Write a wise saying and your name will live forever.
— Anonymous

6 Discussion

Contents

This thesis had the aim of developing novel strategies for the statistical analysis of rare genetic variants in context of complex disease research. In the time since I began working towards this broadly defined goal, many major milestones have been achieved in human genetic research, in particular due to (still ongoing) advancements in high-throughput sequencing technologies. This facilitated research on a previously unseen scale, and offered a wide range of opportunities to be explored.

One major achievement of human genetic research is seen in the success of genome-wide association (GWA) studies which, within less than a decade, have identified thousands of loci associated to a large number of disease phenotypes. At that time, not much was known about the role of rare variants in complex disease, wherein I saw an opportunity to contribute to current (and highly dynamic) research. I became interested in the development of novel approaches that would allow researchers to harness the growing amount of genomic data to find rare allele associations to disease risk.

The recent past has also seen a major change in the division between areas of applied medical research and the traditionally more theoretical field of population genetics. The line between those fields became more blurred, such that it could be argued that it was never there to begin with. The questions arising from the early discoveries made in the human genome, in particular through the Human Genome Project (International Human Genome Sequencing Consortium, 2001, 2004), have necessitated a deeper understanding of how genomic variation as a consequence of demographic and evolutionary forces

contributes to variation of phenotypic traits. I became fascinated about the possibility to use genomic data to draw inferences about past historic events in populations, and to further use such insights to make predictions about the effects on disease traits. In that regard, I intended to focus on rare variants, which due to their presumed recent origin through mutation could be seen as a source of information about the recent past. My interest grew into what now covers the major parts of this thesis.

6.1 Summary and main conclusions

The following main directions can be distinguished in this thesis. First, I attempted to develop a computational method to integrate different sources of data, so as to increase the number of rare variants that can be interrogated in association analysis. Second, a large part of this thesis is concerned with methods development for inference of haplotype segments that are shared by descent from a common ancestor. Lastly, my primary goal was to develop the methodology and the statistical theory required to computationally estimate the age of an allele observed at a single locus. In the following, I briefly review the methodology I developed and give a summary of the main challenges, findings, and conclusions.

6.1.1 Imputation and association analysis or low-frequency alleles

In Chapter 2, I attempted to develop a method to combine independent genomic datasets through genotype imputation as a way to improve statistical power to implicate rare variants in GWA studies. Rare variants are less likely to exert high risk effects on complex disease phenotypes, or otherwise could be picked up through conventional linkage analysis. Variants at lower frequencies may nonetheless play a role in disease aetiology, but are often highly population or cohort specific. Imputation from a single reference panel may therefore not produce genotype data where low-frequency alleles would be likely to be implicated in disease risk through association tests.

I developed a computational tool (*meta-imputation*) to combine genotype data obtained in separate imputations from independent reference panels. The intuition was that the information contained in different studies could be leveraged by bringing these datasets together through imputation into the same study sample. I thereby attempted to capture variants at lower frequencies or those specific to one or few source panels. The method produces a single, canonical genotype dataset that can be used in subsequent association analyses.

The method was evaluated, first, in terms of the achieved genotype accuracy, which was compared to each of the separately imputed datasets that were previously combined through meta-imputation. An second evaluation was performed in a series of simulated GWA studies. This, however, turned out to be particularly challenging due to substantial computational demands. Thousands of simulated datasets had to be generated, which were used as sample for imputations from multiple reference panels, such that each dataset was treated as an independent GWA study.

The main findings are summarised as follows.

- I showed that the method was able to improve overall genotype accuracy when data imputed from multiple studies were combined.
- The accuracy of meta-imputed genotypes improved notably in cases where data from more diverse population groups were available.
- Statistical power in association analysis was increased at low-frequency variants with intermediate or high penetrance.
- Rare variants with low penetrance were unlikely to reach statistical significance.
- Differences in power seen for common risk variants were negligibly small.

Note that I used Phase I data from the 1000 Genomes Project (1000G). Shortly after my work on this project was completed, 1000G Phase III was released. I decided not to repeat the analysis conducted for the evaluation of meta-imputation with the newly released dataset, because the larger sample size and higher marker density would entail that the time and the computational load needed to repeat the analysis would be too prohibitive.

In light of the imputation reference panel that became available through the Haplotype Reference Consortium (HRC) (McCarthy *et al.*, 2016), potential applications of the meta-imputation method may be limited to specific niche problems. For example, for populations that are currently underrepresented in the HRC panel, or when novel datasets become available that are more suited for imputations into a given study cohort than the HRC alone.

6.1.2 Shared haplotype inference around rare variants

Recent advancements in high-throughput sequencing technologies have enabled the study of the rare variation present in the human genome. It is assumed that frequency is indicative for the time since an allele was created through a mutation event. Rare alleles are therefore likely to indicate recent relationships among haplotypes, which is informative about recent demographic history and population structure, within and among populations. Given deeper insight into the sharing structure of alleles, it would be possible, for example, to infer the timing of demographic events. Such inferences could be useful to make further statements with regard to selection or other forces that shaped the genetic variation observed in a population.

