Parsimonious Reconstruction of Ancestral Networks

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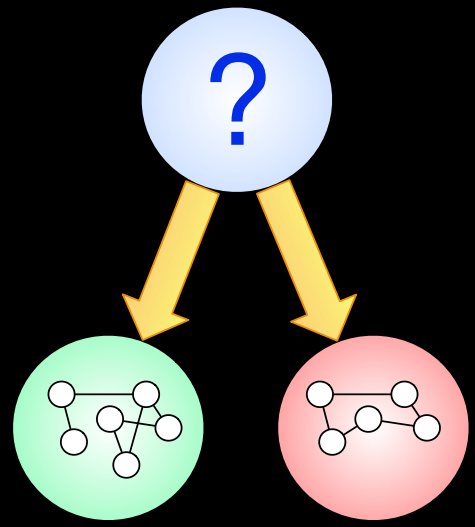
Ancestral Network Reconstruction

What?

Reconstruct the biological networks — regulatory, protein interaction or signaling pathways — of ancestral species

Why?

- Study the evolution of functional modules
- Learn what interactions are conserved
- Understand robustness & evolvability of biological networks
- Improve network-based alignment & phylogeny



Related Work

Reversing Network Growth:

- Gibson and Goldberg (2009) – Multiple networks, not parsimony or ML
- Navlakha and Kingsford (2011) – Single network, greedy model reversal

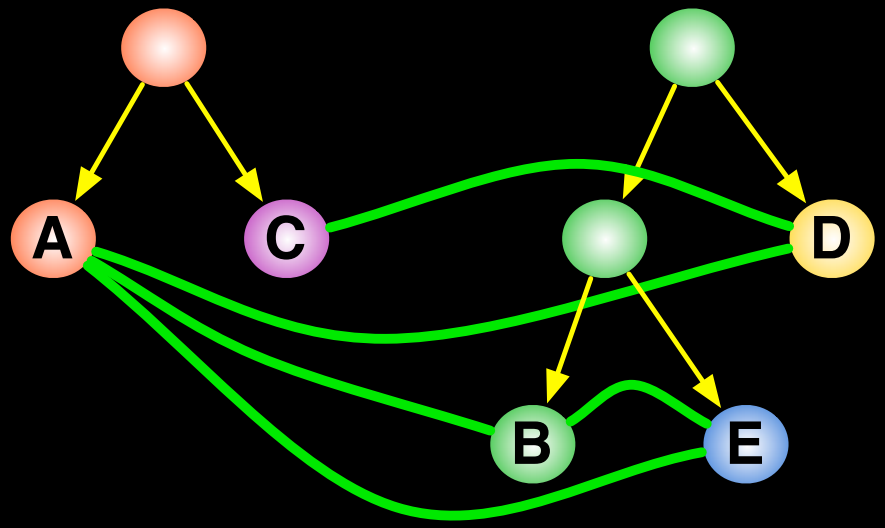
Ancestor Reconstruction (Maximum Likelihood, require total ordering):

- Pinney et al. (2007)
- Dutkowski and Tiuryn (2007)
- Zhang and Moret (2008/10) – Used to improve regulatory inference

Metabolic Network Reconstruction:

- Mithani et al. (2009) – Fixed node set; Gibbs sampling

Represent Network Evolution Histories



Leaf nodes exist in the extant network

Duplication tree specifies (partial) time constraints
  Child nodes exist after their ancestors

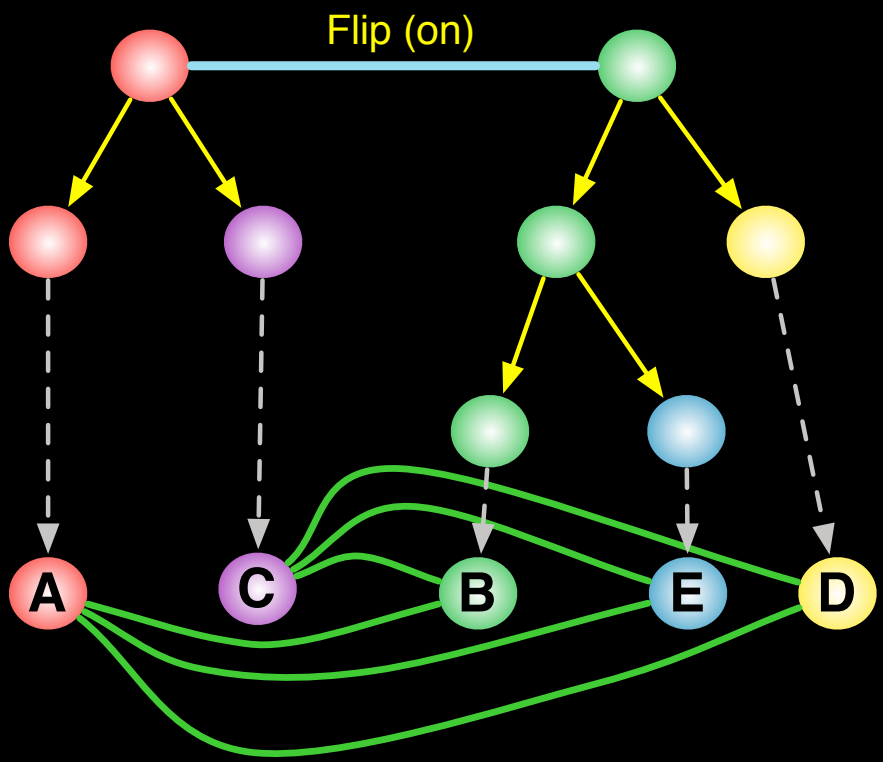
Edges between leaf nodes represent extant interactions

