Analysis of Y-STR data using the discrete Laplace model

DNA in Forensics 2014

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Motivation

- Haplotype probability distribution (statistical model)
- Enables a wide range of inferences using one model:
  - Haplotype frequency estimation (observed and unobserved)
  - Cluster analysis
  - Mixtures (e.g. separation and *LR*)
  - ...
- Not a new ad-hoc tool for each task
- Statistical model gives desirable properties:
  - $P(h)$: probability mass function
  - Consistent:

$$\sum_{h \in \mathcal{H}} P(h) = 1$$

Model

- Y-STR: Loci not statistically independent
- Our approach: Condition on [something] to obtain independency between loci

Discrete Laplace distribution

Discrete Laplace distributed $X \sim DL(p, \mu)$:

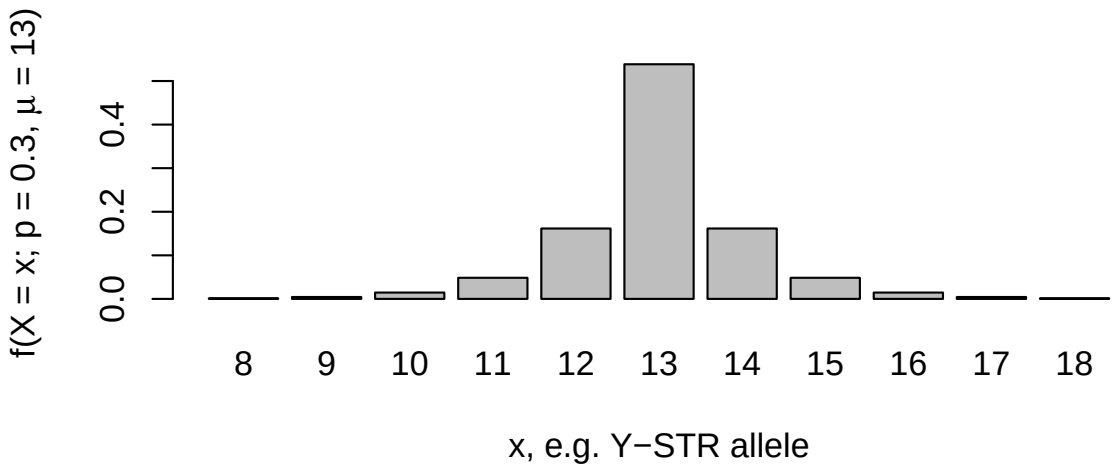
- Dispersion parameter $0 < p < 1$ and
- Location parameter $\mu \in \mathbb{Z} = \{\ldots, -2, -1, 0, 1, 2, \ldots\}$

Probability mass function:

$$f(X = x; p, \mu) = \frac{1-p}{1+p} \cdot p^{|x-\mu|} \quad \text{for } x \in \mathbb{Z}.$$

Perfectly homogeneous population with 1-locus haplotypes:

$$P(X = x) = f(X = x; p, \mu)$$



Statistical model for Y-STR haplotypes

Perfectly homogeneous population with r-locus haplotypes:

$$P(X = (x_1, x_2, \ldots, x_r)) = \prod_{k=1}^{r} f(x_k; p_k, \mu_k)$$

- $\vec{\mu} = (\mu_1, \mu_2, \ldots, \mu_r)$: central haplotype
- $\vec{p} = (p_1, p_2, \ldots, p_r)$: discrete Laplace parameters (one for each locus)
- Mutations happen independently across loci (relative to $\vec{\mu}$)

