Dottorato di Ricerca in Informatica - Ciclo XXII
Dipartimento di Informatica, Sistemistica e Comunicazione
Facoltà di Scienze Matematiche, Fisiche e Naturali
Università degli Studi di Milano–Bicocca

Combinatorial Problems in Studies of Genetic Variations: Haplotyping and Transcript Analysis

September 8, 2009

Student: Yuri Pirola
Supervisor: Prof. Paola Bonizzoni
Tutor: Prof. Lucia Pomello

Outline

Aims and Motivations

Studies of genetic variations are one of the most important task in the post-genomic era.

But...

- Lot of data are needed
- Cost/technological reasons limit data availability

Aim

Analysis and design of combinatorial methods that enable large-scale studies of genetic variations.

Original Contributions

Haplotype Inference:

- Exact and approximate algorithms for two haplotyping problems:
  - Pure Parsimony Xor Haplotyping (PPXH)
  - Haplotyping on Pedigrees with Mutations and Recombinations (MEHC)

Transcript Analysis:

- Efficient algorithm which exploits redundancy to perform gene structure prediction

Haplotype Inference

Haplotype Inference Problem

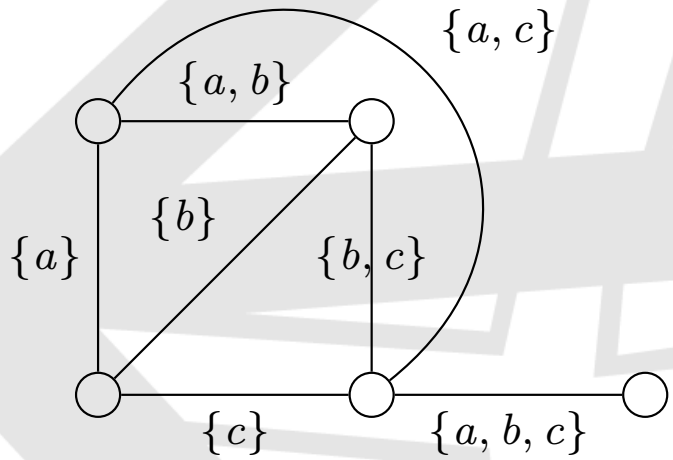
For each individual in a population, distinguish the genome inherited from each parent accordingly to a reference genetic model.

- Well-known problem, studied under different assumptions.
- Pure Parsimony Xor Haplotyping (PPXH)
- Minimum Events Haplotype Configuration (MEHC)

Pure Parsimony Xor Haplotyping

Pure Parsimony Xor Haplotyping

Characterization of solutions as graphs $\longrightarrow$ Xor graph



A Xor-Graph

PPXH - Exact Algorithms

PPXH is *fixed parameter tractable*

- $O(2^{k^2}nm)$ time algorithm
  (parameter k = size of a optimal solution)

Polynomial-time algorithms for specific (and motivated) restrictions:

- PPXH(*,2)
- PPXH(2,*)

