Bayesian Networks for the Analysis of DNA Mixtures

Steffen Lauritzen[1]
University of Oxford

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[1] Based on joint work with Cowell, Dawid, Mortera, Vicard, and others

An area on a chromosome is a *locus*.

The DNA composition, i.e. a particular sequence of the four *bases*, represented by the letters A, C, G and T, on a given locus is an *allele*.

A locus thus corresponds to a (random) variable and an allele to its realised state.

A DNA *marker* is a known locus where the alleles can be identified in the laboratory.

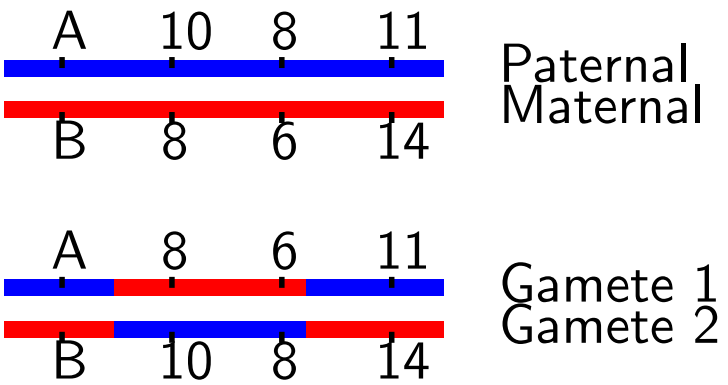
A *genotype* of an individual at a locus is an unordered pair of alleles. One allele comes from the father and one from the mother, but one cannot easily distinguish which is which.

Short Tandem Repeats (STR) are markers with alleles given by integers. If an STR allele is 5, a certain word (e.g. CAGGTG) is repeated exactly 5 times at that locus:

...CAGGTGCAGGTGCAGGTGCAGGTGCAGGTG...

A *DNA profile* is typically a list of genotypes at 10-11 known STR markers.

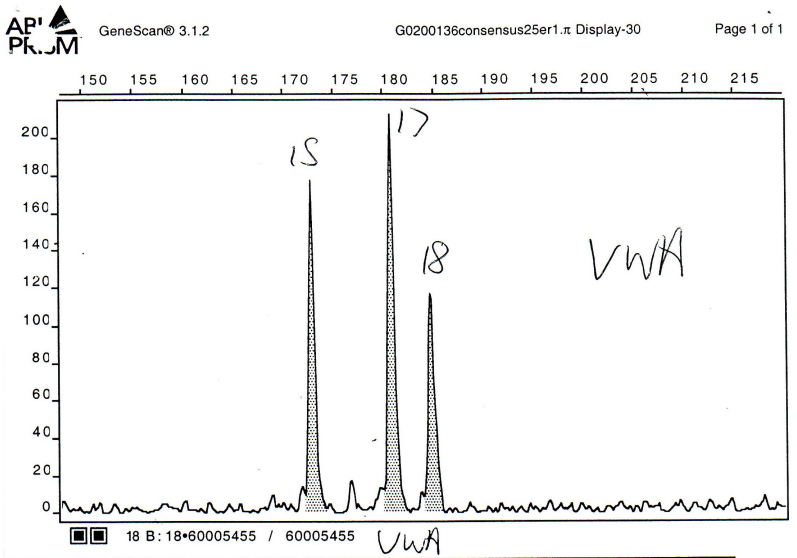
The homologous chromosome pairs are inherited through the process of forming *gametes*, known as *meiosis:*



A child receives one randomly chosen gamete from each parent to form a new homologous pair.

For forensic markers, we can assume independence of alleles within and across markers, as they are located on different chromosomes.

