HapCUT: An efficient and accurate algorithm for Haplotype Assembly

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Genetic variation and disease association

- Different human individuals have small variation in their DNA (genetic variance).
- Small genetic variation often have important phenotypic consequences.

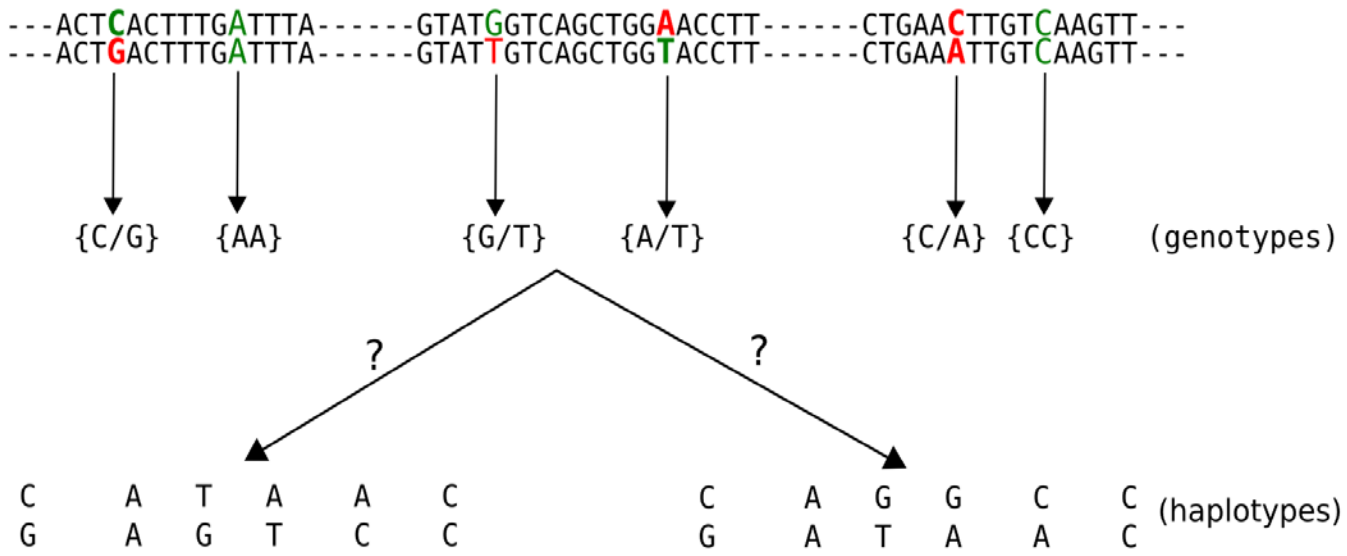
- Therefore variants that are in common in populations are being genotyped and correlated with phenotypes (diseases).

Haplotypes and Disease Association

G	–	T	-	G	*Dis*.
G	–	T	-	G	*Dis*.
G	–	A	-	G	*Nor*.
C	–	A	-	A	*Nor*.
C	–	A	-	A	*Nor*.
C	–	A	-	G	*Nor*.

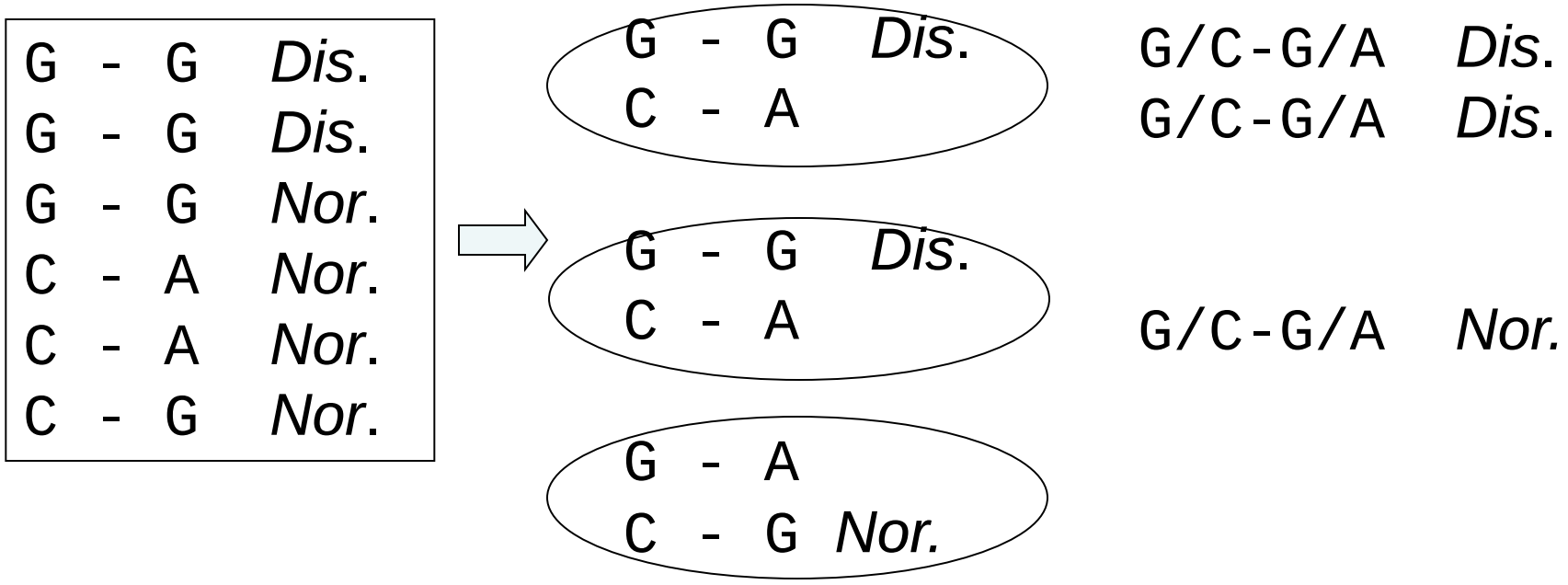
- A haplotype refers to the combination of allelic values on a single chromosome
- Without the causal SNP (A ->T), the haplotype G-G correlates with occurrence of disease, while other haplotypes do not

Humans are diploid



- Humans have two copies of each chromosome
  - Inherited from mother and father
- Genotyping technologies do not maintain the phase

Genotype disease association



- Diploidy and genotyping reduce the power of association!

