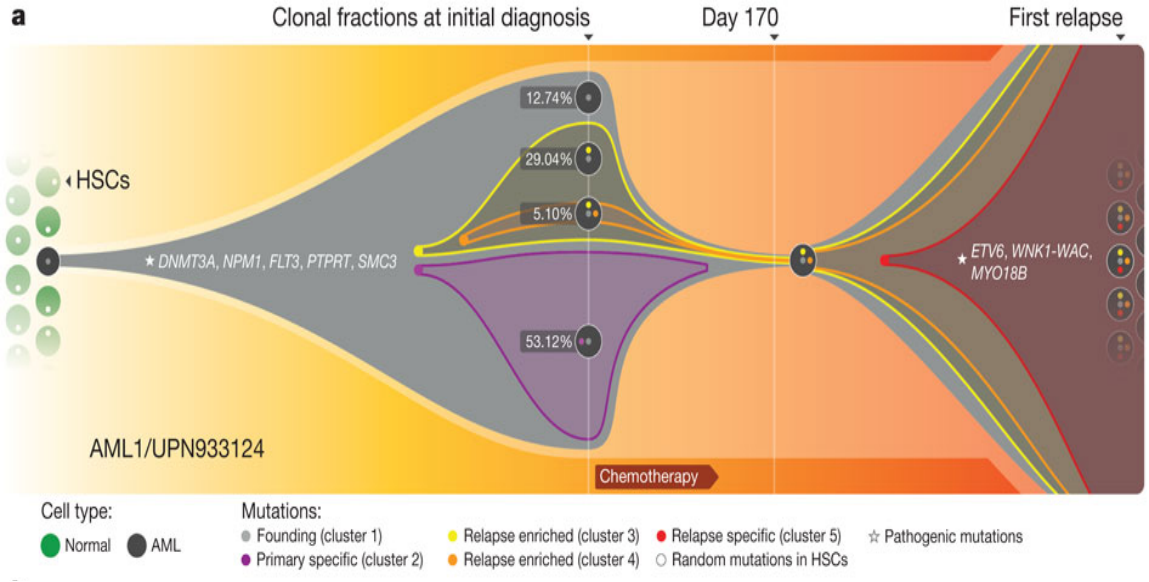
Copy-Number Evolution Problems: Complexity and Algorithms

Mohammed El-Kebir, Ben Raphael, Ron Shamir, Roded Sharan, **Simone Zaccaria**, Meirav Zehavi and **Ron Zeira**

August 23
WABI 2016

Evolution of Cancer

- Cancer is an evolutionary process characterized by the accumulation of somatic mutations
- Different populations of cells form a tumor

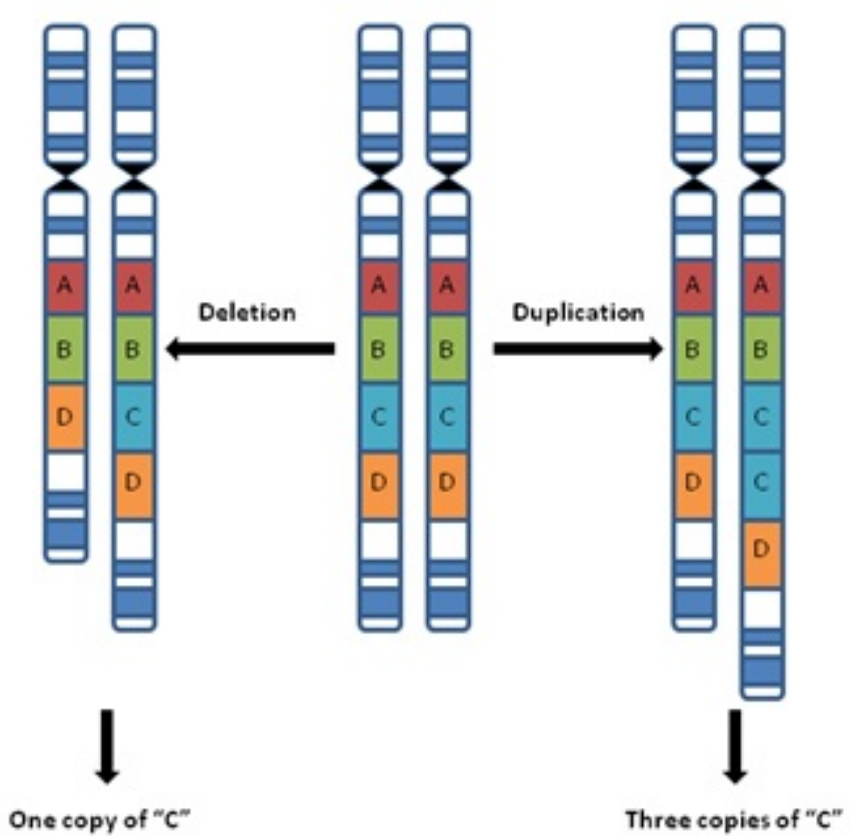


Ding *et al*. Nature 2012

- Inference of evolution for understanding:
  - Order of mutations
  - Dynamics of clones
  - Effects of treatment
  - Driver mutations
  - …

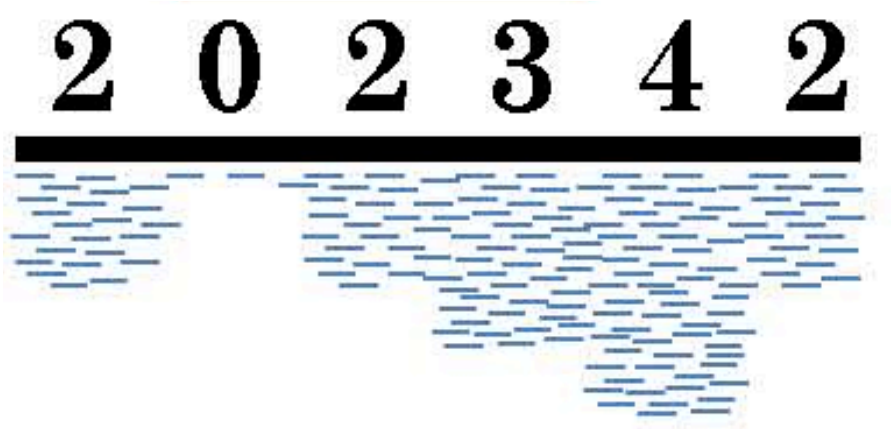
Copy-Number Aberrations

- For most tumor types, *copy-number aberrations* are ubiquitous



Copy-number profiles

- *Copy-number profiles* encode the number of copies of each region along a chromosome.
- Inferred from experimental data (sequencing, aCGH, FISH)