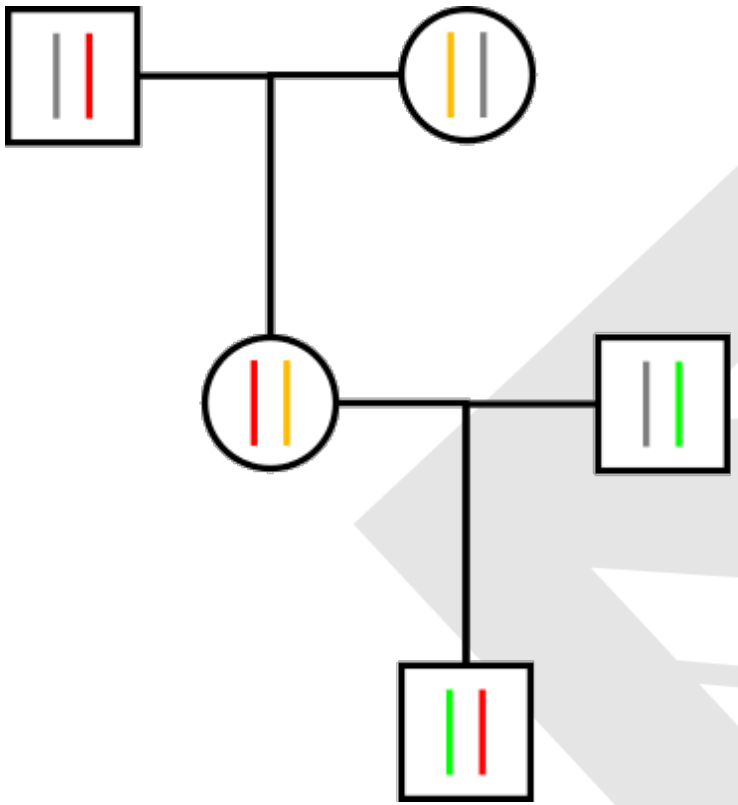
PPXH - Heuristic Algorithm

Heuristic Algorithm:

- Based on Xor-graph reconstruction
- Efficient: $O(\alpha(n, m)n^3m)$ time complexity
- Experimental validation on various kinds of instances
- Experimental observations: performs well
  - approximation factor ≤ 1.57 (often close to 1)
  - time $\leq 1h$ (on big instances)

Haplotyping on Pedigrees

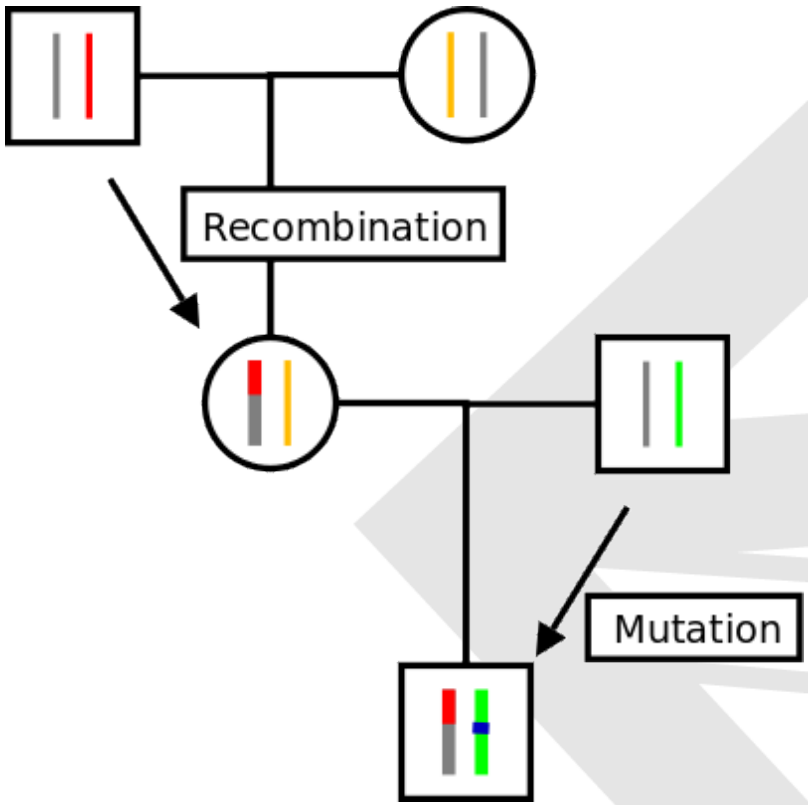
Pedigree $\longrightarrow$ parental relationships



Polynomial if "pure" Mendelian Inheritance

Haplotyping on Pedigrees

Pedigree $\longrightarrow$ parental relationships



Polynomial if "pure" Mendelian Inheritance

Intractable if we admit genetic variation events

Minimum Events Haplotype Configuration

Mutations \ Recombinations	NO	YES
NO	Polynomial	*APX-hard* Randomized algorithm ILP formulation
YES	*NP-hard* Exponential algorithm	

Minimum Events Haplotype Configuration

Mutations \ Recombinations	NO	YES
NO	Polynomial	*APX-hard* Randomized algorithm ILP formulation
YES	*NP-hard* Exponential algorithm APX-hardness	NP-hardness Heuristic

