

The **likeLTD** software: an illustrative analysis, explanation of the model, results of performance tests and version history

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This version coincides with Release 5-4, which includes a new optimisation wrapper function, `evaluate`, that improves the optimisation and provides interim results, as well as a progress bar. Small improvements to the output reports are also included. See Section 1.3.

The previous version (Release 5-3) improved the allele and output reports, which now produce `.doc` files, with the same functionality as previous reports. These include improved layout and presentation, and modifications to the allele report. See Sections 1.2 & 1.4.

The version before (Release 5-2) introduced the function `get.likely.genotypes` that returns the most probable genotypes for each locus, and the most probable whole-profile genotype. See Section 1.5 for more information.

Abstract

likeLTD (“likelihoods for Low Template DNA profiles”) is an **R** package for computing likelihoods for DNA profiles. It is particularly suited for low-template and/or degraded DNA when alleles from some contributors may be subject to dropout. It can handle multiple profiled possible contributors and up to two unprofiled contributors, in addition to the queried contributor. The package also provides input files for an example analysis (the “Hammer Case” described below).

This document shows how to install and run **likeLTD** using an illustrative example. It also describes the model underlying **likeLTD**, for example explaining the “uncertain” category for allele designations, and the dropout and degradation models. We present results of running **likeLTD** on a range of single-contributor and mixed DNA profiles subject to modifications, such as introduction of artificial dropout and dropin. Some of the material here, and some other analyses, are published in Balding (2013).

In all the tests described here, unless otherwise stated we have used Version 5.4.0 of **likeLTD**, with a standard allele frequency database of around 200 UK Caucasians, $F_{ST} = 0.02$ and a sampling adjustment $\text{adj} = 1$ (these are described briefly below).

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1 Installation and example R script

Installing `likeLTD` (only needs doing once on any computer) and loading it (once per R session) are both very simple.

```
install.packages("likeLTD")
require(likeLTD)
```

The `install.packages` command may generate a request for you to choose a site from which to download the package. Choose any site near you.

The example analysis that comes with `likeLTD` is called the Hammer Case. The DNA profiles come from Table 2 of Gill et al. (2007), who introduced the software `LoComatioN` which in some respects is similar to `likeLTD` and also to `LRmix`, available within the `Forensim` R package. The crime scene profile (CSP) consists of two profiling runs at each of 10 loci. These, and reference profiles from a queried contributor Q and two victims (K1 and K2), are available in input files `hammer-CSP.csv` and `hammer-reference.csv`. `likeLTD` allows “uncertain” allele calls but this designation was not used by Gill et al. (2007) and so there are no alleles labelled as uncertain in this example.

There is a total of six alleles, all of them unreplicated, that are not attributable to any of Q, K1 or K2. No more than two of these occurs at any one locus. This suggests a comparison of the following two hypotheses (where H_p stands for the prosecution hypothesis, and H_d stands for the defence hypothesis) for the contributors of DNA to the sample:

$$\begin{aligned} H'_p : & \quad Q + K1 + K2 + U1 \\ H'_d : & \quad X + K1 + K2 + U1 \end{aligned}$$

where X and U1 denote unprofiled, unrelated individuals not related to any of Q, K1 and K2.

1.1 Input

We now show how to calculate likelihoods under H'_p and H'_d using `likeLTD`. The first command below finds out where your system has stored the Hammer Case files, and saves that location in `datapath`. For your own analyses, you will need to create your own CSP and reference files, in the same format as `hammer-CSP.csv` and `hammer-reference.csv`. It is usually most convenient to create these files in a specific directory, and then set that to be the working directory for R using the command `setwd()` or using the R menu option (its location varies across operating systems). For example if your case files are

in the directory `C:/Users/JoeBloggs/Cases/JoeBloggs1` then you enter the command `setwd("C:/Users/JoeBloggs/Cases/JoeBloggs1")`. In that case you can set `datapath = "."` in place of the first command below. A default allele frequency database file is provided with `likeLTD`. To use your own database file instead (must be in same format) set `databaseFile` to the filename, including path if not in the working directory. If you wish to choose a different individual to be Q, or to add or omit one of the other profiled contributors (a K, in the notation used here, standing for “known”) then you must create a new reference file.

```
datapath = file.path(system.file("extdata", package="likeLTD"), "hammer")

# File paths and case name for allele report
admin = pack.admin.input(
  cspFile = file.path(datapath, 'hammer-CSP.csv'),
  refFile = file.path(datapath, 'hammer-reference.csv'),
  caseName = "hammer"
)
```

Values are required for `cspFile` and `refFile`, but `caseName` can be omitted above in which case it defaults to `"dummy"`. Two other arguments have been omitted so that their default values will be used: `databaseFile = NULL` and `outputPath = getwd()`.

1.2 Allele report

```
# Next we generate an allele report
allele.report(admin)
```

The allele report is a `.doc` that will be created in the current working directory (set `outputPath` to specify a different directory). The `.doc` file can be converted to `.pdf` by opening with MS Word or another document editor and saving as a pdf. The report generated by the above command (`hammer-Allele-Report-1.doc`) is shown in Appendix A. It summarises the input data, highlights rare alleles, and suggests values for key parameters (and hence the suitable hypotheses), in particular specifying the number of unprofiled contributors required to explain the observed CSPs under the H_p , and whether modelling dropin is necessary. Here, it indicates that one unknown contributor is sufficient under H_p to explain the observed alleles not attributable to Q/X or K1 or K2 by including dropin. While it is never possible to specify an upper bound on the number of known contributors, specifying more than the minimum required usually has negligible impact on the resulting likelihood ratio (LR). Cowell et al. (2013a) illustrate this with an example

in which a $\log(\text{LR})$ of 14.09 with three contributors barely changes as the number of contributors increases, reaching 14.04 with eight contributors.

1.3 Arguments and optimisation

Based on the allele report we specify the required hypotheses by setting a list of arguments containing the following items:

nUnknowns: The number of unknown contributors under the prosecution hypothesis (either 0, 1 or 2). **likeLTD** automatically adds an additional unknown contributor (X) under the defence hypothesis, who replaces Q from the prosecution hypothesis.

doDropin: Whether to model dropin or not (logical: TRUE or FALSE).

ethnic: The ethnic category of the queried contributor. The default database comes with “EA1”, “EA3” and “EA4”, corresponding to UK residents of Caucasian, Afro-Caribbean and South Asian origin respectively. If you use your own allele frequency database you will choose your own category labels (required even if there is only one category).

adj: Sampling adjustment (scalar). See Section 3.2.

fst: F_{ST} adjustment for distant relatedness (coancestry) of Q and X (scalar). See Section 3.2.

relatedness: Relatedness coefficients for Q and X (vector of length two): the probabilities that they have one and two alleles identical by descent from recent common ancestors (e.g. parents or grandparents). The setting used below is for Q and X unrelated; for siblings use **relatedness** = **c**(0.5,0.25). Note that **likeLTD** does not take into account linkage between markers, which will lead to a slight overstatement of the strength of evidence. The user may prefer to omit one of each pair of syntenic loci, which will instead lead to understatement of the strength of evidence.

```
# Enter arguments
args = list(
  nUnknowns = 1,
  doDropin = FALSE,
  ethnic = "EA1",
  adj = 1,
  fst = 0.02,
```

```

        relatedness = c(0,0)
    )

# Create hypotheses
hypP = do.call(prosecution.hypothesis, append(admin,args))
hypD = do.call(defence.hypothesis, append(admin,args))

# Get parameters for optimisation
paramsP = optimisation.params(hypP)
paramsD = optimisation.params(hypD)

# Run optimisation
results = evaluate(paramsP, paramsD)

```

The entries in `args` shown above are defaults, except for `nUnknowns` which defaults to 0. The function `do.call` calls the function given in its first argument. `prosecution.hypothesis` and `defence.hypothesis` are both functions defined within `likeLTD`, which generate the necessary objects for H_p and H_d respectively. The `evaluate` function is likewise defined within `likeLTD`, and is a wrapper function for the `DEoptim` function that performs optimisation (see Section 2.8), providing improved optimisation, and a progress bar displaying current WoE. The progress bar can be disabled by setting the argument `progBar = FALSE`, which is necessary if you do not have graphical capabilities e.g. running from command line on a server. The `evaluate` function now splits the convergence into a number of steps, with each subsequent step having more stringent convergence tolerance and an increased crossover rate (a parameter for `DEoptim`); the combination of these two behaviours means that the parameter space is searched extensively to start with, and gradually anneals to a more intensive local search towards the end. The number of steps to run is determined by the difficulty of converging the first step. Interim results after each step are available by setting the argument `interim = TRUE`, which writes the most recent results to `Interim.csv`, in the current working directory. The function `optimisation.params` sets the parameter values needed for `DEoptimLoop`. These values can be altered if required but the default settings should be adequate for most analyses.

The object returned by `evaluate` is a list of three elements: `Pros`, `Def` and `WoE`. Both `Pros` and `Def` have the same structure as the object returned by `DEoptim` (see `help(DEoptim)`), with each corresponding to the prosecution and defence results respectively. `WoE` gives the WoE for each step run by `evaluate` in bans, the final WoE can be obtained through the command `results$WoE[length(results$WoE)]`.

1.4 Output report

```
# Generate output report
output.report(hypP,hypD,results)
```

The results are given in the output file `hammer-Evaluation-Report-1.doc` (the numbering of the filename increments automatically, or a custom filename may be specified with `file="fileName.doc"`) which again summarises the input data, similar to the allele report, but also states the hypotheses compared and gives single-locus and overall likelihood ratios (LR) in favour of the prosecution hypothesis relative to the defence hypothesis. Logarithms (base 10) are also given for the LR's, and we will refer to the $\log_{10}(\text{LR})$ values as the weight of evidence (WoE) measured in bans. The output file for the Hammer case analysis is given in Appendix B. The overall WoE was found to be 10.9 bans. The WoE is > 0 (favours H'_p over H'_d) at every locus except D18 (WoE = -0.5 bans). The most incriminating locus is D19 (WoE = 2.6 bans), where the two alleles of Q are rare, replicated in the CSP, and not shared with either K1 or K2.

Dropout rate estimates for each contributor subject to dropout, and each profiling run, are also given in the output file. These estimates are often not precise, particularly under H'_d where there are two unprofiled contributors, but this is not important for assessing the WoE against Q. Note that under H'_d , X and U1 are indistinguishable; we usually take X to be the one with dropout rates most similar to Q, but the labelling in the output file is arbitrary. The single-allele dropout rates for Q/X are estimated at 11%/12% and 0%/1% in the two replicates. The dropout rate estimates for K1 under H'_p/H'_d are 46%/44% for replicate a and 3%/5% for b. The degradation value for K1 (γ_{K1}) is about 0.8% under both hypotheses, while γ_Q and γ_X are both about 0.4%, indicating an increase in dropout rate with fragment length, an effect of degradation, particularly for K1.

Every CSP allele attributable to K2 could also come from K1 or Q, and so under H'_p there is no evidence for DNA from K2. However, under H'_d the DNA of Q is not present, leaving three CSP alleles that can be attributed to K2 but not K1. Nevertheless, `likeLTD` estimates 100% dropout of the alleles of K2 in both replicates and under both hypotheses. This is because the three alleles attributable to K2 under H'_d are all replicated, whereas seven other alleles of K2 do not appear at all, indicating very high dropout, and so `likeLTD` finds that attribution of the three alleles to K2 is unlikely. Although we cannot exclude K2 from contributing any DNA to the sample, these results indicate that including K2 in the analysis brings no explanatory power and so has negligible impact on the WoE implicating Q as a contributor. It isn't necessary to exclude K2 from the analysis, because `likeLTD` has automatically done this by estimating dropout at 100%, but there may be a slight improvement in the likelihood optimisation in running the analysis again without K2, due to fewer nuisance parameters to be estimated.

1.5 Genotype probabilities

LikeLTD can provide a list of the most probable genotypes at each locus for each unprofiled contributor, using function `get.likely.genotypes` (new in Version 5.2). By default only single-locus genotypes with probability > 0.1 are returned; this can be altered using the argument `prob`. The most probable whole-profile genotype, and its probability are also returned (Figure 1). The genotypes and their probabilities add nothing to the assessment of weight of evidence against an alleged contributor of DNA, but can be useful for searches in a database.

```
# Get the most likely single-contributor genotypes
gens = get.likely.genotypes(hypD,paramsD,results$Def)
```

The returned list object is organised into a series of levels, as shown in Figure 1.

It may also be desirable to obtain the probabilities of joint genotypes, rather than genotypes of single contributors. In this case, the argument `joint` can be handed to `set.likely.genotypes`, and if set to `TRUE`, the joint genotypes and probabilities will be returned rather than the single-contributor genotypes and probabilities. For joint genotypes the default probability threshold for single-locus genotypes is 5%. This value can be altered for the single-contributor or joint cases by setting `prob`.

