Quantifying LD decay by quantile regression
A case study

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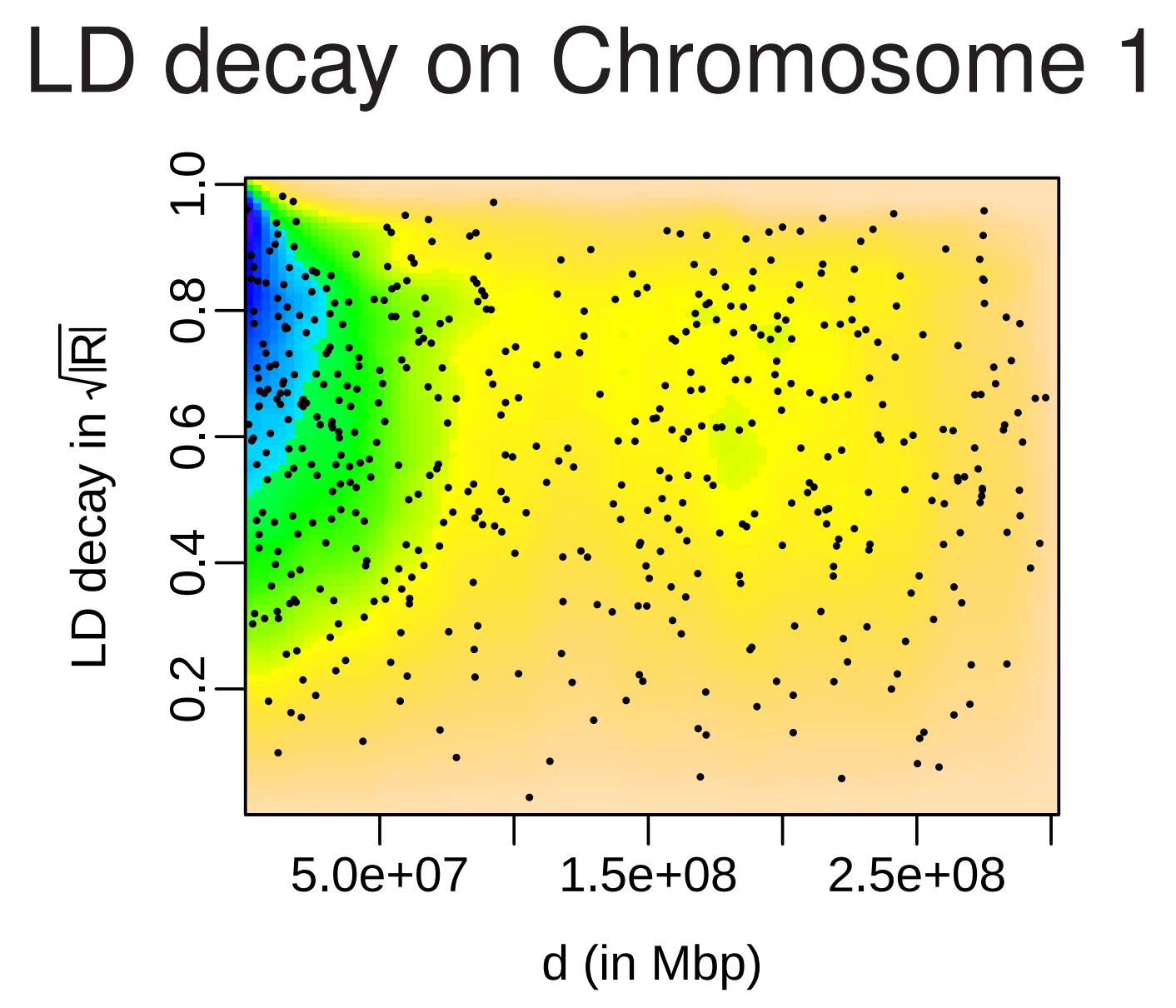
Introduction

- Genome-wide association studies: great tool for the localization of QTLs (quantitative trait loci) in plant and animal breeding programs.
- Investigation of the genetic relatedness (kinship matrix) required for powerful GWAS

→ Insight into LD between genetic markers necessary (Listgarten *et al.*, 2012)


LD decay on Chromosome 1

- Find suitable set of independent markers
- Exploration of LD decay over the whole genome
- LD (linkage disequilibrium) is commonly measured in terms of the squared Pearson correlation coefficient R^2 between pairs of genetic markers (Hill and Robertson, 1968).

Data and Visualization

- Data from Maize population (Fischer *et al.*, 2008), especially from Chromosome 1 with almost 5000 markers → more than 12 million pairwise comparisons
- For these large data: visualization is difficult in a scatterplot.
- Apply a scatterplot smoother (Eilers and Goeman, 2004)

→ Computation of a two-dimensional histogram, smoothing of the counts and display with a color map

- In order to improve the quality of the fit and the visualization → use of $\sqrt{|R|}$ instead of Pearson's R^2.