Original contributions

MEHC - Heuristic Algorithm

Minimum Events Haplotype Configuration (MEHC):

- connected (via L-reduction) to a well-known Information Theory problem (Decoding of Linear Codes)

Heuristic Algorithm (based on the L-reduction):

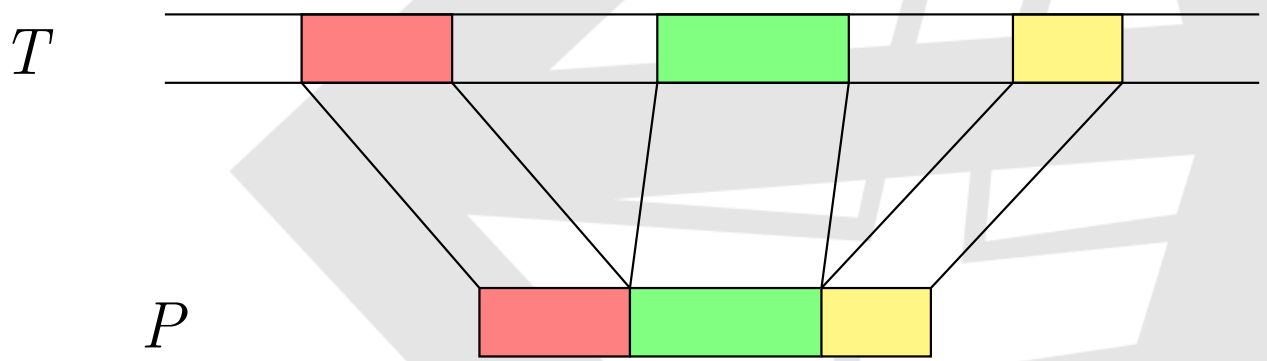
- Efficient: $O(n^3m) + O(n^3m^3 \cdot k)$ time complexity
- Experimentally validated: extremely good performances
  - 99.1% success rate (mutations and recombinations)
  - 100% success rate (only mutations on a real pedigree)
  - 99.8% success rate (only recombinations on a real ped.)
  - time per instance ≤ 16m

Transcript Sequence Factorization

Sequence Factorization Problem

Given two sequences P and T, partition P into a list of factors such that they occur in T in the same order.

Example:



Different factorizations can exist!

Sequence Factorization Problem

Design of an algorithm to find all the "maximal" factorizations of a pair of sequences

- efficient (it uses suffix trees!)
- compact representation of the set of factorizations

How to choose the "right" factorization?

- Idea: exploiting the redundancy of the libraries of transcripts

  $\longrightarrow$ *definition of a new optimization problem!*

Factorization Agreement Problem

Factorization Agreement Problem

Given all the factorizations of a set S of sequences w.r.t. a sequence T, choose the minimum cardinality set F of factors of T such that each sequence of S can be factorized by using only factors that belong to F.

Results:

- NP-hard (by reduction from MinSetCover)
- Size-reduction algorithm + enumeration
  - performs well on some significant genes

Conclusions

Haplotype Inference:

- haplotyping under two different models, PPXH and MEHC
- coping computational intractability using different techniques
  - restrictions, FPT, heuristics, ...

Transcript Analysis:

- algorithm to find alternative factorizations
- gene structure prediction via factorization agreement

Publications

Bonizzoni, Della Vedova, Dondi, **Pirola**, and Rizzi.
"Pure Parsimony Xor Haplotyping".
In *Proceedings ISBRA 2009*, 186–197, 2009.

(An extended version has been submitted to *IEEE/ACM Transactions on Computational Biology and Bioinformatics*.)

Bonizzoni, Della Vedova, Dondi, **Pirola**, and Rizzi.
"Minimum Factorization Agreement of Spliced ESTs".
In *Proceedings WABI 2009*, to appear, 2009.

The work about the *Minimum Events Haplotype Configuration* problem has been carried out while I was a visiting student at *University of California, Riverside* under the supervision of Prof. Tao Jiang (feb–jul 2009).
A manuscript is in preparation.