How do we encode ancestral interactions?

Encoding Ancestral Interactions

Assume a duplicate inherits its parents interactions

Non-tree edges between ancestral nodes show how interactions flip on and off



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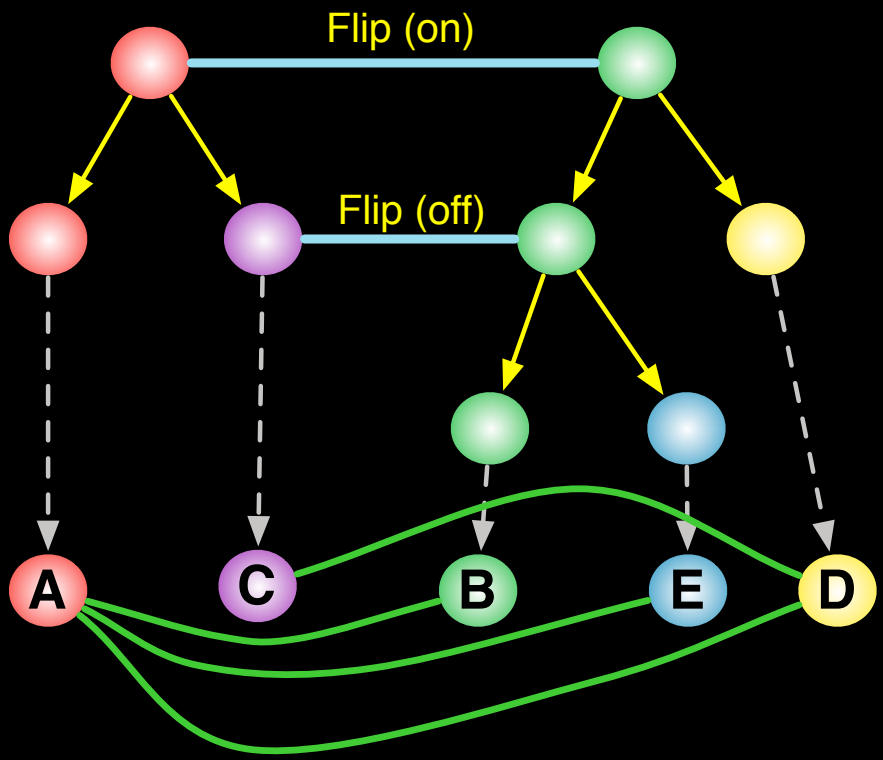