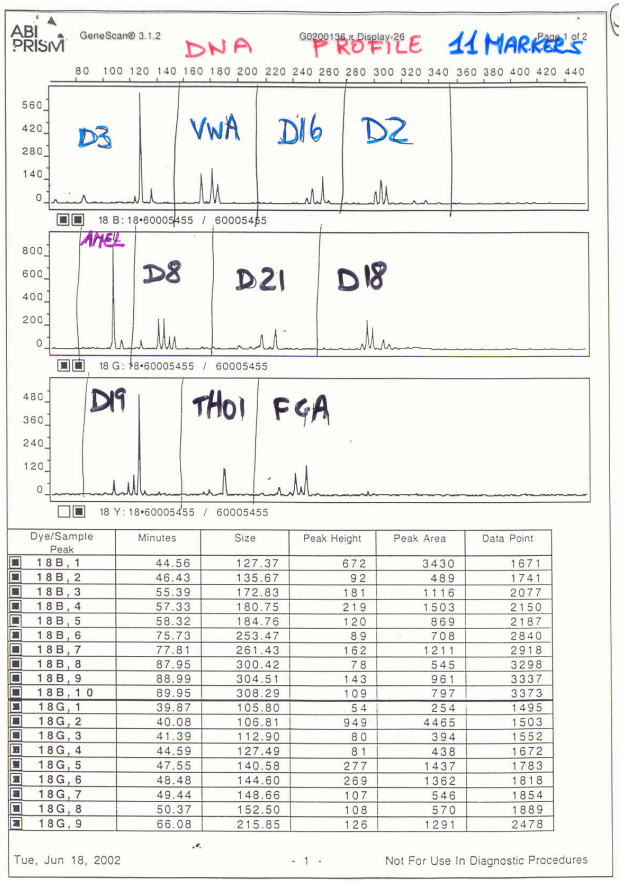
Two-person DNA Mixture profile



Dye/Sample Peak	Minutes	Size	Peak Height	Peak Area	Data Point
18B,6	55.39	172.83	15 181	1116	2077
18B,7	57.33	180.75	17 219	1503	2150
18B,8	58.32	184.76	18 120	869	2187

Marker vWA with *allele repeat number* $\{15, 17, 18\}$, *peak area* and peak height.

DNA profile on 10 markers + Amelogenin



Dye/Sample Peak	Minutes	Size	Peak Height	Peak Area	Data Point
18B, 1	44.56	127.37	672	3430	1671
18B, 2	46.43	135.67	92	489	1741
18B, 3	55.39	172.83	181	1116	2077
18B, 4	57.33	180.75	219	1503	2150
18B, 5	58.32	184.76	120	869	2187
18B, 6	75.73	253.47	89	708	2840
18B, 7	77.81	261.43	162	1211	2918
18B, 8	87.95	300.42	78	545	3298
18B, 9	88.99	304.51	143	961	3337
18B, 10	89.95	308.29	109	797	3373
18G, 1	39.87	105.80	54	254	1495
18G, 2	40.08	106.81	949	4465	1503
18G, 3	41.39	112.90	80	394	1552
18G, 4	44.59	127.49	81	438	1672
18G, 5	47.55	140.58	277	1437	1783
18G, 6	48.48	144.60	269	1362	1818
18G, 7	49.44	148.66	107	546	1854
18G, 8	50.37	152.50	108	570	1889
18G, 9	66.08	215.85	126	1291	2478

Tue, Jun 18, 2002 - 1 - Not For Use In Diagnostic Procedures

Data from a 1:1 mixture of two individuals p1 and p2

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Marker	Alleles	Peak area	Rel. Weight	p1 gt	p2 gt
D2	17	37624	0.573	17	17
	23	9742	0.148		23
	25	18316	0.279	25	
D3	14	56692	0.344	14	
	15	55256	0.335		15
	16	52793	0.321	16	
D8	8	43569	0.412	8	
	9	17423	0.165		9
	13	16227	0.154		13
	14	28488	0.269	14	

A DNA profile gives information on: *allele repeat number* and corresponding *peak area.*

The *peak weight* W_a is the peak area at allele a multiplied by its allele number, the latter to correct for *preferential amplification.*

Evidential calculation

Population gene frequencies are assumed to be *known*. The *evidence* is for example:

$$\mathcal{E} = \{\text{sgt, vgt, mixture profile}\},$$

where sgt,vgt are genotypes of a *suspect* and a *victim*.