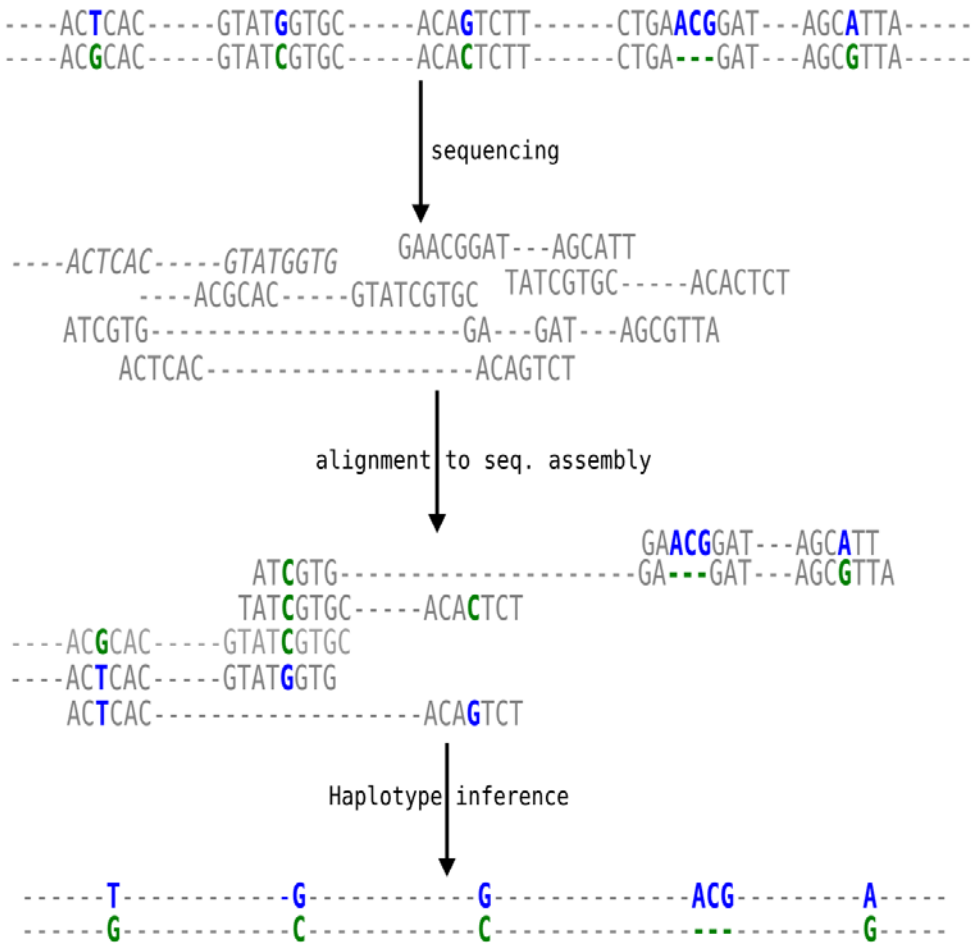
Haplotypes from Genotypes

- The goal of haplotype phasing is to reconstruct the haplotypes from the genotypes
- Haplotypes reconstructed from population genotype data by using correlation between alleles in LD blocks
- Accuracy of haplotypes limited by length of LD blocks (~ 20-50 kb)
- Family genotype data can be used to obtain reliable haplotypes

Reconstucting Haplotypes from sequencing data

- Reads that cover multiple variant sites provide local haplotype information

- Haplotype assembly: use overlap between reads to infer two haplotypes for an individual



Haplotype assembly: Formulation

```
A G A G C T A G C A T G A
C T T T T G G T T C G C G

A G A G - - - - - - - - -
C T T - - - - - - - - - -
- - A G T - - - - - - - -
- - A - - T
- - - G - - - - - - G G -
- - - T C - - - - - - - -
- - - - - T A G - - - - -
- - - - - - A T - A T - -
- - - - - - - G C A - - -
- - - - - - - - - A T G -
- - - - - - - - - - T G A
- - - - - - - - T - - - G
```

- The fragments are aligned to the unphased reference
- Uninformative fragments and columns are removed

Haplotype assembly: Formulation

```
A G A G C T A G C A T G A
C T T T T G G T T C G C G
0 0 0 0 - - - - - - - - -
1 1 1 - - - - - - - - - -
- - 0 0 1 - - - - - - - -
- - 0 - - 0
- - - 0 - - - - - - 1 0 -
- - - 1 0 - - - - - - - -
- - - - - 0 0 0 - - - - -
- - - - - - 0 1 - 0 0 - -
- - - - - - - 0 0 0 - - -
- - - - - - - - - 0 0 0 -
- - - - - - - - - - 0 0 0
- - - - - - - - 1 - - - 1
```

- The fragments are aligned to the unphased reference
- Uninformative fragments and columns are removed
- Relabel the two alleles using 0/1

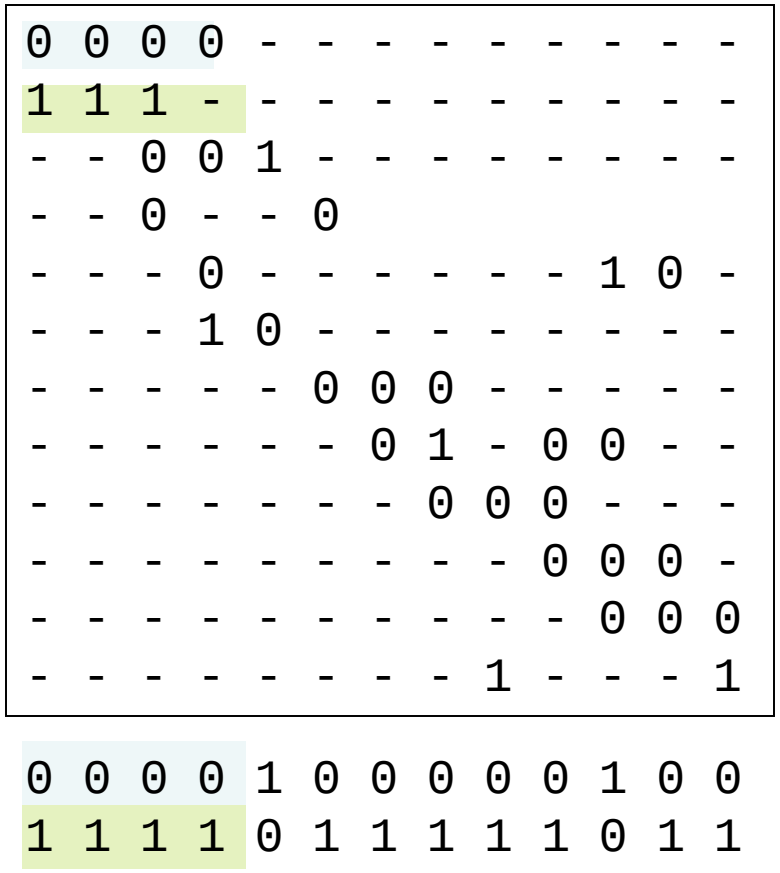
Haplotype assembly: Formulation

```
A G A G C T A G C A T G A
C T T T T G G T T C G C G

0 0 0 0 - - - - - - - - -
1 1 1 - - - - - - - - - -
- - 0 0 1 - - - - - - - -
- - 0 - - 0
- - - 0 - - - - - - 1 0 -
- - - 1 0 - - - - - - - -
- - - - - 0 0 0 - - - - -
- - - - - - 0 1 - 0 0 - -
- - - - - - - 0 0 0 - - -
- - - - - - - - - 0 0 0 -
- - - - - - - - - - 0 0 0
- - - - - - - - 1 - - - 1

0 0 0 0 1 0 0 0 0 0 1 0 0
1 1 1 1 0 1 1 1 1 1 0 1 1
```