Note some of the locus-specific genotypes used to construct the whole profile genotype may have smaller probabilities than the threshold, and will therefore not be displayed in the locus-specific results.

```
# Return joint genotypes and probabilities
gens = get.likely.genotypes(hypD,paramsD,results$Def,joint=TRUE)

# Return joint genotypes with per-locus probability greater than 3%
gens = get.likely.genotypes(hypD,paramsD,results$Def,joint=TRUE,prob=0.03)
```

The returned object here is organised similarly to the single-contributor object, with the dependence on contributor removed from the organising heirarchy, as shown in Figure 2.

If there are three unprofiled contributors to the CSP, the function will return either a genotype list for each contributor if `joint=FALSE`, or a genotype list with six columns (two alleles for each contributor) if `joint=TRUE`. If there is only a single contributor to the CSP, the results will be identical regardless of the value of `joint`, although they will be displayed slightly differently (if `joint=FALSE` the dependence on contributor will still be displayed, but as there is only one contributor this has no real effect).

```

[[1]]
[[1]] [[1]]
[[1]] [[1]]$D2
[[1]] [[1]]$D2$genotypes
[1] "17" "20"

[[1]] [[1]]$D2$probabilities
[1] 0.9460538

[[1]] [[1]]$D21
[[1]] [[1]]$D21$genotypes
[1] "29" "32.2"

[[1]] [[1]]$D21$probabilities
[1] 0.8806254

[[1]] [[1]]$TH01
[[1]] [[1]]$TH01$genotypes
[,1] [,2]
[1,] "6" "9.3"
[2,] "8" "9.3"
[3,] "6" "8"

[[1]] [[1]]$TH01$probabilities
[1] 0.3113742 0.3109442 0.2923899

[[1]] [[2]]
[[1]] [[2]]$D2
[[1]] [[2]]$D2$genotypes
[,1] [,2]
[1,] "17" "24"
[2,] "20" "24"

[[1]] [[2]]$D2$probabilities
[1] 0.3745314 0.2656215

[[1]] [[2]]$D21
[[1]] [[2]]$D21$genotypes
[,1] [,2]
[1,] "29" "31"

[2,] "31" "32.2"

[[1]] [[2]]$D21$probabilities
[1] 0.5306968 0.2493529

[[1]] [[2]]$TH01
[[1]] [[2]]$TH01$genotypes
[,1] [,2]
[1,] "6" "9.3"
[2,] "8" "9.3"
[3,] "6" "8"
[4,] "9.3" "9.3"

[[1]] [[2]]$TH01$probabilities
[1] 0.2776487 0.2232152 0.2017299 0.1318768

$stopGenotypes
$stopGenotypes$genotypes
$stopGenotypes$genotypes[[1]]
[,1] [,2]
D2 "17" "20"
D21 "29" "32.2"
TH01 "6" "9.3"

$stopGenotypes$genotypes[[2]]
[,1] [,2]
D2 "17" "24"
D21 "29" "31"
TH01 "6" "9.3"

$stopGenotypes$probabilities
$stopGenotypes$probabilities[[1]]
[1] 0.2594117

$stopGenotypes$probabilities[[2]]
[1] 0.05518619

```

Figure 1: An example output of `get.likely.genotypes` for a two-contributor, three-locus CSP, obtaining marginal genotype probabilities. The first section of the results shows the single locus genotypes for single contributors and is broken into two subsections, one for each contributor subject to dropout (designated with `[[1]][[1]]` for the first contributor, and `[[1]][[2]]` for the second contributor). Each of these subsections is then further divided into locus sections (designated `$locusName`), which are then each split into genotypes and probabilities for that locus and that contributor. The probabilities correspond to the rows of the genotypes matrices. The second section (designated `$stopGenotypes`) shows the most probable whole-profile genotype for each contributor, and is split into genotypes and probabilities subsections, which are both further subdivided into contributors subject to dropout (e.g. `$stopGenotypes$probabilities[[2]]` indicates the probability of the most probable genotype for the second contributor, which is displayed in `$stopGenotypes$genotypes[[2]]`).

```

$joint
$joint$D2
$joint$D2$genotypes
      [,1] [,2] [,3] [,4]
[1,] "17" "24" "17" "20"
[2,] "20" "24" "17" "20"
[3,] "24" "25" "17" "20"
[4,] "23" "24" "17" "20"
[5,] "19" "24" "17" "20"

$joint$D2$probabilities
[1] 0.35124052 0.23496616 0.07399688 0.07061620 0.06122807

$joint$D21
$joint$D21$genotypes
      [,1] [,2] [,3] [,4]
[1,] "29" "31"  "29" "32.2"
[2,] "31" "32.2" "29" "32.2"
[3,] "30" "31"  "29" "32.2"
[4,] "31" "32.2" "29" "29"

$joint$D21$probabilities
[1] 0.49921332 0.16146173 0.08830646 0.08789113

$joint$TH01

$joint$TH01$genotypes
      [,1] [,2] [,3] [,4]
[1,] "6"  "9.3" "8"  "9.3"
[2,] "8"  "9.3" "6"  "9.3"
[3,] "9.3" "9.3" "6"  "8"
[4,] "6"  "8"  "6"  "9.3"
[5,] "6"  "9.3" "6"  "8"
[6,] "6"  "6"  "8"  "9.3"

$joint$TH01$probabilities
[1] 0.15636400 0.15062049 0.13187676 0.11295039 0.10912104 0.09935616

$stopGenotypes
$stopGenotypes$genotype
      [,1] [,2] [,3] [,4]
D2    "17" "24" "17" "20"
D21   "29" "31" "29" "32.2"
TH01  "6"  "9.3" "8"  "9.3"

$stopGenotypes$probability
[1] 0.02741748

```

Figure 2: An example output of `get.likely.genotypes` for a two-contributor CSP, obtaining joint genotype probabilities. The first section (`$joint`) displays the joint genotype probabilities at each locus for those genotypes with probability greater than `prob` (`$joint$locusName$genotypes`), as well as their associated probabilities (`$joint$locusName$probabilities`). Once again the probabilities correspond to rows in the genotypes matrices. The second section (`$stopGenotypes`) displays the most likely whole-profile joint genotype (`$stopGenotypes$genotype`) as well as its associated probability (`$stopGenotypes$probability`).

2 Overview and description of the model

2.1 Overview

`likeLTD` is an R package for evaluating likelihoods for a crime scene DNA profile (CSP) given the reference profiles of possible contributors of DNA and a specified number of unprofiled contributors. It is particularly appropriate for low template DNA (LTDNA) profiles in which allelic dropout is considered possible for some or all contributors. `likeLTD` is described, and results of some illustrative analyses presented, in Balding (2013) (much, but not all, of the material in that paper is also found here). It is a development of earlier algorithms described in Balding and Buckleton (2009).

We consider a single crime stain which may have been profiled multiple times from replicate PCRs of the original sample. Forensic DNA profiling predominantly assays autosomal short tandem repeat (STR) loci, using technology in which an allele in the profiled sample is represented by a peak in an electropherogram (epg). See Butler (2010) for background on forensic DNA profiling, and Buckleton et al. (2004); Balding (2005) for introductions to statistical methods for evaluating DNA profile evidence. (We plan a new edition of Balding (2005) giving more attention to low-template profiles, to appear early in 2014.)

2.1.1 The contributors of DNA

It is assumed that we are interested in comparing the likelihood given that a profiled individual Q as a contributor with the likelihood when Q is replaced with an unprofiled individual X. The ratio of those two likelihoods, each maximised over the nuisance parameters, is the likelihood ratio (LR). There can be up to two further unprofiled possible contributors of DNA, U1 and U2, and multiple profiled uncontested contributors (K1, K2, ...). The U are always assumed to be subject to dropout, but if all alleles of Q or any of the K are observed in every replicate, then the dropout rate for that individual is fixed at zero.

There can be several LRs of interest, considering X of different ethnicities and different relatedness with Q (the more genetically similar X is to Q, the smaller the LR). `likeLTD` allows X to be related to Q with two relatedness coefficients. In addition, we use an F_{ST} adjustment to allele fractions that allows for possible remote shared ancestry of Q with X. Within `likeLTD`, this adjustment only affects the alleles of Q and does not take into account any other profiled contributors. We assume U1 and U2 to be mutually unrelated, and they and the K are all assumed unrelated to X.

Because the relatedness coefficients and F_{ST} account for the positive correlations across

loci due to shared ancestry of Q and X, it is reasonable to compute full-profile LR_s by multiplication of single-locus LR_s, which is standard practice in the assessment of DNA profile evidence (Buckleton et al., 2004). We thus focus below on the single-locus case.

2.1.2 The parameters

Some parameters are defined in terms of a reference individual who is X under the defence hypothesis. Under the prosecution hypothesis, the reference individual is Q if Q is subject to dropout, otherwise the first K subject to dropout, if any, otherwise the first U, if any. If there are no contributors subject to dropout, then there is no need for a reference individual – the parameters defined in terms of this individual are not used.

The “nuisance” parameters, which must be eliminated under each multi-locus likelihood before taking their ratio, are

- the dropout rates (one per replicate) for the reference individual;
- the contributions of DNA, relative to that from the reference individual (one parameter for each contributor subject to dropout other than the reference individual); the relative contribution from an individual is used to compute dropout rates – see below;
- the parameters of the dropout model: locus adjustment (one per locus), power parameter (one), and degradation parameters (one for each contributor subject to dropout);
- a dropin parameter (optional, see below).

`likeLTD` maximises a (penalised) likelihood over these parameters using the R `DEoptim` function.

2.1.3 Key features of `likeLTD`

Some key features of `likeLTD`:

- It can accept “uncertain” allele calls, in addition to present/absent, which mitigates the “cliff edge” effect of calls that are restricted to present/absent.
- It combines information across all DNA profiling runs, thus avoiding the need for a “consensus” profile (Gill et al., 2000).
- It allows a different dropout rate for each contributor in each profiling runs.

- The dropout probability for a given dose of DNA, relative to unit dose (for the reference individual), uses the model of (Tvedebrink et al., 2009).
- Dropout rates can increase with fragment length, based on the model of Tvedebrink et al. (2012b).
- As a consequence of estimating the dropout rate for contributors, a potential contributor can be considered in an hypotheses without implying that their DNA is present, because the contribution of DNA from that individual can be estimated at zero.
- Because the penalised likelihoods are maximised over the nuisance parameters, combining information over alleles, loci, replicates and individuals, there is little need for external calibration data. This is only required for a few hyperparameters – the parameters of the penalty functions and a rate parameter of the dropout model (for which we use results from Tvedebrink et al. (2009), see below). The underlying parameters are allowed flexibility to best fit the CSP data under each hypothesis, constrained by penalty functions that depend on these hyperparameters.
- `likeLTD` does not use peak height information directly; it is used indirectly by the forensic scientist when making the present/uncertain/absent designations. Peak heights would provide more information and hence greater statistical efficiency for many CSPs, but typically require extensive calibration data specific to the profiling protocol used for the CSP. Because DNA evidence is so powerful, statistical efficiency is not usually an urgent priority; robustness is usually more important and the results below show that `likeLTD` has good robustness properties. In the presence of multiple replicates there is often very little loss of information from using present/uncertain/absent rather than peak heights, but if only a single profiling run is available the loss of information can be substantial.

For a comparison between `likeLTD` and other software packages for computing forensic DNA LR's see Steele and Balding (2014).

2.2 Single-locus LR with dropout

Consider first a single profiling run in which the CSP showed two alleles, A and B. If the contributors under the competing hypotheses are

$$H_p^1: Q \quad \text{and} \quad H_d^1: X,$$

and $Q \equiv AB$, where “ \equiv ” denotes “has genotype”, then the LR under usual assumptions (Buckleton et al., 2004; Balding, 2005) is

$$Q \equiv AB, \text{ CSP} = AB: \quad \text{LR} = \frac{(1+F_{ST})(1+2F_{ST})}{2(F_{ST} + (1 - F_{ST})p_A)(F_{ST} + (1 - F_{ST})p_B)} \quad (1)$$

where the p are population allele fractions. We henceforth assume that sampling and F_{ST} adjustments have been made to the p as described below, so that we can ignore F_{ST} and the LR simplifies to $1/(2p_A p_B)$.

Dropout refers to any allele of a hypothesized contributor that is not observed in the CSP. If $\text{CSP} = A$, and low epg peak heights suggest that dropout is possible, then under a standard model (Balding and Buckleton, 2009; Gill et al., 2012) the LR can be written as

$$Q \equiv AB, \text{ CSP} = A: \quad \text{LR} = \frac{D(1-D)}{p_A^2(1-D_2) + 2p_A(1-p_A)D(1-D)} \quad (2)$$

where D denotes the probability of dropout for a heterozygote allele, while D_2 denotes the probability of a homozygote dropout. The numerator is the probability that the B allele of Q has dropped out (D), while the A has not ($1-D$). In the denominator, either X is AA and there has been no dropout (1st term), or (2nd term) X is heterozygous but the non-A allele has dropped out.

Logically, D in the numerator of the LR is different from D in the denominator. However, typically a similar range for D is supported under both hypotheses and they are often taken to be equal for illustrative calculations (Gill et al., 2007).