Operations on profiles

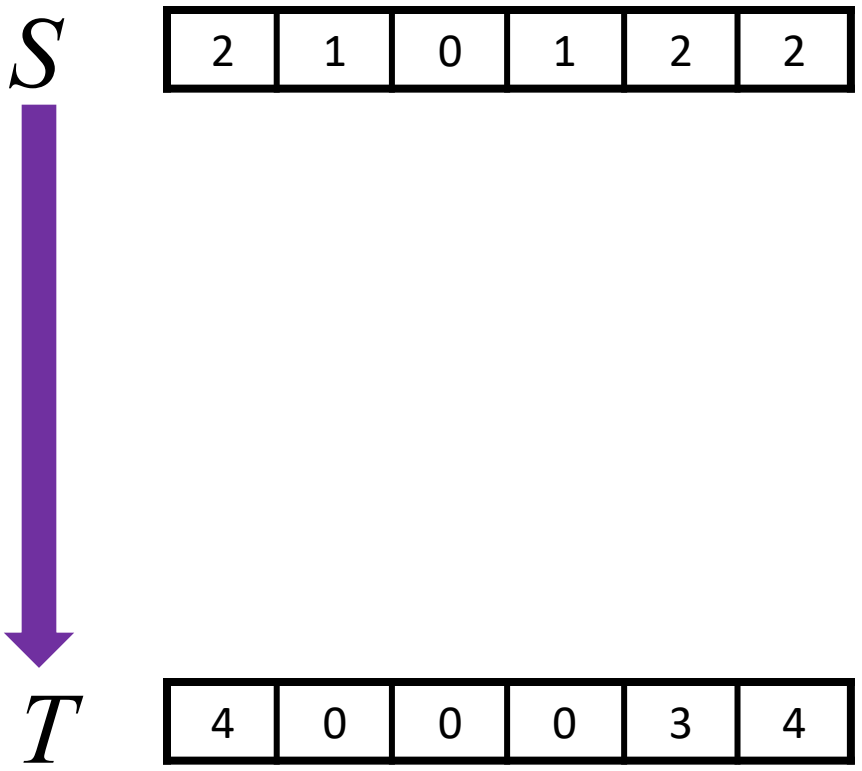
Chromosome =
Copy number profile

S

Operations on profiles

Chromosome = *Copy number profile*

Evolves by copy number change events

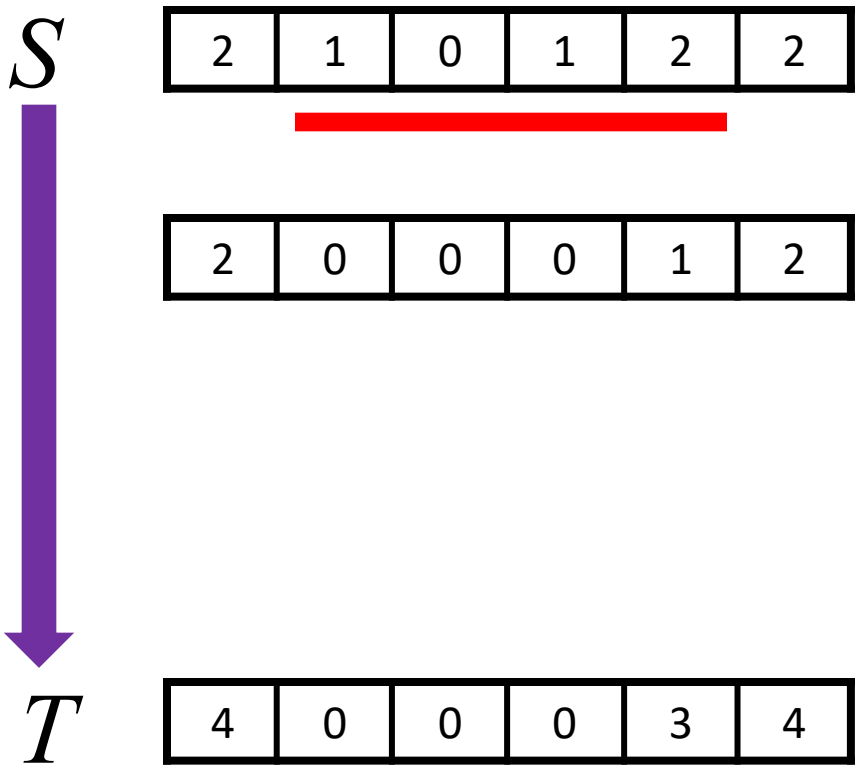


Operations on profiles

Chromosome = *Copy number profile*

Evolves by copy number change events

Event: segmental *duplication* / *deletion*



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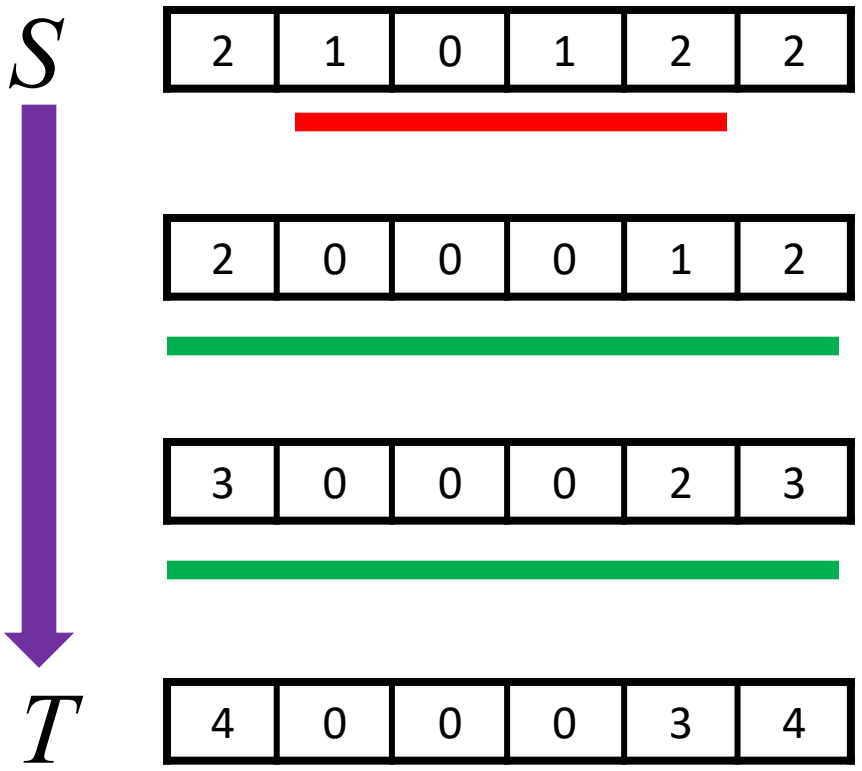