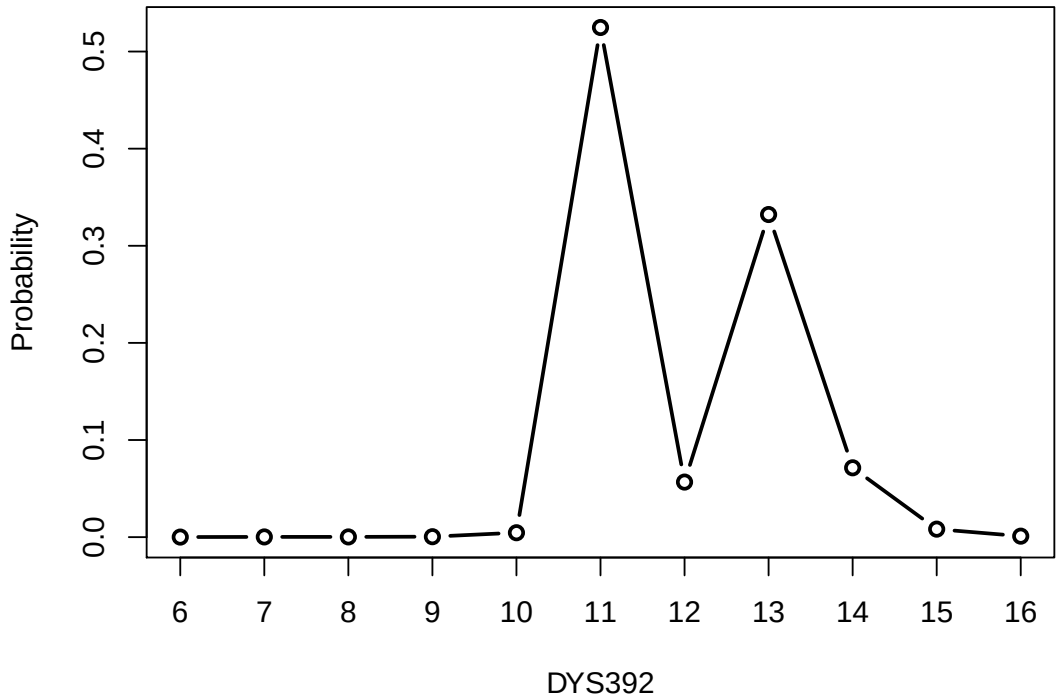
Statistical model for Y-STR haplotypes

Non-homogeneous population with c subpopulations and r-locus haplotypes:

$$P(X = (x_1, x_2, \ldots, x_r)) = \sum_{j=1}^{c} \tau_j \prod_{k=1}^{r} f\left(x_k; p_{jk}, \mu_{jk}\right)$$

- τ_j: a priori probability for originating from the j'th subpopulation ($\sum_{j=1}^{c} \tau_j = 1$)
- $\vec{\mu_j} = (\mu_{j1}, \mu_{j2}, \ldots, \mu_{jr})$: central haplotype for the j'th subpopulation
- $\vec{p_j} = (p_{j1}, p_{j2}, \ldots, p_{jr})$: parameters for all loci at the j'th subpopulation
- Parameter estimation from observations using `R` library `disclapmix`