2.3 Effect of an “uncertain” allele designation

If now we assume $\text{CSP} = A[B]$, where $[]$ denotes an “uncertain” allele designation, while again $Q \equiv AB$, then the LR becomes

$$\text{CSP} = A[B]: \quad \text{LR} = \frac{1-D}{p_A^2(1-D_2) + 2p_A p_B(1-D) + 2p_A(1-p_A-p_B)D(1-D)}. \quad (3)$$

In the numerator we only know that Q ’s A allele has not dropped out ($1-D$), whereas we do not know if B has dropped out and so the corresponding term is one. In the denominator, the three terms correspond to $X \equiv AA$, AB and AZ , where Z is any allele other than A or B.

Figure 3 (solid curves) shows the LRs (1) through (3) as a function of dropout rate D for a locus with $p_A = p_B = 0.1$ (after adjustments). The computation of D_2 from D is discussed in Section 2.5. As expected, the LR for $\text{CSP} = A[B]$ (red curve) is always intermediate between those for $\text{CSP} = AB$ (black) and $\text{CSP} = A$ (green). When D is high the red and green curves are similar, because in the presence of high dropout both

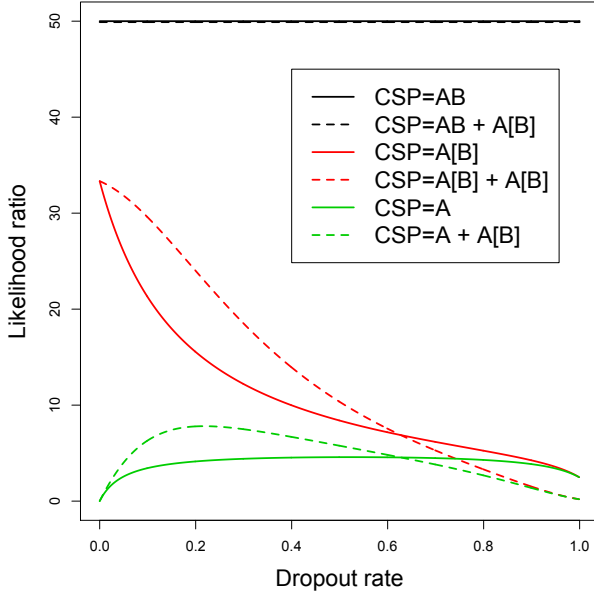


Figure 3: **Single-locus, single-contributor LRs for three CSPs with 1 profiling run (solid curves) and three with 2 runs (dashed curves).** In the legend box, + separates the two runs and [] denotes an uncertain allele call. Allele A is observed in every case, whereas the designation of allele B in the first run varies over present, uncertain, and absent; it is uncertain in the second run. The LRs are expressed as a function of the dropout rate D , assumed to be the same for all alleles. For purposes of illustration, D has the same value in numerator and denominator.

an uncertain and an absent designation for B convey little information about whether or not X has a B allele. However when D is small the two LRs differ substantially as $\text{CSP} = A$ is inconsistent with $X \equiv AB$, whereas $\text{CSP} = A[B]$ is consistent with both $X \equiv AA$ and $X \equiv AB$.

Next consider the LRs when the three CSPs considered above constitute only the first run, and there is a second run that gives $A[B]$ in each case (Figure 3 dashed curves). We assume the same D for both runs. When $\text{CSP} = AB + A[B]$, we must have $X \equiv AB$ (we ignore dropin here, see Section 2.7) and the LR is again (1). The LRs in the other two cases are

$$\begin{aligned} \text{CSP} = A + A[B]: \quad \text{LR} &= \frac{D(1-D)^2}{p_A^2(1-D)^2 + 2p_Ap_B D(1-D)^2 + 2p_A(1-p_A-p_B)D^2(1-D)^2}, \\ \text{CSP} = A[B] + A[B]: \quad \text{LR} &= \frac{(1-D)^2}{p_A^2(1-D)^2 + 2p_Ap_B(1-D)^2 + 2p_A(1-p_A-p_B)D^2(1-D)^2}. \end{aligned}$$

Note that we assume that the different runs are independent, conditional on the genotypes of all contributors (Curran et al., 2005).

We see from Figure 3 that observing $A[B]$ in the 2nd run increases both LRs when D is small but decreases them when D is large. In fact, when D is very high, observing either A or $A[B]$ in just one run yields $\text{LR} > 1$, favouring H_p^1 , whereas two such observations in independent runs gives $\text{LR} < 1$, against H_p^1 . This is because $X \equiv AA$ under H_d^1 then provides a better explanation of the replicate observations than H_p^1 , since homozygotes are much less likely to drop out than a heterozygote allele.

2.4 Additional contributors

LRs such as (2) and (3) can be rewritten more generally as

$$\text{LR} = \frac{P(\text{CSP}|\text{Q} \equiv \text{AB})}{\sum_{g \in \Gamma} p_g P(\text{CSP}|\text{X} \equiv g)} \quad (4)$$

where Γ denotes the set of possible genotypes, while p_g denotes the population fraction of genotype g . Equation (4) makes explicit the requirement to sum over all possible genotypes for the unprofiled contributor X. When there is an additional unprofiled contributor U1, we proceed in the same way as for X. We sum over all possibilities for each unknown genotype, multiplying each term by the genotype probability:

$$\text{LR} = \frac{\sum_{g \in \Gamma} P(\text{CSP}|\text{Q} \equiv \text{AB}, \text{U1} \equiv g)}{\sum_{g1, g2 \in \Gamma} p_{g1} p_{g2} P(\text{CSP}|\text{X} \equiv g1, \text{U1} \equiv g2)}. \quad (5)$$

Each term in these sums follows the same well-established and simple rules that have been used for Q and X above, now applied additionally to the current genotype for U1.

Individuals contribute different amounts of DNA to the mixed-source sample, and multiple individuals can have one or two copies of a given allele. Thus we need to model the dropout probability at an allelic position as a function of the total amount of DNA from all contributors with that allele.

2.5 Multi-dose dropout model

At each step in the likelihood calculation, there is a set of individual hypothesized contributors of DNA to the CSP and each has a genotype (tentatively assigned for the unprofiled contributors). Dropout refers to any allele of these hypothesized contributors that is not observed in the CSP. The dropout model used here (Tvedebrink et al., 2009) can be written

$$\frac{D(k)}{1-D(k)} = (\alpha_s k)^\beta, \quad (6)$$

where s indicates the locus. Note that β is β_1 in the notation of Tvedebrink et al. (2009), and α_s is proportional to $\exp(\beta_{0,s}/\beta_1)$. Here we choose the scale by fixing the mean over loci of α_s at one. The estimates of $\beta_{0,s}$ obtained by Tvedebrink et al. (2009), from experimental non-degraded LTDNA profiled at the ten loci of the SGM+ system, imply an SD for α_s of 0.141. Because they may depend sensitively on the experimental protocol employed, we do not use the Tvedebrink et al. (2009) estimates directly, but instead estimate the α_s under each hypothesis from the observed CSP. To keep the estimates realistic, we impose a gamma distribution prior on the α_s , here assigning mean = 1 and SD = 0.141, although a different SD may be appropriate for example in highly-degraded

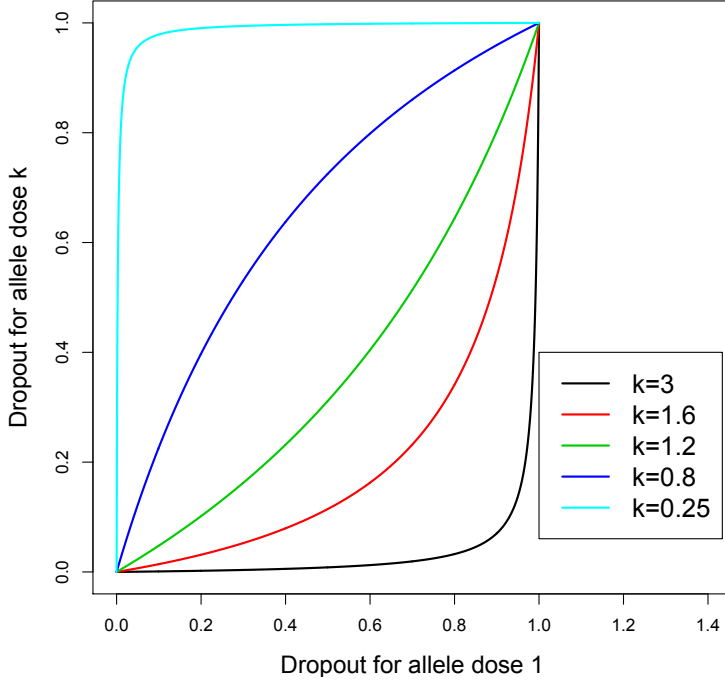


Figure 4: **Dropout probabilities for dose k of DNA (y axis) against those for a unit dose (x axis).** The values of k are shown in the legend box. For this figure the power parameter β was fixed at -4.35 .

samples. For the global parameter β , we adopt a normal distribution with mean -4.35 and SD 0.38 . These both derive from the work of Tvedebrink et al. (2009), but the SD value was not published in the paper and was supplied in personal correspondence with Dr Tvedebrink.

Figure 4 illustrates $D(k)$ as a function of $D(1)$ for several values of k , evaluated by substituting $\alpha_s^\beta = D(1)/(1-D(1))$ in (6). We see for example that if $D(1) = 0.5$, then $D(1.2) \approx 0.3$ and $D(0.8) \approx 0.7$, and so just a 20% change in DNA dose can have a large impact on dropout probabilities.

We take $k = 1$ to correspond to a single heterozygote allele of the reference individual (see Section 2.1.2). Thus $D(1)$ is the heterozygote dropout probability, and $D(2)$ is the homozygote dropout probability, for the reference individual. For k large

$$\frac{D(2k)}{D(k)^2} \approx \left(\frac{2}{\alpha_s k} \right)^\beta > 1,$$

so a homozygote dropout can be *more* likely than independent dropout of both alleles, which is implausible. However, this inequality only applies for low dropout probabilities (Tvedebrink et al., 2012a) and so this defect of the model is unimportant in practice.

The problem of calculating likelihoods for LTDNA profiles was not addressed by Tvedebrink et al. (2009); they validated their model by comparing theoretical and empirical dropout rates. To achieve this, they estimated the amount of DNA from each contributor using the heights of peaks due only to that contributor over the whole profile.

This is problematic for calculating LTDNA likelihoods, because it ignores information from allele peaks with multiple contributors, and requires alleles of individual contributors to be distinguished, which is frequently not possible. Here, we directly specify the likelihood for each replicate in terms of $D(k)$ at every allelic position, with k calculated according to the contributions of DNA and the genotypes of all the hypothesised contributors. We thus use present/uncertain/absent information at every allelic position to provide information about amounts of DNA.

2.6 Degradation model

DNA degrades over time, at a rate that depends on temperature, humidity and environmental exposure. In forensic DNA profiling, degradation is manifested in higher dropout rates for alleles with large fragment lengths. Our model for the effect of degradation is based on that of Tvedebrink et al. (2012b), who posited a geometric distribution for the effective amount of DNA as a function of allele fragment length. Thus, the average allele dose k from the i th contributor subject to dropout is modified at an allele with fragment length l base pairs (centred to have mean zero) according to

$$k' = k(1+\gamma_i)^{-l},$$

where $\gamma_i > 0$. Shorter fragments ($l < 0$) correspond in effect to an enhanced allele dose, while longer fragments generate a smaller effective allele dose. An STR allele consists of flanking regions in addition to the tandem repeats, and so the repeat number that characterises the allele is not a good proxy for fragment length, which can be obtained for many DNA profiling systems at www.cstl.nist.gov/div831/strbase/.

In the spirit of shrinkage regression methods, **likeLTD** incorporates a weak penalty (exponential, mean 0.02) on each γ_i . An example below (Section 3.6) illustrates the effect of this penalty, which is a slight tendency to shrink the parameter estimates towards zero, which is usually negligible but avoids inflated values when there is very little information (for example, in the presence of high dropout or substantial masking).

2.7 Dropin

Dropin refers to an allele in the CSP that is not included in the genotype of any hypothesized contributor, profiled or unprofiled. Dropin alleles can arise from individuals contributing a very low level of DNA to the sample, perhaps generated from fragments of the DNA molecule that persist for some time after the death and decay of a cell. Forensic scientists often restrict “dropin” to lab-based contamination which can be measured by control runs and is usually found to be rare. However, we cannot usually determine

the source of any dropin (Gill et al., 2000), so for the purposes of evaluation we do not distinguish distinguish dropin according to its source. It follows that lab-based estimates of drop-in rates are of limited usefulness.

Each dropin allele does come from an individual, but it may arise from very few and possibly degraded cells so that very little of this individual’s DNA is reflected in CSP peaks. It is computationally inefficient to sum over all possible genotypes, as in (5), for such low-level contributors, and so we allow the possibility of modelling dropin more simply, as independent Bernoulli trials (Curran et al., 2005). Dropin is non-dropout of an allele of a low-level contributor, and so we model the dropin probability as a constant (c) times the non-dropout rate for each replicate. As for the γ_i , we impose a weak penalty on c (exponential, mean 0.5) to discourage solutions with c large, reflecting background information that dropin is usually rare.