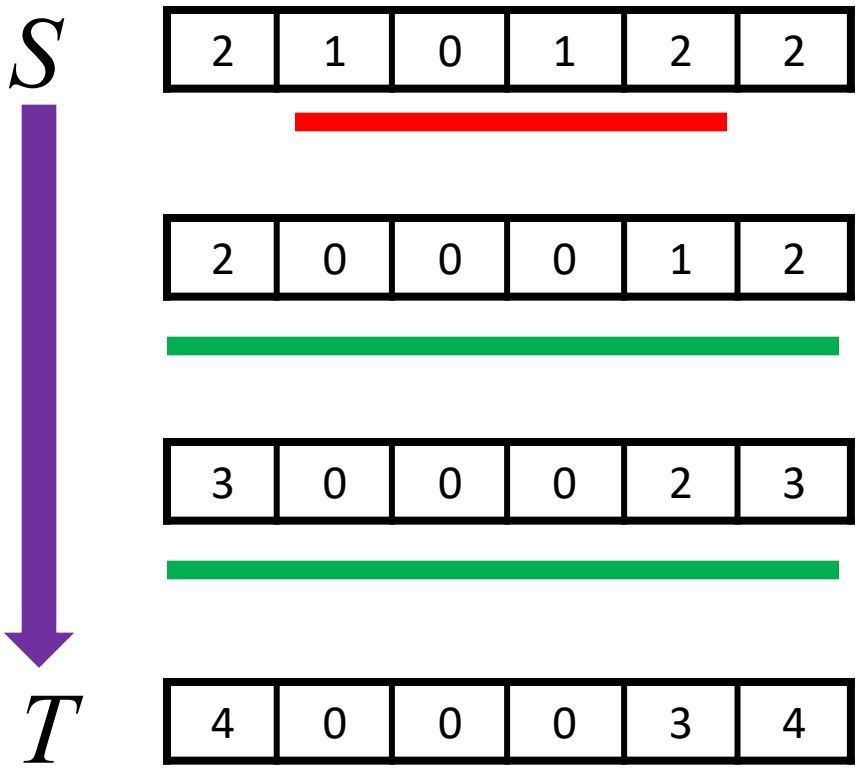
Operations on profiles

Chromosome = *Copy number profile*

Evolves by copy number change events

Event: segmental *duplication* / *deletion*

Distance from S to T: *least no. of operations*



$$dist(S,T) = 3$$

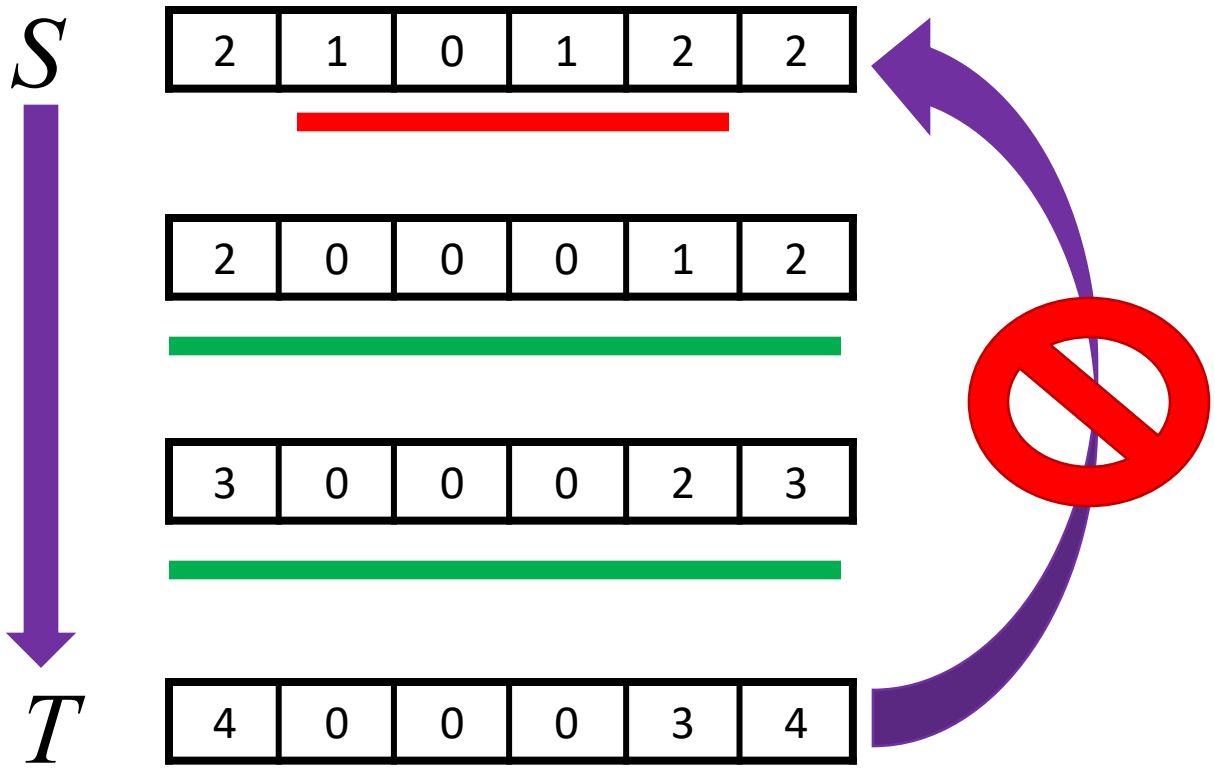
Operations on profiles

Chromosome = *Copy number profile*

Evolves by copy number change events

Event: segmental *duplication* / *deletion*

Distance from S to T: *least no. of operations*



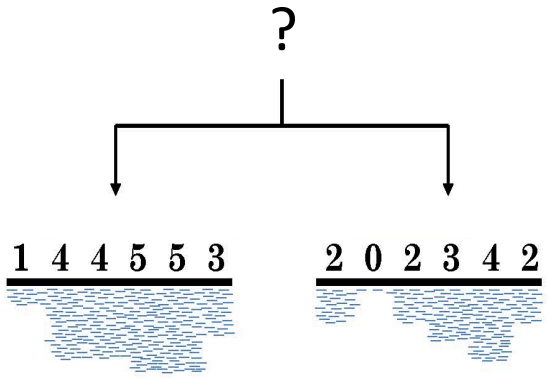
$$dist(S,T) = 3$$

Previous work

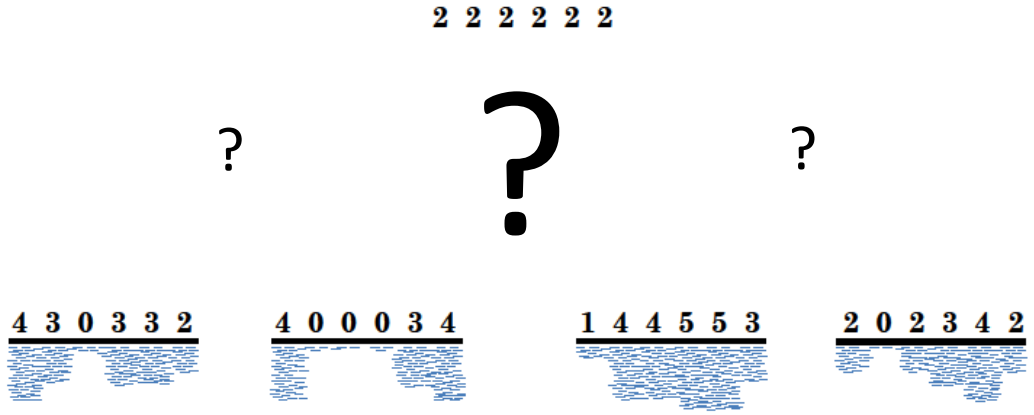
- Schwarz et al. PLoS CB 2014:
  - Presented model, developed a heuristic procedure for tree reconstruction
  - Reconstructed ovarian cancer sample phylogeny.
- Shamir, Zehavi, and Zeira CPM 2016:
  - A linear time algorithm for S → T distance.

This work

- Copy-number triplet (CN3):

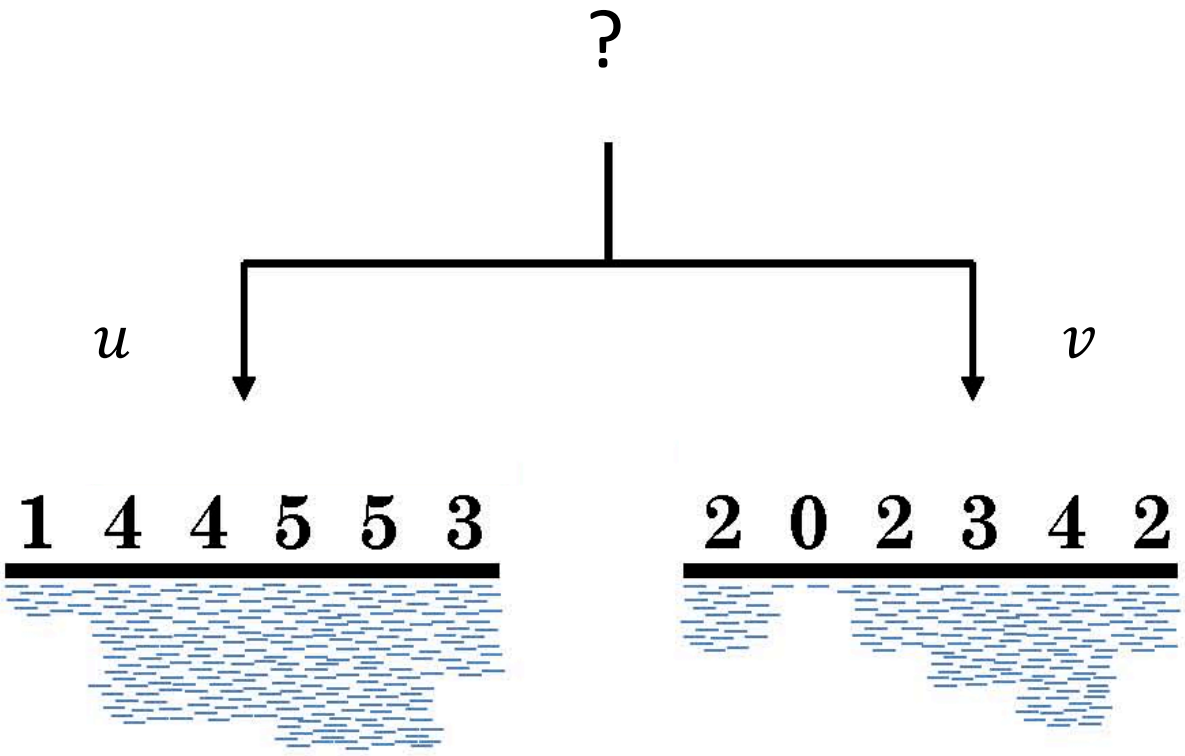


- Copy-number tree (CNT):



Copy-Number Triplet Problem (CN3)

- Given two profiles, find a parent profile minimizing the sum of distances to them.



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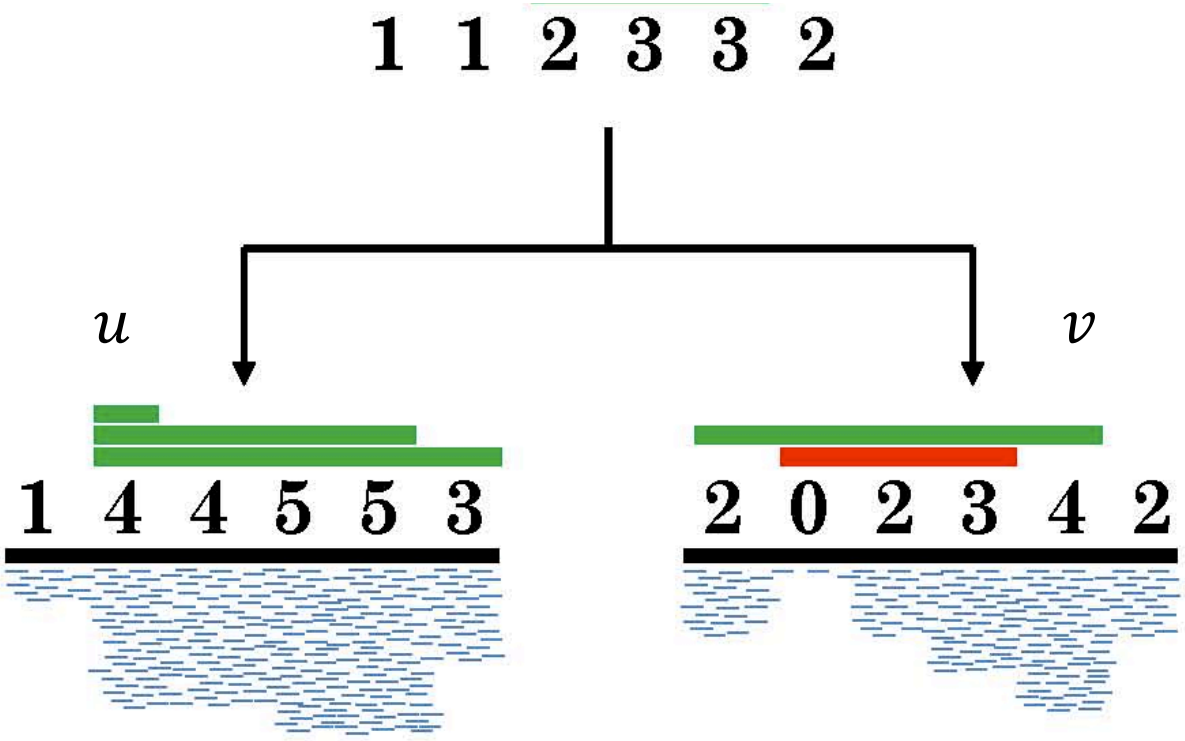


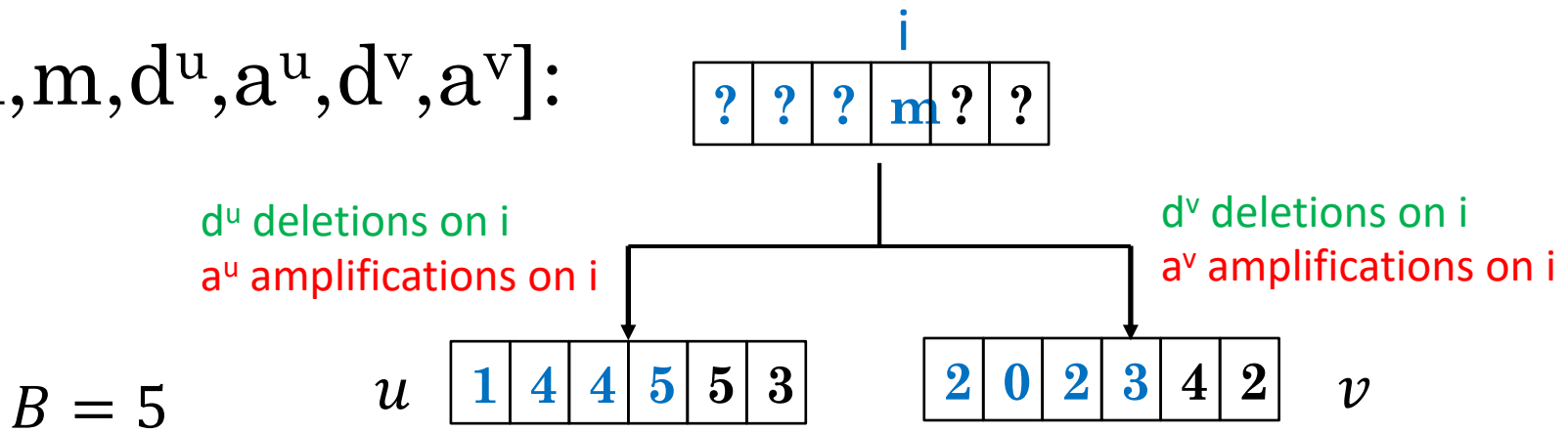
Problem properties

- Shamir et al. 2016:
  - There is an optimal S→T sorting scenario where all deletions precede all amplifications.
  - Let B be the maximal copy-number. There is an optimal S → T sorting scenario that deletes/amplifies each position ≤ B times.