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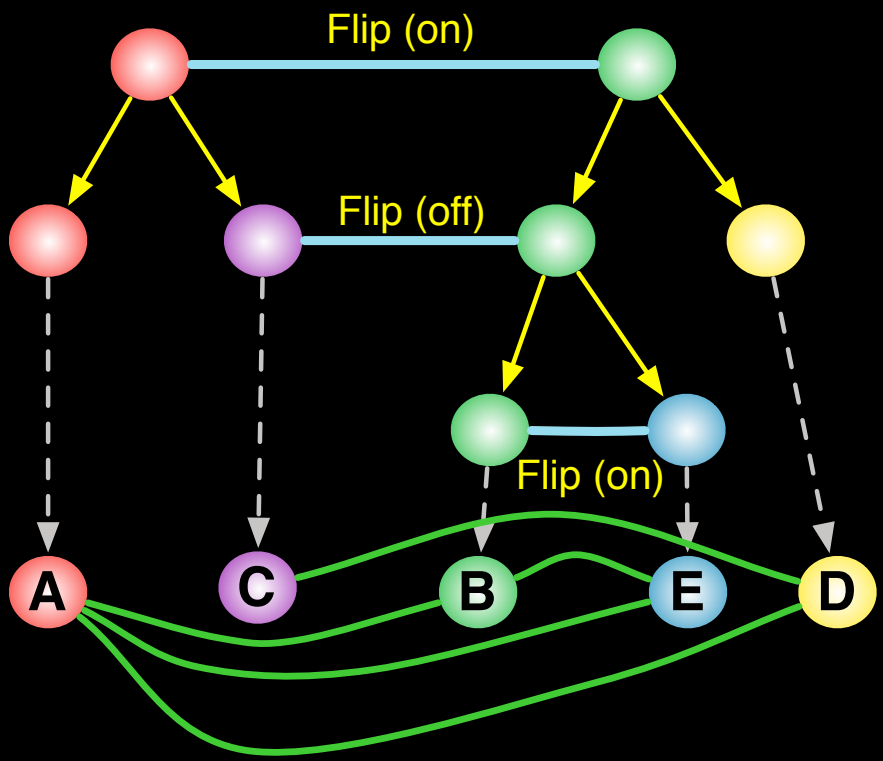
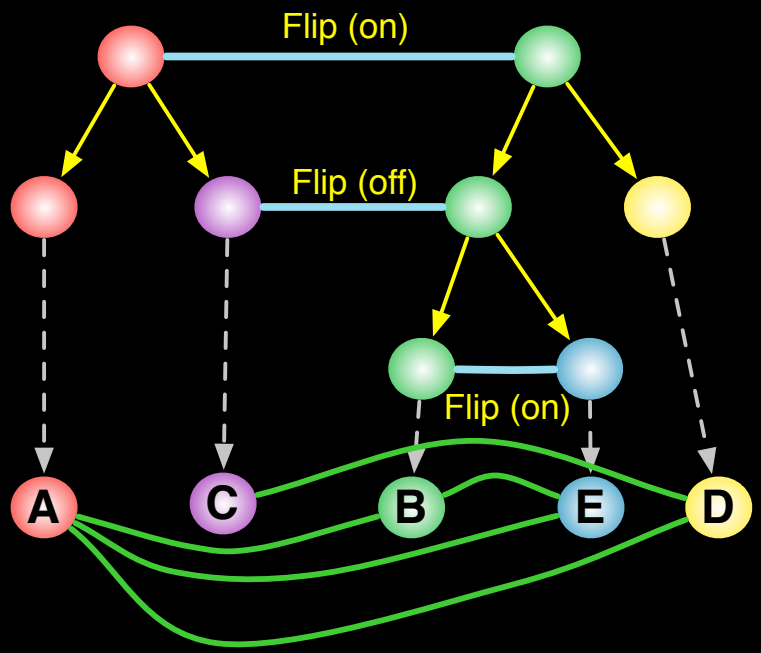


A set of flips that reconstructs the extant networks encodes a possible history of interaction gain and loss

Encoding Ancestral Interactions

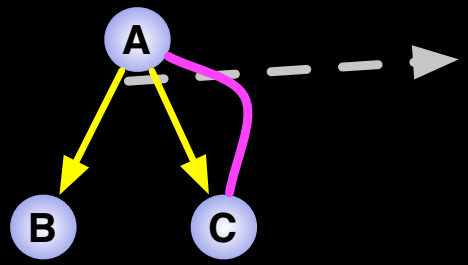


For any pair (u, v) of nodes in the trees and paths p_u and p_v from u and v to their (possibly distinct) roots, the parity of flips between these paths encodes the state of the inferred edge

Even $\implies$ no edge, odd $\implies$ edge

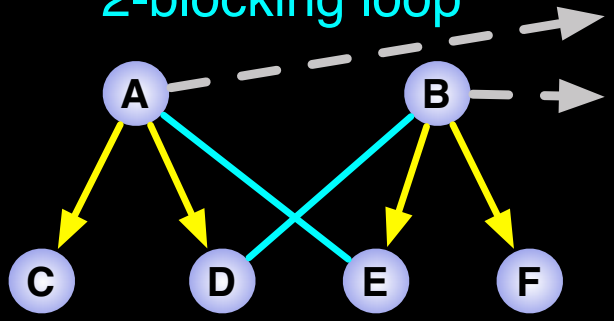
Not all sets of flips (histories) are valid

