Subset-Based Ant Colony Optimisation for the Discovery of Gene-Gene Interactions in Genome Wide Association Studies

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ABSTRACT

In this paper an ant colony optimisation approach for the discovery of gene-gene interactions in genome-wide association study (GWAS) data is proposed. The subset-based approach includes a novel encoding mechanism and tournament selection to analyse full scale GWAS data consisting of hundreds of thousands of variables to discover associations between combinations of small DNA changes and Type II diabetes. The method is tested on a large established database from the Wellcome Trust Case Control Consortium and is shown to discover combinations that are statistically significant and biologically relevant within reasonable computational time.

Categories and Subject Descriptors

J.3 [Life and Medical Sciences]: Biology and Genetics; G.1.6 [Numerical Analysis]: Optimization—Stochastic programming, Global optimization

Keywords

Ant Colony Optimisation, Genome Wide Association, Type II Diabetes, Single-Nucleotide Polymorphisms

1. INTRODUCTION

The entire human genome has been known for less than a decade, and yet next-generation sequencing methods mean that sequencing genomes has never been cheaper, and are about to fall below the $1,000 barrier. Researchers therefore are now able to sequence many hundreds or thousands of individuals, allowing an unprecedented view of disease and variation in traits across populations. These studies, known as genome-wide association studies (GWASs), investigate the relationship between small changes in the genome called Single Nucleotide Polymorphisms (SNPs) and the propensity to develop certain diseases such as Type I and Type II diabetes. These studies offer the potential to illuminate the genetic causes of disease and provide an opportunity for early treatment and planning for patients leading to profound social and economic benefits.

From a computational perspective GWASs present a significant challenge as the number of variables per individual is large (approximately 500,000 in this study) per individual and in the majority of studies these are recorded for thousands of individuals. Any computational approaches used to analyse these data therefore must be scalable in the face of these large-scale data. This paper presents a subset-based tournament ant colony approach to the analysis of full-scale GWAS data with the aim to find combinations of SNPs (gene-gene interactions) that have association with Type II diabetes across a population of 5,003 individuals.

1.1 Previous Research

Many examples of GWAS data analysis exist in the literature that demonstrate the association between a single SNP and disease. There are known single associations for Type II diabetes and traits such as height for instance. However, there is a considerable amount of missing heritability, for example only about 10% of variation in height can be explained by traditional GWAS. This missing heritability could be due to rare variants, or to the combination of SNPs (gene-gene interactions) which have rarely been explored in the past. Standard GWAS analyses are carried out through full enumeration and with modern hardware, the association of hundreds of thousands SNPs with a disease can be determined within reasonable computational time. However, when combinations (pairs, triplets and higher) are considered, the computational load becomes highly burdensome or completely intractable. This has led to the adoption of metaheuristics [13] for this purpose and previous research has shown ant colony optimisation (ACO) to be a promising technique [7] [1].

ACO has also been shown to deliver excellent results on discrete combinatorial test problems [3] and has been widely applied to real-world problems ranging from water distribution system optimisation [19, 17] to bioinformatics.

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Copyright 2013 ACM 978-1-4503-1963-8/13/07 ...$15.00.
It is worth noting that here, a metaheuristic is successfully applied to a full set of GWAS data, comprising many SNPs and individuals without expert knowledge. Whereas previously ACO has only been applied to a single chromosome of real data [1] or with expert knowledge and test data [7].

1.2 Type II Diabetes

Type II diabetes (T2D), characterized by insulin resistance, affects more than 170 million people worldwide [12] and the heritability of this disease has been shown widely in previous studies [16]. Zeggini et al. [20] provide insight into the genetic architecture of T2D detecting replicated diabetes association signals. Glyn et al. [6] evaluated the role of genetic variants to confirm if they increase risk of T2D and Grant et al. [14] identified a common genetic variant in Type II diabetes mellitus and it does not appear to be in a coding region. However identifying genetic risk in T2D has met with only limited success [8] and therefore remains a formidable challenge [10].

1.3 Data

This research uses the database of The Wellcome Trust Case Control Consortium (WTCCC) which is a collection of GWAS studies relating to a variety of diseases including Type II Diabetes [2]. In this database, a total of 5003 human genomes are provided, with ∼500,000 SNPs recorded for each individual in the database. Each SNP represents a small change in the genome and consists of two alleles (two letters among A, C, G, T). Due to the diploid nature of human genomes, there are three possible genotypes for each SNP (e.g. CC, GG, CG).

