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Haplotype resolved genomes

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Dutch summary (Nederlandse samenvatting)

Het in dit proefschrift beschreven werk is gericht op de uitdagingen en mogelijkheden die de analyse van compleet gefaseerde diploide genomen middels single-cell strand sequencing (Strand-seq) ons bieden. Ons initiële doel was het ontwikkelen van een robuuste, gecomputeriseerde methode voor het samenstellen van accurate haplotypes uit single cell Strands-seq libraries. Het volgende doel was het valideren van de resultaten van de phasing methode tegenover de “gold standard” haplotypes uit het HapMap project, alsmede het demonstreren van de toepasbaarheid van mijn Strand-seq phasing methode. Tot slot werden de mogelijkheden onderzocht om Strand-seq met andere sequencing methoden te combineren om de kosten te verminderen en de compleetheid van de geanalyseerde haplotypes te vergroten.

Hoofdstuk 1 bevat een algehele introductie bestaande uit een samenvatting van huidige en voorgaande haplotyping technologieën. Hierin wijs ik op het belang van haplotype informatie in zowel fundamentele als klinische onderzoeken. In dit hoofdstuk leg ik een sterke nadruk op opkomende technologieën zoals single-cell sequencing, linked-read sequencing en long-read technologieën en analyseer ik de capaciteit van deze technologieën op genomen te genereren waarbij de haplotype informatie correct onderscheiden wordt. Ondanks de kracht en het potentieel van Strand-seq zijn er op het moment weinig rekenkundige en gecomputeriseerde methoden beschikbaar voor de analyse van deze data. In hoofdstuk 2 omschrijf ik de ontwikkeling van een nieuwe bio-informatica pipeline die in staat is om kleine nuances in Strand-seq data te detecteren. Met name beschrijf ik een methode om breekpunten en haplotype phasing te extraheren uit Strand-seq data.

De validatie van deze tools wordt gepresenteerd in hoofdstuk 3. Voor de validatie hebben wij gekozen voor een bekend familie trio van het HapMap project te gebruiken, alsmede onafhankelijke bronnen als PacBio RNA-seq en andere single cell phasing methoden. Dit onderzoek bevestigde de hoge accuraatheid van Strand-seq phasing. Deze werd verder geverifieerd in een vergelijking met *de novo* assembly gebaseerde phasing. In hoofdstuk 4 bijschrijf ik de toepassing van genoom-wijde haplotypering met Strand-seq om zowel meiotische recombinaties alsmede haplotype verschillen in kaart te brengen in een familie trio. Verder demonstreer ik de phasing van grotere genetische varianten als deleties, duplicaties en inversies.

Om de kosten en de vereiste werklust die nodig is voor het phaseren van het genoom van een enkel individu te verlagen heb ik de mogelijkheden verkent om de globale phasing van Strand-seq te integreren met andere sequencing

technologieën zoals PacBio of Illumina. In hoofdstuk 5 stel ik een geïntegreerde phasing methode voor. Hierbij worden globale Strand-seq haplotypes gecombineerd met DNA fragmenten waarvan de sequentie bepaald is. Een combinatie van Strand-seq phasing met andere technologieën kunnen complete genomen voor lagere kosten phasieren, met een grotere compleetheid en een hogere accuraatheid. Op basis van onze resultaten verwachten wij dat toekomstige studies naar haplotypes een combinatie van Strand-seq en long-read technologieën zullen gaan gebruiken om complete haplotypes over hele chromosomen vast te stellen. Single-cell sequencing technieken worden steeds toegankelijker. Wij verwachten dat het haplotyperen middels Strand-seq een belangrijke rol zal gaan spelen in de *de novo* constructie van haplotype-bepaalde persoonlijke genomen. Naar verwachting zal dit belangrijke gevolgen hebben voor studies naar genetische variatie in relatie met gezondheid en ziekte.



Glossary

Allele – two or more alternative forms of a piece of DNA that resides on the same locus in the genome.

BreakPointR – software package specifically tailored to search for change-points in template strand inheritance using Strand-seq data.

Compound heterozygosity – the presence of two deleterious variants located in the same gene either in cis (on the same homologue) or in trans (on different homologues) conformation.

Crick – a positive, plus (+) strand of the reference genome and also a read that aligns in this direction.

Direct (experimental) haplotyping – direct observation of alleles on a single molecule of DNA which represent haploid part of the genome.

Fosmid – an artificial construct consisting of bacterial DNA that includes section of cloned genomic DNA of ~ 40kb in length.

Genetic haplotyping – the process of assignment the phase to the observed alleles in a form of genotypes according to the principles of Mendelian segregation of alleles in pedigrees.

