Efficient maximum likelihood pedigree reconstruction

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Abstract

A simple and efficient algorithm is presented for finding a maximum likelihood pedigree using microsatellite (STR) genotype information on a complete sample of related individuals. The computational complexity of the algorithm is at worst \(O(n^{3n})\), where \(n\) is the number of individuals. Thus it is possible to exhaustively search the space of all pedigrees of up to thirty individuals for one that maximizes the likelihood. A priori age and sex information can be used if available, but is not essential. The algorithm is applied in a simulation study, and to some real data on humans.

Key words: Pedigree reconstruction, Bayesian network, maximum likelihood

1. Introduction

There are a number of situations in which reconstructing the pedigree of related individuals from genetic data is of interest and importance, both in human and non-human populations. Biologists interested in (preserving) endangered species may have an interest in pedigree reconstruction, as it may help in inferring the population size, and the amount of inbreeding within the species. This in turn could help to determine both the genetic variability and viability of the species.

Mass-grave scenarios, or disasters in which the remains of many people are found and can only be identified by DNA profiles, can also lead to the prob-

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lem of reconstructing pedigrees. A quite famous historical case concerns that of the Russian royal family who disappeared during the Russian revolution of 1917. In July 1991, in a shallow grave 20 miles from Ekaterinburg, Russia, nine skeletons were found. From the size of some of the bones three were identified as children. The remains were believed to be the remains of Tsar Nicholas II, his wife, three of their five children, together with some servants, and the Royal Physician. A sophisticated DNA analysis of the remains, including comparison of mitochondrial DNA obtained from the remains to that obtained from blood donated by the Duke of Edinburgh (a grand-nephew of the Tsarina) confirmed the identification of the members of the Romanov family (Gill et al., 1994).

One approach to pedigree reconstruction using genotypic data is to find the pedigree having the maximum likelihood. This was developed by Thompson (1976) (see also (Thompson, 1986)) using age and sex information, and more recently by Almudevar (2003) who presented a simulated annealing algorithm that can run either with or without age and sex information. Both of these authors used a complete sample of individuals. This means that a parent of an individual is either in the sample, or if not he or she is unrelated to all other members in the sample. Under this assumption, the likelihood function for a given pedigree decomposes into a simple multiplicative form: this paper will also assume a complete sample. For recent reviews of pedigree reconstruction, see Jones and Ardren (2003) and Blouin (2003).

In recent years Bayesian network expert systems (Cowell et al., 1999) have been applied to model and analyse problems of forensic genetics. Dawid et al. (2002) describe how to use Bayesian networks to analyse problems of disputed paternity. Mortera (2005) and Cowell et al. (2007) have developed Bayesian networks to analyse mixed DNA samples, such as may be found at a crime scene. Lauritzen and Sheehan (2003) provide an overview of various Bayesian network representations for genetic modelling applications.

Within the Bayesian network community there has been much work in inferring Bayesian network structure from data; see, for example, Cooper and Herskovits (1992); Buntine (1996); Heckerman et al. (1994). Learning a pedi-
gree from genotypic data is similar to learning a Bayesian network from data, though the latter tends to be more complex. This is because the graphical structure of a pedigree is constrained so that an individual has at most two parents, and if sex information is available, they are of opposite sex. This considerably reduces the number of possible pedigrees on \( n \) individuals, compared to the number of Bayesian networks on \( n \) nodes; nevertheless the number of pedigrees still grows rapidly with \( n \).

Following on from work by Koivisto and Sood (2004), a Bayesian network structure learning algorithm capable of searching the complete space of Bayesian networks for up to \( n = 25 \) variables was proposed by Singh and Moore (2005). Subsequently a simpler and more efficient (and currently state-of-the-art) algorithm was proposed by Silander and Myllymäki (2006) that is able construct maximum scoring Bayesian networks with up to 32 variables. In this paper the latter algorithm is specialised and adapted to the purpose of reconstructing pedigrees using a complete sample. The algorithm is efficient—finding the maximum likelihood pedigree with 20 individuals takes around 1 second, whilst with 29 individuals the time rises to just over 8 minutes.\(^1\) Previously, an exhaustive search over all pedigrees on more than nine individuals would have been prohibitive (Egeland et al., 2000). As the complexity is similar to the Bayesian network learning algorithm of Silander and Myllymäki (2006), the pedigree reconstruction algorithm proposed in this paper will also be feasible for up to 32 individuals, the limit they suggest for their algorithm.