2. METHOD

2.1 Memory Management

The database on which the research is based is composed of a sample of the genome of 1,999 individuals with Type II diabetes (Cases) and 3,004 control individuals. Each sample of genome is composed of 490,294 single-nucleotide polymorphisms (SNPs) that can have the values unknown, common homozygous e.g. CC, heterozygous e.g CG, rare homozygous e.g. GG. The sample of the genome of the 5,003 individuals were stored on a hard drive in files. It required 95 minutes to open and to read these files using a machine with a 1TB 7200RPM hard-drive and an Intel Core i7-2600 CPU @3.40GHz processor.

An ACO run may require over a million fitness function evaluations and so even a small improvement in complexity of this function will have a large impact on performance. A function that requires the searching of a database on disk will lead to run times orders of magnitude longer than one in which the data are stored in memory. However, with more than 2 billion elements to represent (5,003 individuals × 490,294 SNPs), each SNP cannot be represented by more than 1-2 bytes in memory for normal desktop memory sizes (the above machine has 8GB RAM). The representation below implements a lossless compression of the data that enables it to be kept in memory when considering whole genome analysis.

In order to reduce the time to access to the database, two files ‘diabetes’ and ‘controls’ were generated. In these two files, the four values 0, 1, 2 and 3 for SNPs encode respectively unknown, common homozygous, heterozygous and rare homozygous, such that four SNPs of an individual are encoded in one byte (4^4 = 256). For example, if snp1 is heterozygous, snp2 is unknown, snp3 is common homozygous and snp4 is rare homozygous, then the encoding is 147 (64 × 2 (Heterozygous) + 16 × 0 (Unknown) + 4 × 1 (Common homozygous) + 1 × 3 (Rare homozygous)).

Using this encoding only 1 minute 13 seconds is required to open and to read the files ‘diabetes’ and ‘controls’ using the same machine specification.

Using this representation the size of the database is 490,294 (number of SNPs) × 5,003 (number of individuals) / 4 (number of SNPs per byte) = 0.585 Gigabytes therefore it is possible to store the database entirely in RAM, significantly reducing loading times and greatly reducing the run time of the ACO method.

2.2 Exclusion of SNPs

GWAS data have to undergo a series of quality control tests before it can be used. Therefore there are some exclusion criteria that must be applied to ensure the quality of the remaining data. The SNPs that were kept are those that met these four conditions in the 3,004 control samples.

- Hardy-Weinberg equilibrium Exact Test > 10^{-4}
- Minor allele frequency > 1 % for these 3,004 individuals
- Studywise missing data proportion < 5% for these 3,004 individuals
- Studywise minor allele frequency > 5% for these 3,004 individuals or studywise missing data proportion < 1% for these 3,004 individuals

and meeting these two conditions in the 1,999 samples of genomes of individuals with Type II diabetes:

- Hardy-Weinberg equilibrium Exact Test > 10^{-4}
- Minor allele frequency > 1% for these 1,999 individuals

The resulting filtered dataset contains 405,139 SNPs.

2.3 Tournament ACO Algorithm

As described above, this paper is concerned with the combinations of two SNPs that can discriminate Type II diabetes (T2D). The type of combination that is considered here is the following: An individual is positive if and only if

\[ \text{value}_1 \neq \text{value}_2 \]

for these 3,004 individuals

\[ \text{value}_1 \neq \text{value}_2 \]

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Readers are asked to refer to the GWAS literature for more information on these criteria [5].

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- Minor allele frequency > 1 % for these 3,004 individuals
- Studywise missing data proportion < 5% for these 3,004 individuals
- Studywise minor allele frequency > 5% for these 3,004 individuals or studywise missing data proportion < 1% for these 3,004 individuals

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and subset problems differ in the way the pheromone trail is laid on the construction graph. For ordering problems, the connections between elements of the problem receive the pheromone whereas the components themselves receive pheromone in subset problems. The ACO algorithm uses the representation described by Leguizamon and Michalewicz as the ordering of SNPs is not important in the problem formulation.

2.4 Algorithm

Ant Colony Optimisation (ACO) is used to search for combinations of SNPs that can discriminate the T2D and control populations. A value is associated to every SNP that represents how good the combination of SNPs is at discriminating between these two classes. This value \( P(n) \) is called the amount of pheromone of the SNP \( n \). The amount of pheromones \( P \) is used to guide a tournament selection process to select SNPs for new combinations.

The algorithm can be described as follow:

1. Initialise pheromone on each SNP
2. Repeat
3. For all the \( nbant \) ants:
4. Select two SNPs via tournament selection (see section below)
5. Calculate the fitness of the combination
6. End
7. Updated pheromone of the two SNPs with the best fitness
8. For all SNPs: apply evaporation rate \( e \)
9. End

Where:
- \( nbant \): numbers of ants of the algorithm;
- \( e \): evaporation rate;

2.4.1 Initialisation of the Pheromone Trail

The pheromone trails were initialised to the highest allelic odds ratio of each individual SNP, although in additional experiments the uniform initialisation of trails to 1 was found to produce similar results.