1-blocking loop



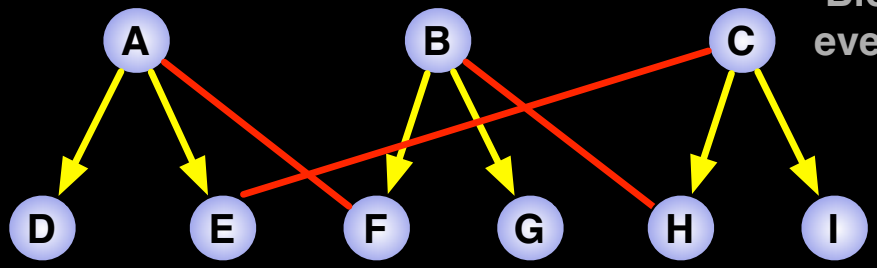
A ceases to exist here, after it duplicates

2-blocking loop



The duplication of A depends on the duplication of B and vice-versa

3-blocking loop



Blocking loops imply that the duplication events can't be consistently ordered while respecting the inferred interactions

A history H is valid $\iff$ it contains no blocking loops

Given: a duplication forest F and extant networks G_1 and G_2

Find: H — a valid interaction history reconstructing G_1 and G_2, with a minimum cost set of edge flips (i.e. the most parsimonious solution).

Despite the exponential number of flip encodings constructing G_1 and G_2, we can discover a maximally parsimonious set of flips in $O(N^2)$ time.

Duplication forest:

- Trees explain node duplication and node loss
- Leaves in extant networks, internal nodes in ancestors

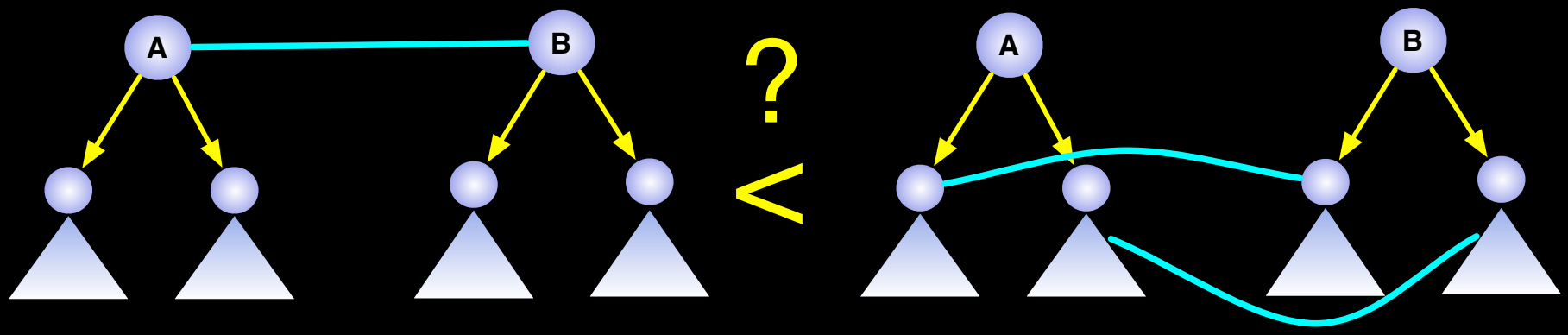
Interaction encoding:

- Non-tree edges represent interactions
- Edge gain/loss affects descendants

Basic idea: Recurse down the tree, finding the minimum cost set of edge flips that construct the extant networks

At each internal node, decide:

Is it better (lower cost) to add an edge here or separately in subtrees?



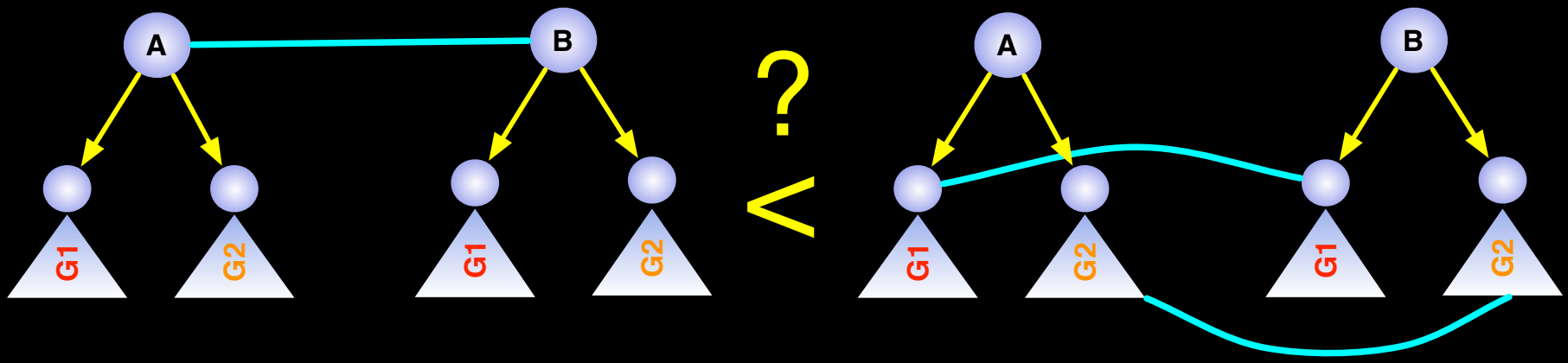
We avoid 2-blocking loops by design

Algorithm recurses into either the left or right subtree; never both simultaneously