- The fragments are aligned to the unphased reference
- Uninformative fragments and columns are removed
- Relabel the two alleles using 0/1
- Goal: Reconstruct the binary string, and its complement, given substrings

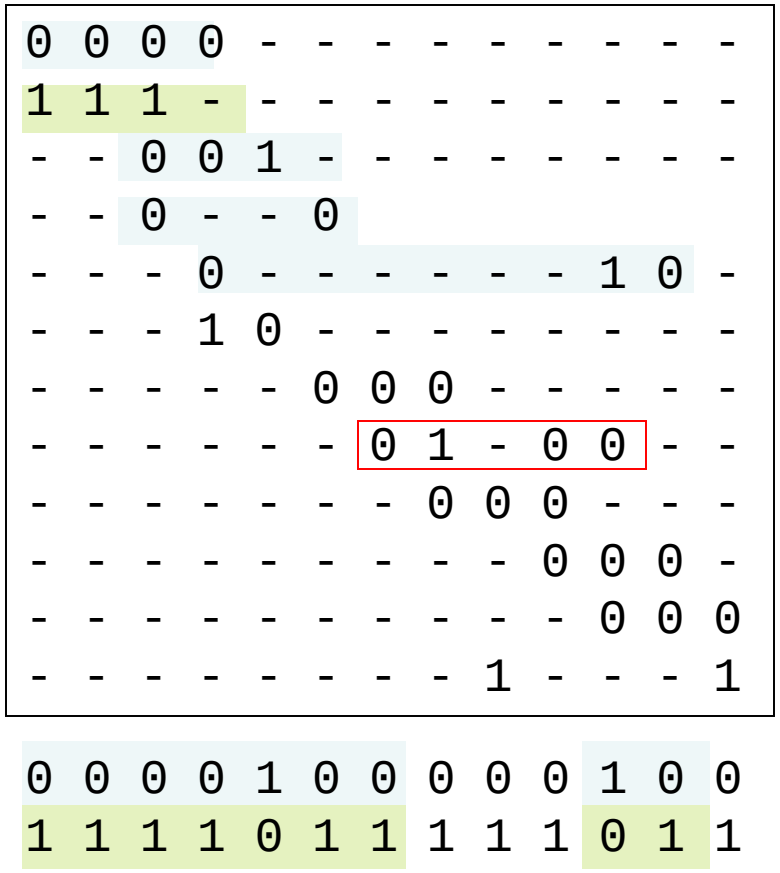
A simple greedy approach

- Greedily select a fragment that extends the current haplotype



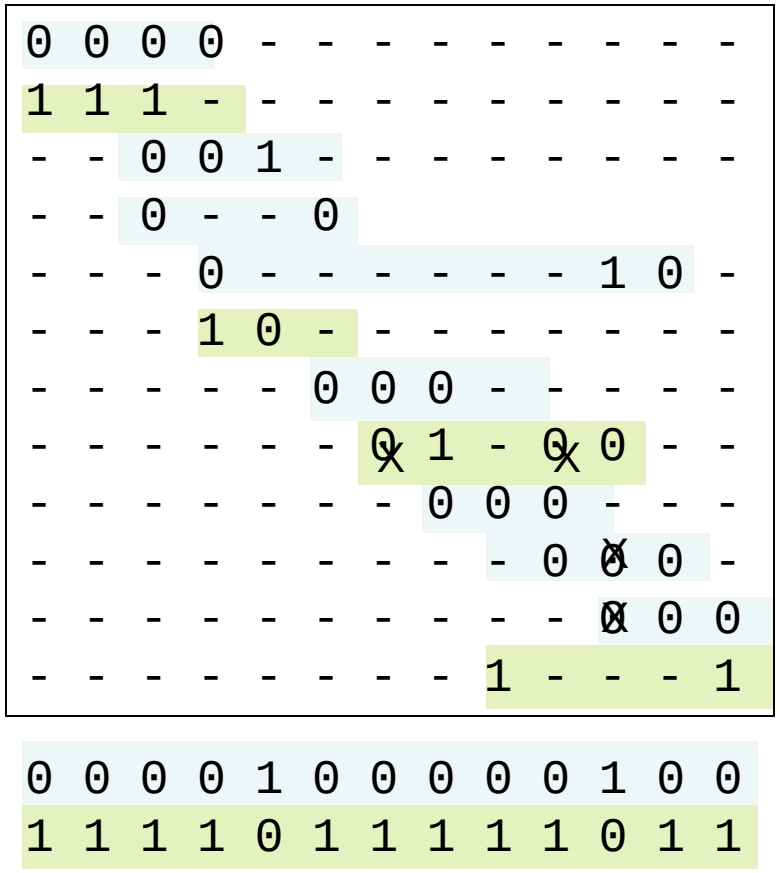
A simple greedy approach

- Some fragments will not match without error
- These are ‘assigned & corrected’ greedily