Quantile Regression

- Using non-parametric quantile regression with a monotonicity constraint (Bollaerts *et al.*, 2006; Muggeo *et al.*, 2013)
- Monotone decreasing curve is in line with biological assumptions.
- $\mu_\tau = s_\tau(d)$, μ_τ quantile function at percentile τ, d SNP distance between pairs of markers and $s_\tau(\cdot)$ smooth and unknown function
- $P-$splines for a smooth functional form, therefore: $\min \sum_k^K b_{k\tau} B_k(d)$ subject to $b_k < b_{k-1}$ for $k = 2, \ldots, K$, with $b_{k\tau}$ coefficient of the B_k-th spline of quantile τ, K dimension of the design matrix.

Global/local LD

- Usually analysis focusses on the global LD decay (per chromosome) → general picture about the linkage desequilibrium and linkage between the markers
- Here: emphasis on local LD decay to get more insight on a smaller scale
  - Overlapping sliding windows of 2.5 Mbp → around 1000 windows on chromosome 1 with on average 2000 points per window
  - Fit a set of quantile curves to each of the windows (here $\tau = 0.25, 0.5, 075$)
  - Choose threshold T in terms of R^2 and collect the associated distances $\Delta_.$ from whereon LD decay is lower than T

Results

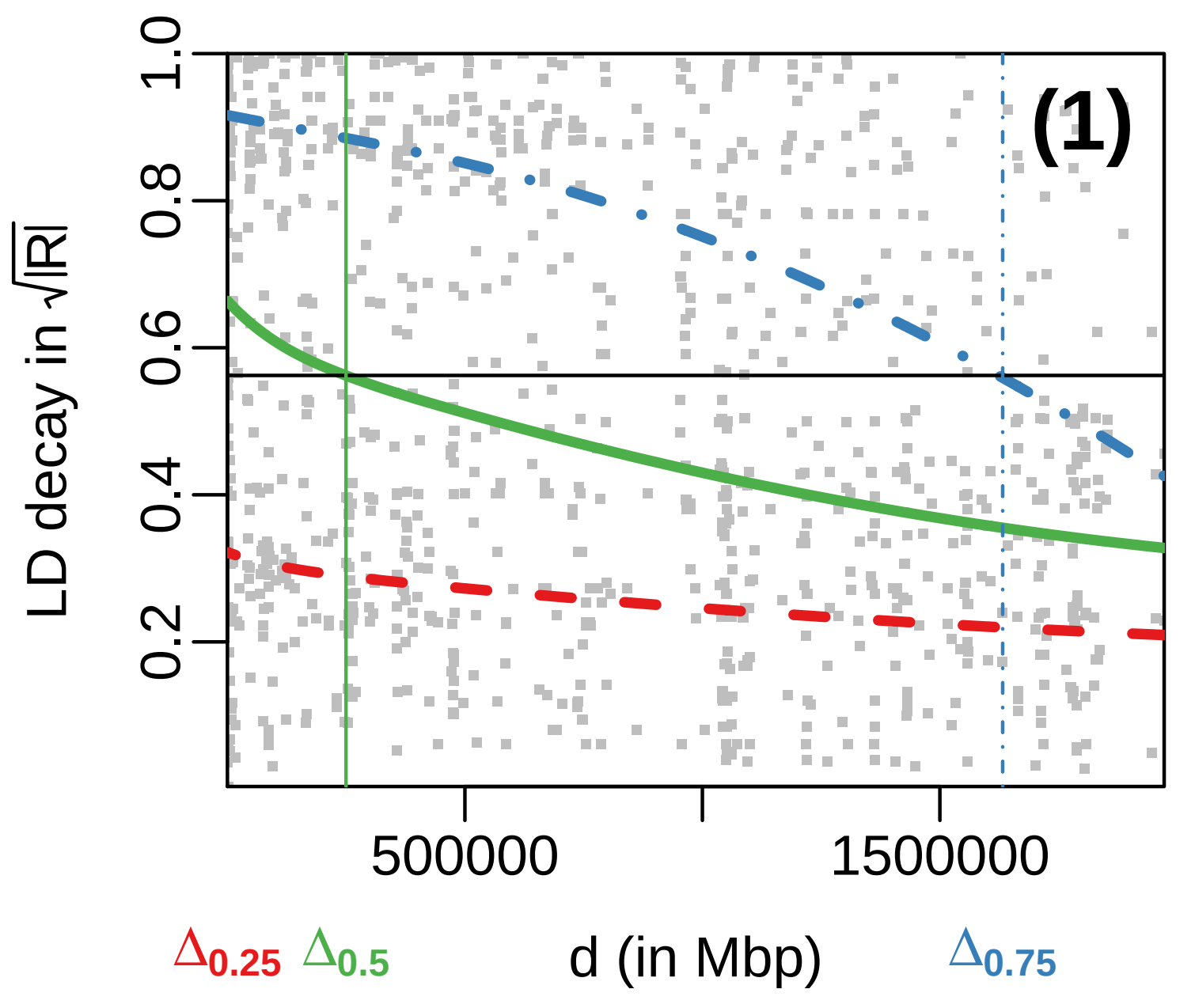
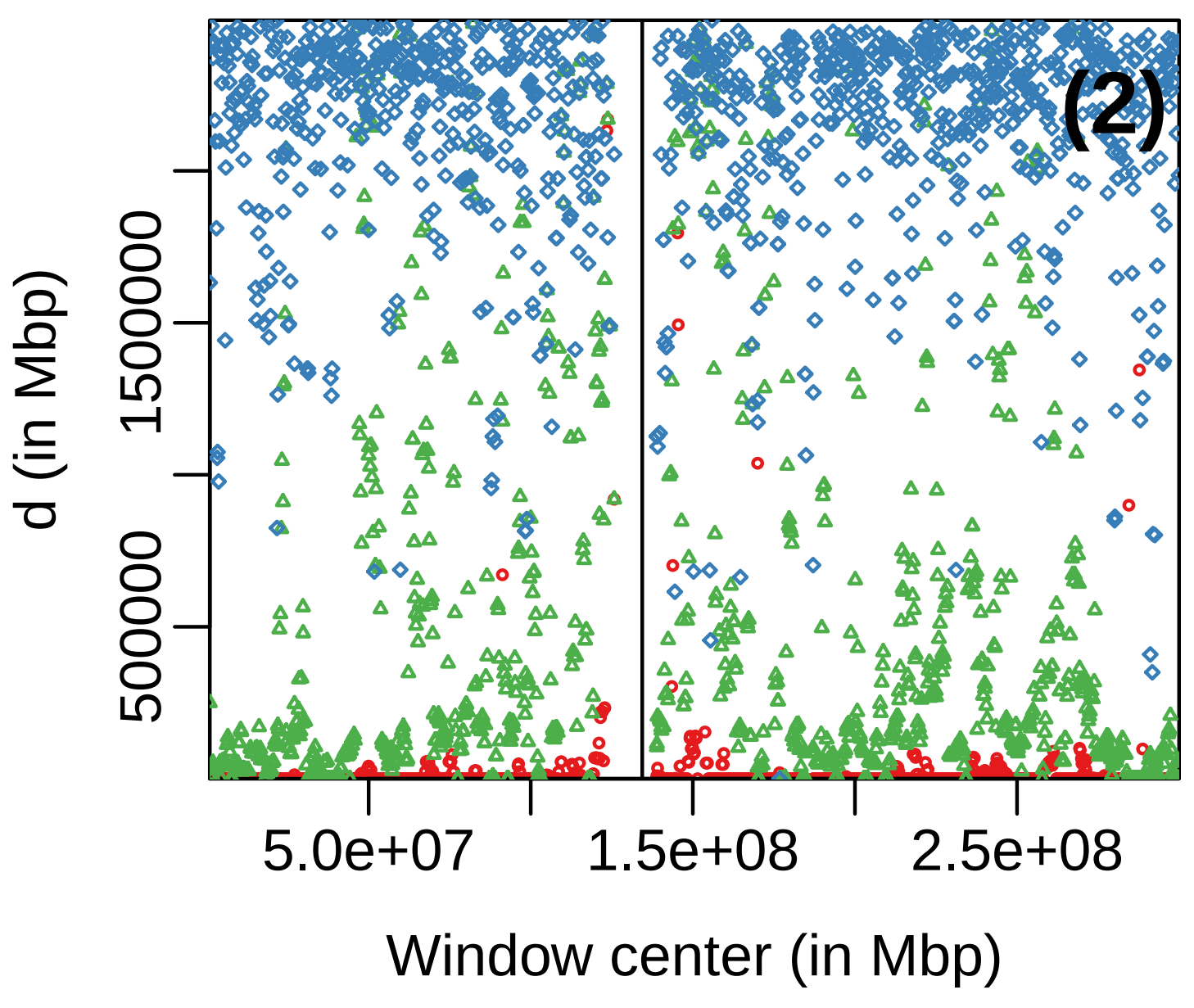
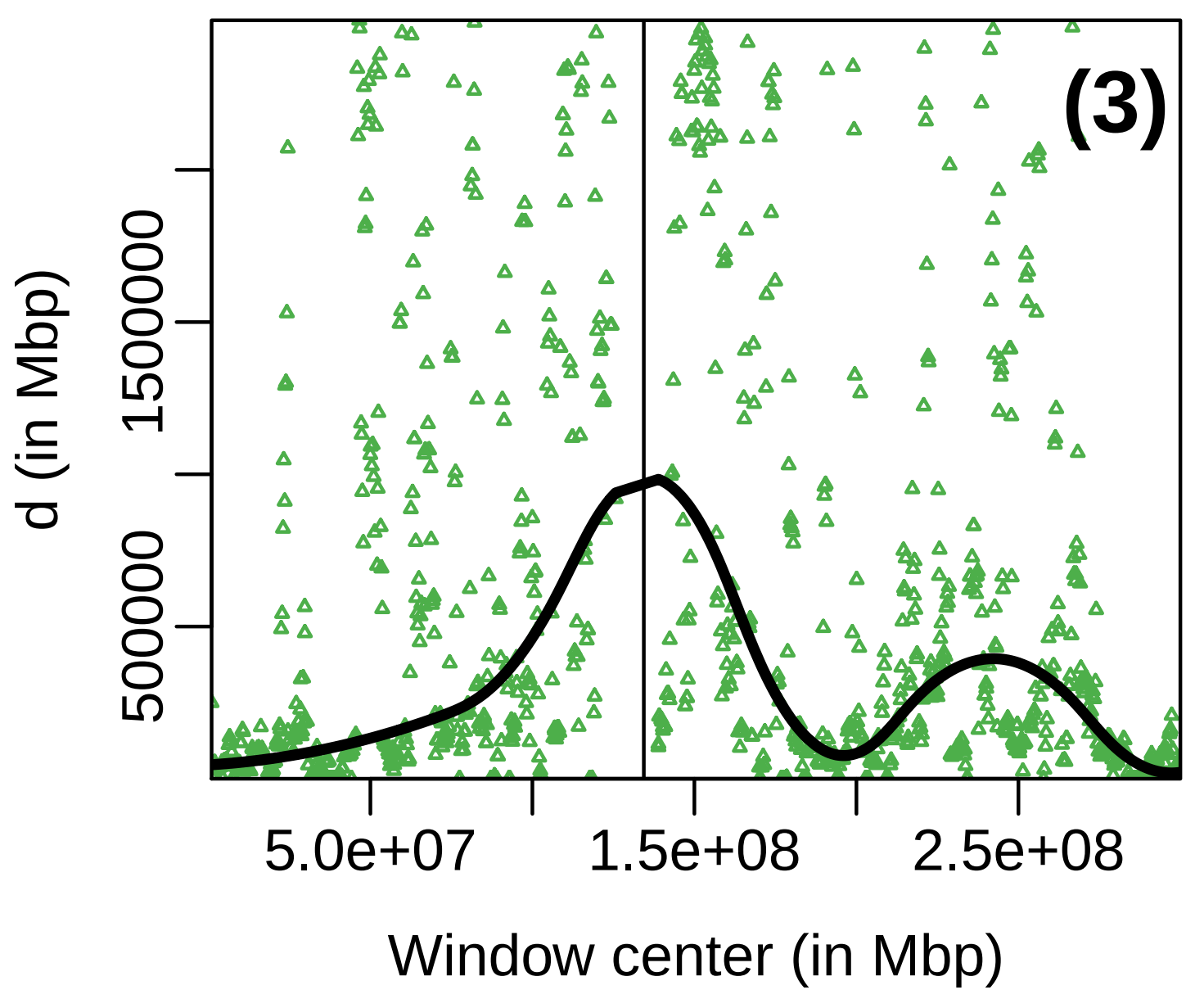


Figure (1) Quantile curves for $\tau = 0.25, 0.5, 0.75$ for a subsample. The distance associated to threshold T is indicated at $\Delta_{0.25,0.5,0.75}$.

Figure (2) Collection of $\Delta_{0.25,0.5,0.75}$ (with indication of centromere)

Figure (3) Smooth fit to $\Delta_{0.5}$





Conclusion and Discussion

- Case study of how to explore and quantify local LD decay patterns in Maize using quantile regression with monotonicity constraints for a first summary of the LD decay.
- Applying $P-$splines to smooth the median local LD decay → easy to interpret and inspect for the collaborating biologists
- In depth exploration of local LD decay (in comparison to global LD decay) leads to new insight.
- In addition to a good tool to quantify local LD decay → also an instrument in identifying problems with the underlying genotypic data that have previously been overlooked.
- Can serve as a diagnostic tool
  - Discovering of undercoverage through sliding windows with low sample sizes
  - Clustering of correlation values → unknown phenomenon in the data, adjustment in subsequent analysis

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