If there are sufficient unprofiled contributors to explain all observed alleles, it is unnecessary to model dropin explicitly. If dropin is not modelled, any proposed allocation of alleles to the unprofiled contributors that does not explain every CSP allele is impossible, and the corresponding likelihood calculations can be avoided. We are unable to model the effect of degradation on dropin probability, because dropins are too rare to estimate γ_i , so it is preferable to avoid use of the dropin model when possible. We suggest that the dropin model be used when there are one or two unreplicated alleles in a 10-locus profile that cannot be accounted for by the hypothesized contributors.

2.8 Maximising the penalised likelihood

To compute the LR, it is necessary to deal with the “nuisance” parameters under each hypothesis. These are: the $D(1)$ (one per replicate), the dropout model parameters α_s (one per locus) and β , the contributions of DNA, relative to the reference individual, and the γ_i (one of each for every contributor subject to dropout), and possibly a dropin parameter c (see above). `likeLTD` seeks to maximise a penalised likelihood over these parameters, with penalties on α_s , β , γ_i and c as described above. These penalties can be thought of as prior distributions, but we do not use a Bayesian approach since we maximise over unknown parameters rather than integrate. The primary purpose of the penalty is to avoid the maximisation algorithm from exploring unrealistic regions of the parameter space.

We use the R `DEoptim` function to maximise the penalised likelihoods, which is a genetic algorithm utilising differential evolution optimisation to find the global minimum of a function (since we want to maximise and not minimise, it is necessary to multiply the log-likelihoods by -1).

The results from `DEoptim` consist of two lists, `DEoptim` and `member`. `DEoptim` consists

of four parts:

bestmem: The parameter values that gave the maximum likelihood.

bestval: The negative log likelihood at these parameter values.

nfeval: The number of evaluations of the objective function that were carried out during optimisation.

iter: The number of generations for the optimisation.

while **member** consists of:

lower: The lower bounds of the parameters used.

upper: The upper bounds of the parameters used.

bestvalit: A vector containing the maximum likelihood at each generation.

bestmemit: A matrix containing the parameters that gave the maximum likelihood at each generation.

pop: The set of parameter values generated for the last generation.

storepop: The sets of parameters generated for previous generations.

See the DEoptim help page for more information.

Rather than estimate the nuisance parameters, they can be set to fixed values if desired, by setting the upper and lower bounds. For example

```
tofix = "dropout"
value = 0.2
# Create index of which parameters are dropout parameters
index = grep(tofix,names(paramsP$upper))
# Set those parameters upper value to the fixed value for prosecution
paramsP$upper[index] = rep(value,times=length(index))
# Set those parameters lower value to the fixed value for prosecution
paramsP$lower[index] = rep(value,times=length(index))

# Repeat for the defence uppers and lowers
index = grep(tofix,names(paramsD$upper))
paramsD$upper[index] = rep(value,times=length(index))
paramsD$lower[index] = rep(value,times=length(index))
```

2.9 Computing time and memory requirements

The Hammer case analysis described above required 49 minutes to run, while the three contributor test (see Section 3.4) requires 117 minutes to run. These timings were made on a desktop computer with 15Gb of RAM, and an eight core Intel i7 processor (at 3.1GHz per core). Computing times may vary across machines. Most desktop computers will have enough memory to run all cases except when dropin is modelled and there are three unknown contributors under H_d . In that case up to 1Gb of RAM may be required per locus, depending on the number of alleles, and so 3 unknowns + dropin analyses will only be possible on large-memory machines.

The number of generations used for optimisation by `DEoptim` is not fixed in advance, but is determined by the function `evaluate`. Each step is a separate optimisation, with a geometric pattern in the crossing over rate (see `DEoptim::DEoptim.control`) and convergence tolerance. Each step checks for convergence after every 75 generations; convergence occurs if $\log_{10}(|1 - L_c/L_{c-75}|) \leq t$ where L denotes likelihood, c the current generation and t the tolerance for the given step.

As discussed previously the major determinant of runtime is now the number n of steps required by `evaluate` runs for convergence, n . This is computed as $n = \max(4, 4\lceil \log_2(\bar{x}) \rceil) + r_d$ where r_d is the number of `rcont` parameters handed to `DEoptim` under the defence case, and \bar{x} is the mean of σ_p and σ_d , where σ_p is the standard deviation of the likelihood for the first phase (iterations 1-75) of the first step of optimisation for the prosecution (σ_d is the same, but for defence). We can see that the minimum number of steps is 4, and that the number of steps increases with both complexity and difficulty of optimisation.

A key parameter determining the `DEoptim` run time is the size of the population (number of random starts per generation). Larger values tend to generate higher likelihoods, but there is a rapidly diminishing benefit with increasing population size, while run time increases approximately linearly. `likeLTD` sets the population size to be four times the number of parameters varied in the optimisation (NP). For the Hammer timings above this implies a population size of 80, while for the three contributor test (Section 3.4) the population size was 72. NP, and hence population size and run time, depend on the number of contributors subject to dropout, since there is an effective amount of DNA and a degradation parameter for each of these. Run time is also affected by the number of unprofiled contributors: these are always subject to dropout, and summation over their possible genotypes adds to run time and to the memory requirement. Below we show that `likeLTD` can handle up to four contributors subject to dropout, of which up to two can be unprofiled under H_p . In previous versions (5.3 and earlier), an increased NP was necessary for proper optimisation when close relatedness is taken into account, however, this need has been negated with the `evaluate` function introduced in version 5.4, which

performs well without any increase in NP.

3 Performance tests of likeLTD

3.1 Validation of likelihood ratios

Laboratory procedures to measure a physical quantity such as a concentration can be validated by showing that the measured concentration consistently lies within an acceptable range of error relative to the true concentration. Such validation is infeasible for software aimed at computing an LR, because there is no underlying true value (no equivalent of the true concentration). The underlying truth that is being probed is whether or not an individual Q is a contributor of DNA to the crime scene profile (CSP), which is a yes/no and not a quantitative event. Even if I know all the contributors to a complex mixture there is still no “correct” value of the LR. Probabilities measure our certainty about the true state of nature, and there is no “true” level of certainty about an unknown fact, it depends on the data available (for example details of the CSP) and on modelling assumptions, e.g. about dropout and dropin. However, forensic LRs are expected to behave in a particular manner, particularly they should not exceed the inverse of the match probability (Cowell et al., 2013b), which can be used to validate any given software package. We have shown (Steele et al., 2014) that likeLTD adheres to this behaviour with multiple replicates, and demonstrated that the inverse match probability is fit for purpose as a validation tool.

For a given set of input data and modelling assumptions, there may be an exact value for the likelihood, but there are always other plausible modelling assumptions that can give different values. In practice, the different programs that are available or in development for the evaluation of LTDNA profiles do make different assumptions and obtain different answers, though of course the differences should be, and in practice are, small relative to the 10 or more orders of magnitude over which LRs range in practical applications. It follows that it is fruitless to insist on very high precision of likelihood calculations under any specific model. It was recognised by Turing over a half-century ago that evidence is best measured in units of base 10 logarithms, a unit that he called the ban. An error of 1 deciban ($\approx 26\%$ on the natural scale) should be regarded as negligible, because the implications of different, reasonable, modelling assumptions are often larger than this, and so bans should not be reported to one decimal place. Moreover, we show below that routine sampling and F_{ST} adjustments can make a difference of between one and two bans, and these are designed to err substantially in favour of defendants, typically by at least several decibans.

There is a convenient analogy between the measurement of WoE and earthquakes.

Both are logarithmic scales that should usually be reported to at most one decimal place, and typical values range up to about 10. There is no maximum for WoE but in practice in the UK any value above 9 bans (LR > 1 billion) is reported as “over a billion”.

While there is no “true” value of the LR, even for simulated cases, many checks on the performance of `likeLTD` are possible, using simulated and real profiles. We report below the performance of `likeLTD` under an extensive set of tests. For example, we check if an allele in the reference profile of Q is removed from the CSP, then the LR is reduced, whereas if an allele not in Q’s reference profile is removed this increases the resulting LR. We check that if we wrongly assume an extra contributor, either profiled or unprofiled, the LR computed by `likeLTD` is little changed, and similarly if a small number of alleles is modelled either using a dropout term in the model, or as the alleles of an additional contributor with heavy dropout. We check that when large fragment length alleles are removed from the CSP, the degradation parameter estimate is high. When different numbers of dropouts occur in different replicates, we show that the estimates of the dropout rates for those replicates differ accordingly. We also check that `likeLTD` produces answers consistent with those generated by a similar program, in that any discrepancies can be qualitatively understood in terms of the different modelling assumptions of the programs. We further provide simulations to illustrate the search length required for stable estimates of the LR over replicate runs of `likeLTD`.

3.2 A one-contributor CSP with dropout and dropout

Three CSPs were analysed (Table 1(i)), to which Q (Table 1(i), row 1) is the only true contributor, but both dropout and dropout are introduced for CSPs 2 and 3. Thus H_p^1 (page 14) is the truth, and in the analyses below this is compared with H_d^1 .

CSP1: Exactly the profile of Q (Table 1, row 1) appears in each replicate of CSP1 (rows 2,3). There would be no need to use `likeLTD` for this perfect single-contributor match, but we apply it here in order to check that `likeLTD` works correctly in this setting. The WoE (Table 1, row 1) is 11.3 bans. A naive application of the product rule using the allele counts in Table 1 gives 12.9 bans (Table 2), but using the allele fractions in the bottom two rows of the table, adjusted for coancestry ($F_{ST} = 0.02$) and sampling ($\text{adj} = 1$), reduces this to 11.43 bans.

The sampling adjustment “adj” is a value added to the database counts for the alleles of Q, to reduce the risk of understating the population frequency, particularly for rare alleles. Except in the first column of Table 2, we always use $\text{adj} = 1$. Balding (1995) advocated $\text{adj} = 2$ in the absence of an F_{ST} adjustment, but since F_{ST} has a big impact on low-frequency alleles, $\text{adj} = 1$ is adequate when an appropriate F_{ST} adjustment is

Locus	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
Q	15,16	15,18	11,11	17,24	13,13	29,31	10,16	13,14	6,9,3	22,24
CSP1a	15,16	15,18	11	17,24	13	29,31	10,16	13,14	6,9,3	22,24
CSP1b	15,16	15,18	11	17,24	13	29,31	10,16	13,14	6,9,3	22,24
CSP2a	15,16	15,18	11	17,24	13	29,31	10,16	13,14	6,9,3	22
CSP2b	15,16,17	15,18	11	17	13	29,31	10,16	13,14	6,9,3	22,24
CSP3a	15,16	15,18	11	17,24	13,15	29,31	10,16	13,14	6,9,3	22
CSP3b	15,16,17	15,18	11	17	13	29,31	16	13,14	6,9,3	22
count	116,106 (396)	38,80 (384)	130 (418)	90,35 (388)	118 (384)	74,28 (384)	2,56 (384)	102,133 (396)	77,151 (384)	75,47 (384)
fraction	0.302,0.278	0.117,0.221	0.341	0.244,0.108	0.338	0.206,0.0918	0.027,0.161	0.268,0.343	0.214,0.398	0.209,0.139

(i)

Contributor 1Contributor 2

CSP	WoE	Hyp	L	DO a	DO b	γ	DO a	DO b	γ	DI	Power
CSP1	11.3	H_p^1	4.6							0.00	-4.35
		H_d^1	-6.8	0.00	0.00	0.00				0.00	-4.35
	11.3	H_p^2	4.6	1.00	1.00	0.00					-4.35
		H_d^2	-6.8	1.00	1.00	0.00	0.00	0.00	0.00		-4.35
(ii) CSP2	11.2	H_p^1	-0.4	0.03	0.03	0.00				0.07	-4.37
		H_d^1	-11.6	0.03	0.03	0.00				0.09	-4.37
	11.3	H_p^2	0.1	0.05	0.02	0.00		1.00	0.99		-4.37
		H_d^2	-11.2	1.00	0.99	0.01	0.05	0.02	0.00		-4.37
CSP3	8.8	H_p^1	-3.6	0.03	0.11	0.00				0.15	-4.38
		H_d^1	-12.3	0.00	0.14	0.00				0.09	-4.37
	9.4	H_p^2	-2.9	0.05	0.13	0.00		0.96	0.98		-4.40
		H_d^2	-12.3	0.97	0.99	0.01	0.04	0.12	0.00		-4.38

Table 1: **One contributor profile simulation experiments.** (i) Observed alleles for three crime scene profiles (CSP), each profiled in duplicate (a and b). Also shown are database counts for the alleles of Q (locus total) and the allele fractions after sampling and F_{ST} adjustments ($\text{adj} = 1$, $F_{ST} = 0.02$). (ii) Weight of evidence (WoE) and corresponding parameter estimates, from 1likeLTD analyses of the three CSPs. DO and DI denote dropout and dropin, while gamma and Power are degradation/dropout parameters described in the text as γ and β . The labelling of Contributors 1 & 2 is arbitrary. Under H_p^1 there is only one contributor who is not subject to dropout, so no dropout or degradation results are shown.