- **Lemma**: There is an optimal solution to CN3 where all positions in the parent are ≤B.

Dynamic programming solution

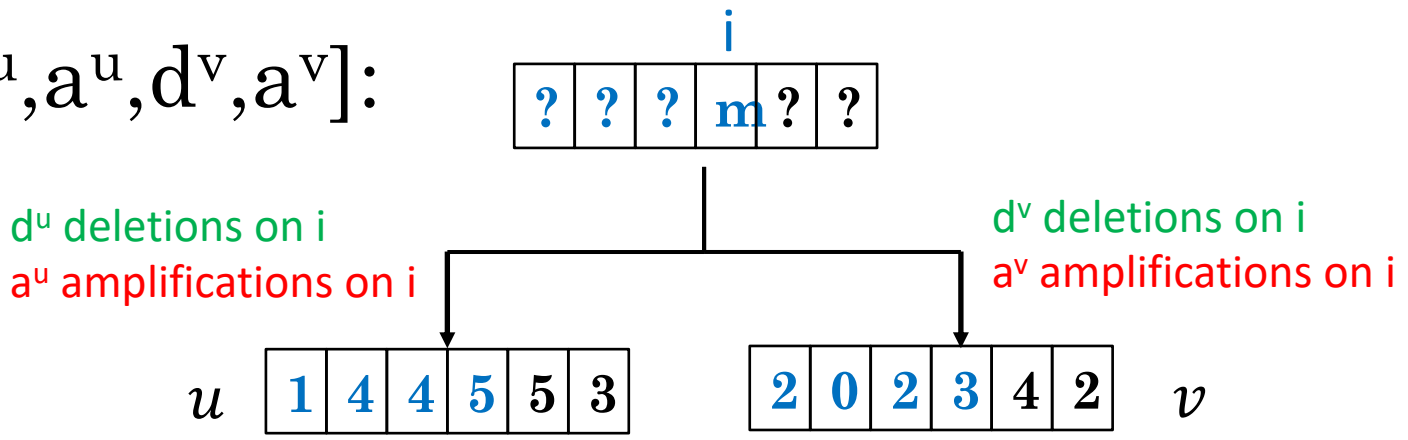
- L[i,m,d^u,a^u,d^v,a^v]:



L: Optimal value of solution for prefixes 1,..i given the values of the parameters.

Dynamic programming solution

- L[i,m,d^u,a^u,d^v,a^v]:



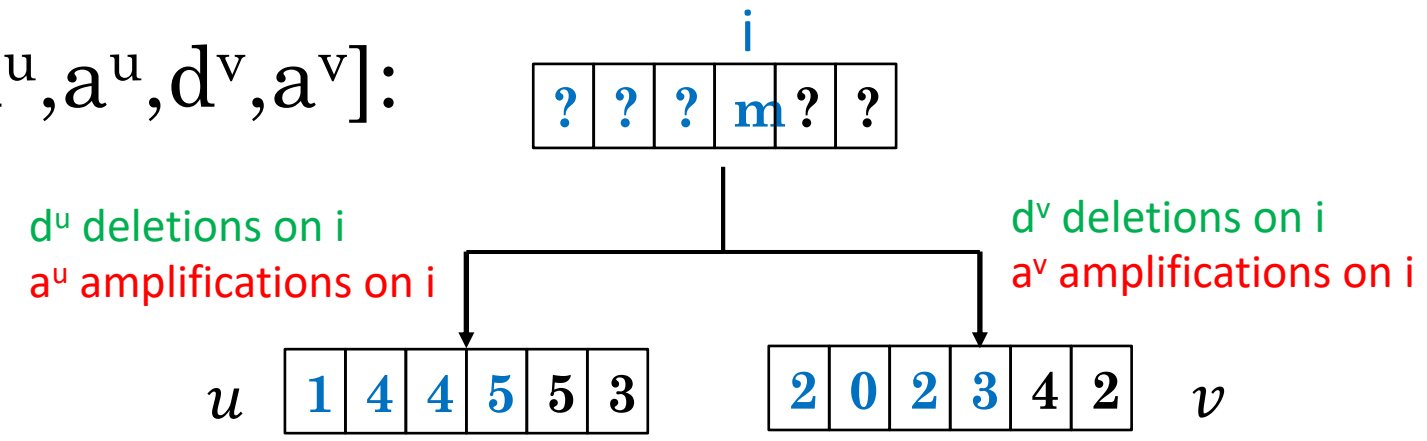
$$\mathrm{L}[i,m,d^{\mathbf{u}},a^{\mathbf{u}},d^{\mathbf{v}},a^{\mathbf{v}}] = \min_{\substack{0\le m'\le N \\ 0\le d^{\mathbf{u}\prime},a^{\mathbf{u}\prime},d^{\mathbf{v}\prime},a^{\mathbf{v}\prime}\le N}} \Big\{ \mathrm{L}[i-1,m',d^{\mathbf{u}\prime},a^{\mathbf{u}\prime},d^{\mathbf{v}\prime},a^{\mathbf{v}\prime}] + \max\{d^{\mathbf{u}}-d^{\mathbf{u}\prime},0\} + \max\{a^{\mathbf{u}}-a^{\mathbf{u}\prime},0\} + \max\{d^{\mathbf{v}}-d^{\mathbf{v}\prime},0\} + \max\{a^{\mathbf{v}}-a^{\mathbf{v}\prime},0\} \Big\}$$

new deletions

new amplifications

Dynamic programming solution

- L[i,m,d^u,a^u,d^v,a^v]:



$$\mathrm{L}[i, m, d^{\mathbf{u}}, a^{\mathbf{u}}, d^{\mathbf{v}}, a^{\mathbf{v}}] = \min_{\substack{0 \le m' \le N \\ 0 \le d^{\mathbf{u}\prime}, a^{\mathbf{u}\prime}, d^{\mathbf{v}\prime}, a^{\mathbf{v}\prime} \le N}} \Big\{ \mathrm{L}[i-1, m', d^{\mathbf{u}\prime}, a^{\mathbf{u}\prime}, d^{\mathbf{v}\prime}, a^{\mathbf{v}\prime}] + \max\{d^{\mathbf{u}} - d^{\mathbf{u}\prime}, 0\} + \max\{a^{\mathbf{u}} - a^{\mathbf{u}\prime}, 0\} + \max\{d^{\mathbf{v}} - d^{\mathbf{v}\prime}, 0\} + \max\{a^{\mathbf{v}} - a^{\mathbf{v}\prime}, 0\} \Big\}$$