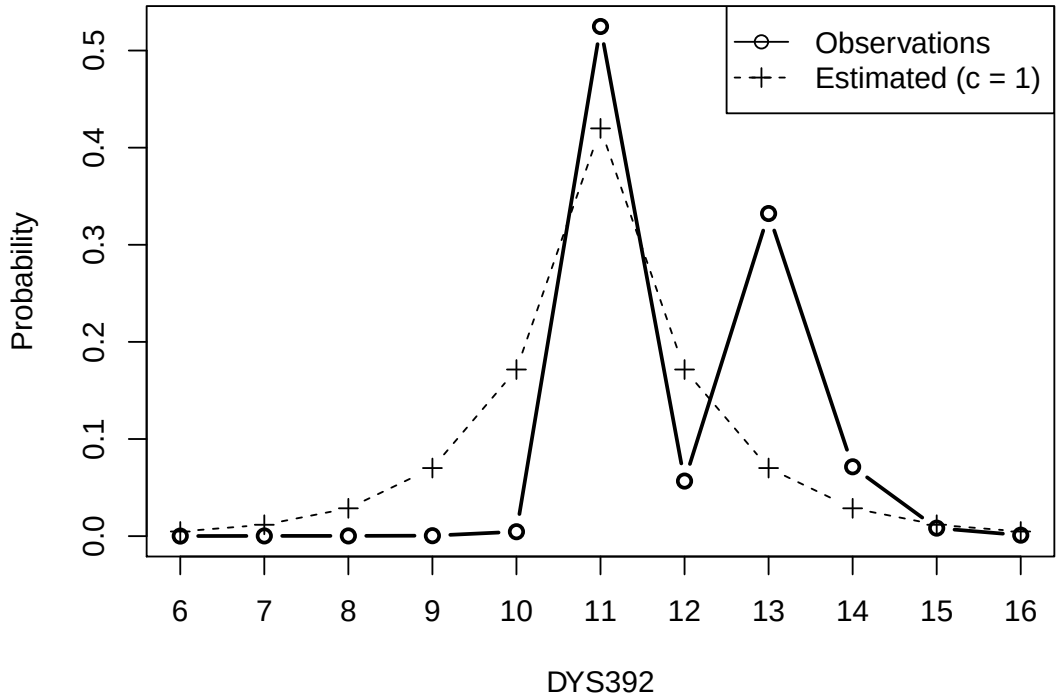
Data and fit



c: Number of subpopulations

$P(X = x) = \sum_{j=1}^{c} \tau_j f(x; p_j, \mu_j)$

Data and fit

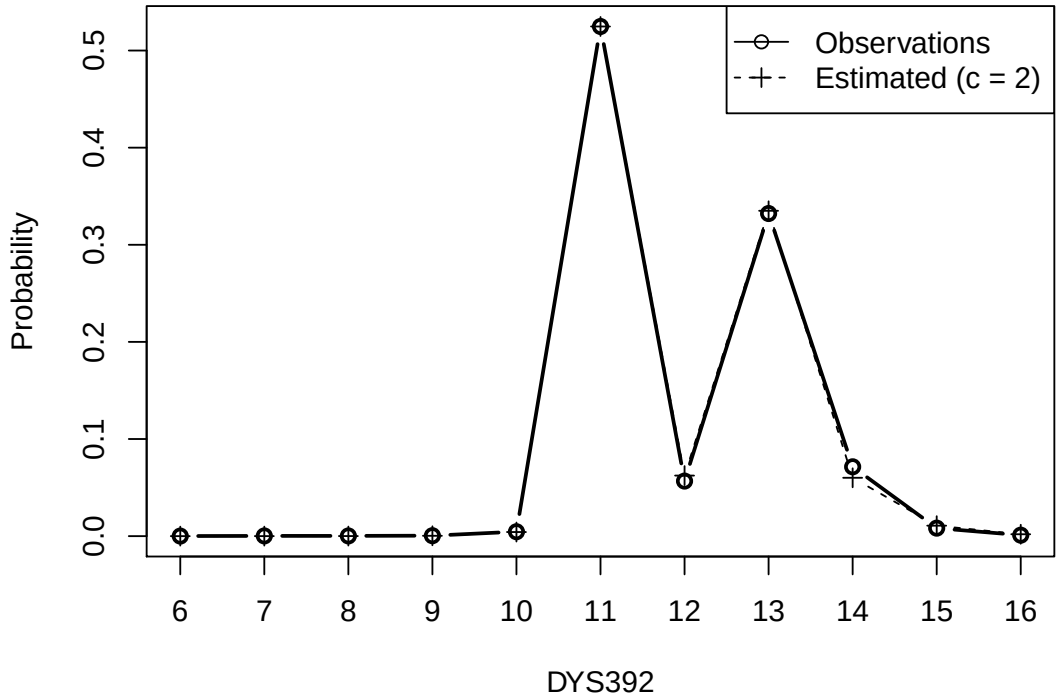


c: Number of subpopulations

$P(X = x) = \sum_{j=1}^{c} \tau_j f(x; p_j, \mu_j)$

$P(\texttt{DYS392} = x) = 1 \cdot f(x; p = 0.41, \mu = 11)$

Data and fit



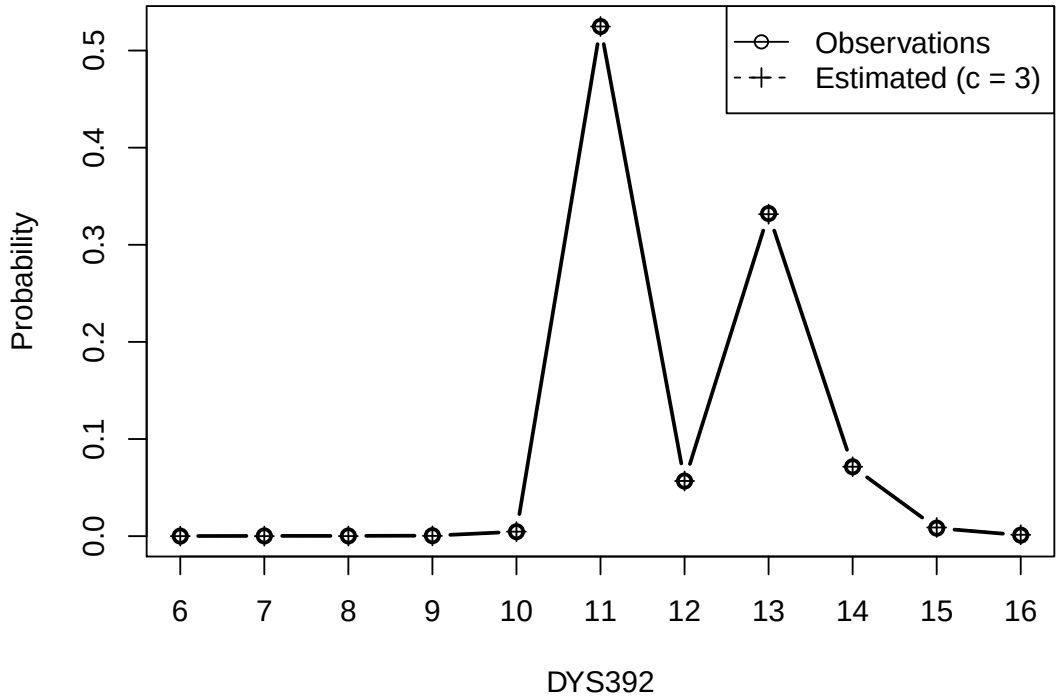
c: Number of subpopulations