2.4.2 Tournament Selection

Selecting SNPs for new combinations based on their pheromone value is a key point of the ACO algorithm. Standard ant colony optimisation algorithms use a roulette wheel type structure for this purpose but for 405,139 SNPs, the implementation of a roulette wheel will slow down the algorithm and a tournament selection was proven to be better for high dimension problems [4]. In the tournament-based approach a number of \( nbt \) SNPs are randomly selected from the possible set to form a tournament and the SNP with the highest amount of pheromone among them is selected as part of this solution. This is the standard method for tournament selection as used in evolutionary algorithms and the tournament size \( t \) can be varied to alter the speed of convergence of the algorithm.

2.4.3 Fitness Function

The value of fitness function depends on the two chosen SNPs \( snp1 \) and \( snp2 \) and the two values \( value1 \) and \( value2 \). For each control and case the following test is performed.

\[ \text{sn}p1 = \text{value}1 \text{ and } \text{sn}p2 = \text{value}2 \]

The numbers of positive and negative controls \( C_p \) and \( C_n \) and the number of positive and negative cases \( D_p \) and \( D_n \) are determined. The expected values \( E.C_p \), \( E.C_n \), \( E.D_p \) and \( E.D_n \) for \( C_p \), \( C_n \), \( D_p \) and \( D_n \) are calculated as shown in table 1.

The chi square for \( value1 \) and \( value2 \) is given by the formula:

\[
\text{Chi}^2_{value1, value2} = \frac{(E.D_p - D_p)^2}{E.D_p} + \frac{(E.D_n - D_n)^2}{E.D_n} + \frac{(E.C_p - C_p)^2}{E.C_p} + \frac{(E.C_n - C_n)^2}{E.C_n}
\]

There are three possible values (Common Homozygous, Heterozygous, Rare Homozygous) for \( value1 \) and again three possible values for \( value2 \). Therefore there are 9 \( (3 \times 3) \) different chi square values and the largest of these is selected as the value \( f \) of the fitness function of the combination of the two SNPs \( snp1 \) and \( snp2 \).

\[ f = \max\{\text{Chi}^2_{value1, value2}\} \text{ such that } (value1, value2) \in \{\text{Common Homozygous, Heterozygous, Rare Homozygous}\}^2 \]

From the chi square the p-value (probability of achieving this result through chance) of the association can be calculated.

2.4.4 Updating Pheromone

The amounts of pheromone of the two SNPs containing in the combination with the highest fitness \( f \) among the \( nbant \) combinations (for each ant a combination of two SNPs is chosen) are updated. For the two amounts of pheromones the following are applied:

\[ P(snp1) = P(snp1) + f \]
\[ P(snp2) = P(snp2) + f \]

2.4.5 Evaporation

For all SNPs, the following equation with an evaporation rate of 1% is applied:

\[ P(snp) = P(snp) \times 0.99 \]

3. EXPERIMENTATION

3.1 Monte Carlo Approach

A key aspect of the analysis of GWAS data is that any discovered associations should be checked to determine the likelihood that they could have been generated by chance. The statistics presented in the tables in later sections provide statistical measures of this by calculating odds ratios, chi-squared and p-values but to gain a more in-depth understanding of the performance of the ACO, and the probability of discovering these results by chance, one million random pairs of SNPs were generated and tested using the above fitness function. The average p-value of these pairs is \( 3.5 \times 10^{-7} \), the best is \( 1.9 \times 10^{-13} \). Figure 1 shows the distribution of the p-value of the one million combinations of SNPs.

3.2 Parameters

The key parameters of the ACO algorithm are:
- \( nbant \): Numbers of ants of the algorithm
- \( nbt \): Number of SNPs in the tournament of the selection process.

An investigation into these parameters was conducted to determine the effect of changing the population size and
Table 1: Calculation of the expected values \( E.C_p \), \( E.C_n \), \( E.D_p \) and \( E.D.n \) for \( C_p \), \( C_n \), \( D_p \) and \( D_n \).