Genotype – represent particular combination of alleles of a given organism, however, relative position of alleles along the single homologue is unknown.

Haplotype – contiguous set of genetic variants that are co-located on the same homologous chromosome and are inherited from the same parent.

Linkage disequilibrium – represents nonrandom segregation of alleles at different loci in a population. Linkage disequilibrium decreases with genomic distance and is not present between alleles residing on different chromosomes.

Long-read sequencing – sequencing technology with raw read average size longer than 1kb. Technologies that rely on assembly of short reads into a long ones belongs here as well.

N50 value – standardized value used to evaluate achieved contiguity of assembled haplotypes and represents the smallest haplotype block in which the sum of that block and all larger blocks total to 50% of the complete haplotype assembly.

Population-based haplotyping – the process of inferring the most likely phasing of common alleles from unordered genotype information based on the frequency of shared haplotype block in a large populations

Homologous chromosomes – pair of chromosomes each inherited from one parent.

Homozygous allele – a locus in the genome where both homologues share the same allele.

Heterozygous allele – a locus in the genome where both homologues chromosomes differ and carry different alleles.

Homozygosity regions – localized regions of the genome at which both homologues chromosomes are identical.

Indel – genetic variant that includes insertions and deletions of relatively short size (< 50bp).

Loss of heterozygosity – loss of the normal, functional allele at a heterozygous locus resulting in a homozygous conformation of alleles.

Paired-end reads – two reads sequenced from the opposite ends of the same DNA fragment, further defined by a specific insert size

Phasing – process of assignment of genetic variants (alleles) to one of two homologous chromosomes. Phase then denotes the relative position of alleles at a given locus.



APPENDICES

Recombination event – position where two homologous chromosomes cross-over and exchange pieces of DNA information during meiosis.

Strand-seq – single cell sequencing technique able to distinguish inherited parental template strands based on the directionality they map to the reference genome.

StrandPhase – software package that specifically interrogates haplotype informative (WC regions) in every Strand-seq library and uses greedy algorithm to obtain consensus haplotypes.

StrandPhaseR – software package that specifically interrogates haplotype informative (WC regions) in every Strand-seq library and uses binary sorting of Watson and Crick strands to obtain consensus haplotypes.

Structural variation – copy number variants (insertion, deletions) or copy number neutral differences between two homologous chromosomes.

Template state – the relative proportion of Watson and Crick reads in a chromosome (or shorter chromosomal region) in a Strand-seq library. We distinguish WW, WC or CC template state in a Strand-seq library.

Watson – a negative , minus ('-') strand of the reference genome and also a read that aligns in this direction.

WC region – a template strand state that consists of approximately equal proportions of reads aligned to the minus ('-') and plus ('+') strand of the reference genome. Such regions are haplotype informative.

Minimal error correction problem – focuses on correction of a minimal number of bases in the error-prone sequencing reads such that they can be partitioned into two conflict free sets representing the two haplotypes. Weighted version of this problem is abbreviated as wMEC.

List of abbreviations

BAIT	Bioinformatic analysis of inherited templates
BAM	Binary alignment map
bp	base pair
BrdU	5-Bromo-2'-deoxyuridine
C	Crick (template strand orientation) or Child's homologue
CC	Crick-Crick (template strand inheritance)
CNV	Copy number variation
Chr	Chromosome
CPT	Contiguity-preserving transposition
DNA	Deoxyribonucleic acid
F	Father's homologue
FACS	Fluorescent activated cell sorting
GC	Guanin-Cytosine pair
H1,2	Homologous one or two
HLA	Human leukocyte antigen
HMW	High molecular weight
kb	kilobase(s)
LD	Linkage disequilibrium
LOH	Loss of heterozygosity
M	Mother's homologue
Mb	Megabase(s)
MDA	Multiple displacement amplification
MEC	Minimal error correction
NGS	Next-generation sequencing
NCBI	National Center for Biotechnology Information
IGV	Integrated genome viewer
PCR	Polymerase Chain Reaction
PE	Paired-end (read)
SCE	Sister chromatid exchange
SCS	Single-cell sequencing
SD	Standard deviation
SE	Single-end (read)
SNV	Single nucleotide variant
SV	Structural variant
VCF	Variant calling format
W	Watson (template strand orientation)
WC	Watson-Crick (template strand inheritance)
WGA	Whole genome amplification
WGS	Whole genome sequencing
WW	Watson-Watson (template strand inheritance)
UCSC	University of California, Santa Cruz



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APPENDICES

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List of publications

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THE END