The plan of the paper is as follows. In the next section the pedigree reconstruction algorithm is presented. It is then applied in a simulation study of two pedigrees involving 20 individuals, and also to the Romanov mass grave dataset. The discussion section examines limitations of and potential uses and extensions of the current work.

\(^1\) All timings refer to calculations carried out using a computer with an AMD dual-core 1.96GHz processor, 2GB of ram running the Debian 4.1 Linux (etch) operating system.
2. The search algorithm

2.1. The likelihood function

We shall represent a given pedigree on $n$ individuals of known genotype graphically using a Bayesian network, in which each node represents the genotype of an individual. If $A$ and $B$ are nodes in the network, then a directed edge from $A$ to $B$ means that $A$ is a biological parent of $B$. Figure 1 shows a simple pedigree for two half siblings and their parents as a Bayesian network.

One property of the Bayesian network is that it is a directed acyclic graph. This means that you cannot start from some node, follow a path along edges in the directions of the arrows, and arrive back where you started. Biologically this corresponds to the logical requirement that an individual cannot be her/his own ancestor.

Suppose we have a given pedigree Bayesian network structure $G$, consisting of nodes $V$ and directed edge set $E$, where each node represents the genotype of an individual, and the genotypes of all individuals are known. Then each node of $G$ has one of three possible parent configurations:

- The node has no incoming arrows. Hence the individual is a *founder* in the pedigree.
- The node has one incoming arrow. Hence the individual has only one parent specified in the pedigree.
- The node has two incoming arrows. Hence both parents of the individual are in the pedigree.
Let $\mathcal{V}_0$ denote the set of nodes that have no incoming arrows, $\mathcal{V}_1$ the set of nodes that have one incoming arrow, and $\mathcal{V}_2$ denote the set of nodes that have two incoming arrows. Then following Almudevar (2003), we let $\alpha_1(g_i|g_j)$ denote the conditional probability that individual $i \in \mathcal{V}_1$ has genotype $g_i$ given one of its parents $j \in V$ has genotype $g_j$. Similarly, $\alpha_2(g_i|g_j, g_k)$ denotes the conditional probability that individual $i \in \mathcal{V}_2$ has genotype $g_i$ given that its two parents $j, k$ have genotypes $g_j$ and $g_k$ respectively. We let $\alpha_0(g_i)$ denote the (marginal) probability that individual $i \in \mathcal{V}_0$ has genotype $g_i$.

We shall assume Hardy-Weinberg equilibrium, so that the founders in the pedigree are unrelated (or marginally independent, in the Bayesian network terminology). Then, under the assumption of a complete sample, the likelihood of the pedigree $G$ decomposes into the product

$$L(G) = L_0(G)L_1(G)L_2(G),$$

where

$$L_0(G) = \prod_{i \in \mathcal{V}_0} \alpha_0(g_i),$$

$$L_1(G) = \prod_{i \in \mathcal{V}_1} \alpha_1(g_i|g_j),$$

$$L_2(G) = \prod_{i \in \mathcal{V}_2} \alpha_2(g_i|g_j, g_k).$$

For simplicity we shall also assume in the examples later in the paper that the STR markers in the marker system that specifies the genotypes are independent (unlinked), and that mutation does not take place. Under these extra assumptions, the likelihood terms $L_i(G)$ factorize further, as described by Almudevar (2003). (The algorithm presented in the next section does not require these additional assumptions, but it does require that the various $\alpha$ probabilities can be evaluated.)

Without loss of generality, we shall label the $|V|$ individuals with the integers $1, 2, \ldots, n$, and use the index 0 to represent a general “absent” individual. Then we may write, for $i, j$ and $k \in \{1, \ldots, n\}$:

$$\alpha_0(g_i) \equiv \alpha_2(g_i|g_0, g_0)$$
\[ \alpha_1(g_i|g_j) \equiv \alpha_2(g_i|g_j, g_0) = \alpha_2(g_i|g_0, g_j) \]

We shall also work with the log-likelihood rather than the likelihood. Thus the log-likelihood may be written as

\[ l(G) = \log L(G) = \sum_{i=1}^{n} \log \alpha(g_i|g_j, g_k) \tag{1} \]

where either or both parents \( j \) and \( k \) of individual \( i \) can take index value 0, indicating untyped individuals not (explicitly present) in the pedigree, and the suffix 2 of \( \alpha_2(\ast|\ast, \ast) \) is now superfluous and so has been omitted.