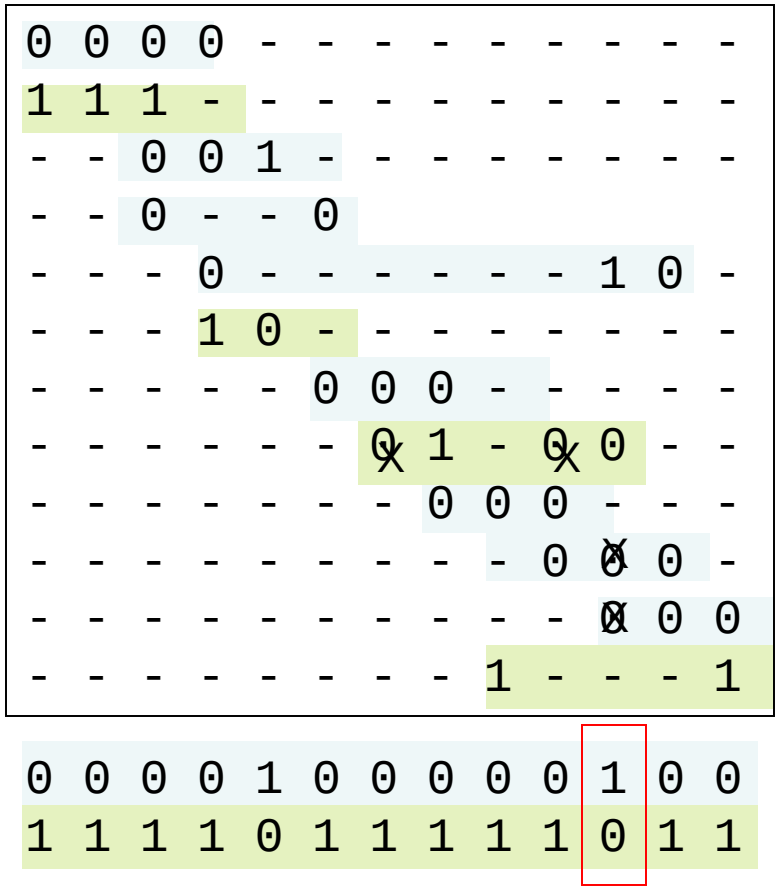
Greedy haplotype assembly

- Minimum Error Correction (MEC): minimum number of variant calls that need to be flipped so that every fragment matches one of the two haplotypes
- MEC is NP-hard



Modifying the haplotypes

- The Greedy approach often leads to suboptimal solutions
- A local flipping of the current haplotype might improve the MEC



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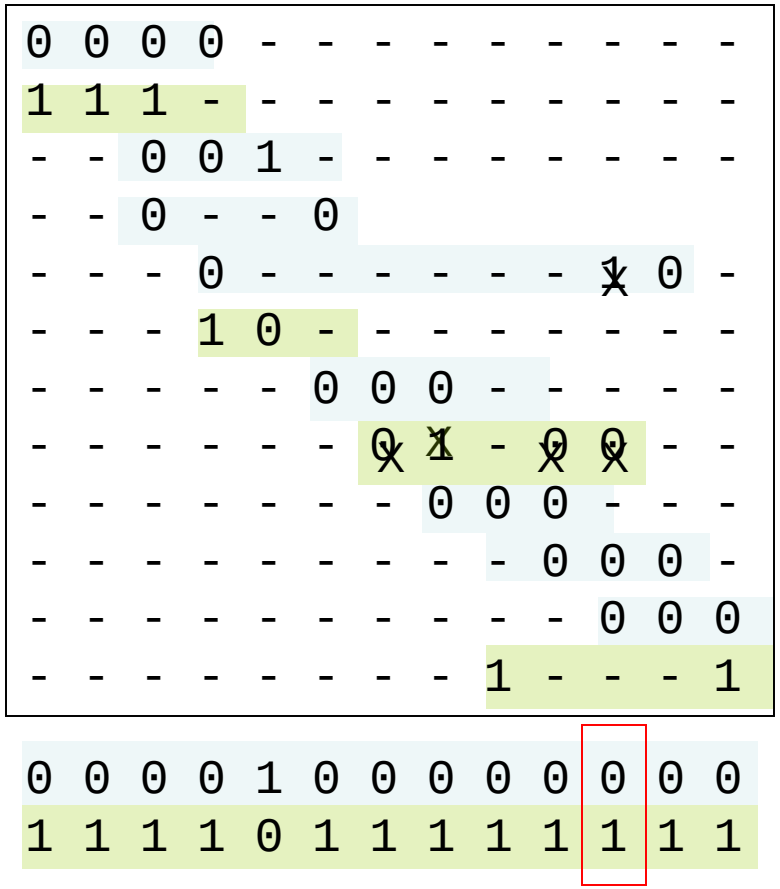
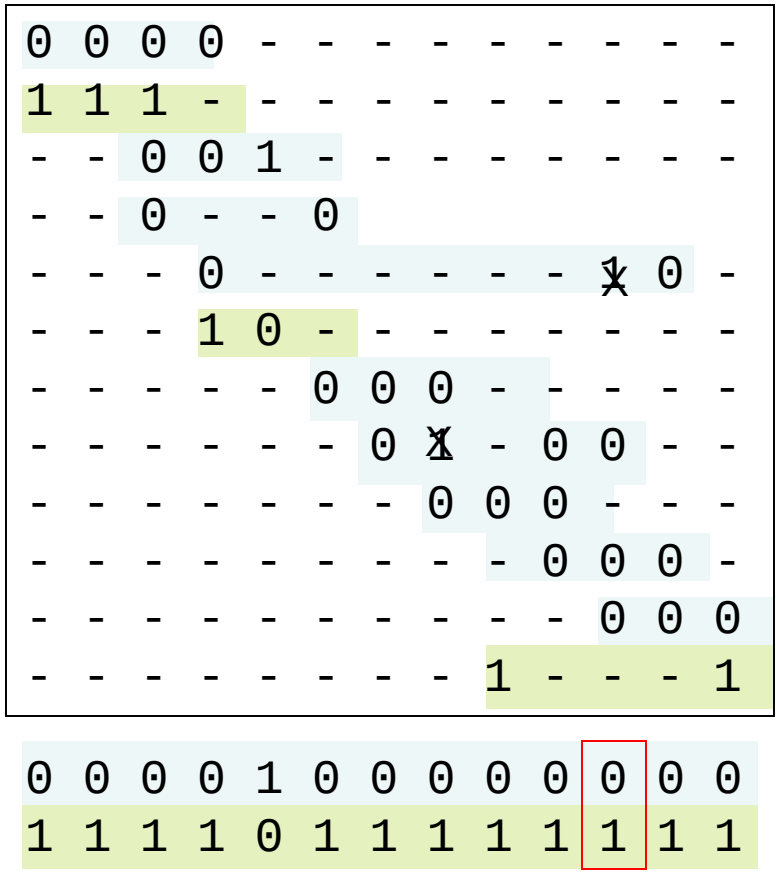


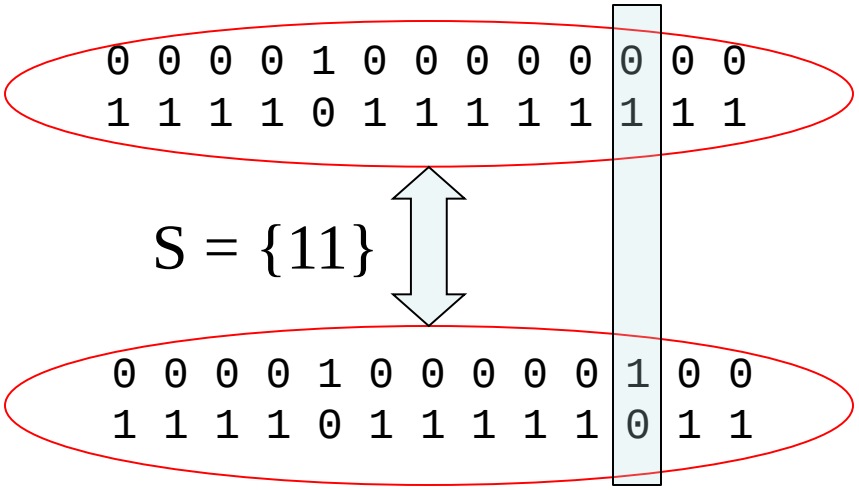
Haplotype to Haplotype

- The haplotype change also involves a reassignment of fragments
- The MEC error reduces to 2
- This suggests a generic strategy
- Start with a haplotype, and move to a new one if it can improve the MEC



