Integer Programming for NP-hard Phylogenetic (and Population- Genetic) Problems

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Phylogeny problems often have data with

> Missing entries
> Homoplasy
> Genotype (conflated) sequences, rather than simpler haplotype sequences

Most of these problems are NP-hard, although some elegant poly-time solutions exist (and are well-known) for special cases.

Question

Can Integer Programming efficiently solve these problems in practice on useful ranges of data? Clearly not genomic or tree-of-life scale.

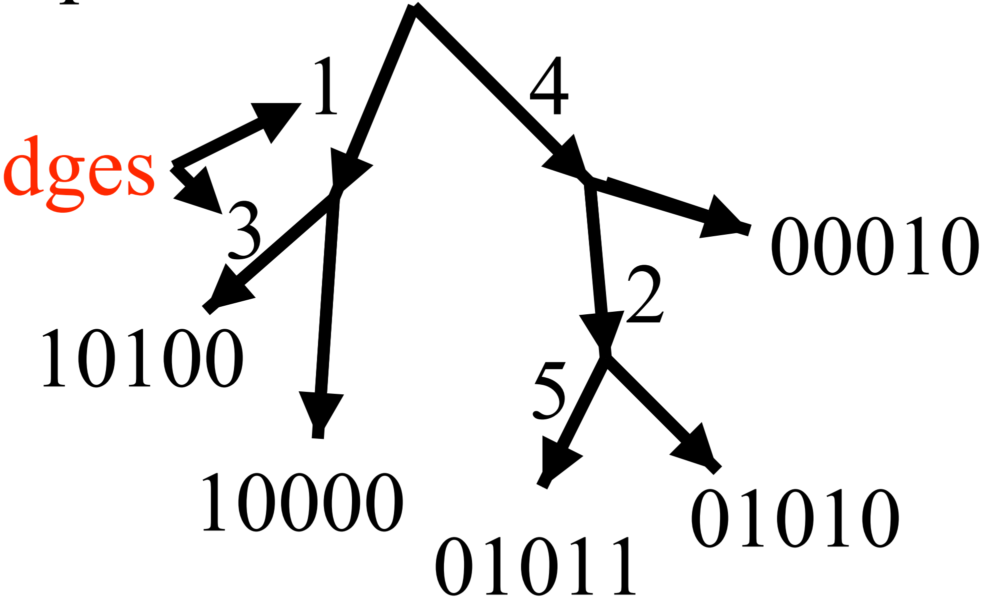
We have recently developed ILPs for over fifteen such problems and intensively studied their performance (speed, size and biological utility). We discuss five related problems in this talk.

Starting Model: Compatibility, Perfect Phylogeny, with binary sequences

Only one mutation per site allowed.

sites 12345

Ancestral sequence 00000



Site mutations on edges

The tree derives the set M:
10100
10000
01011
01010
00010

Extant sequences at the leaves

Everyone here knows

Classic NASC: A set of sequences with no duplicate columns can be generated on a unique perfect phylogeny if and only if no two columns (sites) contain all four binary pairs (gametes):

0,0 and 0,1 and 1,0 and 1,1

This is the 4-Gamete or Compatibility Test

And

The set of splits of a tree uniquely determine the tree.

A pair of sites that has all four binary pairs is called incompatible, otherwise is called compatible.

For M of dimension n by m, the existence of a perfect phylogeny, or the test for pairwise compatibility for M, can be tested in O(nm) time and a tree built in that time, if there is one.

Problem M1: Perfect Phylogeny with Missing Data

Given binary sequences M with some ? entries, change each ? to 0 or 1 in order to minimize the resulting number of incompatible pairs of sites.

Special Case (Existence Problem):

Determine if the ?s can be set to 0, 1so that there are no resulting incompatibilities.

NP-hard in general, but if the root of the required tree is specified, then the problem has an elegent poly-time solution (Pe'er, Sharan, Shamir).