Note, importantly, that the log likelihood is decomposed into a sum of terms, with one term from each of the \( n \) individuals.

2.2. Overview of the reconstruction method

As mentioned in Section 1, the pedigree reconstruction algorithm presented here is based on the method of Silander and Myllymäki (2006). It is, however, simpler because within a pedigree an individual can have at most two parents, whilst in a Bayesian network a node can have more than two incoming arrows. The key observation, also used by Singh and Moore (2005), is that in a directed acyclic graph there is at least one node, called a terminal node or sink, that does not have any outgoing edges. In a pedigree, this will be true for the youngest individual. Removing this sink node results in a directed acyclic graph that also has a sink node.

So suppose that we have \( n \) nodes in a set \( V \) to begin with, labelled from 1 to \( n \). For each node \( i \in V \) we can find the the combination of parents in \( V \setminus i \) that maximizes the contribution \( \alpha(g_i|\ast, \ast) \) to the log likelihood (1). If we could also find for each of the \( n \) sets \( V \setminus i : i = 1, \ldots, n \), each of \( n-1 \) individuals, the maximizing value of the log likelihood over all pedigrees—call this \( l(V \setminus i) \)—then we can identify the “best” or optimum sink as that node \( i \) which maximizes the sum \( \log \alpha(g_i|\ast, \ast) + l(V \setminus i) \). Having found the “best sink” with the “best score”, a pedigree search can then be carried out on the remaining \( n-1 \) individuals.
search algorithm. Silander and Myllymäki (2006) instead use an array in which best scores and sinks are stored and updated as they are encountered during the execution of their algorithm. A key requirement is that the score function is decomposable, which is true of the pedigree likelihood function used here.

2.3. Details of the reconstruction method

There are four main steps to the pedigree reconstruction algorithm.

1. Find the set of possible parent configurations for every individual \( i \).
2. Find the best sinks for all \( 2^n \) subsets of \( V \).
3. Find a best ordering of best sinks.
4. Recover the pedigree using the sink ordering and the best parents of each sink.

The details are as follows:

Step 1: Finding local score contributions.

In this a list \( \Lambda_i \) is constructed for each individual \( i \in V \) that stores the combinations of possible parents and the corresponding local scores \( \alpha(i|j,k) \).

- For each \( i \in V \) and all the valid \((j,k)\) parent combinations (with \( j < k \) or \( j = k = 0 \)) that \( i \) can have using the remaining variables \( V \setminus i \), find the corresponding score contribution \( \alpha(i|j,k) > 0 \), and store the ordered quadruple \((\alpha(i|j,k), i, j, k)\) in the list \( \Lambda_i \).

- Sort each list \( \Lambda_i \) in decreasing order of the score contribution \( \alpha(i|j,k) \) of the quadruples.

Note that each list \( \Lambda_i \) always has at least one element, corresponding to \( j = k = 0 \) which treats \( i \) as a founder, and that the probabilities stored are all strictly positive. Genetic constraints will usually make the number of elements in each list small if there is no mutation, but with mutation, the lists can have up to \( 1 + n(n - 1)/2 \) entries. (These arise as follows: \((n - 1)(n - 2)/2\) two-observed parent entries \( \alpha(i|j,k) \), \( n - 1 \) one-observed parent entries \( \alpha(i|0,k) \) and
the founder entry $\alpha(i|0,0)$.) Hence this part of the algorithm has complexity $O(n^3)$.