Haplotype to Haplotype

- A simple neighborhood is defined by flipping one column at a time (Ex: col. 11)

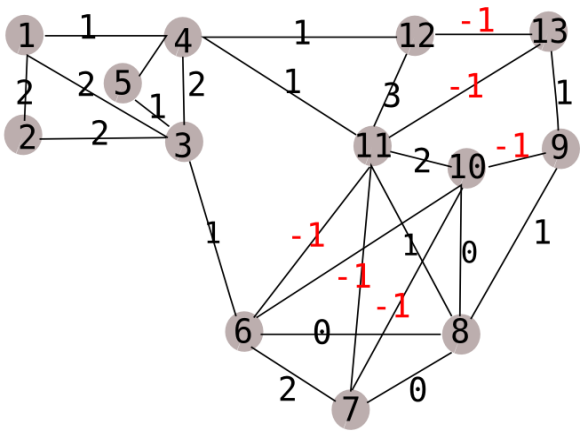


- It is difficult to get out of local minima using single flips
- The “right” move cannot be chosen independently of the fragment matrix and the current solution
- We use the graph structure of the fragment matrix to determine the transitions

Read-haplotype consistency graph

1	2	3	4	5	6	7	8	9	10	11	12	13
A/C	G/T	A/T	G/T	C/T	T/G	A/G	G/T	C/T	A/C	T/G	G/C	A/G
0	0	0	0	-	-	-	-	-	-	-	-	-
1	1	1	-	-	-	-	-	-	-	-	-	-
-	-	0	0	1	-	-	-	-	-	-	-	-
-	-	0	-	-	0	-	-	-	-	-	-	-
-	-	-	0	-	-	-	-	-	-	1	1	-
-	-	-	1	0	-	-	-	-	-	-	-	-
-	-	-	-	-	0	0	0	-	-	-	-	-
-	-	-	-	-	0	0	1	-	0	0	-	-
-	-	-	-	-	-	-	0	0	0	-	-	-
-	-	-	-	-	-	-	-	-	0	0	0	
-	-	-	-	-	-	-	-	-	-	0	0	0
-	-	-	-	-	-	-	-	1	-	-	-	1

0	0	0	0	1	0	0	0	0	1	1	1	0	H
1	1	1	1	0	1	1	1	1	0	0	0	1	

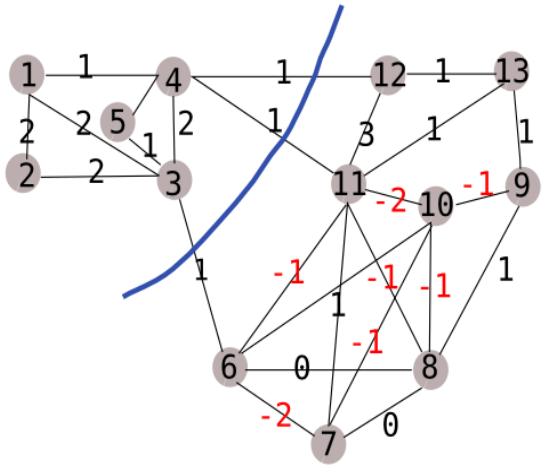


- Each column is a node
- (x,y) is an edge if there is a fragment ‘touching’ columns x and y
- w(i,j) = # fragments matching 'phase' of H - # fragments mismatching 'phase' of H

Cuts

1	2	3	4	5	6	7	8	9	10	11	12	13
A/C	G/T	A/T	G/T	C/T	T/G	A/G	G/T	C/T	A/C	T/G	G/C	A/G
0	0	0	0	-	-	-	-	-	-	-	-	-
1	1	1	-	-	-	-	-	-	-	-	-	-
-	-	0	0	1	-	-	-	-	-	-	-	-
-	-	0	-	-	0	-	-	-	-	-	-	-
-	-	-	0	-	-	-	-	-	-	1	1	-
-	-	-	1	0	-	-	-	-	-	-	-	-
-	-	-	-	-	0	0	0	-	-	-	-	-
-	-	-	-	-	0	0	1	-	0	0	-	-
-	-	-	-	-	-	-	0	0	0	-	-	-
-	-	-	-	-	-	-	-	-	0	0	0	
-	-	-	-	-	-	-	-	-	-	0	0	0
-	-	-	-	-	-	-	-	1	-	-	-	1

0	0	0	0	1	0	1	1	1	0	1	1	1	H
1	1	1	1	0	1	0	0	0	1	0	0	0	

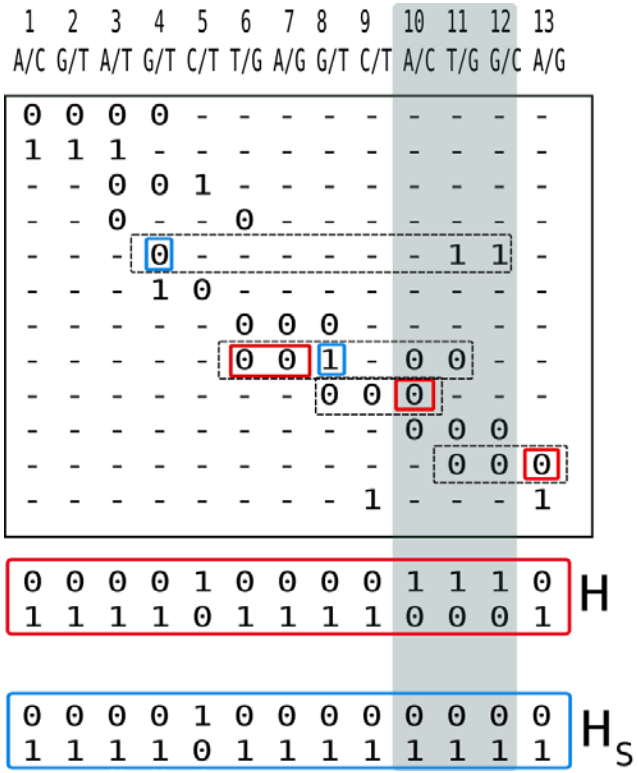


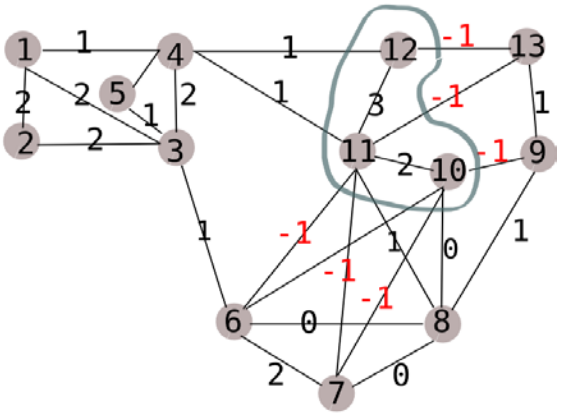
S = { 1,2,3,4,5}

W(S) = 1 + 1 + 1 = 3

- A Cut is a bipartition of the vertices

Negative weighted cuts are ‘good’





- If fragments 'leaving' S are inconsistent with H, the cut S has negative weight
- Such cuts correspond to transitions that reduce the MEC score

A combinatorial scheme

Algorithm HapCUT:

Initialization: Choose an initial haplotype configuration H^1 arbitrarily.