Fst	0.00	0.00	0.01	0.02	0.03
adj	0	1	1	1	1
WoE (bans)	12.3	12.3	11.7	11.3	10.9

Table 2: Overall weight of evidence (WoE) for CSP1.

n. contrib.	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA	WoE
1	2.4	2.9	2.3	2.8	2.1	2.9	3.4	2.2	2.3	2.9	4.1
2	2.4	2.9	2.3	2.8	2.1	2.9	3.4	2.2	2.3	2.9	4.1

Table 3: Single-locus LR_s and overall weight of evidence for CSP1 when X, the alternative source of the DNA, is a brother of Q. Results are shown for both 1- and 2-contributor analyses.

employed. Note that **likeLTD** only adjusts for coancestry between X and Q, by replacing each population allele fraction estimate p (after sampling adjustment) with:

$$\begin{array}{ll}
(1-F_{ST})p/(1+F_{ST}) & \text{for alleles not in the profile of Q} \\
(F_{ST} + (1-F_{ST})p)/(1+F_{ST}) & \text{for a heterozygote allele of Q} \\
(2F_{ST} + (1-F_{ST})p)/(1+F_{ST}) & \text{for a homozygote allele of Q}
\end{array}$$

These F_{ST} adjustments implemented in **likeLTD** are allelic adjustments, rather than the alternative genotype adjustments. Genotype adjustments require a different F_{ST} adjustment depending on the genotype configuration of both Q and X/U. The allelic adjustments can be seen as a approximation of a full F_{ST} genotype adjustment, which should not have a large effect if F_{ST} is low. The largest effect will be seen when both Q and X/U are homozygotes, where the numerator of the genotype adjusted allele probability would include a $3F_{ST}$ term, while the allelic adjusted probability would instead include a $2F_{ST}$ term, as shown in Table 3.2. Note that all allelic F_{ST} adjustment denominators differ from the genotypic F_{ST} adjustments, in that a $1 + F_{ST}$ is replaced with a $1 + 2F_{ST}$. The numerator only differs between the two methods when X is homozygous.

F_{ST} values comparing different parts of mainland Europe are typically < 0.005 , and so 0.02 is a relatively large value, except perhaps for Q and X both from a small population isolate such as a remote island. $F_{ST} = 0.03$, or in extreme cases $F_{ST} = 0.05$, may be more appropriate for small, isolated or heterogeneous populations, such as many migrant populations. See Balding (2005) for further discussion and for more details of F_{ST} adjustments based on the multinomial-Dirichlet distribution.

Brother alternative: Repeating the 1-contributor analysis but now assuming that X is

\mathcal{G}_Q	\mathcal{G}_X	Allele adjustment	Genotype adjustment
AA	AA	$\frac{(2F_{ST}+(1-F_{ST})p_A)(2F_{ST}+(1-F_{ST})p_A)}{(1+F_{ST})(1+F_{ST})}$	$\frac{(2F_{ST}+(1-F_{ST})p_A)(3F_{ST}+(1-F_{ST})p_A)}{(1+F_{ST})(1+2F_{ST})}$
AA	AB	$2\frac{(2F_{ST}+(1-F_{ST})p_A)(1-F_{ST})p_B}{(1+F_{ST})(1+F_{ST})}$	$2\frac{(2F_{ST}+(1-F_{ST})p_A)(1-F_{ST})p_B}{(1+F_{ST})(1+2F_{ST})}$
AB	AB	$2\frac{(F_{ST}+(1-F_{ST})p_A)(F_{ST}+(1-F_{ST})p_B)}{(1+F_{ST})(1+F_{ST})}$	$2\frac{(F_{ST}+(1-F_{ST})p_A)(F_{ST}+(1-F_{ST})p_B)}{(1+F_{ST})(1+2F_{ST})}$
AB	AA	$\frac{(F_{ST}+(1-F_{ST})p_A)(F_{ST}+(1-F_{ST})p_A)}{(1+F_{ST})(1+F_{ST})}$	$\frac{(F_{ST}+(1-F_{ST})p_A)(2F_{ST}+(1-F_{ST})p_A)}{(1+F_{ST})(1+2F_{ST})}$
AB	AC	$2\frac{(F_{ST}+(1-F_{ST})p_A)(1-F_{ST})p_C}{(1+F_{ST})(1+F_{ST})}$	$2\frac{(F_{ST}+(1-F_{ST})p_A)(1-F_{ST})p_C}{(1+F_{ST})(1+2F_{ST})}$
AB	CD	$2\frac{((1-F_{ST})p_C)((1-F_{ST})p_D)}{(1+F_{ST})(1+F_{ST})}$	$2\frac{((1-F_{ST})p_C)((1-F_{ST})p_D)}{(1+F_{ST})(1+2F_{ST})}$

Table 4: F_{ST} adjusted genotype probabilities for all combinations of matching/non-matching alleles between Q and X, with both the allelic F_{ST} adjustment used in `likeLTD` and the full genotypic F_{ST} adjustment.

an unprofiled brother of Q gives 4.1 bans (Table 3). The single locus LRs computed by `likeLTD` follow very closely the usual formula for a sibling (Balding, 2005), which in the heterozygote (homozygote) case is:

$$\text{LR} = \frac{4}{1 + p_a + p_b + 2p_ap_b} \quad \left(\frac{4}{(1 + p_a)^2} \right)$$

Note that the single-locus LR can never exceed 4 for the brother alternative. Also, there is no explicit F_{ST} adjustment in the formula above because the allele fractions p have been adjusted as described above: this provides a reasonable approximation to the adjustment based on the multinomial-Dirichlet distribution.

Assuming two contributors: If we wrongly guessed that there were two contributors to CSP1, we could compare the hypotheses

$$H_p^2 : Q + U1 \quad \text{with} \quad H_d^2 : X + U1$$

where X and U1 denote unprofiled individuals that are unrelated to each other and to Q. In this case `likeLTD` correctly estimates near 100% dropout for U1 under both hypotheses (Table 1(ii), row 2) and the WoE is almost unchanged from assuming one contributor. Similarly, when X is a brother of Q, the single-locus LRs and overall WoE computed by `likeLTD` are almost identical to the 1-contributor case (Table 3). The package does not take into account linkage between markers, so these results will be slightly overstated (see Section 1.3 for more information).

CSP2: The two replicates of CSP2 differ from those of CSP1 due to one dropin and two dropouts (Table 1(i), rows 4,5). The two dropouts both affect loci with large fragment lengths, consistent with the effects of DNA degradation. Because the dropin allele is at a

heterozygous locus where the two alleles of Q are replicated, and the two dropout alleles each appear in the other replicate, the evidence implicating Q remains very powerful and the WoE is only slightly reduced, to 11.2 bans (Table 1, rows 5,6). The dropout parameter estimates are similar over the four replicate/hypothesis combinations. The γ_Q/γ_X estimates are, as expected, moderately large at around 0%. Since the dropin allele must have come from somebody, it is possible to analyse CSP2 as a two-contributor profile without a dropin term in the model, which implies very heavy dropout for the second contributor, U1. We see from (Table 1(ii), rows 7,8) that this analysis gives a slightly stronger WoE (11.3 bans), closer to the WoE for CSP1. The dropout rates for U1 are, as expected, very high, and γ_{U1} is also high (about 1 because the dropin allele is at a short fragment length locus, so when attributed to U1 it gives further support to the pattern of dropout increasing with DNA fragment length).

CSP3: One further dropin and two more dropouts have been introduced into CSP3 relative to CSP2 (Table 1(i), rows 6,7). The extra dropin is at a locus for which Q is homozygous, so while it must be a dropin under H_p^1 , that is not so under H_d^1 . The two additional dropouts again both affect loci with large fragment lengths, and this time an allele of Q has dropped out in both replicates (FGA 24), which has a substantial impact on the evidence implicating Q as a contributor. While the evidence remains powerful, the overall WoE is now reduced by at least two bans compared with CSP2 (Table 1(ii), rows 9–12). CSP3b is affected by three dropouts, whereas CSP3a by only one, and consequently the dropout rate estimates are much higher for CSP3b than for CSP3a. The difference between modelling CSP3 as a one-contributor profile with two dropins, and a two-contributor profile with substantial dropout for one of the contributors, is now more important (0.6 bans). The two models differ in several respects. The two-contributor model gives the stronger WoE, and the dropin model can be regarded as a simple approximation that reduces computation time, and is more conservative for the examples considered here.

3.3 Two unprofiled contributors

Table 6 presents results from `likeLTD` analyses of two-contributor profiles shown in Table 5. The contributors are Q and an individual treated here as unknown, while the hypotheses compared are those given above (page 27): H_p^2 (the truth) and H_d^2 . Note that under H_d^2 the labels X and U1 for the two unprofiled contributors are arbitrary: in the discussion below we call X the one with dropout rates most similar to Q.

CSP4: shows exactly the alleles of the two contributors in both replicates, with no dropout or dropin. The dropout rates, and γ_Q and γ_X , are all correctly estimated to be

Locus	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
Q	15,16	15,18	11,11	17,24	13,13	29,31	10,16	13,14	6,9.3	22,24
CSP4a	15,16,17	15,18	11,13	17,20,24	10,13	29,31,32.2	10,11,13,16	13,14	6,8,9.3	19,22,24,25
CSP4b	15,16,17	15,18	11,13	17,20,24	10,13	29,31,32.2	10,11,13,16	13,14	6,8,9.3	19,22,24,25
CSP5a	15,16	15,18	11,13	17,24	10,13	29,31,32.2	10,11,16	13,14	6,8,9.3	19,22,24
CSP5b	15,16,17	15,18	11,13	17,24	13	29,31,32.2	10,16	13,14	6,9.3	22,24,25
CSP6a	15,16,17	15,18	11,13	17,20	10,13	29,31,32.2	10,11,13	13,14	6,8,9.3	19,25
CSP6b	15,16,17	15,18	11,13	17,20,24	10,13	29,32.2	11,13	13,14	6,8,9.3	19,25
CSP7a	15,17	15,18	11,13	17,20	10,13	29,31,32.2	10,11,13	13,14	6,8,9.3	19,25
uncertain	(16)	(14),(17)	(10)	(16),(19)	(12)			(12)	(5)	(18),(24)
CSP7b	15,17	15,18	11,13	17,20,24	10,13	29,32.2	11,13	13,14	6,8,9.3	19,25
uncertain		(17)	(12)	(19)		(31.2)	(10)	(12)	(5)	(24)
CSP8a	15	15,18	11	17,20,24	–	29,31	10,11,16	13,14	6,8	19,22
CSP8b	16,17	15,18	13	17,20	10,13	31	10,16	13	6,8	22,24,25

Table 5: **Two contributor profile simulation experiments.** The crime scene profiles correspond to those of Q and one unprofiled contributor, modified by dropout and (for CSP7) stutter generating uncertain allele calls. The layout is similar to Table 1 except that for CSP7 there are additional rows indicating alleles classified as uncertain.

		Contributor 1					Contributor 2				
CSP	WoE	Hyp	L	DO a	DO b	γ	DO a.1	DO b.1	γ	DI	Power
CSP4	6.2	H_p^2	-7.5	0.00	0.00	0					-4.35
		H_d^2	-13.8	0.00	0.00	0	0.00	0.00	0		-4.35
CSP5	9.4	H_p^2	-9.9	0.51	0.69	0					-4.37
		H_d^2	-19.4	0.54	0.72	0	0.00	0.00	0		-4.37
CSP6	5.2	H_p^2	-11.9	0.26	0.40	0	0.00	0.00	0		-4.40
		H_d^2	-17.1	0.67	0.77	0	0.00	0.00	0		-4.39
CSP7	4.1	H_p^2	-11.6	0.29	0.47	0	0.00	0.00	0		-4.38
		H_d^2	-15.7	0.65	0.71	0	0.00	0.00	0		-4.37
CSP8	2.5	H_p^1	-23.1	0.25	0.32	0				0.93	-4.22
		H_d^1	-25.6	0.24	0.18	0				0.52	-4.41
	4.5	H_p^2	-21.4	0.43	0.43	0	0.63	0.63	0		-4.15
		H_d^2	-25.9	0.65	0.65	0	0.42	0.42	0		-4.29

Table 6: Weight of evidence (WoE) and corresponding parameter estimates, from `likeLTD` analyses of the five CSPs of Table 5. See Table1(ii) for explanations.

close to zero. The WoE is 6.2 bans, reduced by over five bans from the case of a single-contributor CSP matching Q (CSP1), because of the additional uncertainty created by the masking effect of the alleles of U1.

CSP5: introduces random 50% dropout for the alleles of U1 not shared with Q. Because of the reduced masking effect, the WoE is much higher than for CSP4, now >9 bans. The dropout rates for X are correctly estimated as close to zero. The actual numbers of dropouts of the alleles of U1 are 4 in CSP5a and 5 in CSP5b, and this is reflected in the dropout rate estimates of 35% for CSP5a and 47% for CSP5b. These estimates cannot be precise because of the masking of the alleles of U1 by those of Q.