**Step 2: Finding best sinks**

This is the heart of the algorithm, and where the computational complexity is greatest. We use two arrays, $scores[]$ and $sinks[]$, each of size $2^n$, with each element corresponding to a subset of $V$. The algorithm proceeds by examining the subsets of $V$ in a particular order: two possible orderings are presented here. In addition, there is a lookup procedure that finds the best parents for an individual $i$ from any subset of $V$ and returns the associated Best Local Score: this will be denoted by $BLS(i,W)$ where $W \subseteq V \setminus i$. It also uses a local variable $skore$. On completion of this step of the algorithm, the array $sinks[]$ stores for each subset of $V$ the best sink.

- For all $W \subseteq V$ in ORDER Do
  > $scores[W] \leftarrow 0.0$
  > $sinks[W] \leftarrow -1$
- For all $i \in W$ Do
  > $U \leftarrow W \setminus \{i\}$
  > $skore \leftarrow BLS(i,U) + scores[U]$
  - If $sinks[W] = -1$ or $skore > scores[W]$ Then Do
    > $scores[W] \leftarrow skore$
    > $sinks[W] \leftarrow i$

Finding the Best Local Score $BLS(i,U)$ is straightforward. One simply traverses the sorted list $\Lambda_i$ inspecting the quadruples $(\alpha(i|j,k), i, j, k)$ in turn. The first quadruple encountered such that $j \in U$ and $k \in U$ gives the best parent set for individual $i$ out of the subset of individuals $U$, and $\log(\alpha(i|j,k))$ is the corresponding value of $BLS(i,U)$. (Note that $0 \subseteq U$ always.)

The heart of the algorithm is in using an appropriate ORDER. What we require for the algorithm to work efficiently is that, in evaluating $scores[W]$,
the best scores of all subsets $U \subset W$ have already been evaluated and stored in elements of $scores[]$, and so can be accessed readily without recalculation. One possible ordering that achieves this is to look at the subsets in an order of non-decreasing size, starting with the empty set. For example, suppose we have three individuals, then the sequence of subsets $W$ of $V$ consisting of $\emptyset, \{1\}, \{2\}, \{3\}, \{1,2\}, \{1,3\}, \{2,3\}, \{1,2,3\}$ will work.

An alternative, used by Silander and Myllymäki (2006), is to use a lexicographic order of bit vectors that implement the sets. Treating the case of three individuals once more, the ordering would be: $\emptyset = 000$, $\{1\} = 001$, $\{2\} = 010$, $\{2,1\} = 011$, $\{3\} = 100$, $\{3,1\} = 101$, $\{3,2\} = 110$ and $\{3,2,1\} = 111$. This is simple to implement, as it corresponds to counting from 0 to $2^n - 1$ in binary and the count variable can be used as the array index.

This step of the algorithm has the greatest computational complexity. In the worst case the complexity of calling $BLS(i, U)$ is $O(n^2)$. For a given $W \subset V$, the For loop is called $1 \leq |W| \leq n$ times. Hence each For loop call has worst case complexity of $O(n^2)$, and is called for each of the $2^n$ subsets of $V$. Hence the worst case running time complexity of the algorithm is $O(n^22^n)$, but will typically be much less than this (but still at least $O(2^n)$). It also requires an array of size $2^n$ to store the $score[]$ values in memory. If memory storage is an issue, then the array sinks[] may be written to a file as generated instead of being stored in an array in memory: the values can re-read into memory for the Steps 3 and 4, for which the scores[] array is not required.

**Step 3: Ordering the sinks**

After Steps 1 and 2, the array sinks[] stores the best sink for each subset of $V$. So the algorithm first finds the best sink $i$ for $V$, then the best sink for $V \setminus \{i\}$, etc. The algorithm is the same as in Silander and Myllymäki (2006), and uses an integer array ord[1, ..., n].

- Initialize $left = \{V\}$.
- For $i = n \text{ step -1 until 1 Do}$
> ord[i] ← sinks[left]
> left ← left \{ord[i]\}

At the end of the algorithm, the array \(ord[]\) is a permuted ordering of the \(n\) individuals, with \(ord[1]\) being a founder and \(ord[n]\) being a childless individual in the maximum likelihood pedigree. With the array \(sinks[]\) in memory, the complexity is linear in \(n\).

**Step 4: Recovering the pedigree**

The final step is to extract the pedigree from the ordering. It uses a lookup function \(BLSet(i, U)\) that is identical to the score function \(BLS(i, U)\) of Step 2, but returns the parent set \((j, k)\) instead of the score \(\alpha(i, j, k)\). This step also uses an array \(parents[1, \ldots, n]\) of sets, a local set variable \(predecs\) of predecessors, and the \(ord[]\) array from Step 3.