Simple ILP for Problem M1

If cell (i,p) in M has a ?, create a binary variable Y(i,p) indicating whether the value will be set to 0 or to 1.

For each pair of sites p, q that could be made incompatible, let D(p,q) be the set of missing or deficient gametes in site pair p,q, needed to make sites p,q incompatible.

For each gamete a,b in D(p,q), create the binary variable B(p,q,a,b),

and create inequalities to set B(p,q,a,b) to 1 if the Y variables for cells for sites p,q are set so that gamete a,b is created in some row for sites p,q.

Example

p	q
0	0
?	1
1	0
?	?
?	0
0	?

D(p,q) = {1,1; 0,1}

To set the B variables, the ILP will have inequalities
for each a,b in D(p,q), one for each row where a,b could be created
in site pair p,q.

For example, for a,b = 1,1 the ILP has:
Y(2,p) <= B(p,q,1,1)   for row 2
Y(4,p) + Y(4,q) -- B(p,q,1,1) <= 1   for row 4

Example continued

p	q
0	0
?	1
1	0
?	?
?	0
0	?

D(p,q) = {1,1; 0,1}

For a,b = 0,1 the ILP has:

Y(2,p) + B(p,q,0,1) => 1   for row 2
Y(4,q) -- Y(4,p) -- B(p,q,0,1) <= 0   for row 4
Y(6,q) -- B(p,q,0,1) <= 0   for row 6

The ILP also has a variable C(p,q) which is set to 1 if every gamete in D(p,q) is created at site-pair p,q.

In the example:

$$B(p, q, 1, 1) + B(p, q, 0, 1) -- C(p,q) <= 1$$

So, C(p,q) is set to 1 if (but not only if) the Y variables for sites p, q (missing entries in columns p, q) are
set so that sites p and q become incompatible.

If M is an n by m matrix, then we have at most nm Y variables; $2m^2$ B variables; $m^2/2$ C variables; and $O(nm^2)$ inequalities in worst-case.

Finally, we have the objective function:

$$\text{Minimize} \sum_{(p,q) \text{ in } P} C(p, q)$$

Where P is the set of site-pairs that could be made to be incompatible.

Empirically, these ILPs solve very quickly (CPLEX 9) in fractions of seconds, or seconds
even for m = n = 100 and percentage of missing values up to 30%.
Data was generated with recombination and homoplasy by the program MS and modifications of MS.
Details are in COCOON 2007, Gusfield, Frid, Brown

Moreover, the ILP solution imputes the missing data with
2% - 5% error rate and improves as nm increases.

Extensions from Problem M1

> Problem R1. Site-Removal Problem for complete data: Remove the minimum number of sites from the data, so that no incompatibilities remain. This is a common approach to incompatible data. NP-hard problem.

> Problem S1. Site-Removal Problem with missing data: Impute values for the missing entries to minimize the solution to the resulting Site-Removal Problem.

ILP for S1 - a simple extension to the ILP for M1

- For each site i, let D(i) be a variable set to 1 if and only if site i is removed.
- For each site-pair p,q in P, add the inequality D(p) + D(q) -- C(p,q) => 0

to the M1 formulation. If sites p,q are

incompatible (depending on how the missing values are set), then one of them must be removed.

Change the objective function to

Minimize Sum_i D(i)