<table>
<thead>
<tr>
<th>( E.D_p )</th>
<th>( E.D_n )</th>
<th>( D_p + D_n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{D_p + D_n \times (D_p + C_p)}{D_p + D_n + C_p + C_n} )</td>
<td>( \frac{D_p + D_n \times (D_n + C_p)}{D_p + D_n + C_p + C_n} )</td>
<td>( \frac{D_p + D_n \times (C_p + C_n)}{D_p + D_n + C_p + C_n} )</td>
</tr>
</tbody>
</table>

\( E.D.p \) = \( \frac{(D_p + D_n) \times (D_p + C_p)}{D_p + D_n + C_p + C_n} \)

\( E.D.n \) = \( \frac{(D_p + D_n) \times (D_n + C_p)}{D_p + D_n + C_p + C_n} \)

\( E.D.p \) = \( \frac{(C_p + C_n) \times (D_p + D_n)}{D_p + D_n + C_p + C_n} \)

\( E.D.n \) = \( \frac{(C_p + C_n) \times (D_n + D_n)}{D_p + D_n + C_p + C_n} \)

Table 4: Result of the association rs7031174 = Het. and rs7045471 = Com. Hom.

<table>
<thead>
<tr>
<th>Rs number</th>
<th>position</th>
<th>Chromosome</th>
<th>Allelic OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7031174</td>
<td>36651528</td>
<td>9</td>
<td>1.178</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>1397</td>
<td>443</td>
<td>15</td>
</tr>
<tr>
<td>Controls</td>
<td>2266</td>
<td>557</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 3: SNP of rs number 7045471.

<table>
<thead>
<tr>
<th>Rs number</th>
<th>position</th>
<th>Chromosome</th>
<th>Allelic OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7045471</td>
<td>30603003</td>
<td>9</td>
<td>0.821</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>1647</td>
<td>321</td>
<td>17</td>
</tr>
<tr>
<td>Controls</td>
<td>2388</td>
<td>393</td>
<td>37</td>
</tr>
</tbody>
</table>

4. RESULTS

The best results of 10 algorithm runs over 10000 generations with 100 ants and 50 items in the tournament size were saved into files. With these parameters, a generation of the algorithm lasts on average 1.28 seconds so a run lasts an average of 3 hours and 32 minutes using a machine with a processor and a hard drive as outlined in the method section.

The ACO algorithm found good results for combinations of two SNPs. The first combination presented here has not previously been known to discriminate T2D where the second is known to discriminate T2D. The last subsection presents a sample of the best combinations that were discovered.
However, SNPs in similar regions on the genome are often correlated through a phenomenon known as linkage disequilibrium (LD), and these two SNPs have very similar locations on the genome (36651528 and 36603003) meaning this association is therefore likely to be an artefact of LD, despite it being the strongest statistical signal discovered within this dataset.

There is evidence that this run of the algorithm has found a combination of SNPs that are statistically significantly associated with Type II Diabetes, although LD meant that the result had to be rejected.

There is some evidence that at least one of the SNPs has previously been found to be significant, although not in Type II Diabetes. In [18], the SNP of rs number 7031174 has been found:

The locus rs7031174 resides at the intron of gene MELK. MELK has been found significantly over-expressed in the great majority of breast cancer cells (Involvement of maternal embryonic leucine zipper kinase (MELK) in mammary carcinogenesis through interaction with Bcl-G, a pro-apoptotic member of the Bcl-2 family).

Also the SNPs rs7031174 and rs7045471 are discussed in a previous study [15].

For the combination shown in Table 4, an individual is positive if and only if the SNP rs7031174 is heterozygous and the SNP rs7045471 is common homozygous:

Positive $\iff$ rs7031174 = CA AND rs7045471 = AA

4.2 Combination of SNPs

Although the previous combination is likely to be due to LD, the population-based nature of the ACO algorithm permits the exploration of other combinations that are more promising from a biological perspective. The SNPs that appear individually in tables 5 and 6 and in combination in table 7, are located on different chromosomes and therefore cannot be in LD and demonstrates one the best results discovered by the algorithm across two chromosomes.

This combination is clearly not as statistically significant as the previous one with a p-value of $4 \times 10^{-15}$. However, it is still far in exceedance of the p-values obtained by monte-carlo search ($10^{-13}$). Additionally, there is evidence in the biology literature that at least one of the SNPs has been previously associated with Type II diabetes. The SNP of rs number 7901695 is in the gene TCF7L2 that is described as follows in [20]:

TCF7L2 transcription factor 7-like 2 (T-cell specific, HMG-box) [ Homo sapiens ], This gene encodes a high mobility group (HMG) box-containing transcription factor that plays a key role in the Wnt signaling pathway. The protein has been implicated in blood glucose homeostasis. Genetic variants of this gene are associated with increased risk of type II diabetes. Several transcript variants encoding multiple different isoforms have been found for this gene.

The second SNP has not yet been identified as significant.
### Table 5: SNP of rs number 7901695.