- \(predecs ← \emptyset\)
- For \(i\) from 1 step 1 to \(n\) Do
  - \(parents[ord[i]] ← BPSet(ord[i], predecs)\)
  - \(predecs ← predecs ∪ \{ord[i]\}\)

At the end of the algorithm the array element \(parents[i]\) contains the parent set for the individual \(i\). Taken together for all individuals \(i ∈ [1, \ldots, n]\), this defines a pedigree having the maximum likelihood. (Note that there could be more than one pedigree that achieves the same maximum likelihood value.)

**3. Evaluation and results**

**3.1. Example 1: Simulation using two pedigrees**

Figure 2 and Figure 3 show two pedigrees each with twenty individuals, the second highly inbred, that were used in a simulation study. Genetic profiles for all individuals were simulated using the assumptions of Hardy-Weinberg equilibrium, independence of markers and no mutation. Four pedigree reconstruction scenarios were carried out for both pedigrees:
Figure 2: A pedigree of twenty individuals with slight inbreeding. Note that the offspring of individual 7 are all half-siblings, as are the offspring of individual 12.

Figure 3: An inbred and incestuous pedigree of twenty individuals.
- Use 10 markers, without sex information
- Use 10 markers, using sex information
- Use 15 markers, without sex information
- Use 15 markers, using sex information

In both pedigrees, in using sex information, the even numbered individual were assigned as male, and the odd numbered individuals as female.

Allele frequencies were taken for the American Caucasian population given by (Butler et al., 2003). For the first two scenarios, the following markers were used: CSF1PO, FGA, THO, TPOX, VWA, D3, D5, D7, D8, and D13. The following additional five markers were used for the second pair of simulations: D16, D18, D21, D2 and D19. None of the simulations used age or generational information from the true pedigree. For each scenario, 1000 genetic profiles for the individuals were simulated. Both the likelihood of the profile according to the true pedigree, and the maximum likelihood were found. Typically it took approximately 1.1 seconds to find the maximum likelihood pedigree for each pedigree profile.

Figures 4 and 5 show the distribution of the differences in the log-likelihood of the true pedigree and the value obtained for the maximum log-likelihood, (that is, the log-likelihood ratio), for the subsets of simulations for which the difference is non-zero, that is, when the algorithm found a pedigree having a higher likelihood than the true pedigree. (The logarithms are to base-10 in all plots.) As is to be expected, as the number of markers is increased, and also information about the sex of individual is used, the number of times the maximum likelihood exceeds the likelihood of the true pedigree decreases. We also see on the plots the excess values bunching closer to zero. Perhaps surprisingly the reconstruction algorithm appears to perform better on the highly inbred pedigree of Figure 3 than the pedigree of Figure 2 when comparing the excess totals in each scenario. This might be because in the highly inbred pedigree, apart from the 5 founders the remaining 15 individuals have both of their parents present.
Figure 4: Simulation results for pedigree in Figure 2. The histograms show the distribution of the difference of the maximum log-likelihood value and the log-likelihood value according to the true pedigree, for the subset of simulated profiles for which these quantities were different. (That is, the $\log_{10}$ likelihood ratio between the maximum-likelihood and true pedigree.) The caption of each histogram gives the total number of such different values from 1000 simulations.
Figure 5: Simulation results for pedigree in Figure 3. The histograms show the distribution of the difference of the maximum log-likelihood value and the log-likelihood value according to the true pedigree, for the subset of simulated profiles for which these quantities were different. The caption of each histogram gives the total number of such different values from 1000 simulations.
Table 1: Romanov STR data

