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A new type of genetic map:
Locus ordering based on pair-wise linkage disequilibria

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Contents

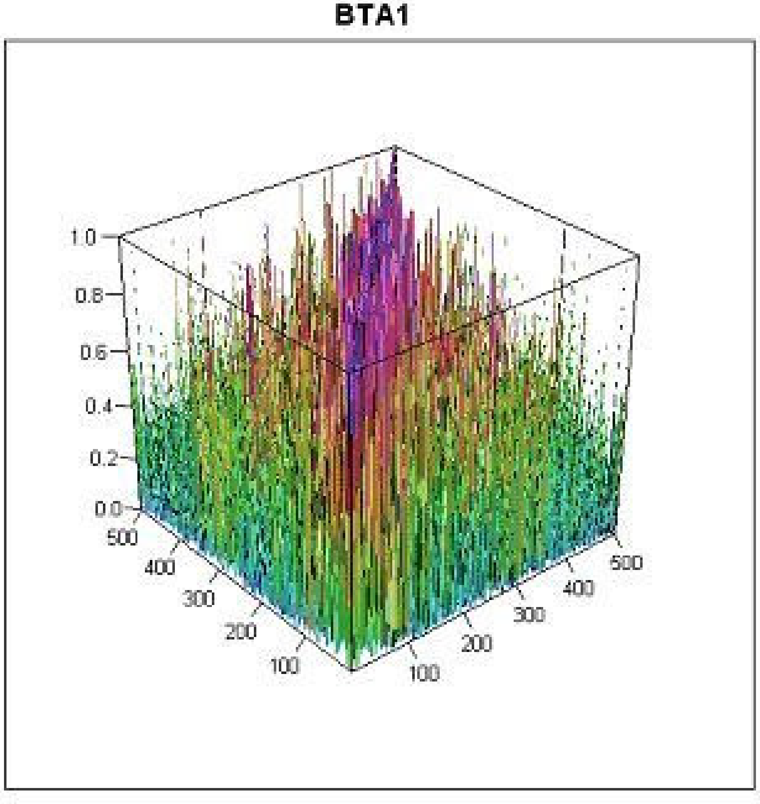
- Estimators of LD
- Ordering method
- Ordering of bovine SNP
- Alignment and positioning of unaligned SNP
- Application to human sets
- Potential utilities of the LODE map

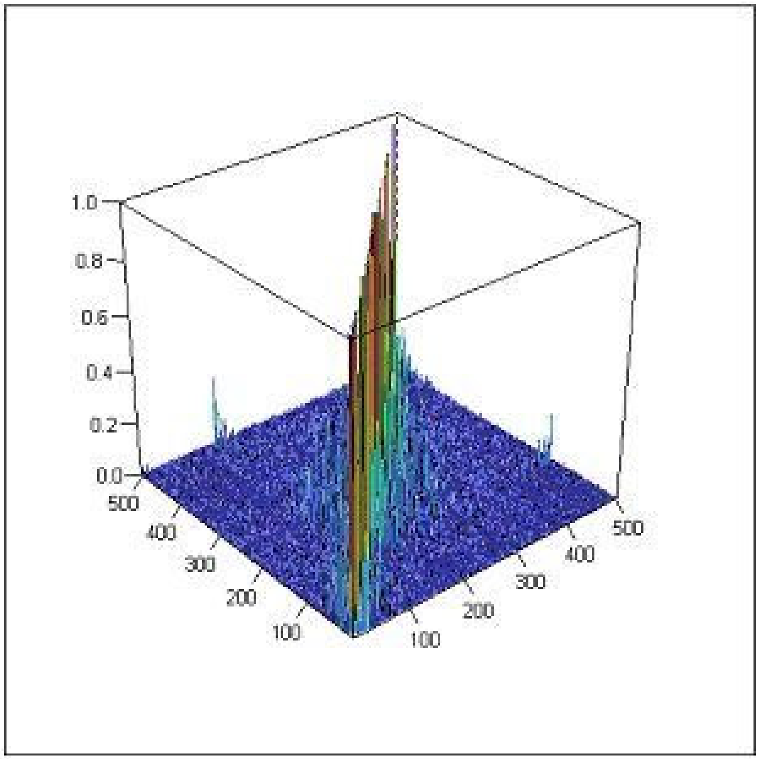
Measurement of LD

- Quantify the degree of association between pairs of markers
- Depends on haplotype and allele frequencies
- A large number of statistics have been developed

$$D' = D/D_{max} \; (D = p_{AB} - p_A p_B)$$

$$r^2 = D^2/p_A p_a p_B p_b$$


BTA1



LODE map

- Target
  - Construct a genetic map based purely on linkage disequilibria of SNP markers: D‘ or/and r^2
- Input
  - Matrix of pairwise LD
- Expected output
  - Order of markers, close to the true order