The *hypotheses* are for example

$$H_0 : s\&v, \quad H_1 : U\&v.$$

The *weight of the evidence* is the likelihood ratio:

$$LR = \frac{\Pr(\mathcal{E} \mid H_0)}{\Pr(\mathcal{E} \mid H_1)} = \frac{\Pr(H_0 \mid \mathcal{E})}{\Pr(H_1 \mid \mathcal{E})} \frac{\Pr(H_1)}{\Pr(H_0)}.$$

Choose uniform prior to make calculation simple.

Separation of DNA profiles

Identifying the genotype of each of the possibly unknown contributors to the mixture.

Calculate either

$$P\{\text{sgt} \mid \text{vgt}, \text{mixture}\}$$

or

$$P\{\text{p1gt}, \text{p2gt} \mid \text{mixture}\}$$

and find most probable combination.

Important in investigative phase.

So is evidential calculation which can be used to decide whether it is worthwhile to search for supporting evidence against a suspect.

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  - η determines *scale* and ρ is the *amplification factor*.

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- PCR reaction is fundamentally a branching process. Simplest such has gamma distributed final population size
- Simulation model produces data indistinguishable from a gamma when number of initial molecules is ≥ 5

R_a denotes *relative weights* $R_a = W_{+a}/W_{++}$ so

$$\{R_a, a \in A\} \sim Dir(\rho B_a, a \in A),$$

where $B_a = \gamma \sum_i \theta_i n_{ia}$ is the weighted allele number and $B_+ = \sum_a B_a = 2\gamma$ is twice the total amount of DNA γ.

Note η disappears and

$$\mathbb{E}(R_a) = \mu_a = B_a/B_+ = \sum_i \theta_i n_{ia}/2$$

and

$$\mathbb{V}(R_a) = \mu_a(1-\mu_a)/(\rho B_+ + 1) = \sigma^2 \mu_a(1-\mu_a).$$

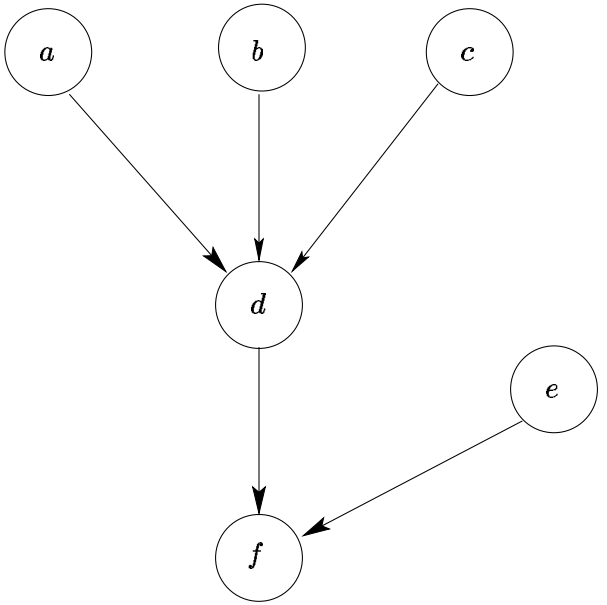
We used $\sigma^2 = 0.01$ which conforms with values of a minor/major peak area ratio reported in the literature.