<table>
<thead>
<tr>
<th>Skeleton</th>
<th>HUMVWA/31</th>
<th>HUMTHO1</th>
<th>HUMF12A1</th>
<th>HUMFES/FPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (servant)</td>
<td>14,20</td>
<td>9,10</td>
<td>6,16</td>
<td>10,11</td>
</tr>
<tr>
<td>2 (doctor)</td>
<td>17,17</td>
<td>6,10</td>
<td>5,7</td>
<td>10,11</td>
</tr>
<tr>
<td>3 (child)</td>
<td>15,16</td>
<td>8,10</td>
<td>5,7</td>
<td>12,13</td>
</tr>
<tr>
<td>4 (Tsar)</td>
<td>15,16</td>
<td>7,10</td>
<td>7,7</td>
<td>12,12</td>
</tr>
<tr>
<td>5 (child)</td>
<td>15,16</td>
<td>7,8</td>
<td>3,7</td>
<td>12,13</td>
</tr>
<tr>
<td>6 (child)</td>
<td>15,16</td>
<td>8,10</td>
<td>3,7</td>
<td>12,13</td>
</tr>
<tr>
<td>7 (Tsarina)</td>
<td>15,16</td>
<td>8,8</td>
<td>3,5</td>
<td>12,13</td>
</tr>
<tr>
<td>8 (servant)</td>
<td>15,17</td>
<td>6,9</td>
<td>5,7</td>
<td>8,10</td>
</tr>
<tr>
<td>9 (servant)</td>
<td>16,17</td>
<td>6,6</td>
<td>6,7</td>
<td>11,12</td>
</tr>
</tbody>
</table>

In contrast, in the other pedigree, there are 4 founders, (1, 2, 3 and 5) and two groups of three half-siblings (13,14,15) and (18,19,20). However the distribution of excess values appears concentrated closer to the origin in the pedigree with only a slight amount of inbreeding.

3.2. Example 2: The Romanov family

Table 1 shows STR genotype data for the nine skeletons found in a shallow grave 20 miles from Ekaterinburg, Russia, and believed to be the remains of the Romanov family, some servants and the family doctor (Gill et al., 1994), described in Section 1. Five of the individuals including all the children were female, the remaining four individuals were male.

Two pedigrees reconstructions were carried out, one using sex information the other not. In both cases age information was not used. In the absence of suitable population allele frequencies, each marker was assumed to consist of eight alleles, (inclusive of the ones in the table), with a uniform distribution. Figure 6 shows the maximum likelihood pedigree that results without using the sex information. Although the pedigree places the members of the Romanov family in the correct group, the relationships are incorrect. Using age information, having the children $c_3$ and $c_6$ as parents of the Tsar and Tsarina would
have been ruled out. Using the sex information would also rule this out, as the children were all female. Using sex information\(^2\) gives the pedigree in Figure 7, in which the royal family group is now correctly established. Note that both reconstructions suggest that the doctor \(d_2\) is related to two of the three servants. Pedigrees in which \(s_9\) is the father of the doctor, and the doctor is the parent of \(s_8\), or in which \(s_8\) and \(s_9\) are half siblings with the doctor as the common parent, would be equally likely. However, these familial relationships between the doctor and the two servants are most probably reconstruction errors resulting from the use of only four genetic markers.

A set of simulations similar to those of Section 3.1 was carried out in which 10,000 genetic profiles for a pedigree consisting of mother, father and three daughters were generated. Figure 8 summarizes the excess log-likelihood values obtained from these simulations, using 4, 10 or 15 markers, and either using or not using sex information. We see that using only 4 markers the true pedigree is recovered in less than half the simulations without using sex information, and in less than 30% of the simulations when sex information is used. Thus the pedigree reconstructed in Figure 6 is not so unusual considering the low number of markers used.

4. Discussion

This paper has presented what is believed to be the state-of-the-art algorithm of an exhaustive search of pedigrees of up to 31 or so individuals, for reconstructing pedigrees using a complete sample. The algorithm can utilize age and sex information, but does not require either. The algorithm was applied in a simulation study on two pedigrees of twenty individuals, and on the historical data of the Romanov mass grave skeletons. In the examples consid-

\(^2\)The paper of Gill et al. (1994) states that the children are all female, and which skeletons correspond to the Tsar and Tsarina. It does not say which sex the remaining skeletons have. However in this case, the result will be the same regardless of how sex is assigned to the remaining four individuals.
Figure 6: Reconstructed pedigree of Romanov mass grave skeletons without using sex or age information. This pedigree had a log likelihood of -86.3172. Note that reversing the parentage assignment from s8 to d2 (so that s8 and s9 are half-siblings), or reversing both this and the parentage assignment from d2 to s9 (so that s9 is a grandparent of s8) yield pedigrees having the same likelihood.