new deletions

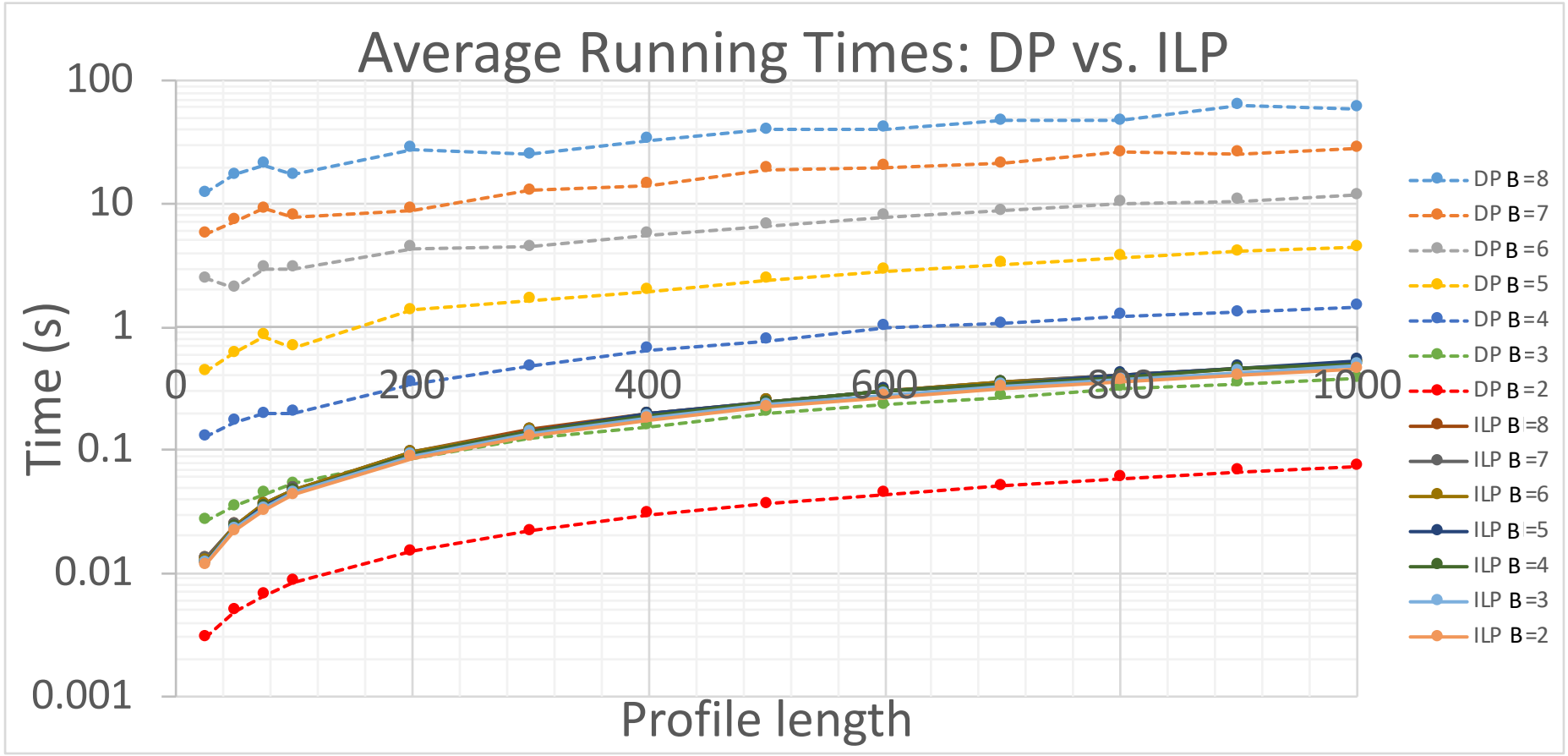
new amplifications

$O(nB^{10})$ time
$O(nB^5)$ space

Can be improved to $O(nB^7)$ time, $O(nB^4)$ space

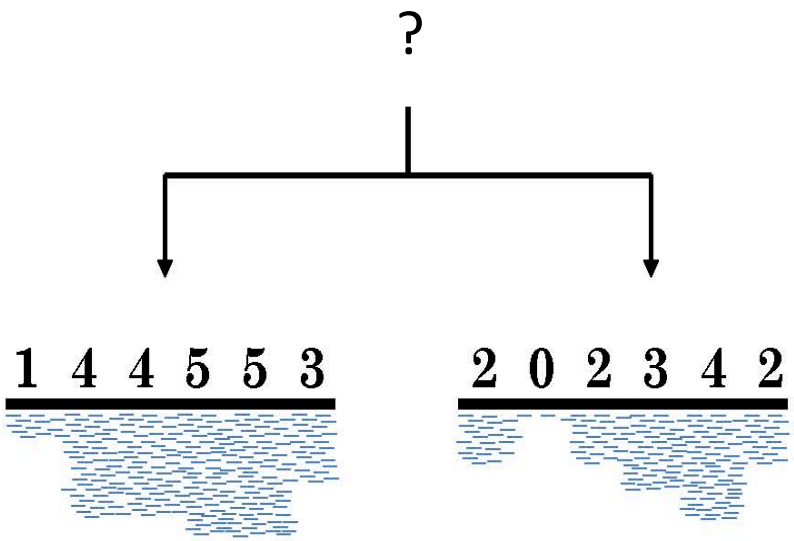
CN3 simulations results

- Comparing DP and an ILP with O(n) variables and constraints

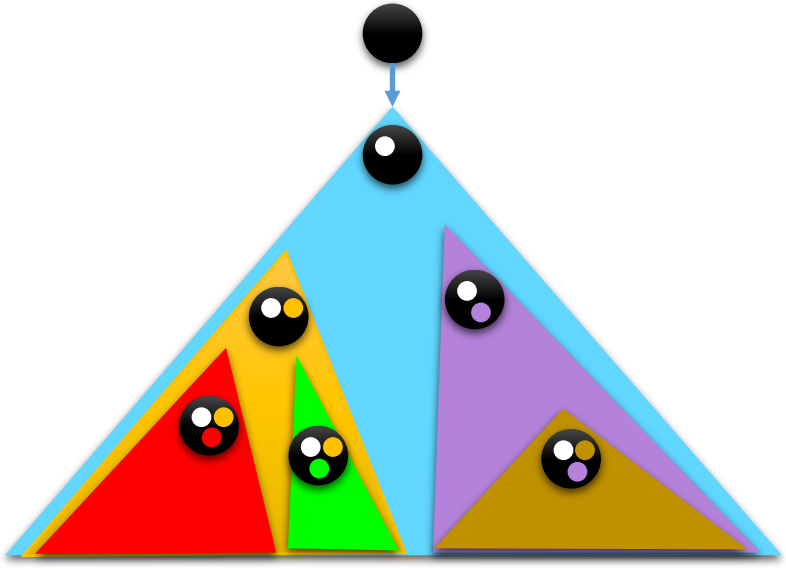


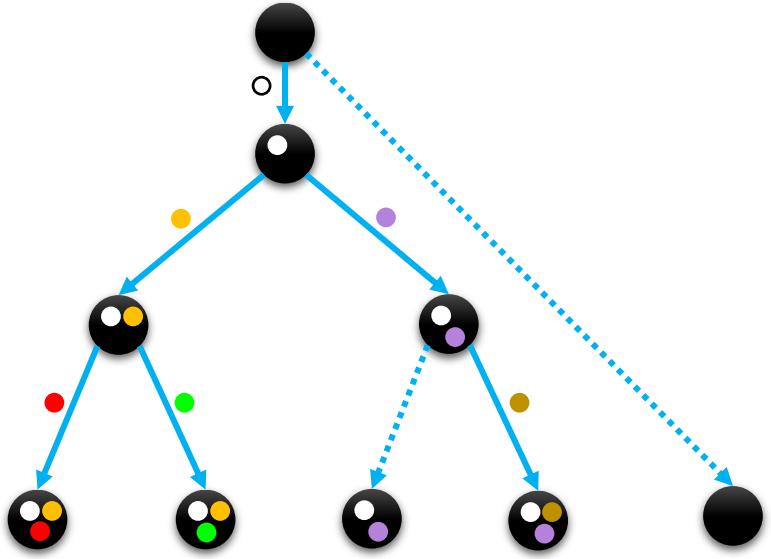
CN3 Conclusions

- DP alg for CN3: linear in n, pseudo-polynomial ($O(nB^7)$)
- An ILP with O(n) variables and constraints
- In simulations: ILP runs faster than DP, obtains the optimum, independent of B
- Complexity of CN3 is still open!

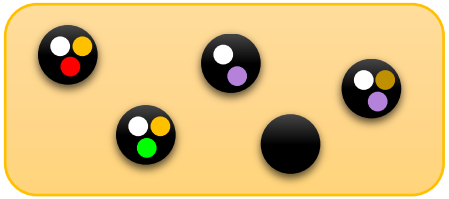


Tree for tumor evolution





Extant clones inferred from multi samples

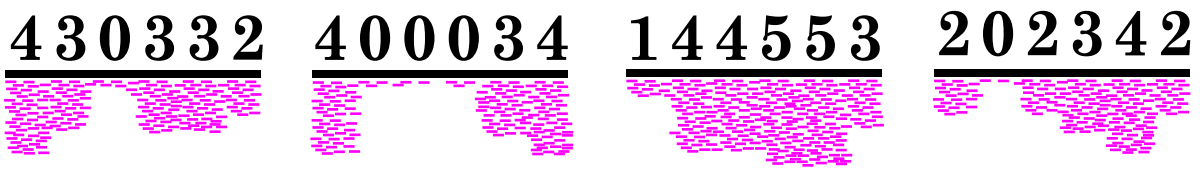


Evolutionary history of clones is modelled by a phylogenetic tree:

1. Leaves correspond to extant clones
2. Edges are labeled by mutations

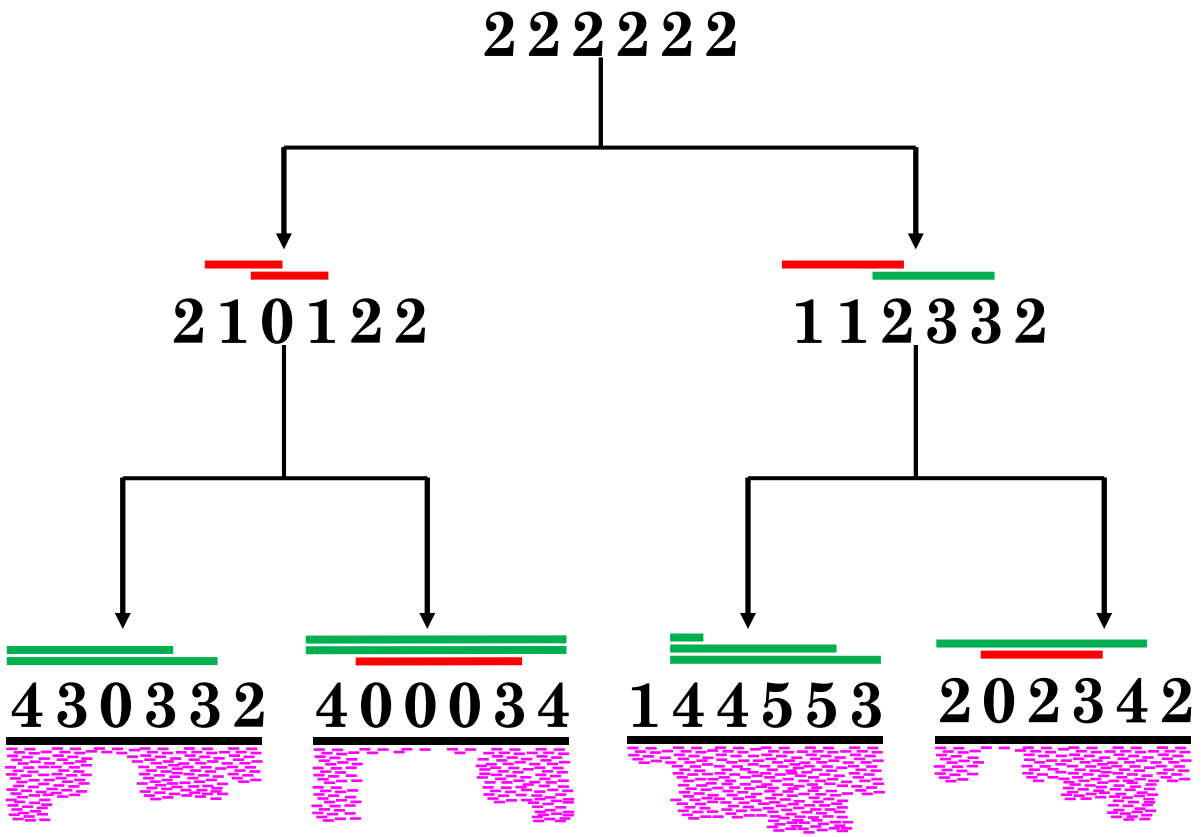
Copy-Number Tree (CNT)