$P(X = x) = \sum_{j=1}^{c} \tau_j f(x; p_j, \mu_j)$

$P(\texttt{DYS392} = x) =$

$0.519 \cdot f(x; p = 0.004, \mu = 11) + 0.481 \cdot f(x; p = 0.179, \mu = 13)$

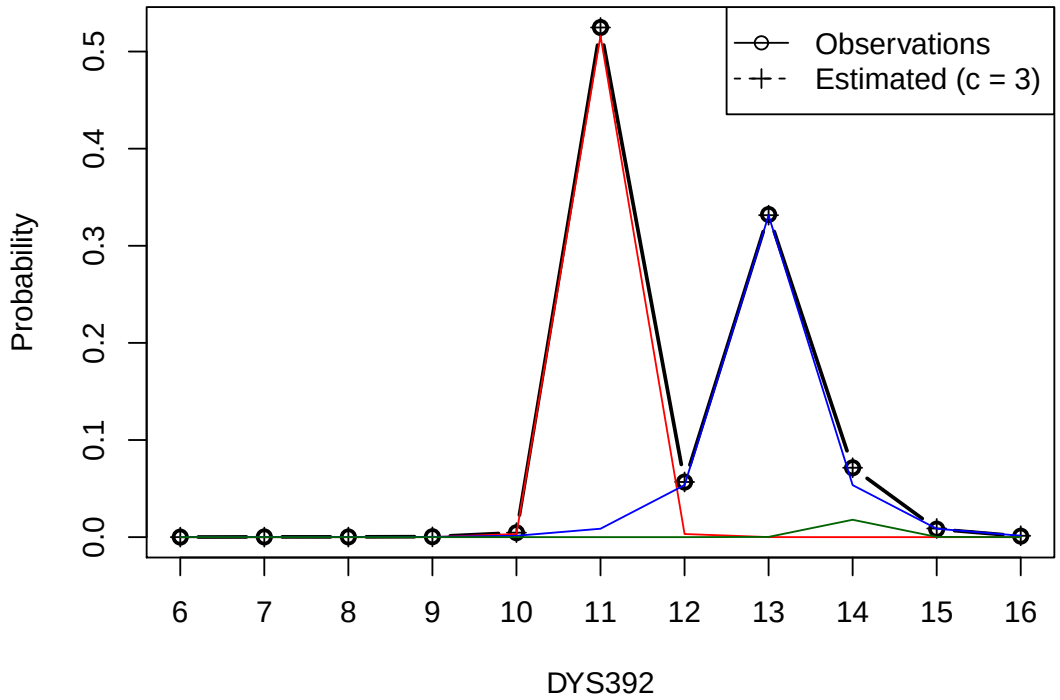
Data and fit



c: Number of subpopulations

$P(X = x) = \sum_{j=1}^{c} \tau_j f(x; p_j, \mu_j)$

Data and fit



c: Number of subpopulations

$P(X = x) = \sum_{j=1}^{c} \tau_j f(x; p_j, \mu_j)$

- 3 subpopulations:

$\hat{\mu}_j$	11	13	14
$\hat{\tau}_j$	52%	46%	2%

- Observed vs expected:

Allele	11	12	13	14	15
Observed	0.5248	0.0567	0.3322	0.0714	0.0083
Expected	0.5248	0.0567	0.3315	0.0715	0.0089

Estimate match probability

Journal of Theoretical Biology: *The discrete Laplace exponential family and estimation of Y-STR haplotype frequencies*

1. Simulate population (e.g. 20 mio. individuals)
2. Draw random database of individuals (e.g. 1,000)
3. Estimate haplotype frequency and compare to true value

Result: smaller prediction error than those with existing estimators

Cluster analysis of European data

FSIGEN: *Cluster analysis of European Y-chromosomal STR haplotypes using the discrete Laplace method*

- European 7-loci Y-STR database from 2004 consisting of 12,727 individuals in 91 European sample locations
- First analysed in 'Signature of recent historical events in the European Y-chromosomal STR haplotype distribution' by Roewer *et al.* in 2005
- Our study
  - Fit a discrete Laplace model
  - Parameters (genetic information) versus known sample locations
  - Discrete Laplace model does not know about sample locations, it infers 'genetic' subpopulations (or clusters)

Cluster analysis of European data

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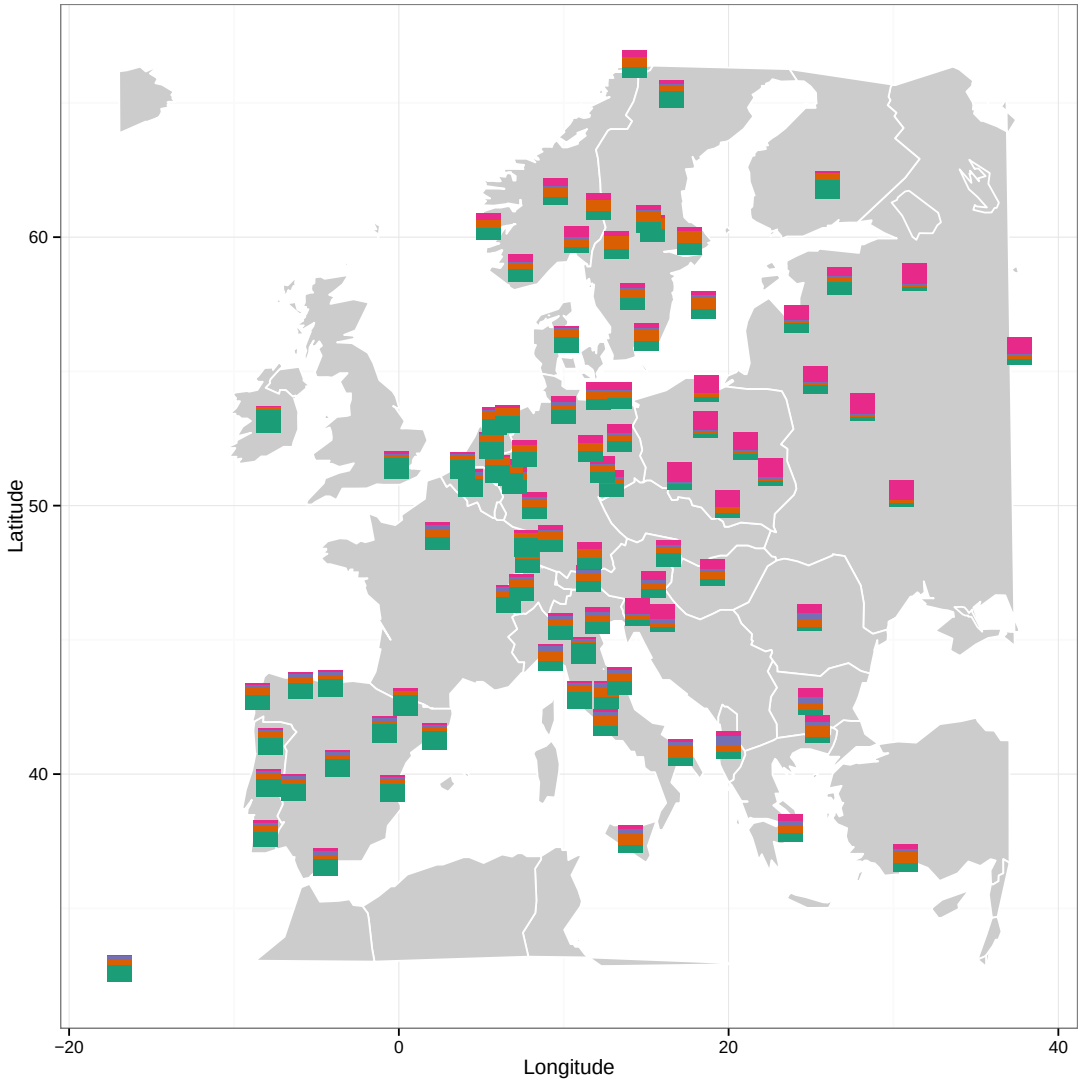