Extension to non-binary characters

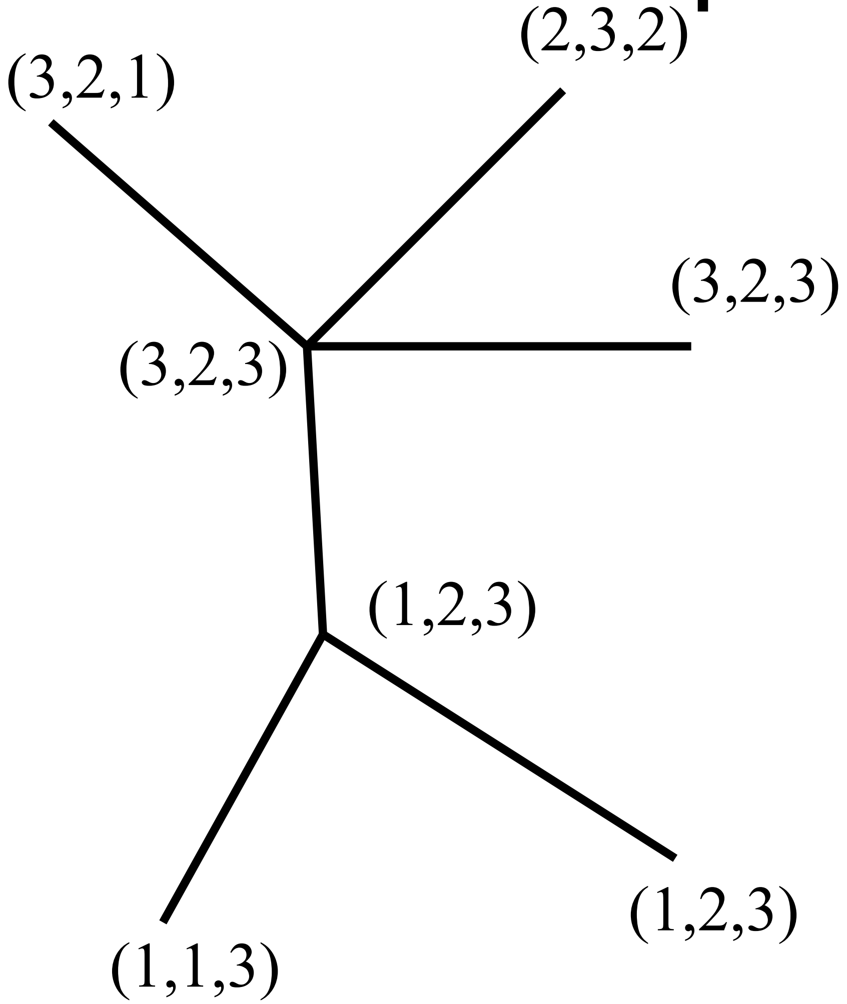
We detail the case of three and four allowed states per character.

What is a Perfect Phylogeny for non-binary characters?

- Input consists of n sequences M with m sites (characters) each, where each site can take one of k values (states).
- In a Perfect Phylogeny T for M, each node of T is labeled with an m-length, k-ary sequence.
- T has n leaves, one for each sequence in M, labeled by that sequence.

- For each character-state pair (C,s), the nodes of T that are labeled with state s for character C, form a connected subtree of T. It follows that the subtrees for any C are node-disjoint