Handling Multiple Graphs

To infer the ancestral interactions using data from multiple graphs:

Lower cost to add an interaction in the ancestor or separately in the extant species?



Same as single-graph DP step, except don't consider flips between species

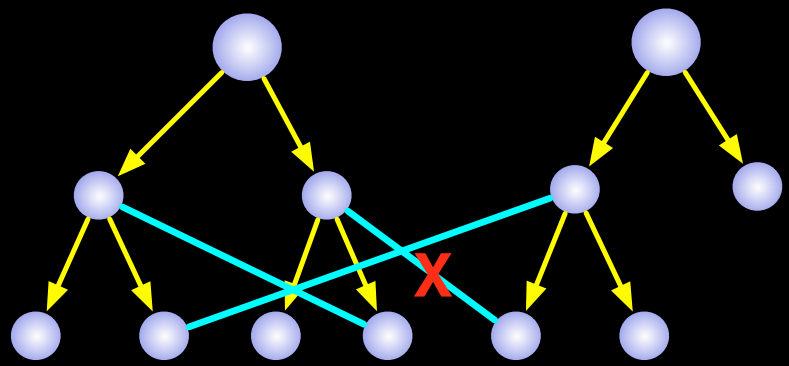
Breaking Blocking Loops

Blocking loops of order ≥ 3 handled post-hoc

If there are no blocking loops, we've found the optimal solution

while any blocking loop ℓ exists:

$e =$ some edge of ℓ
Forbid e
Re-run the dynamic program



Gives us an upper bound on $\Delta(OPT)$

Loop-free solution is at least as costly as initial (loopy) solution

Benefits of Our Approach

- Can encode directed & undirected networks

  PPI and regulatory networks, signaling pathways

- Can encode networks both with and without self-loops
- Does not require branch lengths (total ordering of duplications)
- Can handle asymmetric edge creation and deletion costs

Experimental Setup (Synthetic)

Consider 3 models to generate synthetic regulatory networks

1) Foster, Kauffman, and Socolar 2006:
   - Based on node duplication
   - In & Out edges removed probabilistically after duplication
   - Nodes lost only when they have no incident edges