14,13,16,25,11,13,13 (R1b1b2a2g)
14,13,16,25,10,13,13 (R1b1b2a1)
14,13,16,24,10,13,13 (R1b1b2a2c)
14,13,17,24,10,13,13 (R1b1b2a2g)
14,13,16,23,10,13,13 (R1b1b2a2c)
14,13,17,23,11,13,12 (R1b1b)
14,13,16,23,11,13,13 (R1b1b2a1)
15,13,16,24,11,13,13 (R1b1b2a2g)
14,13,17,24,11,13,13 (R1b1b2a2c)
14,13,16,24,11,13,13 (J1a)
14,14,16,24,11,13,13 (R1b1b2a2c)
14,14,16,24,11,14,14 (N1c)
14,14,16,23,11,14,14 (N1c1)
15,13,16,23,10,14,14 (N1c)
15,14,17,23,10,12,14 (I2b)
15,13,17,23,10,12,14 (I2b)
15,12,17,22,10,11,14 (G2a3)
15,12,17,22,10,11,13 (G2a3b)
15,12,16,22,10,11,13 (G2a3)
14,12,17,22,10,11,13 (I1)
14,12,16,22,10,11,13 (I1)
14,12,16,23,10,11,13 (I1)
15,12,16,24,10,11,12 (J2b2)
15,13,16,23,10,11,12 (J1)
14,13,17,23,10,11,12 (J1e)
14,13,16,23,10,11,12 (J2a8)
13,14,16,24,9,11,13 (E1b1b1b)
13,13,17,24,10,11,13 (E1b1b1a2)
13,13,18,24,10,11,13 (E1b1b1a)
14,13,16,24,11,11,13 (R1b1b2a2g)
16,13,18,24,11,11,13 (I2a)
16,13,18,24,10,11,13 (I2a)
16,13,16,24,10,11,13 (R1a1a)
16,13,16,25,10,11,13 (R1a1a7)
16,13,17,25,10,11,13 (R1a1a)
15,13,17,25,10,11,13 (D2)
15,13,17,25,11,11,13 (R1a)
16,13,17,25,11,11,13 (R1a)
17,13,17,25,11,11,13 (R1a)
17,13,17,25,10,11,13 (R1a1a7)

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Cluster analysis of European data

FSIGEN: *Cluster analysis of European Y-chromosomal STR haplotypes using the discrete Laplace method*

Pairwise population distances:

- 7-locus, 12,727 European males (91 locations): Correlation(AMOVA, discrete Laplace) = 0.90
- 10-locus, 2,736 African males (26 locations): Correlation(AMOVA, discrete Laplace) = 0.82

Mixture separation

Yfiler trace (DYS385a/b removed), 15 loci left:

Locus	Alleles
DYS19	14, 15
DYS389I	13, 14
DYS389II'	16, 17
DYS390	24, 26
DYS391	10, 11
DYS392	11, 13
DYS393	13
DYS438	11, 12
DYS439	10, 11
DYS437	14, 15
DYS448	19, 20
DYS456	15, 16
DYS458	14, 18
DYS635	23
Y GATA H4	12, 13

$2^{13-1} = 4{,}096$ possible contributor pairs.