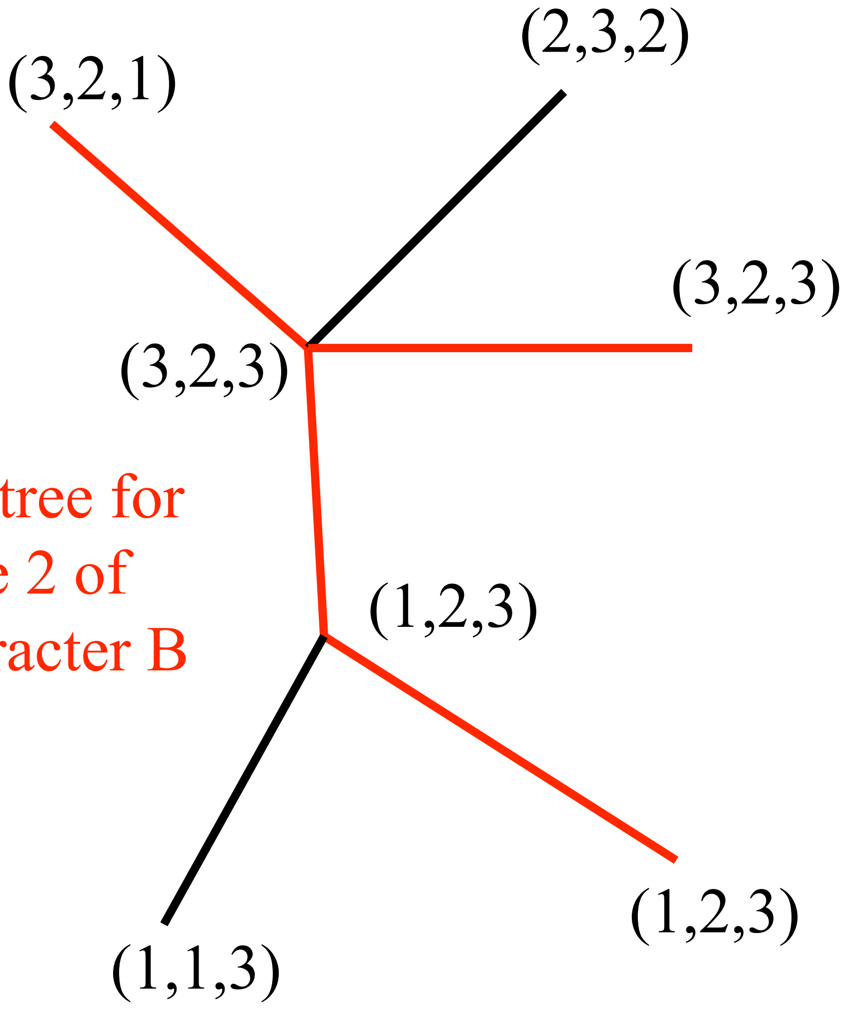
Example: A perfect phylogeny for input M



	A	B	C
1	3	2	1
2	2	3	2
3	3	2	3
4	1	1	3
5	1	2	3

M

n = 5
m = 3
k = 3



The tree for State 2 of Character B

	A	B	C
1	3	2	1
2	2	3	2
3	3	2	3
4	1	1	3
5	1	2	3

M

n = 5
m = 3
k = 3

Three problems

- TR1: Given a ternary (1,2,3) matrix M, Remove the fewest sites (characters) of M so that the resulting matrix has a 3-state perfect phylogeny.
- TS1: Given a ternary matrix M with some ?s, Set each ? to 1,2, or 3 to minimize the solution to Problem TR1.
- Existence Problem: Is there a way to set the ?s so there is a 3-state perfect phylogeny?

Dress-Steel solution for 3-state Perfect phylogeny given complete data (1991)

- Recode each site M(i) of M as three binary sites M'(i,1), M'(i,2), M'(i,3) each indicating the taxa that have state 1, 2, or 3.
- Theorem (DS) There is a 3-state perfect phylogeny for M, if and only if there is a 2-state perfect phylogeny for some subset of M' consisting of exactly two of the columns

  M'(i,1), M'(i,2), M'(i,3), for each column i of M.

Example

M

	A	B	C
1	3	2	1
2	2	3	2
3	3	2	3
4	1	1	3
5	1	2	3

M’

	A,1	A,2	A,3	B,1	B,2	B,3	C,1	C,2	C,3
1	0	0	1	0	1	0	1	0	0
2	0	1	0	0	0	1	0	1	0
3	0	0	1	0	1	0	0	0	1
4	1	0	0	1	0	0	0	0	1
5	1	0	0	0	1	0	0	0	1
	↑	↑		↑		↑	↑	↑	

Compatible subset

ILP for the DS solution

S(i,1), S(i,2), S(i,3) are binary variables indicating which columns of M' associated with column i in M will be selected. Then we need inequalities

S(i,1) + S(i,2) + S(i,3) = 2

S(i,x) + C(i,x; j,y) + S(j,y) <= 2 etc. for x,y = {1,2,3}, and

C(i,x;j,y) is the variable (essentially from the M1 ILP) that is forced to 1 if columns (i,x) and (j,y) in M' are incompatible.