CSP6: Here, the opposite scenario is considered of a random 50% dropout of the alleles of Q not shared with U1. As expected, this reduces the WoE relative to CSP4, by one ban. At locus FGA both alleles of Q have dropped out in both replicates; the WoE is -0.74 at this locus and is > 0 at all other loci (not shown). There are again four dropouts in CSP6a but five in CSP6b, which is reflected in different dropout rates over the two replicates. The dropouts were predominantly at the loci with large fragment lengths (D2, D18 and FGA) and so γ_Q is moderately high, at 0.6%.

CSP7: A new difficulty is introduced: in addition to 50% dropout for the alleles of Q, 50% of the alleles of U1 generate stutter peaks that have a non-negligible probability of masking an allele of Q. Each of these peaks is classified as “uncertain” for the `likeLTD` analysis, irrespective of whether or not Q has an allele at that position. This additional ambiguity in the CSPs reduces further the WoE, to 4.1 bans. Once again the dropout and γ_i parameter estimates are broadly reasonable, noting that high precision is not possible here because of the masking effects of the stutters and alleles of U1.

CSP8: Random 50% dropout affects the alleles of both Q and U1. Once again all the dropout and γ_i estimates are reasonable for the two-contributor analysis, and the WoE is 4.5 bans. Even though the CSPs were created assuming two contributors, there are now only three replicate/locus combinations (out of 20) at which > 2 alleles were observed. Thus, it would be possible, though not recommended, to analyse this case assuming one contributor plus dropin. The results (Table 6(ii) two rows) again show that this simplified analysis gives a conservative result, with the WoE now 2.5 bans.

We repeated the computation of the likelihoods for CSP7 and CSP8 (2 contributors) varying the tolerance of `evaluate`, which sets the tolerance for convergence of the last step of optimisation (Table 7). We find no variance in the WoE with any of the tolerance levels, suggesting advanced users may wish to reduce the tolerance to gain some speed increases. However, while this is true for these results, this may not apply to other CSPs;

user discretion is advised.

3.4 Three unprofiled contributors

We generated an example with three unprofiled contributors using the profiles from the Hammer Case (see above) but omitting K2 and treating K1 as if unprofiled. The hypotheses compared were then

$$H_p^3 : Q + U1 + U2 \quad \text{with} \quad H_d^3 : X + U1 + U2.$$

Once again the tolerance has no effect on the final WoE. This comes with the same caveat that this may only apply to the cases shown here; any decision by the user to reduce the tolerance threshold should be investigated thoroughly before implementation. Minor changes to tolerance should cause no problem (e.g. 1e-4), however, larger changes may cause suboptimal optimisation for more difficult CSPs (e.g. 1e-1).

In `likeLTD` the population size of each iteration (NP) was determined as a factor multiplied by the number of parameters to optimise over. In earlier versions of the program, factor=1 was inadequate for the three-contributor case, but with improvements implemented in version 5.4 this is no longer the case and the overall WoE is accurate even when factor=1 (results not shown).

3.5 Complex Case

We simulated a complex CSP with four replicate profiling runs. The genotypes of the four contributors (Q, K1, U1 and U2) were generated randomly assuming HWE and allele fractions from the Caucasian database (EA1). The probabilities of dropout were 0.2, 0.4, 0.6 and 0.7 for Q, K1, U1 and U2, respectively, each constant over runs. Dropout of the two alleles of a homozygote, and/or multiple contributors with the same allele, were treated as independent events (so the allele dropped out only if each copy from each contributor dropped out according to the probabilities above). This makes dropout at such alleles more likely than predicted under the multi-dose dropout model, generating an inflated dropout rate estimates in `likeLTD`

At any locus and in any replicate, with probability 0.95 there were no dropins, otherwise exactly one dropin, chosen according to the allele fractions.

At locus D2 there are three alleles that cannot be explained by Q or K1 (17,22,23), all three of which are replicated and so cannot be explained by drop-in, thus indicating the presence of at least two unprofiled contributors. We therefore compared the following hypotheses:

(a)

Tolerance	Time	WoE	Lp	Ld	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
0.1	4	4.1	-11.58	-15.68	0.6	4.1	1.8	3.8	1.8	11.1	8.6	2.3	3.5	0.6
0.01	5	4.1	-11.58	-15.68	0.6	4.1	1.8	3.8	1.8	11.1	8.6	2.3	3.5	0.6
0.001	5	4.1	-11.58	-15.68	0.6	4.1	1.8	3.8	1.8	11.1	8.6	2.3	3.5	0.6
1e-04	5	4.1	-11.58	-15.68	0.6	4.1	1.8	3.8	1.8	11.1	8.6	2.3	3.5	0.6
1e-05	5	4.1	-11.58	-15.68	0.6	4.1	1.8	3.8	1.8	11.1	8.6	2.3	3.5	0.6
1e-06	5	4.1	-11.58	-15.68	0.6	4.1	1.8	3.8	1.8	11.1	8.6	2.3	3.5	0.6

(b)

Tolerance	Time	WoE	Lp	Ld	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
0.1	11	4.5	-21.41	-25.88	2	11.6	0.7	3.2	0.5	10.3	46.4	2.9	0.2	4.3
0.01	12	4.5	-21.41	-25.88	2	11.6	0.7	3.2	0.5	10.3	46.4	2.9	0.2	4.3
0.001	13	4.5	-21.41	-25.88	2	11.6	0.7	3.2	0.5	10.3	46.5	2.9	0.2	4.3
1e-04	13	4.5	-21.41	-25.88	2	11.6	0.7	3.2	0.5	10.3	46.5	2.9	0.2	4.3
1e-05	13	4.5	-21.41	-25.88	2	11.6	0.7	3.2	0.5	10.3	46.4	2.9	0.2	4.3
1e-06	14	4.5	-21.41	-25.88	2	11.6	0.7	3.2	0.5	10.3	46.4	2.9	0.2	4.3

(c)

Tolerance	Time	WoE	Lp	Ld	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
0.1	84	8.3	-17.1	-25.38	8.1	12.1	9.9	3.6	1.6	17.3	3.6	91.3	1.3	4.6
0.01	85	8.3	-17.1	-25.39	8.1	12	10	3.8	1.6	17.2	3.5	92.6	1.3	4.5
0.001	89	8.3	-17.1	-25.38	8.1	12.1	10	3.7	1.6	17.3	3.5	90.2	1.3	4.7
1e-04	92	8.3	-17.1	-25.38	8.1	12.1	9.9	3.7	1.6	17.6	3.5	92.1	1.3	4.6
1e-05	96	8.3	-17.1	-25.38	8.1	12	10	3.6	1.6	17.1	3.6	90.3	1.3	4.7
1e-06	111	8.3	-17.1	-25.38	8.1	12.1	10	3.7	1.6	17.3	3.5	90.7	1.3	4.7

Table 7: Summary of results from likeLTD analyses for two 2-contributor CSPs: (a) CSP7, (b) CSP8, and (c) a 3-contributor CSP (Section 3.4), using different tolerances for the evaluate function. The first column gives the tolerance to which the last step of optimisation must reach before it is deemed as having converged. WoE is in bans, computed as the difference between Lp and Ld which are the overall log likelihoods under the prosecution and defence hypotheses. The LR is reported for individual loci. Results from the default tolerance are shown in bold. Time shows the time taken in minutes for optimisation to be completed.

$$H_p^4 : Q + K1 + U1 + U2 \quad \text{with} \quad H_d^4 : X + K1 + U1 + U2.$$

Hp	K1	Q	U1	U2
Dropout a	0.558	0.271	0.726	0.730
Dropout b	0.559	0.272	0.727	0.730
Dropout c	0.653	0.357	0.798	0.801
Dropout d	0.624	0.328	0.777	0.780

Hd	K1	X	U1	U2
Dropout a	0.542	0.669	0.635	0.605
Dropout b	0.541	0.668	0.634	0.604
Dropout c	0.633	0.746	0.717	0.690
Dropout d	0.602	0.721	0.690	0.661

Table 8: Dropout rate estimates for the complex case (Section 3.5)

The dropout estimates returned by `likeLTD` tend to overestimate the known values slightly under H_p^4 , due to the the independent assignment of drop-out as discussed above. Under H_d^4 , the differences in DNA contribution from the three unprofiled contributors are, as might be expected, not well distinguished.

The log likelihoods returned were -55.3 under H_p and -62.44 leading to a WoE of 7.1 bans. Here, H_p^4 is true and so the strong WoE in favour of this hypothesis is encouraging. However, the WoE has been tempered by the presence of substantial masking from the one profiled and two unprofiled other contributors of DNA.

3.6 Modifying the model

In this section we introduce various modifications to the model underlying the Hammer Case analysis of Section 1.

3.6.1 Including a dropout term

In the original analysis we did not explicitly model dropout because the CSPs show at most three alleles not attributable to the victims, so they are consistent with two unknown contributors and no dropout. We now investigate the effect of introducing an explicit dropout term, retaining U1 so that the algorithm could account for the unreplicated alleles either as dropout or as alleles of U1. Allowing the possibility of dropout had a noticeable impact

Hammer	Standard	Drop-in	Unc	Beta		locAdj σ^2		deg
				-3.97	-4.73	0	0.32	
D3	1.0	1.1	1.0	1.1	1.1	1.1	1.1	1.3
vWA	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
D16	1.5	1.4	1.3	1.4	1.4	1.4	1.4	1.5
D2	0.9	1.4	0.9	1.4	1.3	1.5	1.3	1.5
D8	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
D21	1.5	1.6	1.5	1.6	1.6	1.6	1.6	1.5
D18	-0.5	-0.5	-0.5	-0.5	-0.5	-0.4	-0.5	-0.9
D19	2.6	2.6	1.7	2.6	2.6	2.6	2.6	2.5
TH01	0.9	0.8	0.9	0.8	0.8	0.9	0.8	0.8
FGA	1.1	1.2	0.7	1.2	1.2	1.1	1.2	1.3
Overall	10.9	11.6	9.5	11.6	11.6	11.7	11.6	11.4

Table 9: Single-locus and overall WoE values for analyses of the Hammer case imposing various modifications to the dropout model.

on the overall WoE (Table 9). The most important single-locus difference was an increase of 5 decibans at D2. This is the only locus at which more alleles were observed in CSPa than in CSPb: overall there are 11 more alleles observed in CSPb than in CSPa, and consequently the dropout rate for U1 in CSPa is high (estimate 95% under H'_p , compared with 38% for CSPb). This makes the unreplicated D2 23 allele in CSPa better explained as a dropin. However, the fact that the dropin model does not adequately account for the evidence for a high dropout rate in CSPa reflects a limitation of the model, and a reason to prefer the standard analysis above that does not include a dropin term.

3.6.2 Uncertain allele calls

The capability of `likeLTD` to treat an allelic position as “uncertain” was not available in `LoComatioN` and so this designation was not made in the Hammer Case CSPs. Additional features of `likeLTD` not incorporated in `LoComatioN` include dropout rate estimates per replicate and per contributor, and modelling of DNA degradation.

To illustrate its impact on WoE, we recoded seven CSP alleles as “uncertain”. Overall, this weakens the evidence but it remains very strong at 9.5 bans (Table 9). However, the consequence of changing an allele call to “uncertain” varies, depending for example on whether it affects an allele of Q or a profiled contributor or both. For each allele the change in the computed WoE matches intuition we briefly describe some examples:

- Locus D16, CSPa, allele 11. This is an allele of Q, not shared with K1, and so changing its status from present to uncertain reduces the WoE, but only slightly because the allele is called in CSPb: the single-locus WoE is decreases slightly from 1.5 bans to 1.3 bans (Table 9, column 4).
- Locus D8, CSPa, allele 11 and CSPb allele 15. These are both alleles of K1 not shared with Q, and both are called as alleles in the other run. The WoE is unchanged at 0.9 bans.
- Locus D19, CSPa and CSPb, allele 15.2. This is a rare allele, included in the profile of Q but not K1 or K2, and so changing its status in both CSPs substantially reduces the WoE, by 9 decibans.

There are also indirect effects on all loci, because the changes in allele calls impact the support for dropout parameter values.

In the following subsections, we investigate the effects on WoE of various modifications to the dropout model (6).

3.6.3 Varying the dropout power parameter

We performed new analyses assigning $\beta = -3.97$ and $\beta = -4.73$. These values represent one SD above and below the central estimate of -4.35 reported by Tvedebrink et al. (2009). The overall WoE values are identical at 11.6 bans, and 11.6 bans, respectively.

3.6.4 Varying the dropout locus adjustments

The locus-adjustment parameter α_s allows for differences in dropout rates over loci, beyond the dependence on fragment length that is captured with the degradation model. In the standard analysis, **likeLTD** imposes a gamma distribution penalty term with both parameters equal to 50, implying a prior variance in α_s of 0.14. We first fixed α_s at one (variance = 0), so that the dropout probability of an allele of a given fragment length is the same for all loci. The overall WoE was 11.7 bans. The converse change was to weaken the gamma penalty by changing its prior SD from 0.14 to 0.32 (the two parameters of the gamma distribution penalty changed from both = 50 to both = 10). This reduced the overall WoE to 11.6 bans.