- Input: collection of CN profiles



Copy-Number Tree (CNT)

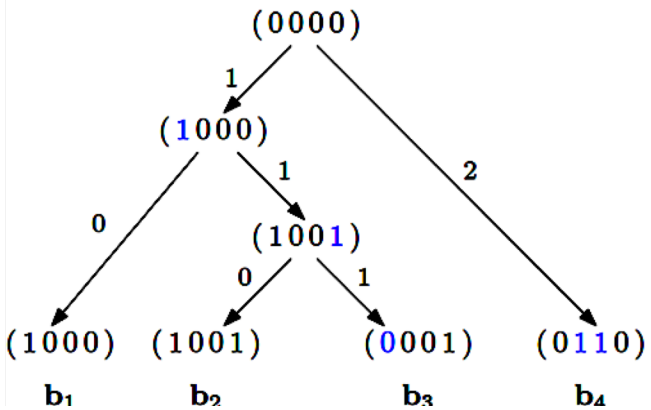
- Input: collection of CN profiles
- Output: copy-number phylogeny:
  - Rooted in the normal diploid profile
  - The leaves are the input profiles
  - Explained by the minimum number of events



Computational Complexity

- CNT is NP-hard
- Reduction from the NP-hard Steiner Problem in Phylogeny (also called Maximum Parsimony Phylogeny):
  - Binary vectors
  - Events are single flips

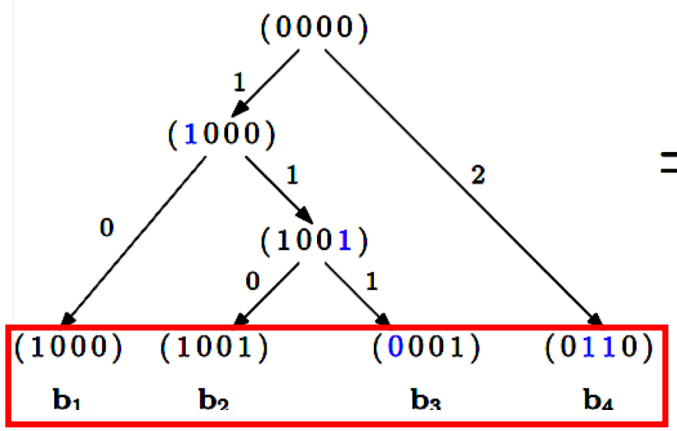
MPP instance and solution T with cost $\Delta(T) = 5$



Computational Complexity

- Transformation:
  - 0 → 2 and 1 → 1 (real copy-numbers)
  - A wall Ω (21⋯12) between consecutive real copy-numbers, large enough

MPP instance and solution T with cost $\Delta(T) = 5$



$\Rightarrow$

$\Omega = (2 \quad 1 \quad \cdots \quad 1 \quad 2)$

$|\Omega| = nk = 20$

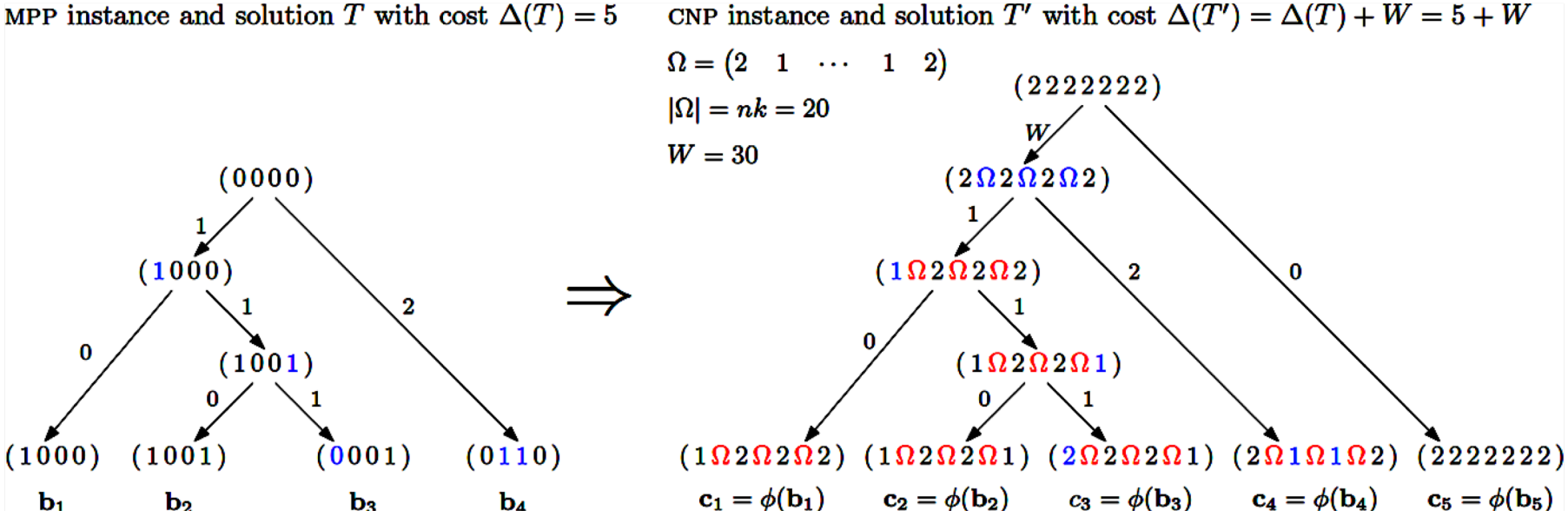
$(1\Omega 2\Omega 2\dot{\Omega}2)$ $(1\Omega 2\Omega\dot{2}\Omega 1)$ $(2\Omega\dot{2}\Omega 2\Omega 1)$ $(2\dot{\Omega}1\Omega 1\Omega 2)$ $(\dot{2}222222)$

$\mathbf{c}_1 = \phi(\mathbf{b}_1)$ $\mathbf{c}_2 = \phi(\mathbf{b}_2)$ $\mathbf{c}_3 = \phi(\mathbf{b}_3)$ $\mathbf{c}_4 = \phi(\mathbf{b}_4)$ $\mathbf{c}_5 = \phi(\mathbf{b}_5)$

Computational Complexity

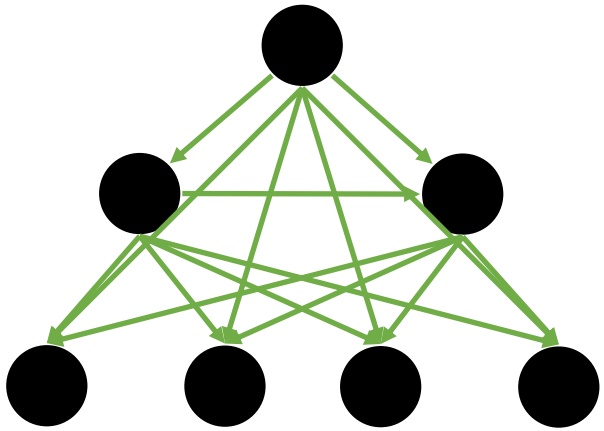
- Key observation: no amplification or deletion breaches the wall Ω

  ➔ Amplifications and deletions correspond to flips



ILP Model

1. Build a spanning tree from a DAG that contains all the possibilities



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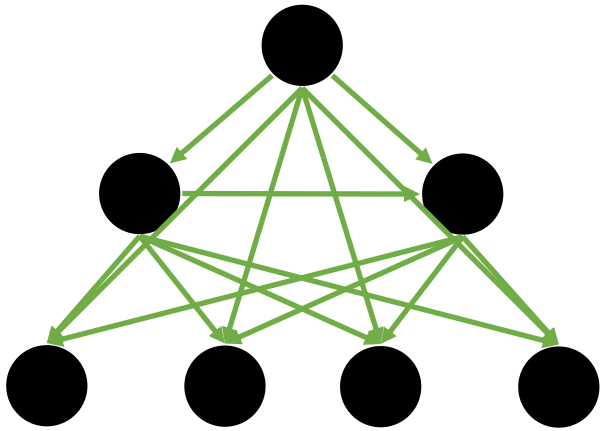
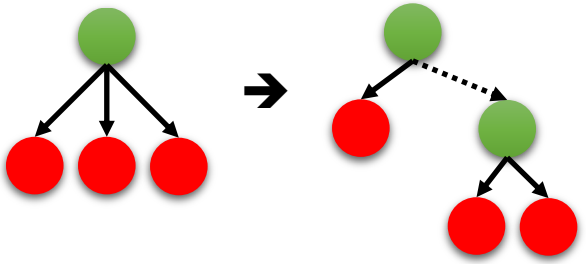
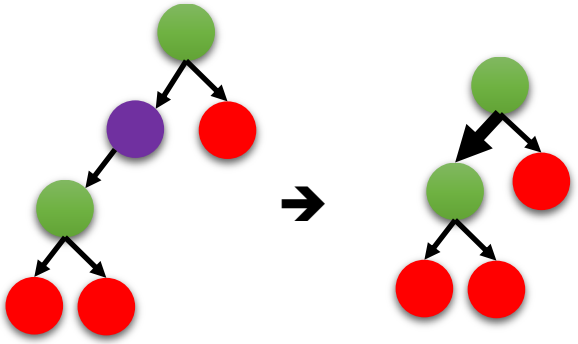


Assumptions

1. Tree is binary, w.l.o.g. by splitting high degree vertices



2. Tree is full binary, w.l.o.g. by collapsing outdegree-2 internal non-root vertices and solving an additional instance adding the root to the leaves