Figure 7: Reconstructed pedigree of Romanov mass grave skeletons using sex but not age information. This pedigree had a log likelihood of -89.2075.
Figure 8: Simulation results for a “Romanov family” structured pedigree consisting of mother, father and three daughters. The number in the caption of each plot gives the total count, out of 10,000 simulations, that the maximum likelihood exceeded the likelihood of the true pedigree.
Figure 9: An inadmissible pedigree. It is not possible to assign sexes to the founders such that each child has two parents of opposite sex.

The marker systems were assumed to be independent; however linked loci can readily be handled by the method presented here, provided that a suitable recombination model is incorporated into calculating the contributions to the likelihood terms in (1). Similarly, the examples did not take into account possible mutation, but this too can be handled by the reconstruction algorithm provided a suitable modification to the likelihood contributions in (1) can be evaluated. All of the examples used STR markers, but the algorithm should also be applicable to pedigree reconstruction using SNP data.

The algorithm can use sex information on individuals if available. The effect of including sex information is potentially to remove some of the child-parent triples in the $\Lambda_i$ lists, introduced in Section 2.3, that contain a child with two parents of the same sex. If not using sex information, the reconstructed pedigree should be checked to ensure that sexes can be assigned to the individuals in the pedigree in a consistent manner.\(^3\) An example of an inconsistent pedigree is shown in Figure 9.

Age information can also be incorporated into the reconstruction algorithm, where age constraints are available for some pairs of individuals. Thus for example if individual $i$ is known to be older than individual $j$, then $j$ will be excluded as a parent of $i$ in the $\Lambda_i$ lists. Note, however that this information will be strictly local to exclude parent-child links only. (An exception may be that individual $j$ is known not to be old enough to have offspring, in which case $j$ will not appear as a potential parent in any $\Lambda_i$ list.) Although such age constraints

\(^3\)This consistency check was not carried out in the simulations.
will exclude a pedigree being constructed which has $j$ being a parent of $i$ if $j$ is younger than $i$, it will not prevent $j$ being considered as a grandparent or other ancestor of $i$. Hence, when using age constraints, the final reconstructed pedigree should be checked for possible violations extending beyond parent-child relationships.

The consistency considerations of the previous two paragraphs highlight a weakness of the current algorithm. If the maximum likelihood pedigree is found to be inconsistent, then the algorithm does not suggest a maximum likelihood consistent alternative. This is because the algorithm does not explicitly construct all of the possible pedigrees as it goes along. Work on removing this problem is being pursued.

There are two other notable limitations of the assumptions used in algorithm. One is that it treats the founders in a pedigree as unrelated individuals. The other is that the algorithm cannot take account of the presence of null alleles.

However, despite these limitations, the algorithm should prove useful in practical problems and for theoretical use. The time and memory requirement complexity of the algorithm limits its practical applicability to a maximum of around thirty or so individuals. The Romanov example showed its use in a mass-grave scenario involving nine individuals. It also showed the apparent clustering of the nine individuals into three distinct groups. For mass graves or other disaster scenarios involving more than thirty people, it may be possible to identify smaller subgroups of related individuals, and then carry out the reconstruction algorithm on each subgroup. (Such an approach was suggested in Cowell and Mostad (2003).) One way to do this is to construct an undirected graph on the individuals as follows. Start with a graph in which the nodes are the individuals, and there are no edges between any pair of individuals. Then join each pair of individuals with an undirected edge if it is genetically consistent for one to be the parent of the other. After processing all pairs of individuals, the graph will consist of one or more connected components. The reconstruction algorithm may be carried out on the individuals of each connected component separately, provided the number of individuals in the component is around thirty or less.
The other use of the algorithm is as a benchmark for monitoring the efficacy of heuristic algorithms for pedigree reconstruction, such as greedy search or Monte-Carlo search algorithms. The algorithm presented here is guaranteed to find a maximum likelihood pedigree, thus it can be used to check the convergence of other proposed methods providing an insight into their effectiveness and efficiency, particularly for use in larger problems that cannot be handled by the method of this paper.

References