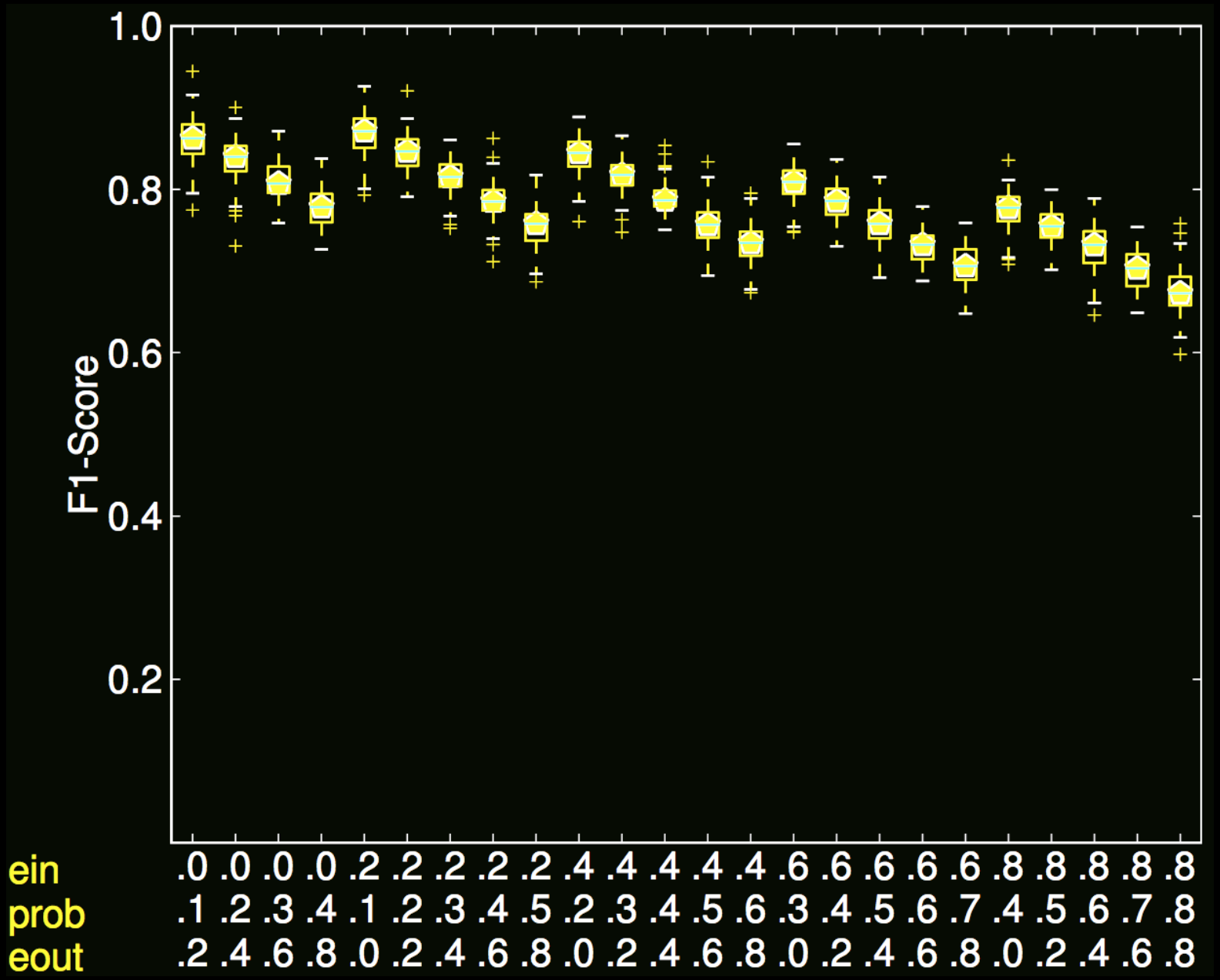
2a) Degree-independent variant

2b) Degree-dependent variant

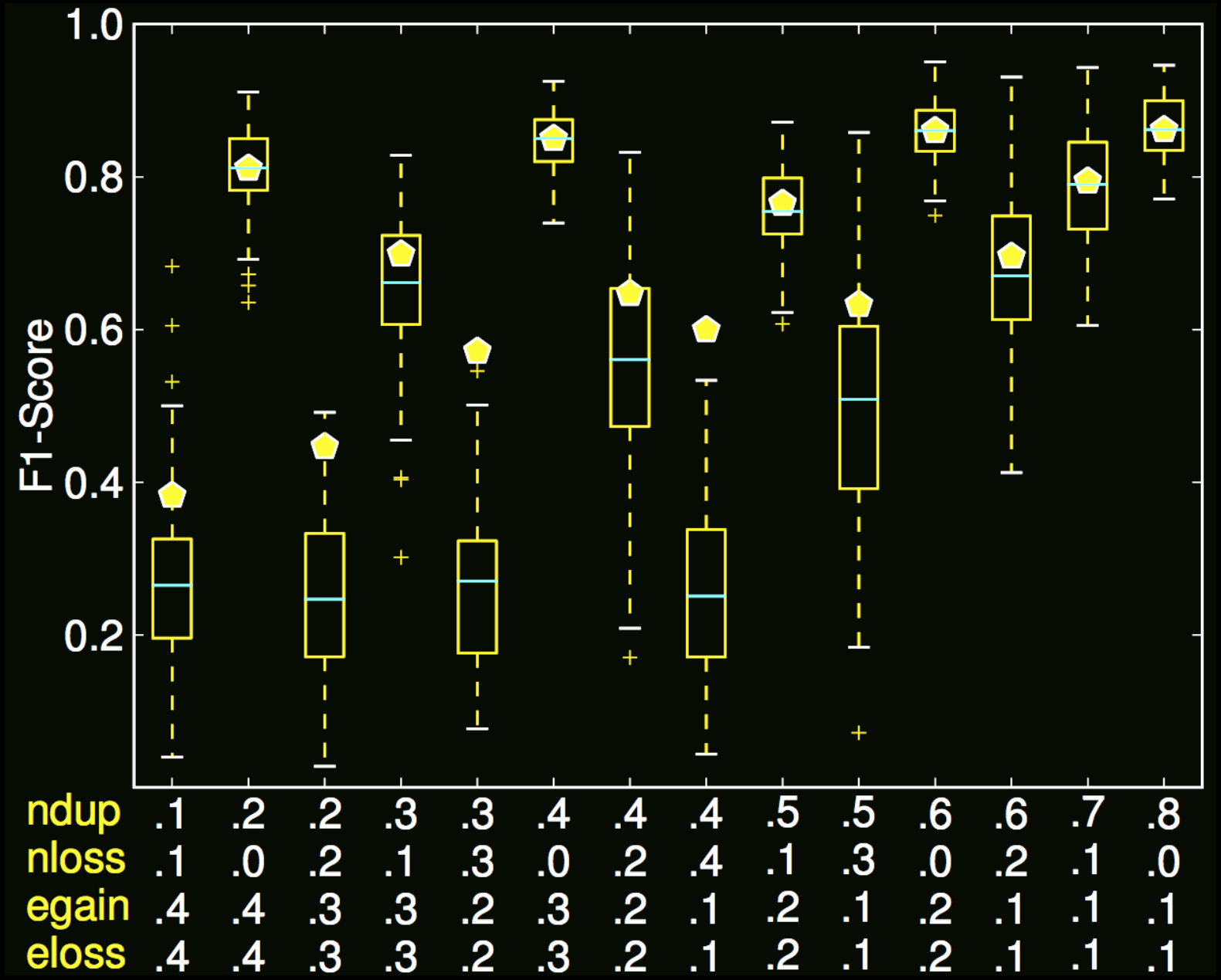
} General model:
- Arbitrary edge gain, loss
- Node duplication
- Arbitrary node loss

