Institution: University of Oxford

Unit of Assessment: 10

Title of case study: Pharmaceutical and biotechnology companies gain economic benefits from novel statistical methods for imputing genotypes

1. Summary of the impact

In genetic studies of human disease it is now routine for studies to collect genetic data on thousands of individuals with and without a particular disease. However, the genetic data collected is incomplete, with many millions of sites of the genome unmeasured. The novel methods and software (IMPUTE) developed by researchers at the University of Oxford predict unobserved genetic data using reference datasets.

IMPUTE has been adopted by the company Affymetrix in the design of custom genotyping chips. Affymetrix recently won the tenders by the UK Biobank and UKBiLEVE studies to genotype >500,000 participants, with a total study cost of ~£25M. The company states that IMPUTE gave their project bid a significant competitive advantage. Affymetrix also purchased the IMPUTE source code for £250,000. In addition, Roche Pharmaceuticals have used the software in their research on the genetic basis of drug response. The use of imputation has saved Roche ~$1,000,000.

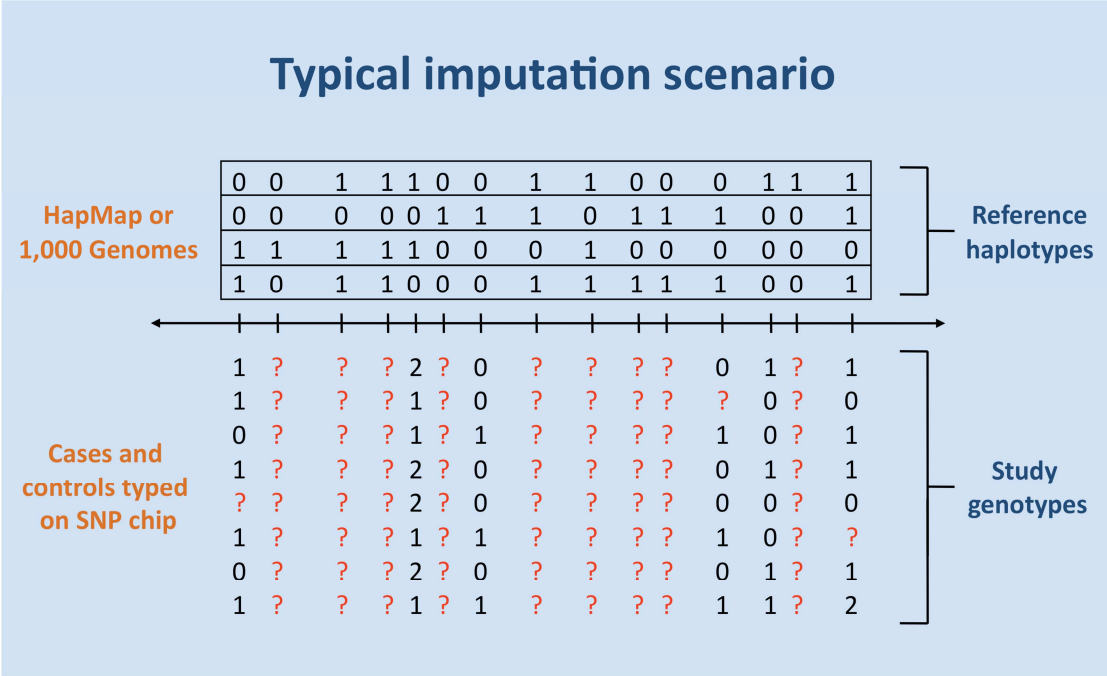
2. Underpinning research

Genome-wide association studies (GWAS) aim to identify genes that increase risk of developing a disease under study. A typical study will measure up to a million variable positions across the genome, called single nucleotide polymorphisms (SNPs), in thousands of subjects, and look for significant differences between individuals with and without the disease. The identification of these disease genes can help understanding of the disease mechanisms. Since only a fraction of sites that are known to vary between humans are measured, there is a substantial amount of genetic data that is unobserved. However, reference databases such as the 1000 Genomes Project (TGP) contain many more SNPs. The July 2012 TGP release contains 38 million SNPs. The methodology developed at the University of Oxford combines the data from a GWAS with the TGP database and predicts the unobserved genotypes.