Iteration: For $t = 1, 2, \ldots$

1. Construct the read-haplotype consistency graph $G(H^t)$
2. Compute a cut S in $G(H^t)$ such that $W(S) < 0$
3. If $\text{MEC}(H^t_S) \leq \text{MEC}(H^t)$, $H^{t+1} = H^t_S$
4. Else $H^{t+1} = H^t$

Final: Return H^t

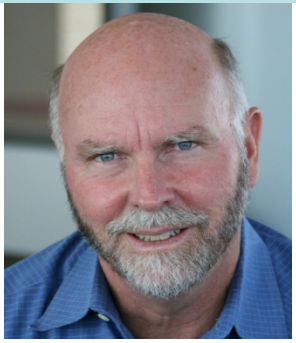
- Cuts computed using a greedy max-cut heuristic
- Stop if no improvement in MEC score for 10 iterations

HapCUT versus sampling

- The HapCUT algorithm uses cut computations in the read-haplotype consistency graph to 'greedily' move towards haplotypes with low MEC
- It can be modified to sample from the haplotype space, instead of searching for haplotypes with lowest MEC

  HASH - “An MCMC algorithm for haplotype assembly from whole-genome sequence data” (Bansal et al. Genome Research, Aug. 2008)

Haplotype assembly for HuRef



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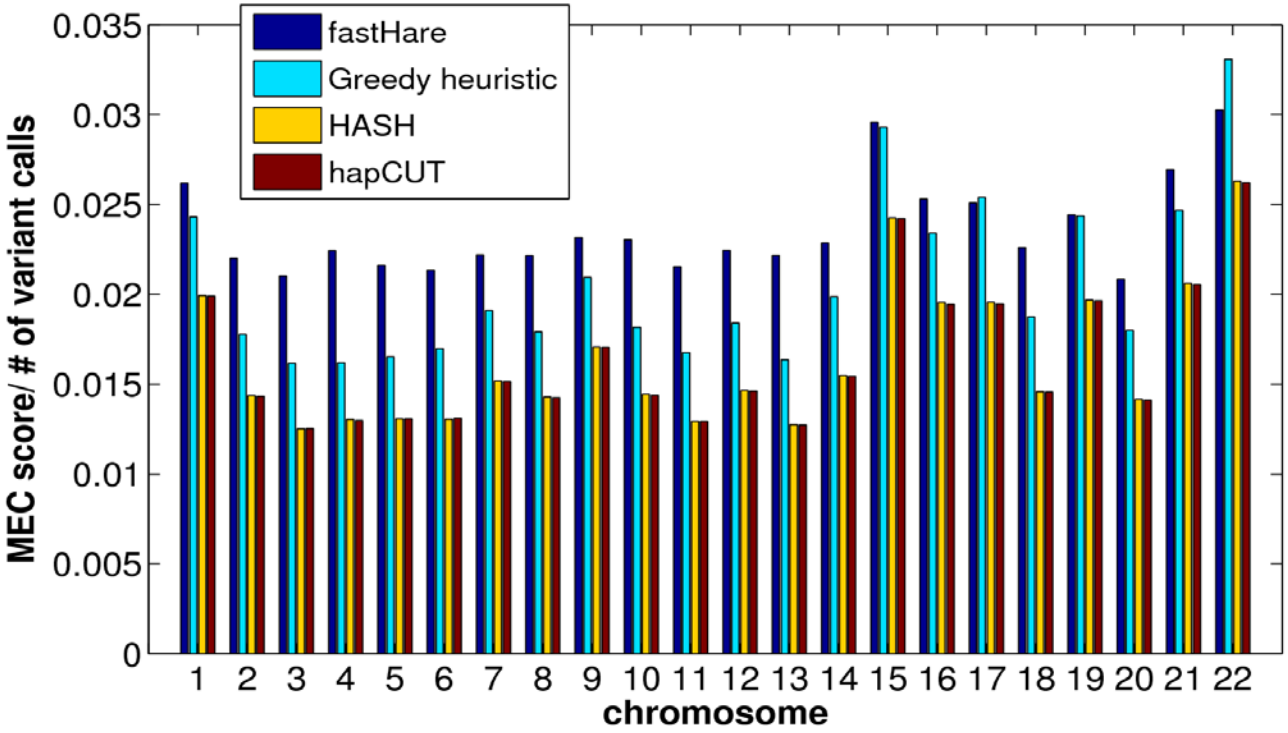
The Diploid Genome Sequence of an Individual Human

Samuel Levy[1*], Granger Sutton[1], Pauline C. Ng[1], Lars Feuk[2], Aaron L. Halpern[1], Brian P. Walenz[1], Nelson Axelrod[1], Jiaqi Huang[1], Ewen F. Kirkness[1], Gennady Denisov[1], Yuan Lin[1], Jeffrey R. MacDonald[2], Andy Wing Chun Pang[2], Mary Shago[2], Timothy B. Stockwell[1], Alexia Tsiamouri[1], Vineet Bafna[3], Vikas Bansal[3], Saul A. Kravitz[1], Dana A. Busam[1], Karen Y. Beeson[1], Tina C. McIntosh[1], Karin A. Remington[1], Josep F. Abril[4], John Gill[1], Jon Borman[1], Yu-Hui Rogers[1], Marvin E. Frazier[1], Stephen W. Scherer[2], Robert L. Strausberg[1], J. Craig Venter[1]

1 J. Craig Venter Institute, Rockville, Maryland, United States of America, 2 Program in Genetics and Genomic Biology, The Hospital for Sick Children, and Molecular and Medical Genetics, University of Toronto, Toronto, Ontario, Canada, 3 Department of Computer Science and Engineering, University of California San Diego, La Jolla, California, United States of America, 4 Genetics Department, Facultat de Biologia, Universitat de Barcelona, Barcelona, Catalonia, Spain