Compute F1-Score over 100 trials for each choice of parameters

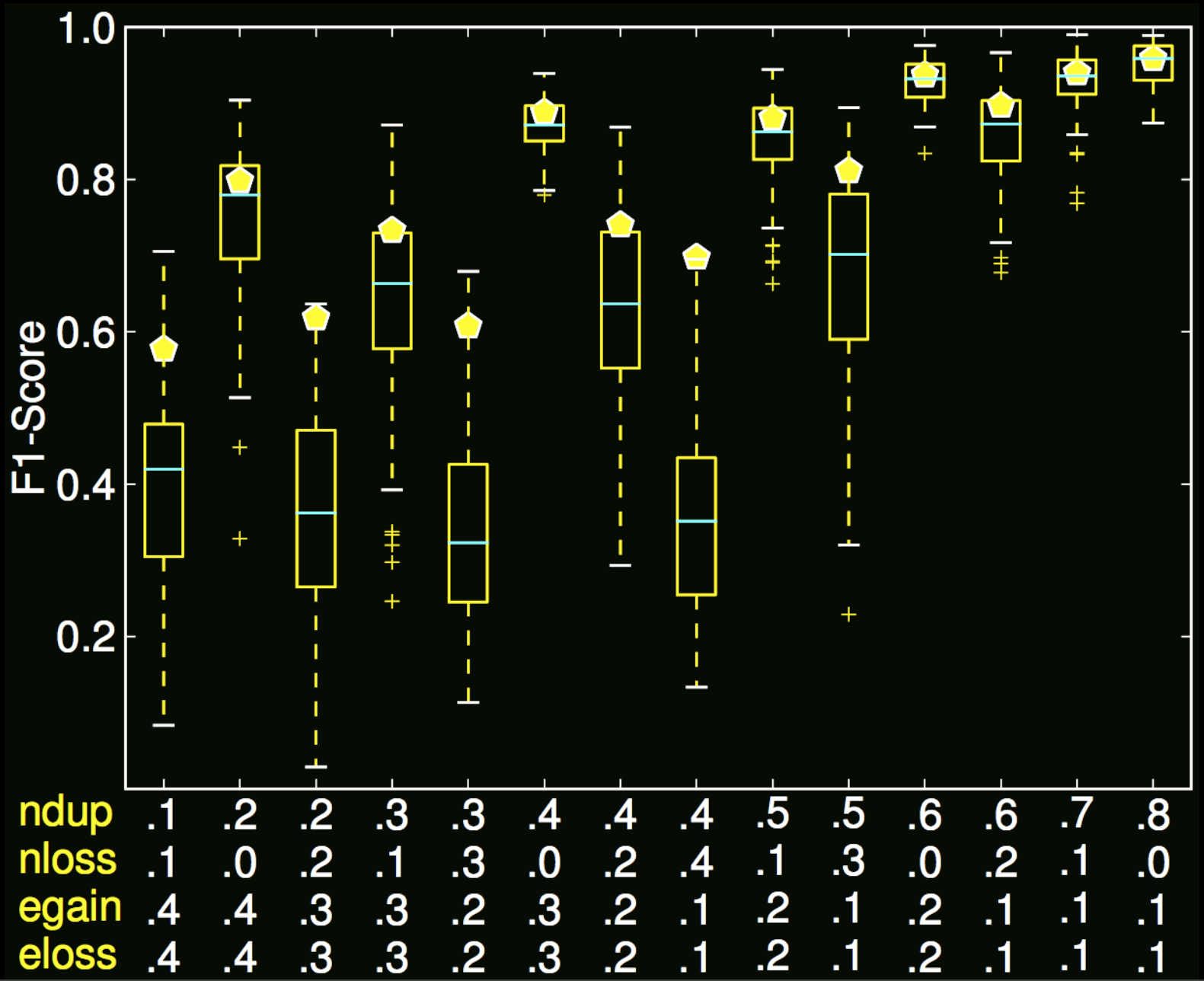
Foster model (1)