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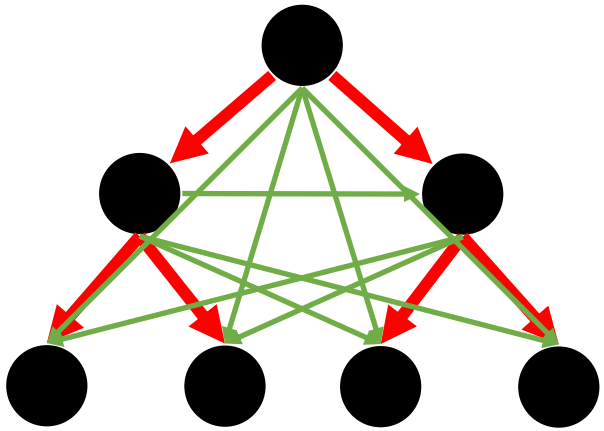

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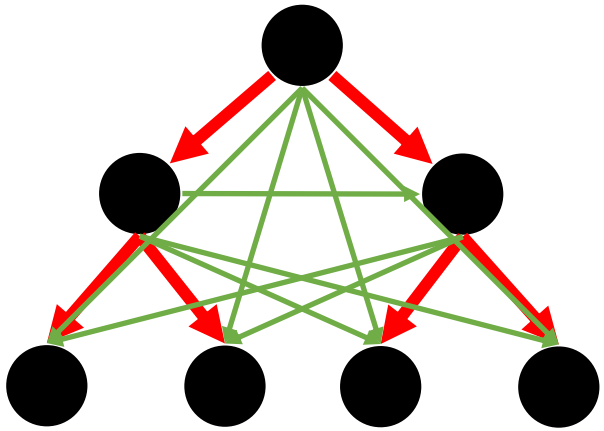

2. Compute the labeling of the internal vertices and the cost of the edges in order to minimize number of events

ILP Model

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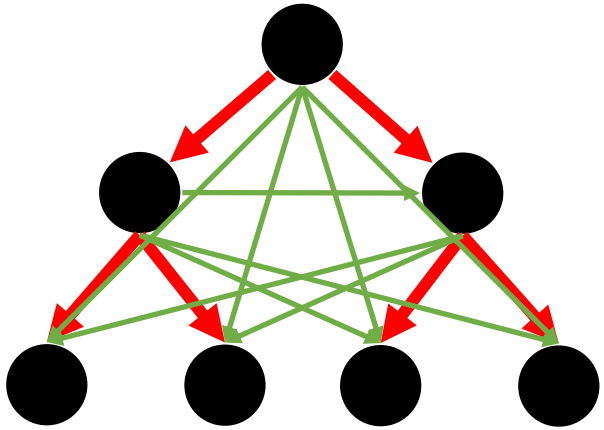

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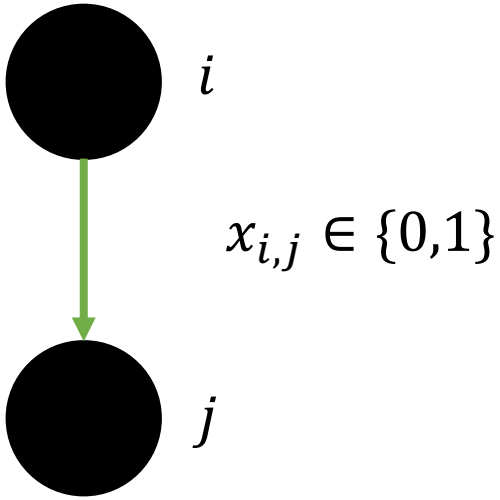

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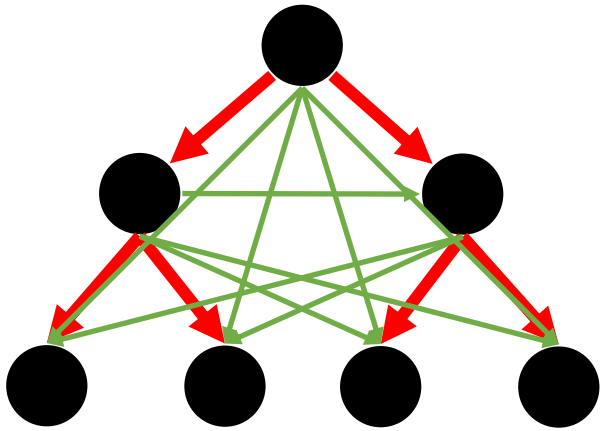

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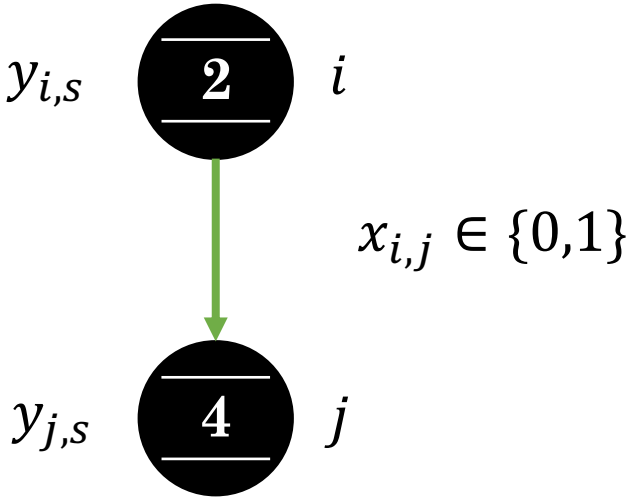

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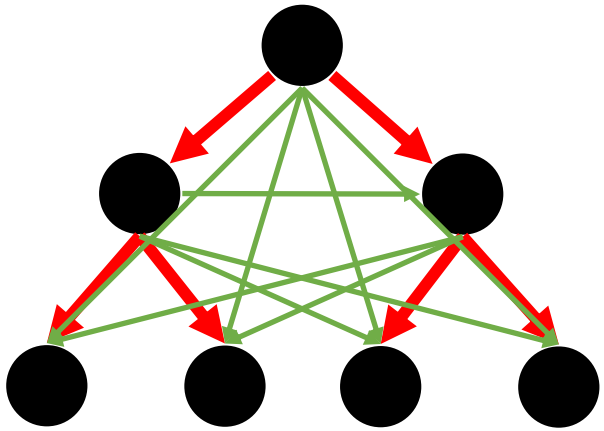

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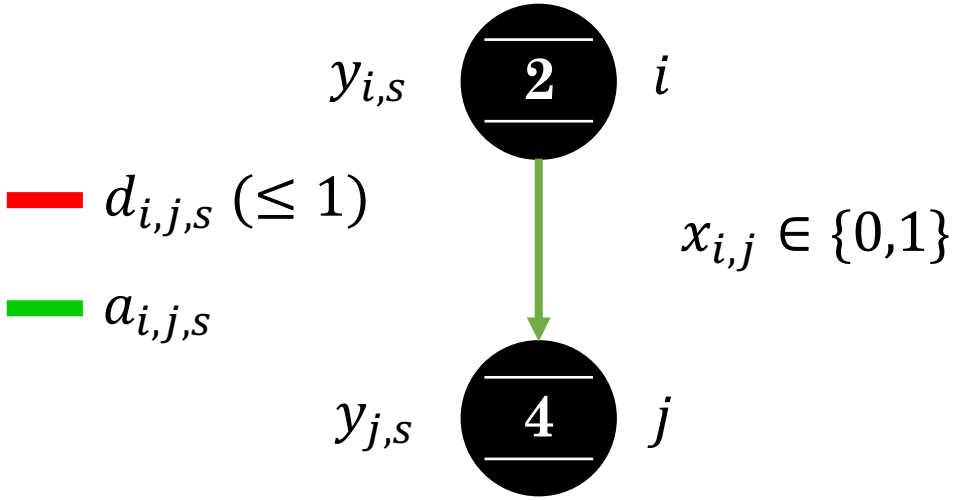
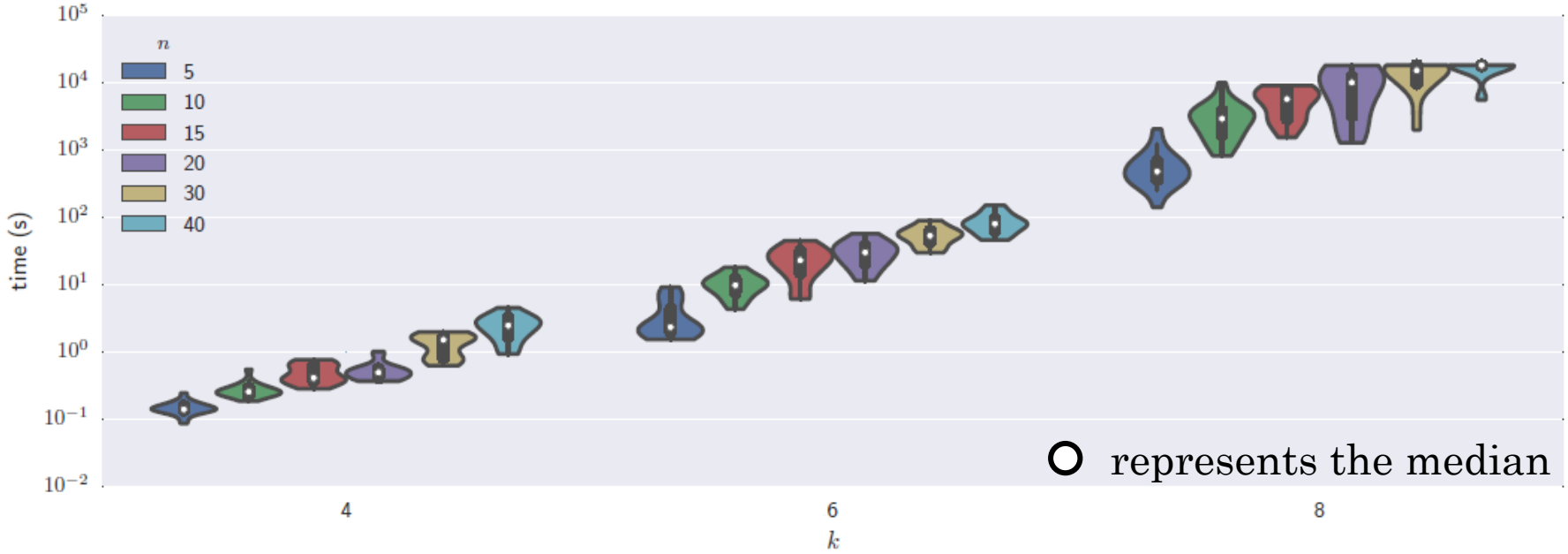