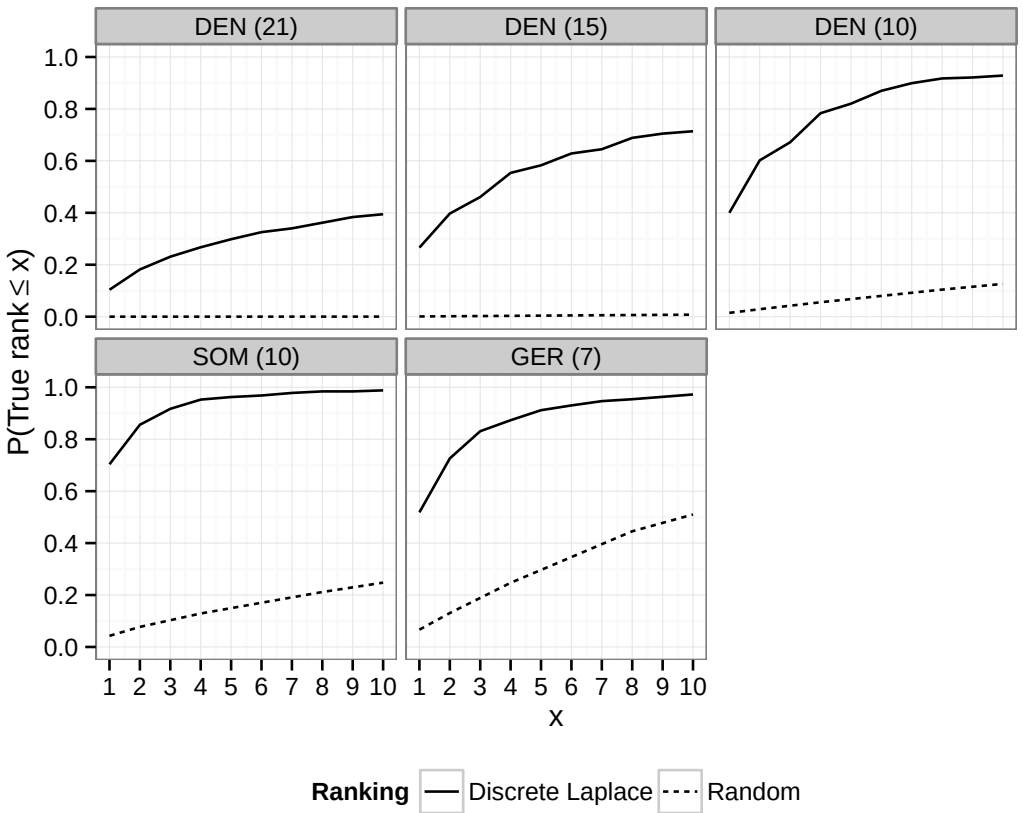
Mixture separation

	DEN (21)	DEN (15)	DEN (10)	SOM (10)	GER (7)
Dataset	All three the same Danish dataset			Somali	Germany
Loci (w/o DYS385a/b)	21	15	10	10	7
Observations	181	181	181	201	3,443
Singletons	181	164	112	56	662
Singleton proportion	1	0.906	0.619	0.279	0.192
Median loci w/ 2 alleles	14	10	6	3	4
Median #pairs	8,192	512	32	4	8

- For each dataset, 550 mixtures were simulated.
- i'th contributor pair $c_i = \{h_{i,1}, h_{i,2}\}$, find $\hat{p}_i = \hat{P}(h_{i,1})\hat{P}(h_{i,2})$
- Order all pairs according to the $\hat{p}_i$ values (highest to lowest)

Mixture separation

	DEN (21)	DEN (15)	DEN (10)	SOM (10)	GER (7)
P(Rank $\leq$ 1)	10%	27%	40%	70%	52%
P(Rank $\leq$ 5)	30%	58%	82%	96%	91%
P(Rank $\leq$ 10)	39%	71%	93%	99%	97%
P(RandomRank $\leq$ 10)	0.03%	0.78%	12.62%	24.76%	51.01%



Conclusion

- Sound statistical properties
- Applications
  - Estimation of Y-STR haplotype population frequencies
  - Cluster analysis
    - Many analyses possible (also those of e.g. AMOVA)
    - Gives results similar to those of previous studies
  - Mixture separation (new) – even for many loci
- Computationally feasible
- Open source software: `R` libraries `disclap` and `disclapmix` (and `fwsim` for simulating populations)