Comparison of Haplotype Motif and Block Models using the Principle of Minimum Description

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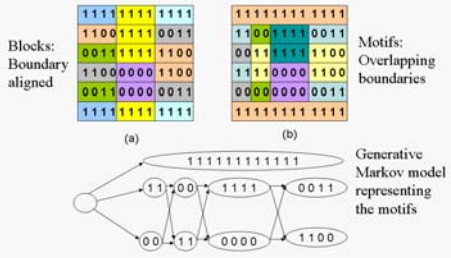
Haplotype Structure

- Haplotypes: Contiguous DNA segments between recombination sites
- Popular models of haplotype structure:
  - Blocks
    - Haplotype boundaries are aligned
    - Built on the recombination hot-spots assumption
  - Motifs
    - Overlapping haplotype boundaries
    - Relaxes the rigidity of the blocks model

Minimum Description Length (MDL)

- Popular measures for comparing models: MDL, information content & compression
- Let
  - M represent the parameters of the model
  - I represent the input
  - E be the 'explanation' of I using M
  - L be the length of encoding
- Objective:
  - Minimize $L(M) + L(E(I)|M)$
- Complicated models are penalized, prevents over-fitting

Example: Blocks and Motifs

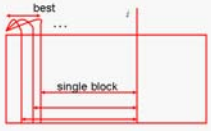


Algorithm for Blocks: Dynamic Program

- Dynamic Program (Koivisto et al. 2003):

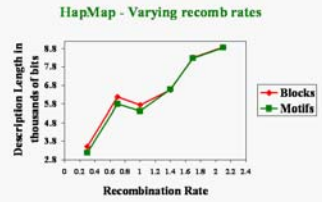
$$F(i) = \min_{1 \le j < i} (F(j) + C(j+1, i))$$

- where $C(j+1, i)$ is the cost of creating a single block from $j+1$ to i.
- Running time: $O(n^2)$
- Work space: $O(n)$

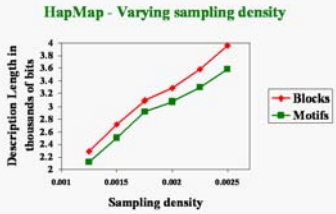


Algorithm for Motifs

- Step 1 - Initial Solution
  - Construct a generative Markov model M of all possible motifs with a 'start' state
  - Initialize transition probabilities of M
  - Repeat maximization-maximization step:
    - For each row r in input I
    - Find maximum likely path P_r (explanation) of r in M
  - Perform maximum likelihood estimate for transition probabilities based on number of times the transitions appear in P
- Step 2 – Simulated Annealing
  - Define motif as a triple (s, e, b)
    - where s, e are columns and $b \in \{0, 1\}^{e-s+1}$
  - Let current solution S be a set of motifs
  - Neighbors of S are solutions that can be obtained from S by one of the following operations:
    - Select a column c; concatenate all $m = (\_, c, b)$ with $m' = (c+1, \_, b')$; add m, m' to S
    - Select a column c; let $S_c \subseteq S$, s.t $\forall (s, e, b) \in S_c$, $s \le c$ and $e > c$; select a subset T_c of S_c; remove T_c from S; for every $(s, e, b) \in T_c$, add (s, c, b_1) and $(c+1, e, b_2)$ to S, where $b = b_1 \circ b_2$

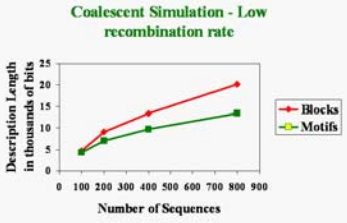


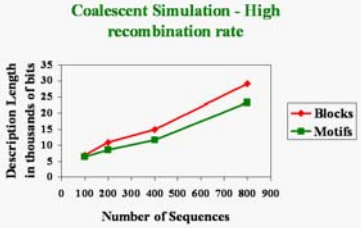
Recombination rates obtained from Jensen-Seaman et.al, 2004



Coalescent Simulation using the ms program (Hudson 2002)

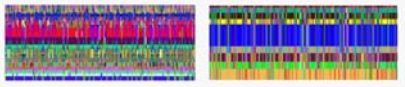
- Length of DNA under simulation: 100kb
- Mutation rate per nucleotide per generation: 2.5×10^{-8}
- Recombination rate per pair of sites per generation:
  - Low rate: 10^{-8}
  - High rate: 2×10^{-8}
- Effective population size: 10,000
- Selected SNP's with minor allele frequency at least 0.1
- SNP density (number of SNPs/physical length of DNA) varied between 0.002 to 0.0025





Motifs and block haplotypes in Daly et.al 2004

Rows: SNPs
Columns: DNA sequences
Identical colors indicate same motif or block haplotype



Motifs Description Length: 6554.93 bits Blocks Description Length: 7342.71 bits

Conclusions

- Motifs better capture haplotype conservation than blocks in most instances
- Results less pronounced in real data sets than in simulations that use the assumption of uniform recombination rate
- Blocks can be easily inferred and used in applications such as association testing
- Motifs are harder to infer but could possibly improve the power of association testing
- Are there better models 'in between' blocks and motifs?

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