$O(k^2n + kn \log e)$ variables and constraints

Simulations: Running time

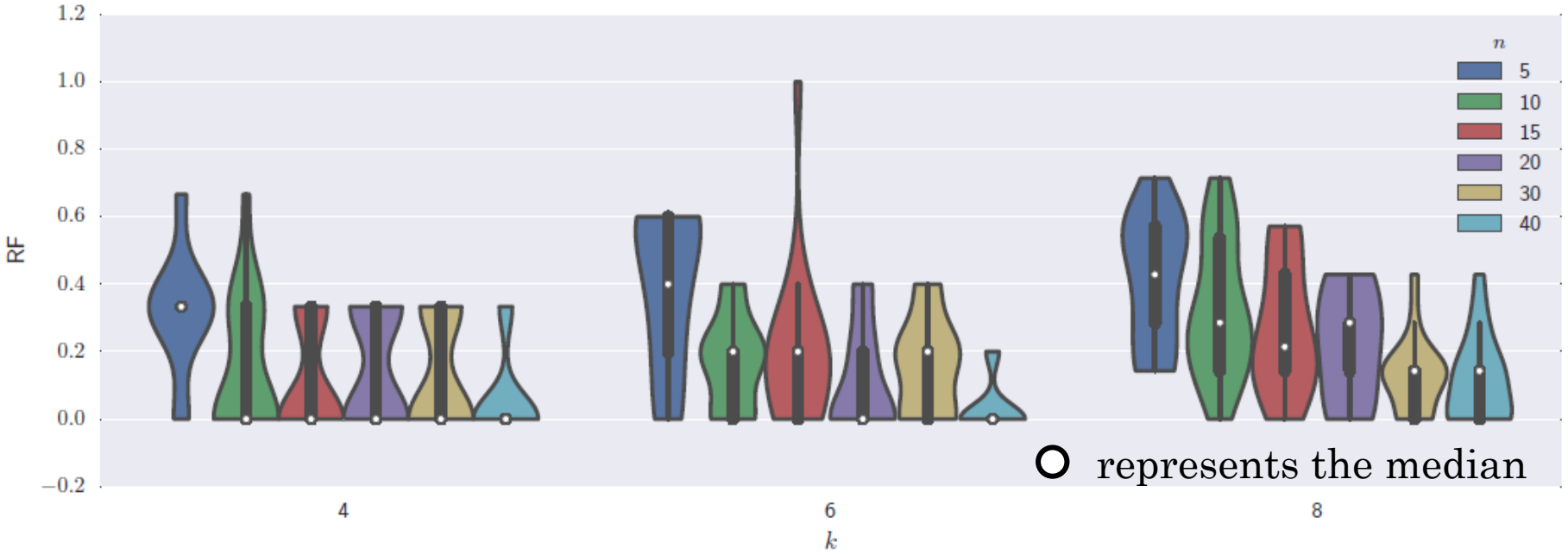
- Implemented in C++ with CPLEX 12.3
- Simulated instances (1 chromosome) were generated varying the profile's length (n), the number of leaves (k), and number of events:
  ➔ $n \in \{5,10,15,20,30,40\}$ and $k \in \{4,6,8\}$ are realistic



(a) Running time in seconds (log scale)

Simulations: Accuracy

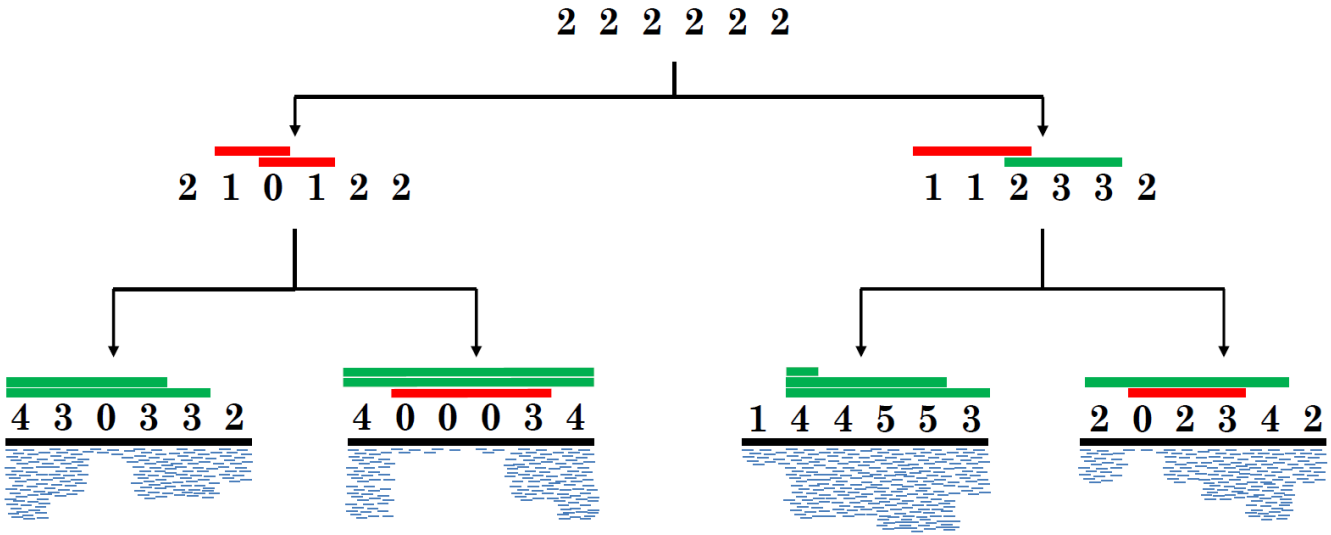
- RF metric – symmetric difference between partitions of two trees – as measure of topological accuracy
- 0 corresponds to identical topologies



(b) Normalized Robinson-Foulds (RF) metric

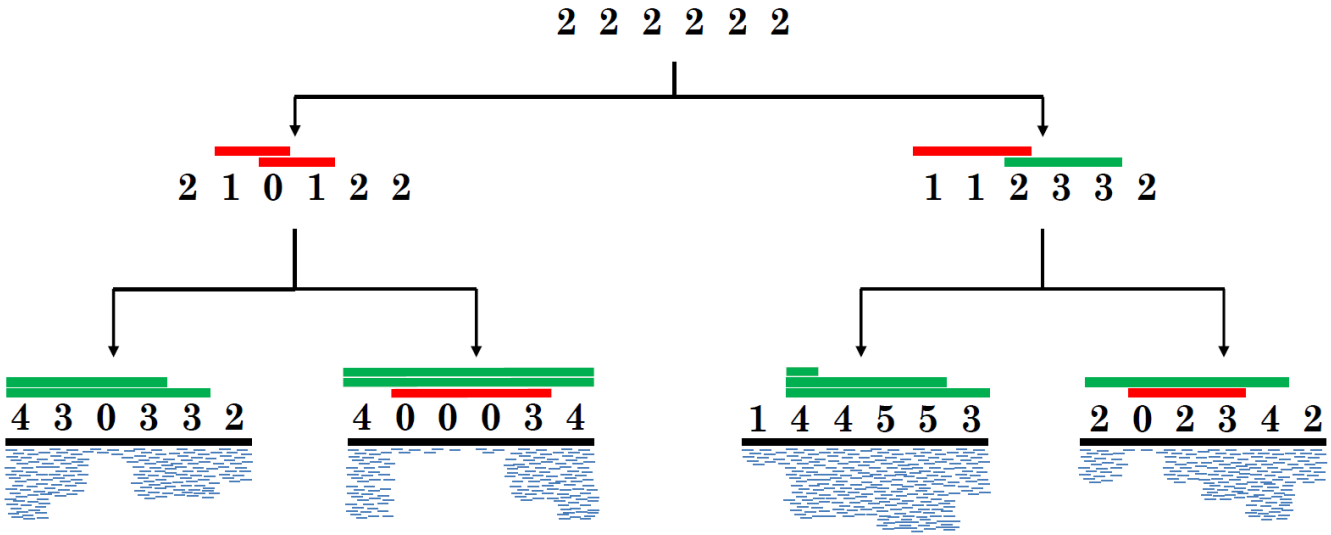
CNT Conclusions

- CNT: NP-hardness, solving algorithm (ILP)
- The results of ILP on simulated data show good accuracy on instances of real size
- Next step: experiments on real data ➔ need of dealing with additional factors as diploid genomes



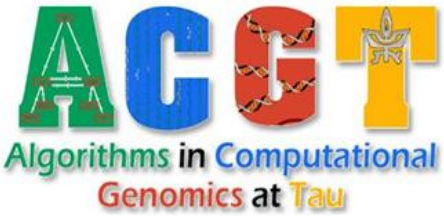
Open Questions

- Computational complexity of CN3
- Computational complexity of the ‘small phylogeny’ for CNT (with fixed topology)



Thanks for the attention.

Questions?



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