3.6.5 Varying the degradation model

Degradation is manifested in higher dropout rates for large fragment length alleles. In the SGM+ system, this has greatest effect for the alleles at D2, D18 and FGA. In Table

9, we note a reduced number of observed alleles relative to other loci at D18 and FGA, but not D2. To investigate the effect of modelling degradation in **likeLTD**, we repeated the analysis but with the degradation parameter $\gamma_i = 0$ for every contributor i , which implies no change in dropout probability with fragment length. This increased the WoE by nearly 6 decibans at locus D2 relative to the standard analysis, but decreased it by 4 decibans at D18.

In contrast with fixing the γ_i , we removing the penalty term (Table 9). The estimates of γ_Q , γ_X , γ_{K1} and γ_{U1} were almost identical to those given in Appendix A, rows 3 and 6, confirming that the penalty term has little effect in the presence of good information. For K2 we have essentially no information, and γ_{K2} was estimated at 0.000 and 0.000 with the penalty, but at 0.001 and 0.003 without it, illustrating that the penalty can prevent inflated γ_i estimates in the presence of little information.

The overall effect on WoE of both the failure to model degradation and the removal of the penalty term was close to zero (Table 9).

3.7 Conclusions

As discussed above there is no “gold standard” test of a likelihood calculation for LTDNA profiles, but we have shown here a good performance of **likeLTD** in analysing a wide range of crime scene DNA profiles, involving complex mixtures, uncertain allele designations, dropin and dropout, degradation, stutter, and relatedness of alternative possible contributors. **likeLTD** behaves gives the same answer as well-established formulas in simple settings. The parameter estimates and WoE change in a coherent and interpretable manner under artificial modifications of the CSPs, and are robust to major modifications of the modelling assumptions.

As well as providing strong WoE in favour of true contributors in simulation experiments, we found in examples that **likeLTD** identified no support for the presence of DNA even when superficially there appeared to be some support. This, together with the decline in WoE as dropins and dropouts were introduced, illustrate that, while powerful, **likeLTD** does not overstate evidential strength, due to a number of features in the algorithm including F_{ST} and sampling adjustments. The introduction of “uncertain” allele calls mitigates the “cliff edge” problem of yes/no allele calls required by other approaches.

Full results are available from the authors, including all input files that enable others to replicate any of the analyses reported here or to make additional tests.

4 Acknowledgments and version history

The underlying mathematical model and its implementation in the `likeLTD` R code were developed by DJB. Input into the model came from John Buckleton, as described in Balding and Buckleton (2009). A number of other academics and forensic scientists have given feedback and encouragement, among them Norah Rudin and Kirk Lohmueller in California, Torben Tvedebrink and Niels Morling in Denmark, Peter Gill (Norway), Hinda Haned (Netherlands), and Roberto Puch-Solis (UK).

Since Version 4.0, DJB has been helped to develop the R code by Adrian Timpson, and more recently Chris Steele has helped improve coding and implement the tests described in this document.

The early work in developing Version 5.0 was done by Adrian Timpson, the bulk of the recoding was done by Mayeul d’Avezac of the Research Software Development team in UCL Information Services Division, and some final enhancements were implemented by Chris Steele.

There has been no external funding for this project, although DJB has benefitted from fees paid to UCL Consultants Ltd for expert witness work. His employer University College London, and in particular the UCL Genetics Institute, have supported the project by continuing to pay him a salary during the many months of work time that he has devoted to it.

- **Version 1**

- Release 1-0, 19/1/10. The initial code had separate files `LR1unk.R` and `LR2unk.R` for 1 and 2 unprofiled contributors. Each included functions `LRnumer()` and `LRdenom()`
- Release 1-1, 23/1/10. Restructured code for `LR1unk.R` to make it more similar to `LR2unk.R`
- Release 1-2, 26/3/10. Fixed small bug reported by Kirk Lohmueller, affecting the assignment of `allfracs` in 3 places
- Release 1-3, 24/5/10. Changed way `dropin` is modelled.

- **Version 2**

- Release 2-0, 21/6/10. Merged previous `LR1unk.R` and `LR2unk.R` into a single file `LTDNALR.R` with the functions `LRnumer()` from those files renamed as `LRnumer1()` and `LRnumer2()`, respectively, and similarly for `LRdenom()`.
- Release 2-1. The change introduced in V2.1 has since been undone in V3.0, by introduction of a better way to deal with rare alleles

- **Version 3**

- Release 3-0, 12/10/11. The previous functions `LRnumer1()`, `LRnumer2()`, `LRdenom1()` and `LRdenom2()` were all replaced by a single function `likeLTD`. There is now a distinct dropout rate for each replicate (DO). The dropout rate for other individuals is determined as a function of DO and the amount of DNA from that individual relative to the amount contributed by the reference individual (Q or U). We now strip out alleles with zero database frequency. If an allele of Q or CSP is not found in `rownames(acbp)` this allele is inserted into `acbp` with count 1. This has speeded up computations so that it now becomes feasible to allow three unprofiled contributors to the crime scene profile when $Q_{cont}=F$, otherwise two unprofileds + Q. The model for dropout is now improved: the previous `kdrop` function has gone, and both dropout and dropin calculations are included in a new function `Calclik()`. Stutter alleles, or other apparent artefacts, can be entered as uncertain alleles allowing the possibility that they could be allelic.
- Release 3-1, 4/1/12. Previously the dropin parameter DI was the non-dropout rate for a hypothetical extra individual, but this is now modified so that the dropin rate for each replicate is DI times the non-dropout rate (1-DO) for that replicate. As before, if $DI=0$ then all CSP alleles must come from one of the specified contributors. We now allow any of the profiled possible contributors to be unaffected by dropout, including Q. This option should only be used if the individual's alleles are observed in the CSP in every replicate at every locus; otherwise an error is generated. Alleles of profiled possible contributors not subject to dropout are converted to uncertain and removed from the CSP in the preprocessing step and (except for Q) don't play any further role in `likeLTD`. There has been some rearrangement of the code so that more work is done in a preprocessing function that is called only once, rather than being repeated in every call to the main function. Some changes have been made to the way parameters are named and passed; function calls to previous versions of `likeLTD` will not work without modification.

- **Version 4**

- Release 4-0, 19/3/12. The main innovation is to allow dropout rates to increase with fragment length. Thus, fragment lengths for each allele in the profiling system being employed must be supplied (in base-pairs, bp, centred so that 0 represents an average length). These are passed to `likeLTD` in column 2 of matrix `afbp`, which replaces vector `allfracs` in Version 3.1; column 1 is the

previous allfracs, and specifies population allele fractions. The program uses the model of Tvedebrink et al. (2012b) and essentially the “dose” of DNA contributed by an individual at an allele is adjusted by a geometric function of fragment length (increased for below-average fragment lengths, and decreased for above-average). The rate of the geometric distribution is a parameter `deg` (for degradation), which is a vector with one entry per contributor subject to dropout.

- Release 4-1, 8/5/12. Improvement to computation of number of simulations used when `denNu=3` and also starting values for `nupa` and `depa`. Release of test document giving results from performance tests of `likeLTD`.
- Release 4-2, 26/6/12. These are mainly minor changes to improve the output and program clarity documentation. The test results document distributed with this code is also updated to include new test results. The most important change is an improved assignment of the simulation size for the likelihood approximation invoked for three unprofiled contributors (i.e. `denNu=3`). For one or two unknown contributors there should be no changes to results from Version 4.1. `BB` is now passed as a parameter rather than being assigned as a constant.
- Release 4-3, 10/8/12. Mostly just a few minor changes to documentation but there is one important bug fix that affected the likelihood calculations when `DI > 0`; thus any V4.2 runs that modelled dropout (`Drin = TRUE` in the wrapper) should be rerun with V4.3. Further improvements to output and to value for `nsim`.
- Release 4-4, 2/11/12. Two changes:
 - * A new block of code can provide much faster computation when `Nump=2` or `3` and `DI=0`. The speed-up is greatest when the CSPs determine many alleles in the genotypes of the unprofiled contributors. The new code uses combinatorial functions that require the R `gtools` library; `library(gtools)` is now included in the Wrapper, but the package must first be installed using `install.packages("gtools")`. The result of the computation is unchanged from the original code that uses “for” loops. Both codes are kept, and the initial likelihood calculation is done once using each code in order to set flags indicating which is quickest; the faster code is then used for all subsequent calculations at that locus (there are separate flags for the calculations under H_p and H_d). Because of this improvement, the previous code that performed a simulation-based approximation to the likelihood

when `Nunp=3` has been removed, and so `nsim` has been removed from the list of parameters passed to `likeLTD`.

- * Locus adjustment terms are now included in the dropout model, as in Tvedebrink et al. (2009). However, rather than estimate the locus effects on dropout from external data, they are estimated from the input data for the profile being analysed. Because this may be relatively little information, a strong prior is imposed on the locus adjustments: gamma with both parameters equal so that the mean is 1. The default value of this parameter (`lap`) is 50, giving a prior standard deviation for the locus adjustments of 0.14, the same as the SD of the estimates of Tvedebrink et al. (2009).

Also the inverse of the exact match probability is output for comparison with the LR for the observed CSP: this is the standard match probability that would apply if the CSP showed exactly the reference profile of Q, and it is assumed that there is only one contributor. The LR for any other CSP should not exceed the inverse of the match probability.

- Release 4-5, 2/11/12. The power parameter β (eq. 6) has been fixed in previous versions at -4.35 (Tvedebrink et al., 2009). In this version it is updated in the simulated annealing, separately under H_p and H_d , subject to a Gaussian prior/penalty with mean -4.35 and SD 0.38 , the values obtained by Tvedebrink et al. (2009). This is a relatively minor and sensible change, and we have checked that it has little impact. However all the test results reported in this document are for V4-4 and not V4-5.

• Version 5

- Release 5-0. This is a complete re-writing of the basic code, which is now established as an official R package on CRAN. The simulated annealing algorithm used in previous versions for parameter optimisation is replaced with a differential evolution algorithm for optimisation. The underlying likelihood model remains the same as version 4.5, however, significant speed improvements have been gained through re-factoring of R code (e.g. converting for loops into vector/matrix operations), re-writing computationally intensive steps in C, and implementing parallel computation of the C code. Steps that have been implemented in C code include the computation of genotype combinations for unknown contributors, computing allele doses for each genotype combination, dose adjustments for relatedness, heterozygosity, dropout and power. Uploading the package to CRAN comes with improved documentation, version control

and ease of access.

- Release 5-1. This update improved the calculation of the LR when close-relatedness is taken into account.
- Release 5-2. This update adds the function `get.likely.genotypes` that returns the most probable genotypes for each locus, and the most probable whole-profile genotype. There is an option to return marginal genotype probabilities for each contributor subject to dropout, or joint probabilities for all contributors subject to dropout.
- Release 5-3. This update improves the generation of both allele and output reports. These are now output as .doc files instead of .pdf files, and will now scale with the number of loci and the number of replicates correctly. The change to .doc files was motivated by client requests, and .pdf files can still be easily obtained by opening the .doc file in MS Word and saving as a pdf. There are additional improvements to the checks for unusual alleles (which will now recognize typos and alleles not present in the database), and to the suggestion of appropriate hypotheses to test.
- Release 5-4. This update improves the optimisation procedure, replacing the simple convergence threshold with a geometric progression of convergence. This includes a geometric progression of the `DEoptim::DEoptim.control CR` variable, which controls the crossover rate of the optimisation algorithm. The combination of these two means that the parameter space is more thoroughly searched in the initial stages, leading to improved optimisation. L_p and L_d are now optimised together (within each step), allowing for estimation of the progress of optimisation (and an associated progress bar). Interim results after each step are now available. These changes are incorporated in the new optimisation function, `evaluate`. Small changes to the outputs are included, namely altered default file names (including the case name in the file name) and including which database file is used in the information section.