- 1.856M variants used for haplotype assembly of HuRef (Craig Venter's genome)
- Chromosome 22 stats:
  - 25K variant sites, 53K ‘useful’ fragments (rows)
  - ~7 fragments per variant
  - 609 disjoint haplotype blocks (largest contains 1008 variants)
  - 50% of the variant sites lie in haplotypes 350kb or greater (N50 haplotype length)

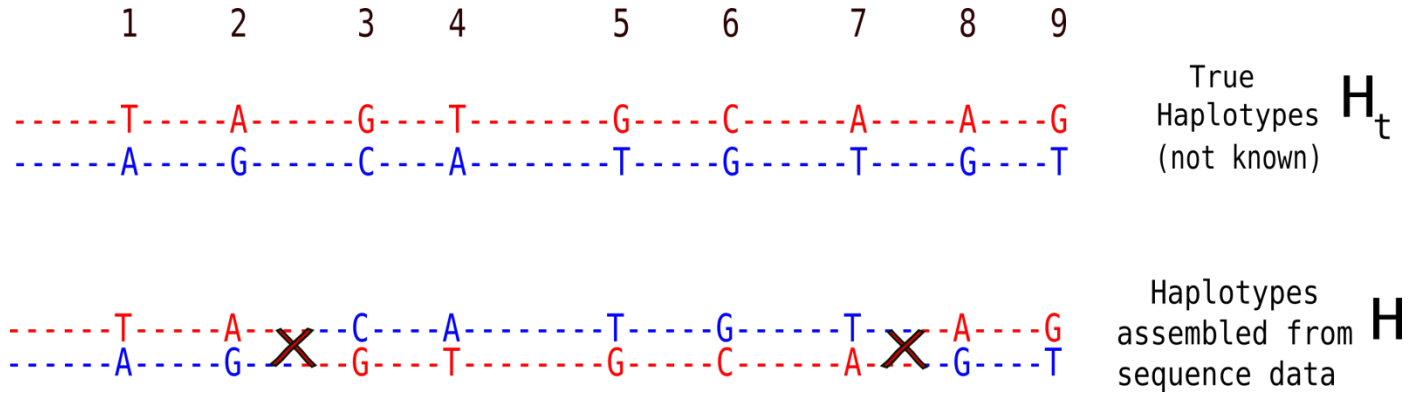
Performance on HuRef



- HapCUT and HASH have nearly identical accuracy
- Both offer > 20% improvement over previous methods
- HapCUT is an order of magnitude faster than HASH

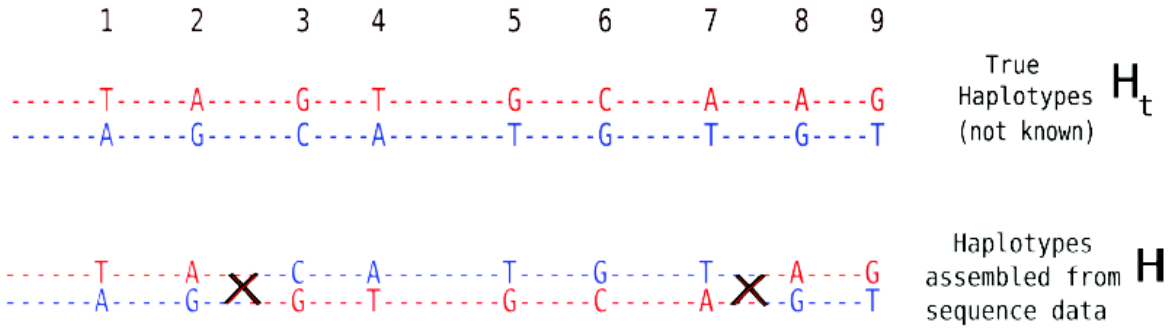
Switch error rate in reconstruction

- MEC error rate measures consistency of haplotypes with the sequenced fragments
- Switch error rate measures absolute accuracy of haplotypes



Switch error rate = 2/8 = 0.25

Using HapMap to estimate switch error rate

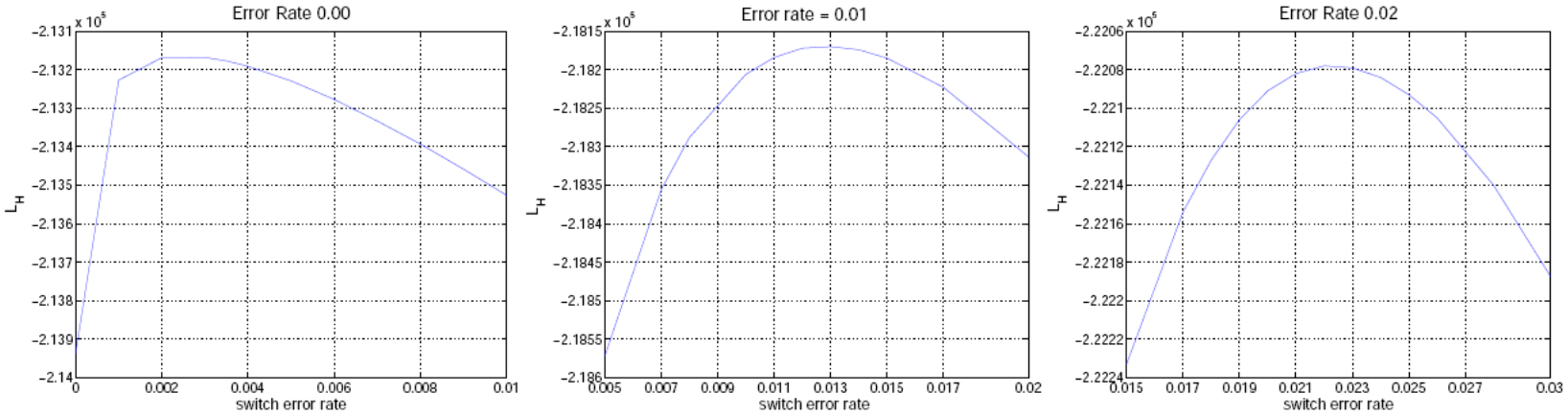


$$L_H(1,2) = (1-\varepsilon_s)\cdot \Pr(H_{12}|H_p) + \varepsilon_s \cdot (1-\Pr(H_{12}|H_p))$$

- For a pair of adjacent SNPs, define a likelihood for the haplotype assembly 'H' conditional on the HapMap haplotypes 'H_p'
- L_H computed as product of pairwise likelihoods