In Chapter 3, an initial attempt was made to develop deterministic (rule-based) methodology that utilises rare variants as "bookmarks" in the underlying genealogy, to identify haplotypes that recently derived from a common ancestor. I presented two approaches that are based on the four-gamete test (FGT) after Hudson and Kaplan (1985), through which the "breakpoint" of a recombination event along the sequence can be detected. While the FGT is based on observing specific allelic configurations in haplotype data, its simplified form, the discordant genotype test (DGT), requires only genotype data. I developed a computational tool (*tidy*) to detect breakpoint intervals around a given focal site in pairs of diploid individuals that carry the focal allele. The resulting interval is assumed to indicate the underlying shared haplotype segment that was inherited "identical by descent" in each pair sharing the focal allele.

In Chapter 4, this idea was extended using a Hidden Markov Model (HMM) that operates on genotype data. The chapter includes a study in which I determined genotype error rates in different sequencing and genotyping datasets, which I used to modify simulated data to perform subsequent evaluations of the developed detection methods in realistic settings. Error rates were also used to construct an empirical emission model to make the HMM robust towards error in applications to real data. I employed a similar approach to additionally construct an empirical model for a second HMM in Chapter 5, but which operates on haplotype data.

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- I showed that the pattern previously seen in the application to real data could be reproduced, confirming the notion that the deterministic, rule-based methods were unsuitable for general applications to real data.

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6.1.3 Allele age estimation

The method for allele age estimation was presented in Chapter 5, which concluded this thesis. Age is estimated for a given allele at a single locus as observed in the sample. This is done in a Bayesian setting in which a composite posterior distribution is computed from posterior probabilities of the time of coalescent events between pairs of haplotypes. According to observed allele sharing in the sample, a number of "concordant" and "discordant" haplotype pairs are formed and analysed in turn to obtain pairwise posteriors. Several models were derived based on the coalescent to obtain such posterior densities. The age of an allele can be estimated directly from the resulting composite posterior distribution.

The methodology developed in this thesis to detect shared haplotypes around a given focal site was essential for the application of the age estimation method. This is because the values of the parameters in the underlying models are determined from the from the data with respect to the shared haplotype structure inferred at a focal site in the sample.

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I developed the theory to estimate the time to the most recent common ancestor (T_{MRCA}) for pairs of haplotypes around a given focal site, for which I presented several statistical models that operate on different genetic parameters that can be observed from the data. Model definitions derive from coalescent theory and are used in a Bayesian setting. I then extended the above to obtain a composite posterior distribution from which allele age can be estimated directly.

This methodology was evaluated, first, using full knowledge of the underlying haplotype structure around a given allele using simulations, so as to established proof of concept. I showed that allele age can be estimated with high accuracy under such ideal conditions. To be able to apply the method to real-world questions, I used the

previously developed methodology for shared haplotype detection to obtain parameter values required by the model. Note that this thesis had a strong emphasis on identity by descent and shared haplotype inference for this reason.

The different approaches for the inference of shared haplotype segments as developed in previous chapters was evaluated in context of the age estimation method. However, I found that none of detection methods devised so far was able to yield reliable results in realistic settings or when real data was used. As a consequence, the previous HMM was substantially revised, in particular, in order to operate on haplotype data. I showed that this modified approach was able to outperform all previously developed detection methods. Specifically,

that were explored, developed, and repeatedly refined in

I showed that compared well to the PSMC model and I showed although implicitly biased due to its use of an empirical emission model the method was nonetheless well suited to estimate the age of alleles that derived from very old mutation events that estimation of allele age was nonetheless

6.2 Future directions

Chapter 2.

Chapter 3. used rare alleles as "bookmarks" of recently inherited shared haplotypes

The intuition was that

thereby changing the focus from a phenotype-oriented view to a variant-centric one.

was a first attempt to derive information about the underlying genealogy of the sample.

The intuition was to use rare variants as "'bookmarks' to find recently co-inherited shared haplotype regions;

However, I showed that ... failed when applied to real data. However, because the approach was strictly deterministic, it failed when applied to real data.

Chapter 4 characterised genotypic error in existing sequencing or genotyping datasets using and used this information to generate realistic error patterns in simulated data.

By applying the methodology devised in Chapter 3 to these data,

This suggested that estimation bias in the deterministic This suggested that error in existing sequencing datasets may affect the estimation of identity by descent regions, where I also showed that existing methodologies may suffer similar consequences. as major contributor to estimation bias in the deterministic may adversely affect inference was a main factor

The empirically measured error rates formed the basis for the development of a genotype-based HMM for inference of recently inherited shared haplotype regions around a rare variants observed the sample data.

I constructed a genotype-based HMM for shared haplotype inference. I showed that the previous

Chapter 5 In the introduction to this thesis, I advocated a variant-centric approach as opposed to a phenotype-focused view. It was my assumption that much could be learned about

Future research will show to what extent the methodology developed in this thesis is useful.

The key test for an acronym is to ask whether it helps or hurts communication.

— Elon Musk

Abbreviations

1000G	1000 Genomes Project
DGT	Discordant genotype test
FGT	Four-gamete test
GWA	Genome-wide association
HMM	Hidden Markov Model
HRC	Haplotype Reference Consortium
$\mathbf{T_{MRCA}}$	Time to the most recent common ancestor

My definition of a scientist is that you can complete the following sentence: 'he or she has shown that . . . '

— E. O. Wilson

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1. *I have told you more than I know* [...].
2. *What I have told you is subject to change without notice.*
3. *I hope I raised more questions than I have given answers.*
4. *In any case, as usual, a lot more work is necessary.*

– Fuller Albright