Potential use

- Alignment of currently non-descript SNP
  - Chromosomal assignment
  - Approximate positioning
- (Bovine) SNP chips

- Ordering of loci in unsequenced species

Method for Data Ordering

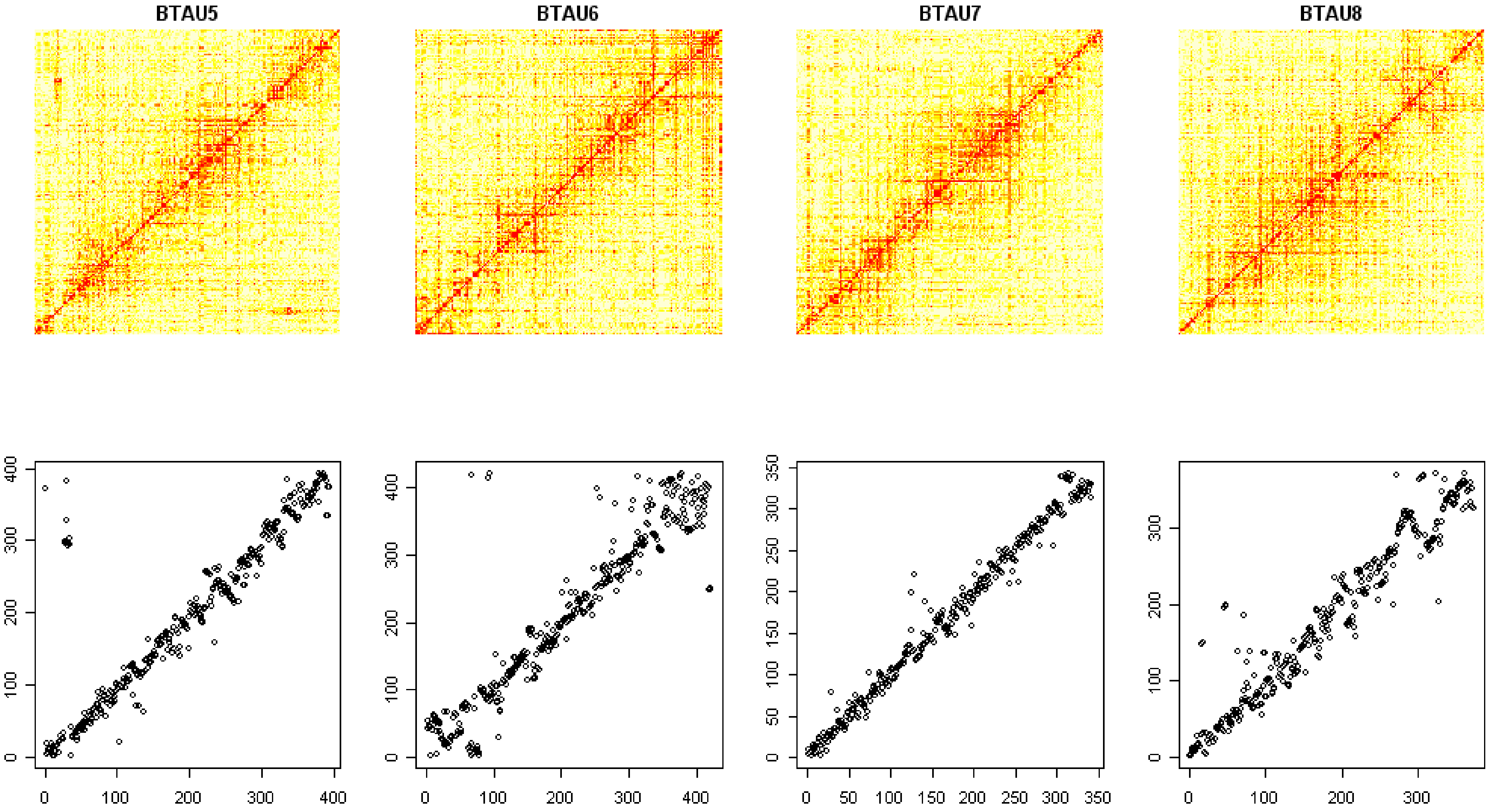
- Sorting Points Into Neighborhoods (SPIN):
  D. Tsafrir et al., 2005. Data Analysis and Visualization by Ordering Distance Matrices. Bioinformatics 21, 2301-2308.
- (approximate) solution to the wandering salesperson problem

Data

- Australian Holstein Friesian (Dairy CRC)
  - 1,546 bulls, 15,036 SNP
  - 1077 not aligned, according to BTAU3.1
- Humans, 2 Finnish isolates
  - 200 persons each, 2,486 SNP on HSA 22

Application of SPIN for the bovine set

- Transform LD into distance $\Rightarrow$ 1–D‘
- Start from a matrix of distances of SNP in random order
- Run sorter repeatedly, successively reducing an indicator for the size of neighbourhood.