<table>
<thead>
<tr>
<th>Rs number</th>
<th>position</th>
<th>Chromosome</th>
<th>Allelic OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7901695</td>
<td>114744078</td>
<td>10</td>
<td>1.371</td>
</tr>
<tr>
<td>Diabetics</td>
<td>721</td>
<td>TT</td>
<td>296</td>
</tr>
<tr>
<td>Controls</td>
<td>1367</td>
<td>TC</td>
<td>295</td>
</tr>
</tbody>
</table>

### Table 6: SNP of rs number 9508846.

<table>
<thead>
<tr>
<th>Rs number</th>
<th>position</th>
<th>Chromosome</th>
<th>Allelic OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>9508846</td>
<td>30306076</td>
<td>13</td>
<td>1.186</td>
</tr>
<tr>
<td>Diabetics</td>
<td>1016</td>
<td>GG</td>
<td>75</td>
</tr>
<tr>
<td>Controls</td>
<td>1823</td>
<td>GA</td>
<td>128</td>
</tr>
</tbody>
</table>

### Table 7: Result of the association rs9508846 = Com. Hom. and rs7901695 = Com. Hom..

<table>
<thead>
<tr>
<th>Combination</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs4506565=TT AND rs17489797=TT</td>
<td>1.2×10^{-17}</td>
</tr>
<tr>
<td>rs12243326=AA AND rs17489797=TT</td>
<td>1.1×10^{-15}</td>
</tr>
<tr>
<td>rs9508846=GG AND rs4506565=TT</td>
<td>2.5×10^{-15}</td>
</tr>
<tr>
<td>rs9508846=GG AND rs7901695=TT</td>
<td>3.8×10^{-15}</td>
</tr>
<tr>
<td>rs4132670=GG AND rs9508846=GG</td>
<td>1.6×10^{-15}</td>
</tr>
<tr>
<td>rs7077039=CC AND rs1935683=TT</td>
<td>4.4×10^{-15}</td>
</tr>
<tr>
<td>rs4506565=TT AND rs1814931=GG</td>
<td>5.6×10^{-15}</td>
</tr>
<tr>
<td>rs7901695=TT AND rs903228=CC</td>
<td>1.4×10^{-14}</td>
</tr>
</tbody>
</table>

### Table 8: Sample of the best combinations and their p-value that were discovered.

In diabetes and it does not correspond to any known gene function at present.

For this combination, an individual is positive if and only if the SNP rs9508846 is common homozygous and rs7901695 is common homozygous:

Positive $\iff$ rs9508846 = GG AND rs7901695 = TT

### 4.3 Sample of the Best Combinations

Table 8 shows a collection of the best results discovered by the ant colony approach on this dataset, again all with significantly smaller p-values than those discovered by the montecarlo search. Rs4506565 that appears multiple times and rs12243326 are both polymorphisms related to the TCF7L2 gene (in addition to rs7901695 reported above) and therefore have been shown to be related to Type II diabetes. This clearly shows that the ACO algorithm is capable of discovering highly discriminatory associations SNP combinations with some biological plausibility.

### 5. CONCLUSION

An ant colony approach to the problem of discovering combinations of SNPs from large-scale GWAS data has been described. The algorithm has been adapted so as to be scalable to the size of dataset both in terms of its memory requirements through the use of a byte-wise representation of genomes and through the use of a tournament path selection to greatly increase execution speeds. These novel modifications to the algorithm are required to permit the execution of ACO on full-scale GWAS data and this is, to the best of our knowledge, the first time that an ACO method has been successfully applied to such data.

The algorithm is also able to discover higher order combinations of SNPs (e.g. 3+ SNPs, not shown) that would not be possible using existing methods. In this paper, combinations of two SNPs that can discriminate type II diabetes patients from controls have been discovered by the approach. The ACO has been able to find some of the strongest statistical signals in the dataset (although as explained above these have been ruled out on biological grounds) and has also found SNPs that have a known biological relationship to diabetes. Although other discovered SNPs do not at present have a known biological function, it is this discovery of plausible known information and targets for further investigation that make the approach a promising addition to the GWAS toolbox.

### 6. FURTHER WORK

A further step could be to determine which p-values can be expected at random in order to gain a more in-depth understanding of the quality of the results. These p-values can be obtained by running the ACO algorithm that is described here on shuffled data.

The ACO method can be applied to any GWAS dataset that conforms to the standard OXSTATS format and so further trials are planned on other disease datasets from the WTCCC, including Type I Diabetes and Rheumatoid Arthritis.

### 7. ACKNOWLEDGEMENTS

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