The first approach at predicting, or imputing, unobserved genotypes was developed by Dr Marchini and Professor Donnelly, both faculty members at the University of Oxford, as part of their involvement in the Wellcome Trust Case Control Consortium (WTCCC) [1], during the period of 2006-2007. They realized that genetic studies of human disease could be substantially improved if unobserved genotypes could be predicted using the existing reference databases, and that recently developed Hidden Markov models developed in the area of population genetics could be adapted to carry out this task. Their approach, IMPUTE v1 [2], was developed by Marchini and applied successfully to all 7 disease studies carried out by the WTCCC. This paper has over 1,000 citations since 2007. The figure below illustrates the typical imputation scenario, where a reference panel of haplotypes is combined with a GWAS. The figure highlights that a large fraction of genotypes are unobserved (indicated by question marks). IMPUTE can predict this missing data using shared patterns of haplotypes between the two datasets. For common genetic variants of interest, the accuracy of imputation is over 95%.

There have been over 1,350 published GWAS since 2005 (www.genome.gov/gwastudies). Imputation has been used in the vast majority of these, evidenced by the large number of citations of our papers on imputation. One key benefit of the method is that once unobserved genotypes have been predicted in several different studies, they can then be combined, via meta-analysis, to produce much more powerful studies. This approach has changed the field of human genetics and groups now routinely share data via this approach. One of the earliest examples of this was in the study of Type 2 Diabetes and lead to the discovery of 6 new disease genes [3].

Subsequently, Marchini and Donnelly realized that as reference panels increase in size, through ongoing projects such as the TGP, the method IMPUTE v1 would not scale well. Marchini led the development of IMPUTE v2 which extends the approach by adaptively selecting a subset of the reference database to use for predicting each individual. Another insight was that this approach naturally allows the use of reference panels from multiple populations. For example, when predicting genotypes in an individual with European ancestry the method would select the subset of the reference database that matches the individual's ancestry [4,5].



A further paper published in Nature Genetics [6] develops a new two-step imputation process, first by estimating haplotypes in the GWAS sample, then using haploid imputation. The second step is very fast and reduces the computational cost needed by a factor of at least 20.

From 2002-2005, Marchini held a Wellcome Trust Postdoctoral Fellowship at the University of Oxford and since 2005 has been a University Lecturer in Statistical Genomics. Donnelly has been a Professor of Statistical Science since 1996. From 2007 he has also been Director of the Wellcome Trust Centre for Human Genetics, University of Oxford.

3. References to the research

*[1] The Wellcome Trust Case Control Consortium (2007) Genomewide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447 661-78. doi:10.1038/nature05911.

*[2] J. Marchini, B. Howie, S. Myers, G. McVean and P. Donnelly (2007) A new multipoint method for genome-wide association studies via imputation of genotypes. *Nature Genetics* 39 906-913. doi:10.1038/ng2088.

[3] E. Zeggini, L. Scott, R. Saxena, B. Voight, J. Marchini et al. (2008) Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nature genetics* 2008;40;5;638-45. doi:10.1038/ng.120.

*[4] B. Howie, P. Donnelly, J. Marchini (2009) A Flexible and Accurate Genotype Imputation Method for the Next Generation of Genome-Wide Association Studies. *PLoS Genetics* 5(6): e1000529. doi:10.1371/journal.pgen.1000529.

[5] B. Howie, J. Marchini, M. Stephens (2011) Genotype Imputation with Thousands of Genomes. *G3 : Genes, Genomes, Genetics*. doi: 10.1534/g3.111.001198.

[6] B. Howie, C. Fuchsberger, M. Stephens, J. Marchini, and G. R. Abecasis (2012) Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nature Genetics* 44, 955-959. doi: 10.1038/ng.2354.

The three asterisked outputs best indicate the quality of the underpinning research. All six papers are in high quality internationally refereed journals.

4. Details of the impact

There are two main areas where IMPUTE software has made an economic impact on companies working in the area of genetics and pharmaceuticals:

- IMPUTE has had a significant impact on the company Affymetrix. It has led to the introduction of new products and has significantly changed a design process. The company has benefited by recently winning a genotyping contract worth ~£25M.
- IMPUTE has led to the improvement of a drug response study carried out by Roche. This saved the company an estimated ~$1,000,000.

Affymetrix licensed the source code for both IMPUTE v1 (2009) and v2 (2010) from Oxford University for £250,000 [A]. Affymetrix use Impute v2 as a central part of the process of designing both generic and custom-made SNP chips (a chip is a collection of microscopic DNA spots attached to a solid surface). In addition, licences for use of the software, without the source code, worth ~£70,000 in total have been sold to Genentech (2008), GlaxoSmithKline (2008), Biocomputing Platforms Ltd. (2009) and PGxHealth (2010) [A]. IMPUTE has also been used in a study of drug response by Roche via a 2011 consultancy agreement with Marchini.

Optimizing product design at Affymetrix using IMPUTE

Genotype imputation is now a central method in human genetics utilized by researchers carrying out GWAS. The method is usually applied to data collected from genome-wide SNP arrays. Affymetrix is a $300M US company that makes such arrays together with the equipment and reagents to run the experiments. Such equipment is essential in any lab carrying out its own GWAS.