Using HapMap to estimate switch error rate

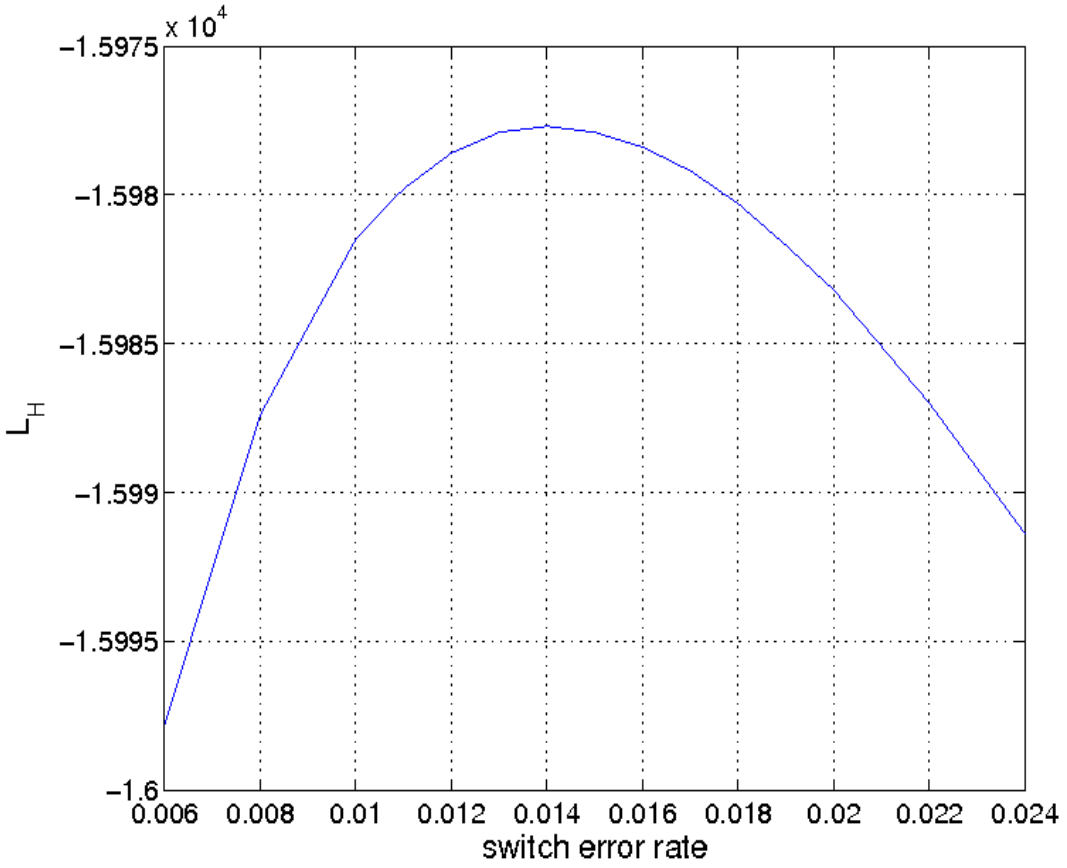
- L_H is a function of Linkage Disequilibrium (LD) in HapMap data and switch error rate ε_s
- *Intuition*: Maximum likelihood value of L_H should track the switch error rate ε_s



- ML estimator works well in simulations (switch errors distributed randomly)

Switch error rate for HuRef haplotypes

- Switch error rate for HapCUT: 0.014
- Switch error rate for greedy heuristic: 0.03
- HapMap switch error rate is 0.005 (CEU) to 0.02 (YRI) even with trios
- Without trios, HapMap error rate is > 0.05



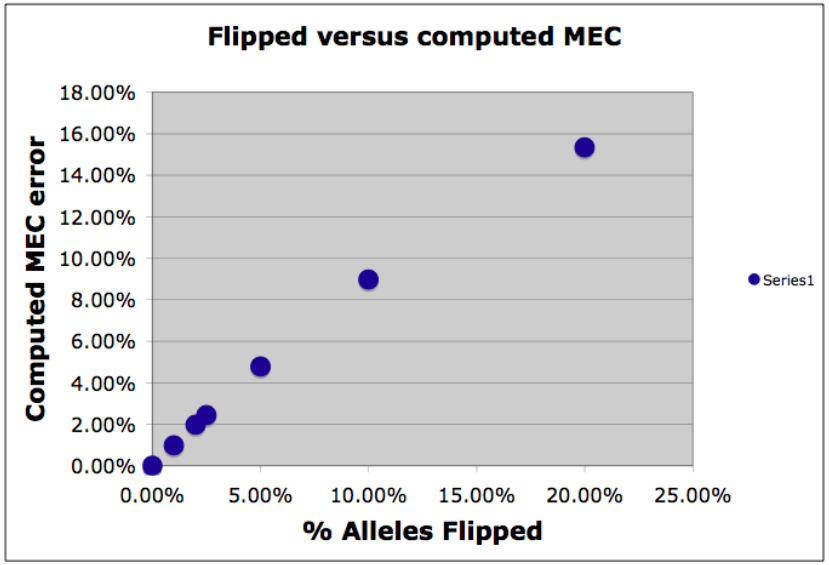
Conclusions

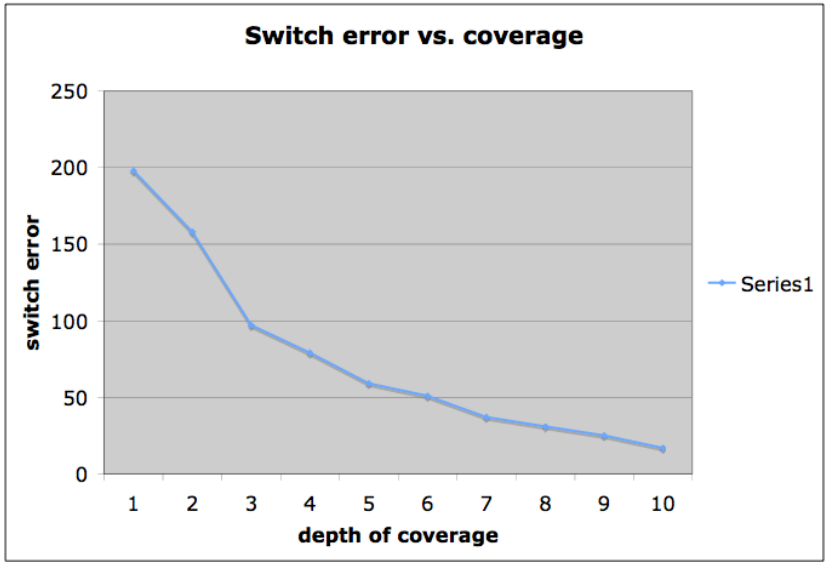
- Haplotype assembly is a feasible approach to haplotype inference, with increasing applicability
- A combinatorial algorithm HapCUT for haplotype assembly with good performance on real data
- Highly accurate haplotypes with low switch error rates based on comparison to HapMap haplotypes

Acknowledgements

- Aaron Halpern
- Sam Levy
- JCV Institute

Simulating errors





- Errors were simulated on HuRef sequences
- The computed MEC error tracks simulated errors
- Switch error in reconstruction is low, and decreases with increasing depth of coverage