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A Allele report for Hammer case

hammer-Allele-Report
hammer

Data provided by forensic scientist

Crime scene profiles (CSP)

run	status	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
1	certain	14,16	15,16,19	11,13,14	20,23,24,25	11,12,13,15	28,31		12,14,15.2,17.2	6,8,9,9.3	22
-	uncertain										
2	certain	14,16	15,16,17,19	11,13,14	20,24,25	11,12,13,15	28,29,30,31,31.2	13,14,16,17	12,13,14,15.2,17.2	6,8,9,9.3	22,23,25
-	uncertain										

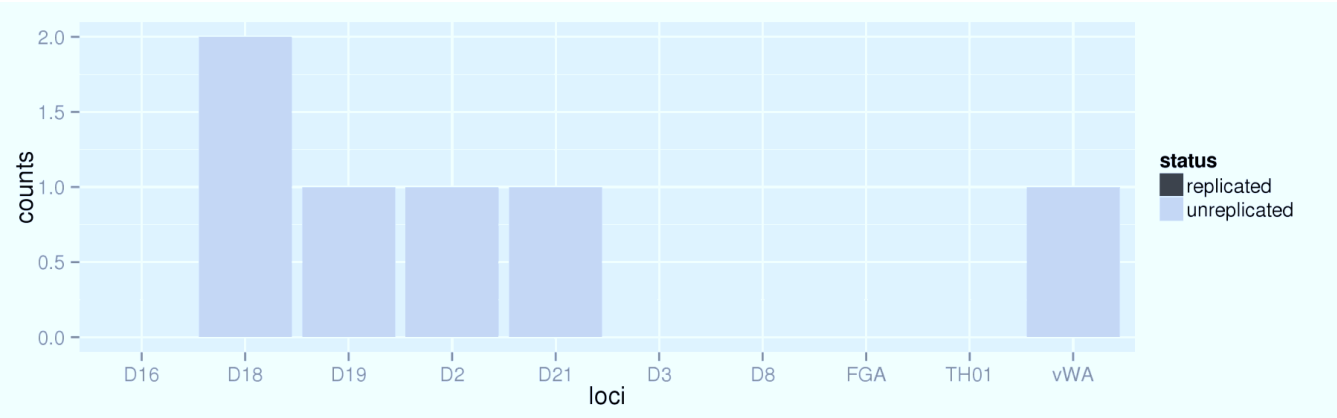
Reference profiles

profile	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
Suspect	14,16	15,19	11,14	24,25	12,13	28,31	14,17	15.2,17.2	9,9.3	22,23
Victim 1	16	15,16	13	20	11,15	29,30	17	12,14	6,8	22,25
Victim 2	15,17	16,19	13,12	25,18	11,13	29,30	17,15	14	6,7	22,20
Other		17		23		31.2	13,16	13		

Alleles that are replicated, unreplicated or absent in the crime scene profile, using the certain designations only.

Summary

Unattributable alleles



The number of 'certain' alleles that cannot be attributed to the known profile(s).

Unusual alleles

source	locus	allele	EA1.freq	EA3.freq	EA4.freq	error
Reference profiles	D19	17.2	0	2	1	-
Crime scene certain	D19	17.2	0	2	1	-

Alleles are automatically checked against the database. An error will be reported if an allele is absent from the database, or present more than once, or if a locus is absent.

Approximate representation

Contributor	Rep 1	Rep 2	Total
Suspect	85	100	92
Victim 1	75	100	88

Contributor	Rep 1	Rep 2	Total
Victim 2	47	63	55

The fraction of an individual's alleles (as a percentage) that have been designated as 'certain' alleles in each replicate. This estimate is not used by likeLTD, and is intended to assist informal assessments of possible known contributors to the CSP. A more formal approach is to do a likeLTD run to compute the likelihood ratio (LR) for that individual contributor.

Suggested parameter values

nUnknowns	doDropin	Recommendation
0	TRUE	
1	FALSE	recommended

Recommended values for 'nUnknowns', choose from 0,1 or 2 (likeLTD automatically adds and additional unknown X to the defence hypothesis in place of the queried profile Q).

Recommended values for 'doDropin', choose from 'TRUE' or 'FALSE'.

All the attributable alleles must either come from an unknown or dropin.

System information

Type	Details
Date report generated:	Sun Jun 29 01:49:57 2014
Package	likeLTD
Title	Tools to determine DNA profile evidence.
Description	Tools to determine DNA profile Weight of Evidence. For further information see the likeLTD guide at the URL provided, or the paper under citation.
Depends	R (≥ 2.10), DEoptim, ggplot2, gtools, rtf
Suggests	svUnit, scales
Imports	gdata, tools, tcltk
Version	5.3.3
Date	2013-03-15
Author	David Balding, Adrian Timpson, Christopher Steele, Mayeul d'Avezac, James Hetherington.

Type	Details
Maintainer	Christopher Steele <c.steele.11@ucl.ac.uk>
License	GPL-3
URL	https://sites.google.com/site/baldingstatisticalgenetics/
Packaged	2014-06-26 12:50:41 UTC; csteele
Built	R 3.0.1; x86_64-unknown-linux-gnu; 2014-06-26 12:50:44 UTC; unix
sysname	Linux
release	2.6.32-358.18.1.el6.x86_64
version	#1 SMP Wed Aug 28 17:19:38 UTC 2013
nodename	ugi-151057.ugi.ucl.ac.uk
machine	x86_64
login	csteele
user	csteele
effective_user	csteele

B Output file for Hammer case

hammer-Evaluation-Report

hammer

Prosecution Hypothesis: Suspect (Q) + Victim 1 + Victim 2 + 1U

Defence Hypothesis: Unknown (X) + Victim 1 + Victim 2 + 1U

Data provided by forensic scientist

Crime scene profiles (CSP)

run	status	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
1	certain	14,16	15,16,19	11,13,14	20,23,24,25	11,12,13,15	28,31		12,14,15.2,17.2	6,8,9,9.3	22
-	uncertain										
2	certain	14,16	15,16,17,19	11,13,14	20,24,25	11,12,13,15	28,29,30,31,31.2	13,14,16,17	12,13,14,15.2,17.2	6,8,9,9.3	22,23,25
-	uncertain										

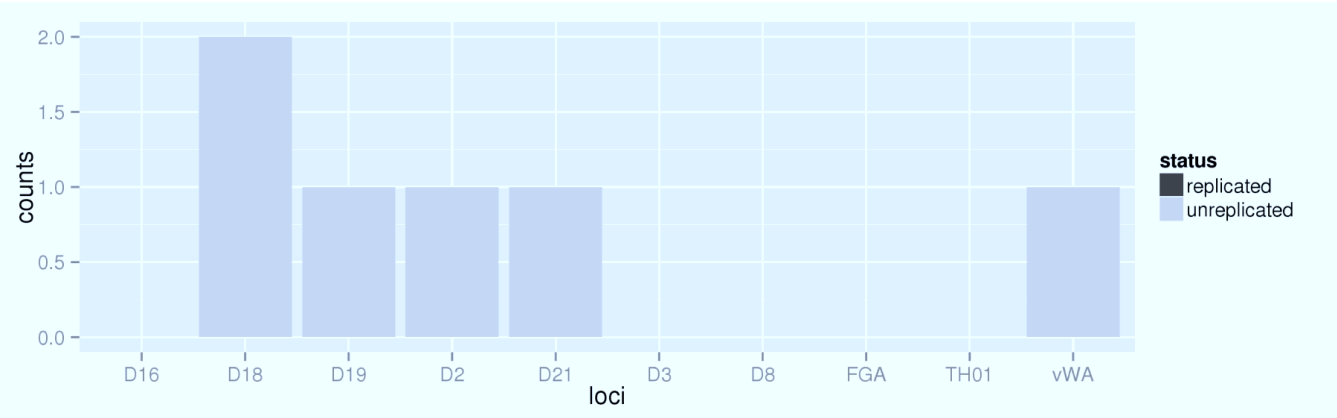
Reference profiles

profile	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
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Victim 2	15,17	16,19	13,12	25,18	11,13	29,30	17,15	14	6,7	22,20
Other		17		23		31.2	13,16	13		

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Crime scene certain	D19	17.2	0	2	1	-

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Approximate representation

Contributor	Rep 1	Rep 2	Total
Suspect	85	100	92
Victim 1	75	100	88

Contributor	Rep 1	Rep 2	Total
Victim 2	47	63	55

The fraction of an individual's alleles (as a percentage) that have been designated as 'certain' alleles in each replicate. This estimate is not used by likeLTD, and is intended to assist informal assessments of possible known contributors to the CSP. A more formal approach is to do a likeLTD run to compute the likelihood ratio (LR) for that individual contributor.

Likelihoods at each locus

Likelihood	D3	vWA	D16	D2	D8	D21	D18	D19	TH01	FGA
Prosecution.log10	0.031	-0.408	-0.168	-3.065	0.126	-1.549	-3.226	-0.418	0.112	-0.910
Defence.log10	-1.013	-1.523	-1.620	-3.935	-0.818	-3.030	-2.691	-3.013	-0.760	-1.993
Ratio.log10	1.045	1.116	1.452	0.871	0.944	1.481	-0.535	2.595	0.872	1.083
Ratio	11.081	13.054	28.299	7.423	8.794	30.300	0.292	393.415	7.451	12.093

Overall Likelihood

calculation	estimate
Prosecution.log10	-9.475
Defence.log10	-20.398
Ratio.log10	10.923
Ratio	83738325729

Theoretical maximum LR

calculation	estimate
likelihood ratio	218884512327670
Log10 likelihood ratio	14.340

Dropout and degradation parameter estimates

hypothesis	contributor	Dropout (Run 1)	Dropout (Run 2)	Degradation (overall)
Prosecution	Victim 1 (K1)	0.465	0.027	0.009
Prosecution	Victim 2 (K2)	1.000	1.000	0.000
Prosecution	Suspect (Q)	0.108	0.004	0.004
Prosecution	U1	0.954	0.397	0.000
Defence	Victim 1 (K1)	0.438	0.046	0.008
Defence	Victim 2 (K2)	1.000	1.000	0.000
Defence	X	0.896	0.347	0.000
Defence	U1	0.117	0.008	0.004

Dropin parameter estimates

hypothesis	dropin
Prosecution	-
Defence	-

User defined parameters

Parameter	User input
caseName	hammer
outputPath	/ugi/home/shared/steele/Dropbox/PhD/likeLTD/likeLTD-5.0/TestResults/hammer-standard
nUnknowns	1
ethnic	EA1
adj	1
fst	0.02
relatedness1	0
relatedness2	0
doDropin	FALSE

Input files

File	Used
CSP	hammer-CSP.csv
Reference	hammer-reference.csv
Database	lgc-allele-freqs-wbp.txt (Default)

Optimised parameters

Prosecution parameters

parameter	estimate	upper bound	lower bound
locusAdjustment1	0.946	1.500	0.500
locusAdjustment2	1.010	1.500	0.500
locusAdjustment3	1.004	1.500	0.500
locusAdjustment4	1.098	1.500	0.500
locusAdjustment5	0.981	1.500	0.500
locusAdjustment6	0.943	1.500	0.500
locusAdjustment7	0.932	1.500	0.500
locusAdjustment8	1.009	1.500	0.500
locusAdjustment9	1.010	1.500	0.500
locusAdjustment10	0.873	1.500	0.500
power	-4.330	-2.000	-6.000
dropout1	0.108	1.000	0.000
dropout2	0.004	1.000	0.000
degradation1	-2.062	0.000	-20.000
degradation2	-16.686	0.000	-20.000
degradation3	-2.360	0.000	-20.000
degradation4	-17.597	0.000	-20.000
rcont1	0.635	100.000	0.000

parameter	estimate	upper bound	lower bound
rcont2	0.000	100.000	0.000
rcont3	0.305	100.000	0.000

Defence parameters

parameter	estimate	upper bound	lower bound
locusAdjustment1	0.946	1.500	0.500
locusAdjustment2	0.999	1.500	0.500
locusAdjustment3	1.013	1.500	0.500
locusAdjustment4	1.088	1.500	0.500
locusAdjustment5	0.994	1.500	0.500
locusAdjustment6	0.937	1.500	0.500
locusAdjustment7	0.878	1.500	0.500
locusAdjustment8	1.014	1.500	0.500
locusAdjustment9	1.022	1.500	0.500
locusAdjustment10	0.908	1.500	0.500
power	-4.401	-2.000	-6.000
dropout1	0.896	1.000	0.000
dropout2	0.347	1.000	0.000
degradation1	-2.110	0.000	-20.000
degradation2	-16.891	0.000	-20.000
degradation3	-17.384	0.000	-20.000
degradation4	-2.374	0.000	-20.000
rcont1	1.725	100.000	0.000
rcont2	0.000	100.000	0.000
rcont3	2.578	100.000	0.000

System information

Type	Details
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Type	Details
Date report generated:	Sun Jun 29 01:49:58 2014
Package	likeLTD
Title	Tools to determine DNA profile evidence.
Description	Tools to determine DNA profile Weight of Evidence. For further information see the likeLTD guide at the URL provided, or the paper under citation.
Depends	R (≥ 2.10), DEoptim, ggplot2, gtools, rtf
Suggests	svUnit, scales
Imports	gdata, tools, tcltk
Version	5.3.3
Date	2013-03-15
Author	David Balding, Adrian Timpson, Christopher Steele, Mayeul d'Avezac, James Hetherington.
Maintainer	Christopher Steele <c.steele.11@ucl.ac.uk>
License	GPL-3
URL	https://sites.google.com/site/baldingstatisticalgenetics/
Packaged	2014-06-26 12:50:41 UTC; csteele
Built	R 3.0.1; x86_64-unknown-linux-gnu; 2014-06-26 12:50:44 UTC; unix
sysname	Linux
release	2.6.32-358.18.1.el6.x86_64
version	#1 SMP Wed Aug 28 17:19:38 UTC 2013
nodename	ugi-151057.ugi.ucl.ac.uk
machine	x86_64
login	csteele
user	csteele
effective_user	csteele