BTAU5
BTAU6
BTAU7
BTAU8
0
100
200
300
400
0
100
200
300
400
0
100
200
300
400
0
100
200
300
400
0
50
100
150
200
250
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350
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150
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300

Chromosomal assignment of currently unaligned SNP

- Run SPIN with 1-r^2 distances starting from the correct order of known SNPs
- Very successful in test runs
  - > 80 % were aligned to only one chromosome, close to the correct position
  - > many non-aligned showed MAF<0.05
- From the currently unaligned SNPs, we could place 2/3 on one chromosome with high confidence

HSA22 in population isolates

Magnitude and distribution of linkage disequilibrium in population isolates and implications for genome-wide association studies

Service et al., 2006

Nature Genetics

11 isolates

200 persons each

2486 SNP

Provided LD for

Fi – general pop.

Fi - Kuusamo

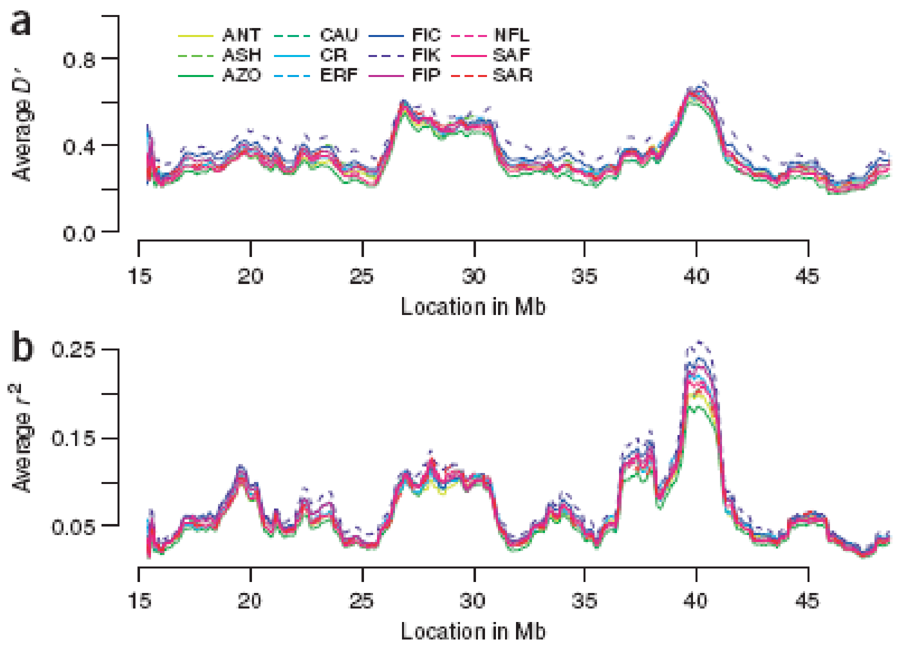
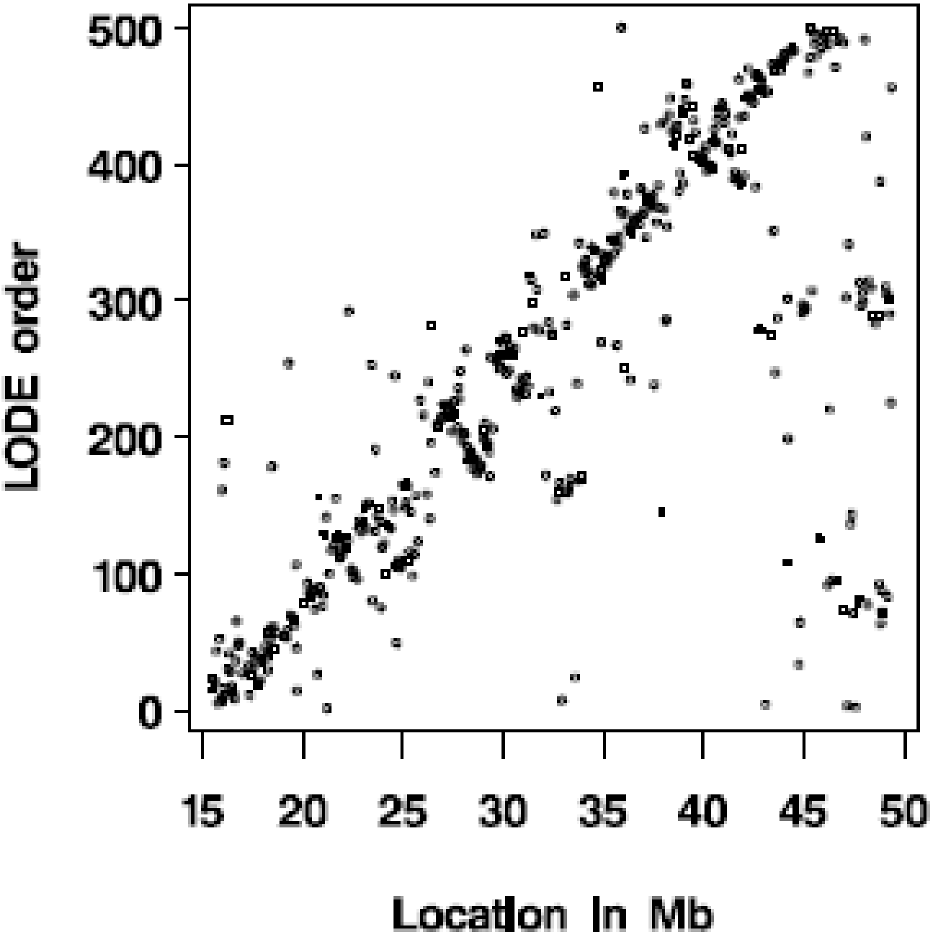
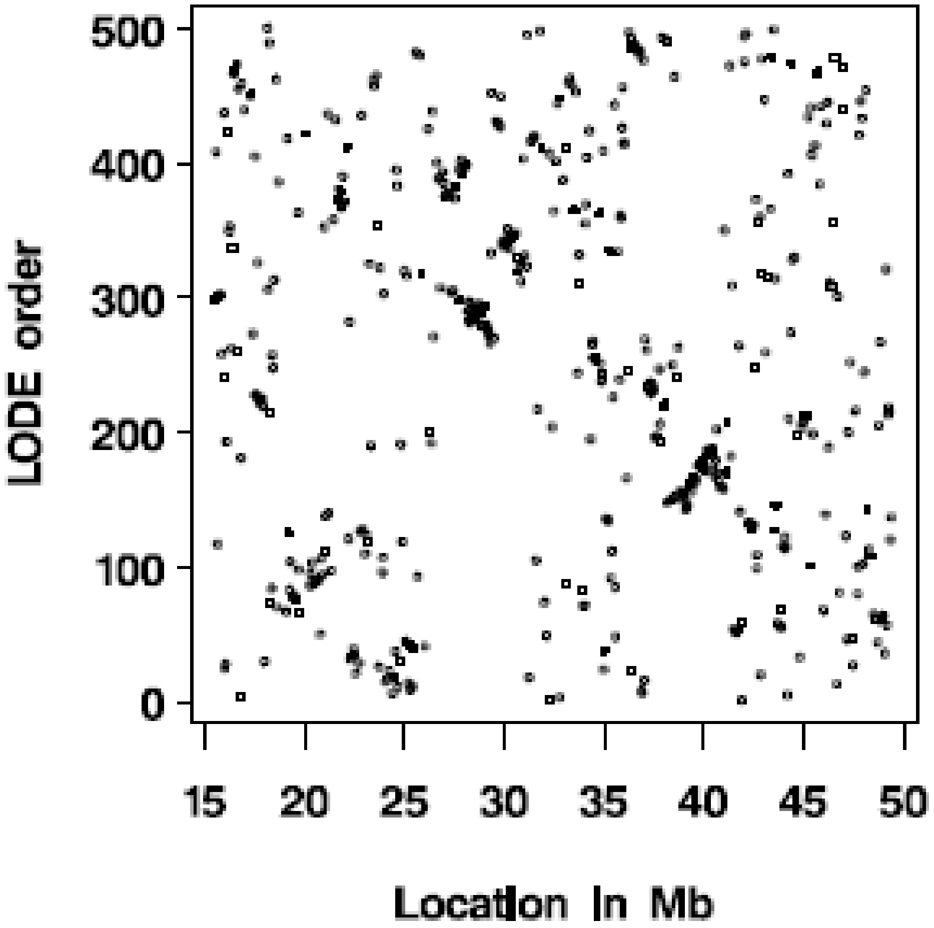


Figure 2 Distribution of linkage disequilibrium on chromosome 22. Average D' (**a**) and r^2 (**b**) coefficients plotted in sliding windows containing all markers separated by less than 500 kb in successive 1.7-Mb segments (1.6-Mb overlap). Population abbreviations are as in **Table 1**.

Finnish isolate Kuusamo



Finland nationwide



Utilities of the LODE map

- Alignment and positioning of unaligned SNP in cattle and other livestock species
  - Illumina Bovine Chip: 54,001 SNP, 1678 not aligned
- A start from less prior infomation (larger proportion of unaligned SNP) in other un-sequenced species is possible
- Extremely useful for populations with extent of LD similar to Holstein Friesian
  - chromosome-wide ordering w.o. prior information