SNP

SINGLE-NUCLEOTIDE POLYMORPHISM - SITE IN HUMAN GENOME WHERE TWO NUCLEOTIDES COMMONLY OCCUR

HAPLOTYPE SPECIFIES NUCLEOTIDES AT n SELECTED POLYMORPHIC SITES ON A CHROMOSOME. THE PATERNAL AND MATERNAL CHROMOSOMES EACH SPECIFY A HAPLOTYPE

GENOTYPE SPECIFIES PAIR OF NUCLEOTIDES AT A SITE, BUT NOT THEIR ASSORTMENT BETWEEN HAPLOTYPES

HAPLOTYPES

A C G & T
T C C G C

GENOTYPE

{A/T} C {C/G} G {C/T}

PHASE PROBLEM

GIVEN THE GENOTYPES OF A POPULATION OF INDIVIDUALS, COMPUTE THEIR HAPLOTYPES

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BASED ON OBSERVATION THAT GENOMIC DNA CAN BE PARTITIONED INTO LONG BLOCKS WHERE RECOMBINATION HAS BEEN RARE AND THE NUMBER OF DISTINCT HAPLOTYPES IS SMALL.

ASSUME THAT, WITHIN A BLOCK, HAPLOTYPES ARE GENERATED BY A PERFECT PHYLOGENY

HAP ESKIN, HALPERIN

MATHEMATICAL MODEL

- m SITES
- AT EACH SITE, THE TWO NUCLEOTIDES DENOTED BY 0 AND 1

HAPLOTYPE $h \in \{0,1\}^m$

GENOTYPE $g \in \{0,1,2\}^m$

2 MEANS THAT BOTH NUCLEOTIDES OCCUR

THE PAIR $(h^{(1)}, h^{(2)})$ OF HAPLOTYPES IS CONSISTENT WITH GENOTYPE g IF $\forall j$

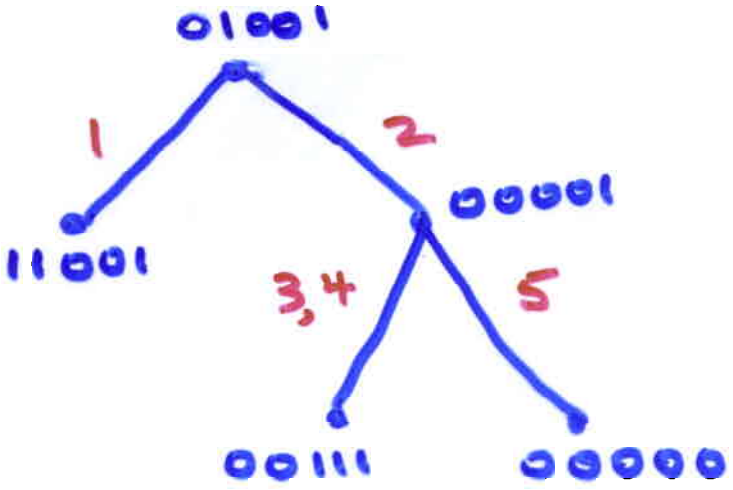
$$g_j = 0 \Rightarrow h_j^{(1)} = h_j^{(2)} = 0$$

$$g_j = 1 \Rightarrow h_j^{(1)} = h_j^{(2)} = 1$$

$$g_j = 2 \Rightarrow h_j^{(1)} \neq h_j^{(2)}$$

PERFECT PHYLOGENY

NO SITE HAS MUTATED MORE THAN ONCE



GUSFIELD POSTULATES THAT, WITHIN EACH BLOCK, THE HAPLOTYPES HAVE EVOLVED WITHOUT RECOMBINATION ACCORDING TO A PERFECT PHYLOGENY

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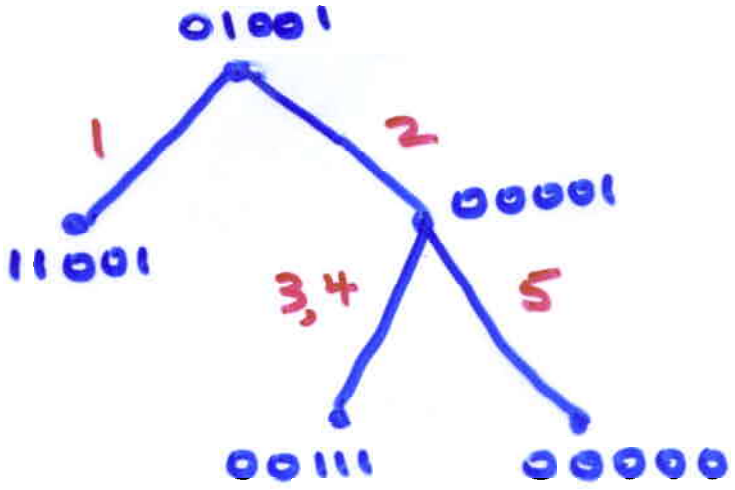