From the DS theorem, the ILP is feasible if and only if there is a 3-state perfect phylogenty for M.

Handling missing values: When there is a ? in cell

(p,q) of M, we use binary variables

Y(p,q,1), Y(p,q,2), Y(p,q,3) to indicate their values in M', and add the equality:

Y(p,q,1) + Y(p,q,2) + Y(p,q,3) = 1

which sets the ? in cell (p,q) of M to either 1,2, or 3.

The resulting ILP is feasible if and only if the ?s in M have been set to allow a 3-state perfect phylogeny.

That ILP solves the Existence Problem for three states per character.

To solve problem TR1: minimize the number of columns of M to remove, so that there is a 3-state solution, use variable R(i) to indicate whether column i of M will be Retained. Then modify the DS ILP:

$S(i,1) + S(i,2) + S(i,3) <= 2$ instead of =
and add $S(i,1) + S(i,2) + S(i,3) – 2R(i) => 0$

so that R(i) can be set to 1 only if two of the three columns M’(i,1), M’(i,2), M’(i,3) have been selected. Finally, use the objective function:

$$\text{Maximize } \sum_{i \text{ in } M} R(i)$$

Probem TS1

To solve Problem TS1, if there is a ? in cell (p,q) of M, we add the equality

Y(p,q,1) + Y(p,q,2) + Y(p,q,3) = 1 to the formulation for TR1.

Empirical Results: The 3-state Existence Problem

	0%	5%	10%	20%	35%	missing values
50 by 25, 3PP exists	0.0098	0.3	0.6	1.16	56.0	seconds
100 by 50 3PP exists	0.03	4.0	6.9	13.9	2492.0	seconds

Times for data where no 3-state Perfect Phylogeny exists were similar, but smaller!

Empirical Results: Problems TR1 and TS1(avg of 100 sets)

	TR1		TS1		
	0%	1%	5%	15%	missing values
30 by 100,	0.065	3.3	13.0	49.7	seconds
r = 1	93.7	93.8	94.12	94.4	# sites remaining

100 by 50		
r = 3	0.17	seconds
	40.18	# sites remaining
100 by 50		
r = 5	0.2558	seconds
	36.68	# of sites remaining

parameter r influences the “closeness” of the data to a tree.

4-state perfect phylogeny

Problem FR1: Given quaternary sequences M, find the fewest number of sites to remove so that the resulting data M’ has a 4-state perfect phylogeny.

Existence Problem: Is there a 4-state perfect phylogeny for M?
We encode the Kannan-Warnow (1991) high-level idea for the existence problem as an ILP: Choose one of five possible tree types for each site and the generic splits that define each tree type, and require that the set of chosen splits be pairwise compatible.

The ILP for Problem FR1 is built on the ILP for the 4-state Existence Problem.

Initial Empirical Results for 4-states

Existence Problem:

30 by 30 0.2 secs for data with a 4-state PP
r = 1 0.49 secs for data with no 4-state PP

50 by 25
r = 3 0.24 secs for data with a 4-state PP
0.27 secs for data with no 4-state PP

Initial Empirical Results for 4-states

Problem FR1:

50 by 25	0.39 secs.
r = 0	25 remaining sites
50 by 25	1.28 secs.
r = 1	23.45 remaining sites
50 by 25	3.16 secs.
r = 3	20.69 remaining sites
100 by 50	70 secs.
r = 5	44 remaining sites

*this would solve faster as an existence problem

Software

Perl script to generate the ILPs (for input to Cplex or other ILP solvers) can be found at:

wwwcsif.cs.ucdavis.edu/~gusfield

The COCOON 2007 paper on the 2-state case is there also.