The company has used IMPUTE in the design process for a new series of population-specific arrays called the "AxiomTM Genome-Wide EUR, EAS, LAT and AFR Arrays", targeted at the European, East Asian, Latino and African populations. These arrays are sold commercially to research groups carrying out GWAS [B,C]. Affymetrix recently won the bids to genotype >500,000 participants for the UKBiLEVE (http://www.mrc.ac.uk/Newspublications/News/MRC008925) and UK Biobank (http://www.ukbiobank.ac.uk/) studies, with a total study cost of ~£25M. The UK Biobank project is the largest single genotyping study on record in the world as well as the largest single project in the Affymetrix Genotypic revenue base [B]. The company states that "*a significant competitive advantage of the Affymetrix proposal was a custom GWAS grid that draws significant power from using IMPUTE2 in its design*" [D].

The Vice President for Informatics at Affymetrix says in [B] "*The impute software that we licenced from Oxford University has been used extensively at Affymetrix and is an essential tool used to compute and describe the coverage of our genotypic arrays.* […] *In particular, the SNPs on these arrays were selected in such a way as to maximize imputation coverage. This has made a significant impact in the way we design arrays and could not have happened without using IMPUTE2, which has been shown to be the most accurate method of imputation in the literature.* […] *Affymetrix had total revenues of about $300 million in 2012 and is using IMPUTE2 in the design and dissemination of all its genotyping products Affymetrix has a significant and rapidly growing share of the worldwide market for genotyping arrays, the size of which is on the order of $600m million annually*."

Roche saved ~$1,000,000 by using IMPUTE in a study of drug response

Pharmacogenetics is a particular type of GWAS applied to subjects that do or do not have an adverse reaction to a particular medication. Many medications exhibit a variable response rate that is thought to be partly genetic. Therefore, there is a great interest in discovering biomarkers that aid physician decision making, through the identification of patients who will or will not respond, and therefore derive greater benefit from a particular therapy.

The pharmaceutical company Roche has investigated the genetics of response to the drug tocilizumab for the treatment of rheumatoid arthritis (RA). Tocilizumab is prescribed to RA patients who had inadequate response to disease modifying anti-rheumatic drugs. Genotype imputation using IMPUTE v2 was used in this study to combine studies together for greater power. Since the subjects in these studies had a variety of different ancestries the use of IMPUTE v2 together with the HapMap3 reference panel provided an ideal and practical solution to the prediction of the unobserved genotypes in each study. The study was able to implicate the involvement of 8 loci in the patient response to tocilizumab treatment. Patients carrying the specific genetic markers had a higher remission compared to those who did not [F].

The Roche study used three different Illumina genotyping chips (550K, Human1M-Duo and HumanOmni1-Quad) on different sets of individuals. A Senior Statistical Scientist at Roche [E] states "*The IMPUTE program was used and generated high quality data for the union set of SNPs on the three chips. This allowed us to analyse the data from all 1600 patients together…..Without the genetic data imputation carried out with IMPUTE, the best way to reproduce the study would be to genotype all study samples using an IlluminaOmni1-Quad chip. This would have involved re-genotyping 1,157 samples at a cost of $750 each plus an additional operational cost of 20%.* Therefore *the total cost saving is ~$1,000,000. In addition to the cost saving, the imputation work also allowed us to save time and complete the analysis in time to meet decision timelines set by the development program*".

5. Sources to corroborate the impact

[A] Letter from Technology Transfer Team Leader, ISIS Innovation, Oxford, held by the University of Oxford, which corroborates licensing deals and software sales for IMPUTE.

[B] Letter from Vice President Informatics, Affymetrix, held by the University of Oxford, which corroborates how Affymetrix have made use of IMPUTE.

[C] Affymetrix press release giving details of their Axiom arrays and how IMPUTE was used to design the arrays, copy held by the University of Oxford

[D] Affymetrix press release giving details of contract with UK Biobank, copy held by the University of Oxford

[E] Letter from Senior Statistical Scientist, Roche, held by the University of Oxford, describing the use of IMPUTE in their pharmacogenetic study of Tocilizumab for the treatment of rheumatoid arthritis.

[F] Paper describing Roche's pharmacogenetic study of Tocilizumab, confirming the use of IMPUTE in their study.

Wang J et al. (2011) Genome-wide association analysis implicates the involvement of 8 loci with response to tocilizumab for the treatment of rheumatoid arthritis *The Pharmacogenomics Journal* 44, 955-960, doi: 10.1038/tpj.2012.8