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$n \times m$ HAPLOTYPE MATRIX H

$H = (h_{ij})$ $h_{ij} \in \{0,1\}$

ROW = HAPLOTYPE

- H IS REALIZABLE IF ITS ROWS BELONG TO A PERFECT PHYLOGENY

DUO 2×2 SUBMATRIX

e.g. $\begin{matrix} & s & t \\ i & 0 & 1 \end{matrix}$

H IS REALIZABLE IFF, IN EACH PAIR OF COLUMNS, AT MOST THREE DISTINCT DUOS OCCUR

(BUNEMAN)

$n \times m$ GENOTYPE MATRIX G

$G = (g_{ij})$ $\quad g_{ij} \in \{0,1,2\}$

ROW = GENOTYPE

G IS REALIZABLE IF EACH GENOTYPE CAN BE REPLACED BY A CONSISTENT PAIR OF HAPLOTYPES SO THAT THE RESULTING HAPLOTYPE MATRIX IS REALIZABLE

G → H

$$\begin{bmatrix} 2000 \\ 2202 \\ 2220 \\ 0122 \end{bmatrix}$$

$$\begin{bmatrix} 0000 \\ 1000 \\ 1000 \\ 0101 \\ 1000 \\ 0110 \\ 0101 \\ 0110 \end{bmatrix}$$

GUSFIELD (2002) SHOWED THAT REALIZABILITY OF G CAN BE TESTED IN SLIGHTLY SUPERLINEAR TIME BY REDUCTION TO TUTTE'S TREE REALIZATION PROBLEM: GIVEN A COLLECTION $\{E_k\}$ OF SUBSETS OF A FINITE SET E, IS THERE A TREE WITH EDGE SET E IN WHICH EACH E_k IS THE EDGE SET OF A PATH?

PRACTICAL $O(m^2n)$ ALGOR'S

BAFNA, GUSFIELD, LANCIA, YOOSEPH JCB 2003

ESKIN, HALPERIN, KARP RECOMB 2003

SIMPLE GENOTYPE REALIZATION ALGORITHM

$G \rightarrow H$

DUOS IN G INDUCE DUOS IN H

[0,2] INDUCES [0,1]

[0,2] " [0,0], [0,1]

[2,1] " [0,1], [1,1]

[2,2] CAN BE RESOLVED EITHER EQUALLY [0,1], [1,0] OR UNEQUALLY [0,0], [1,1]

IN A GIVEN PAIR j, k OF COLUMNS ALL OCCURRENCES OF [2,2] MUST BE RESOLVED THE SAME WAY

$$L(j,k) = \begin{cases} 0 & \text{IF } [2,2] \text{ DUOS RESOLVED EQUALLY} \\ 1 & \text{IF RESOLVED UNEQUALLY} \end{cases}$$

CONSTRAINTS

- IF $\overset{j\ k}{[0,1]}$ AND $\overset{j\ k}{[1,0]}$ ARE INDUCED THEN $L(j,k) = 1$
- IF $\overset{j\ k}{[0\ 0]}$ AND $\overset{j\ k}{[1\ 1]}$ ARE INDUCED THEN $L(j,k) = 0$

IF SOME GENOTYPE CONTAINS 2's IN COL's j, k, l THEN

- $L(j,k) + L(j,l) + L(k,l) \equiv 0 \mod 2$

REALIZABILITY CAN BE TESTED BY SOLVING LINEAR EQUATIONS OVER GF[2]

PARTIAL HAPLOTYPE MATRIX

$\hat{H} = (\hat{h}_{ij})$

$\hat{h}_{ij} \in \{0, 1, x\}$

x INDICATES MISSING DATA

$\hat{H}$ IS REALIZABLE IF ONE CAN OBTAIN A REALIZABLE HAPLOTYPE MATRIX H BY REPLACING EACH x IN $\hat{H}$ BY 0 OR 1

- REALIZABILITY OF $\hat{H}$ IS NP-COMPLETE, BUT DECIDABLE IN LINEAR TIME IF ONE ROW OF H IS GIVEN

PE'ER, PUPKO, SHAMIR, SHARAN
SICOMP (TO APPEAR)