Degree-independent model (2a)



Degree-dependent model (2b)



Summary of Performance on Synthetic Data

Performance is generally good

Arbitrary node loss has the largest single effect:

- This effect can be mitigated by considering more extant species

Blocking loops of size ≥ 3 are rare in practice:

- Occurred in $< 2\%$ of all of our test cases
- Even when they occur, often find a loop-free sol. of the same cost

Real bZIP PPI

bZIP PPI analyzed in the work of Pinney et al. (PNAS 2007)

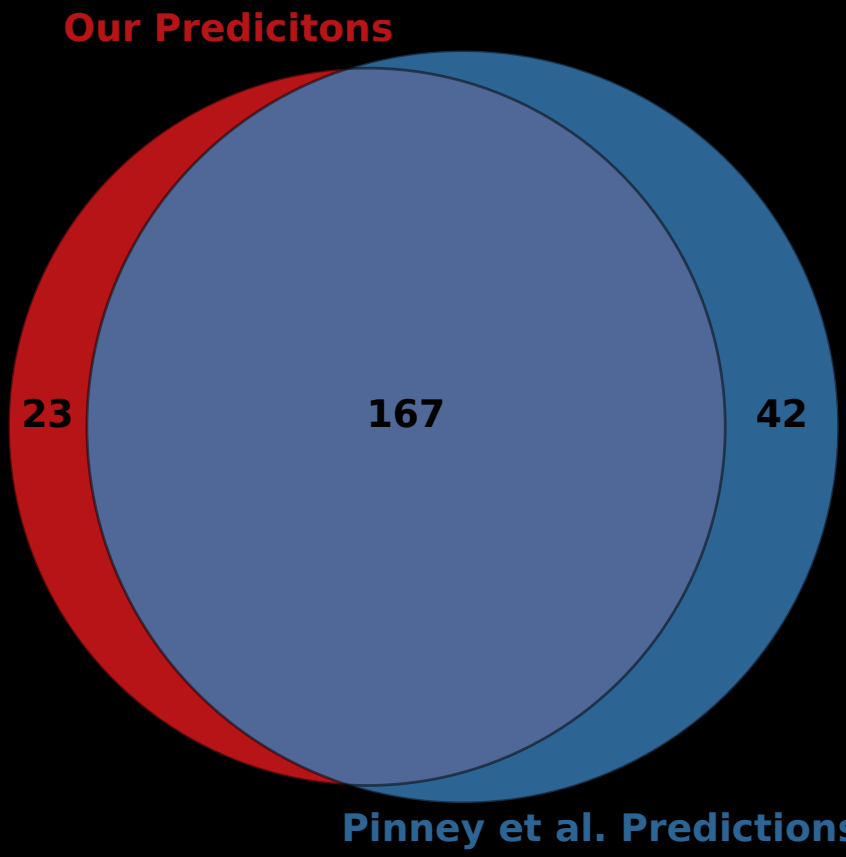
"Ground truth": ancestral interactions predicted using sequence

Reconstruction of ancestral Teleost network:

	Pinney et al. Maximum Likelihood	Our algorithm Parsimony
Precision	0.68	0.78
Recall	0.88	0.90
F1-Score	0.77	0.84

Simple extension of our algorithm to arbitrary # of extant species

Comparison of Inferred Edges



Most predictions are the same

We make fewer total predictions:

- But more of them are correct

Consider a larger space of histories

- Not constrained by edge lengths

Conclusion & Future Work

Parsimony-based reconstruction performs well
    On both real & synthetic data

Dynamic programming solution efficient & accurate
    Doesn't require phylogenetic branch lengths

Future Work :

- Room to improve both sensitivity & specificity
- Study the effect of noise
- Improve uncertain duplication histories (tree inference)
- How many (near) optimal solutions are there, how do they differ?
- Is avoiding general (i.e. $k \geq 3$) blocking-loops $\mathcal{NP}$-hard?

Thanks

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Duplication History Framework