Bayesian network is

- Directed Acyclic Graph (DAG)
- Nodes V represent (random) variables $X_v, v \in V$
- Specify conditional distributions of children given parents: $p(x_v \mid x_{\mathrm{pa}(v)})$
- Joint distribution is then $p(x) = \prod_{v \in V} p(x_v \mid x_{\mathrm{pa}(v)})$
- Algorithm transforms network into *junction tree* so $p(x_v \mid x_A)$ can be *efficiently computed* for all $v \in V$ and $A \subseteq V$ by *probability propagation.*

Variant calculates revised probabilities $p^*(x_v)$ after *likelihood evidence*

$$p^*(x) \propto \prod_{v \in V} p(x_v \mid x_{\mathrm{pa}(v)}) \prod_{a \in A} L_a(x_a).$$



a, b and c (graph) parents of d; f (graph) child of d and e.

$$p(x) = p(x_a)p(x_b)p(x_c)p(x_d \mid x_{\{a,b,c\}})p(x_e)p(x_f \mid x_{\{d,e\}}).$$

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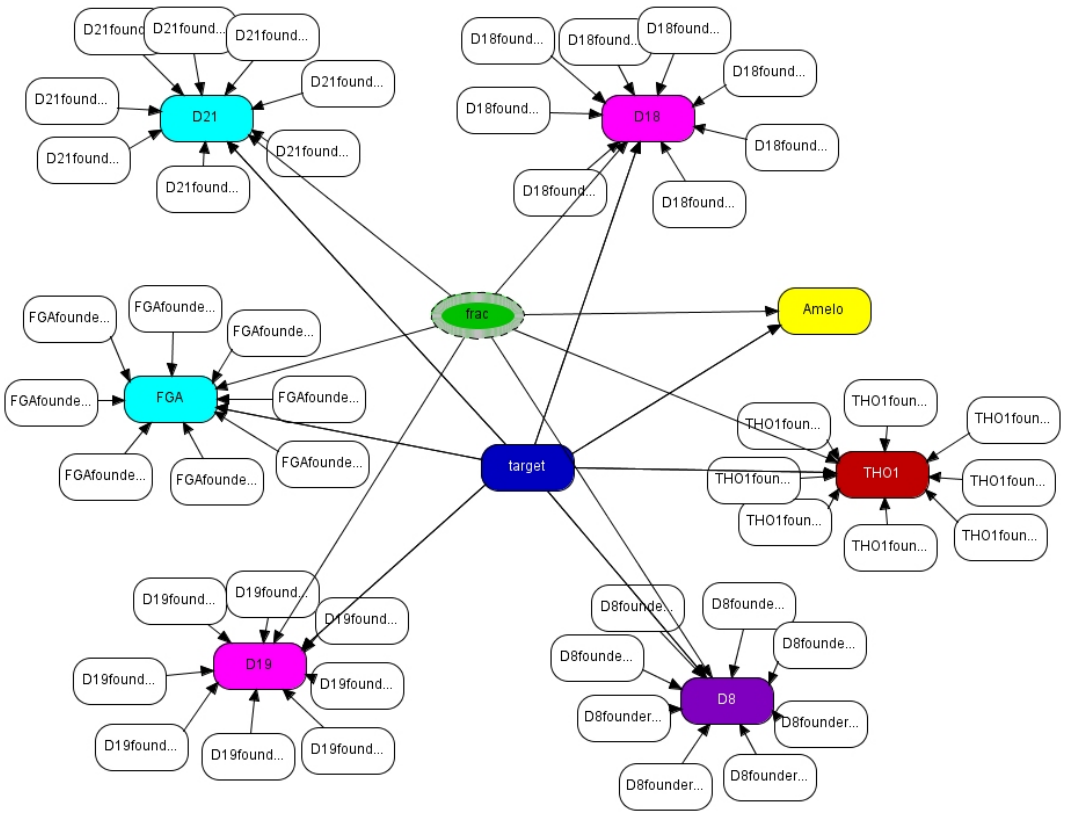
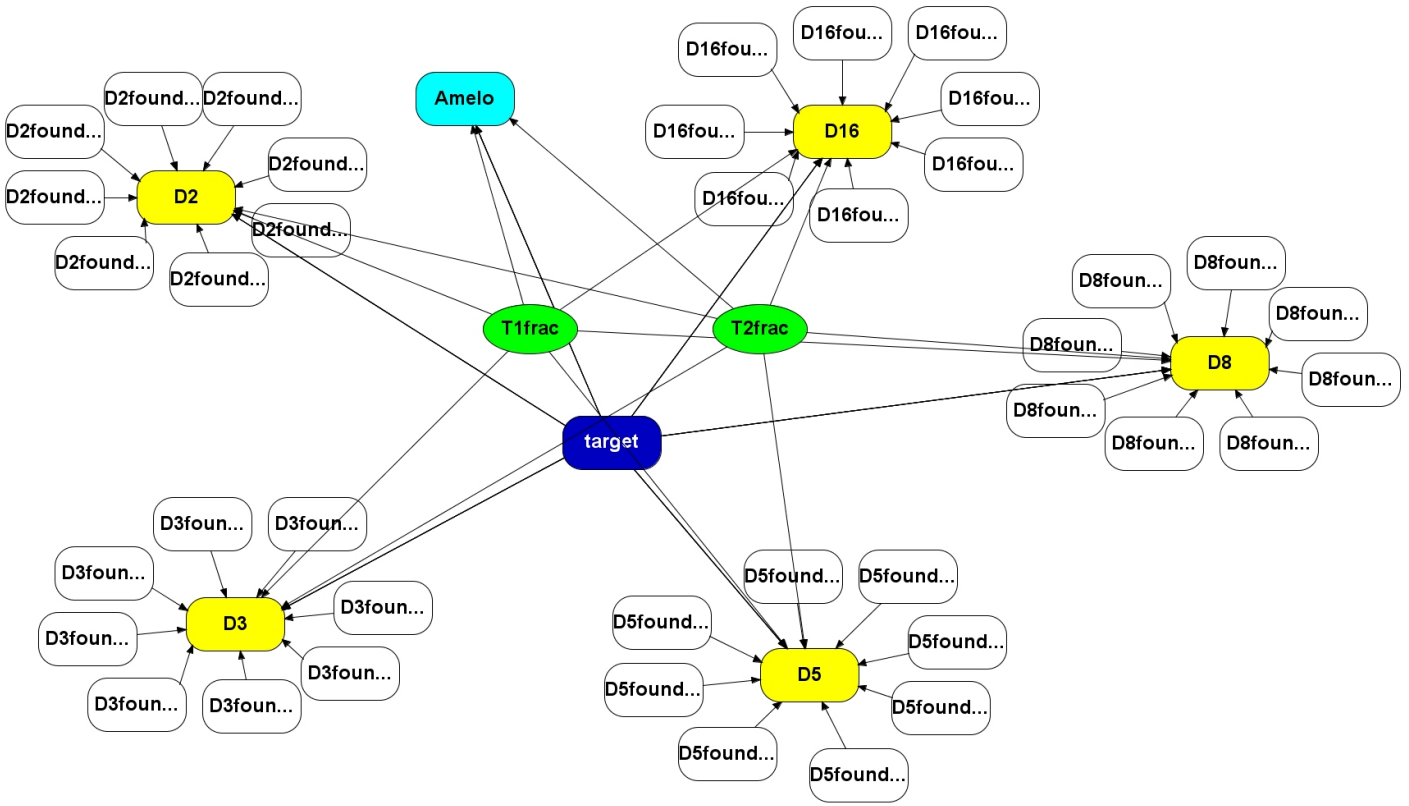
- Objects have *input* and *output nodes*, and also ordinary nodes
- Instances of a given class have identical conditional probability tables for non-input nodes
- Objects are connected by arrows from output nodes to input nodes. These arrows represent *identity links* whereas arrows between ordinary nodes represent *probabilistic dependence*.

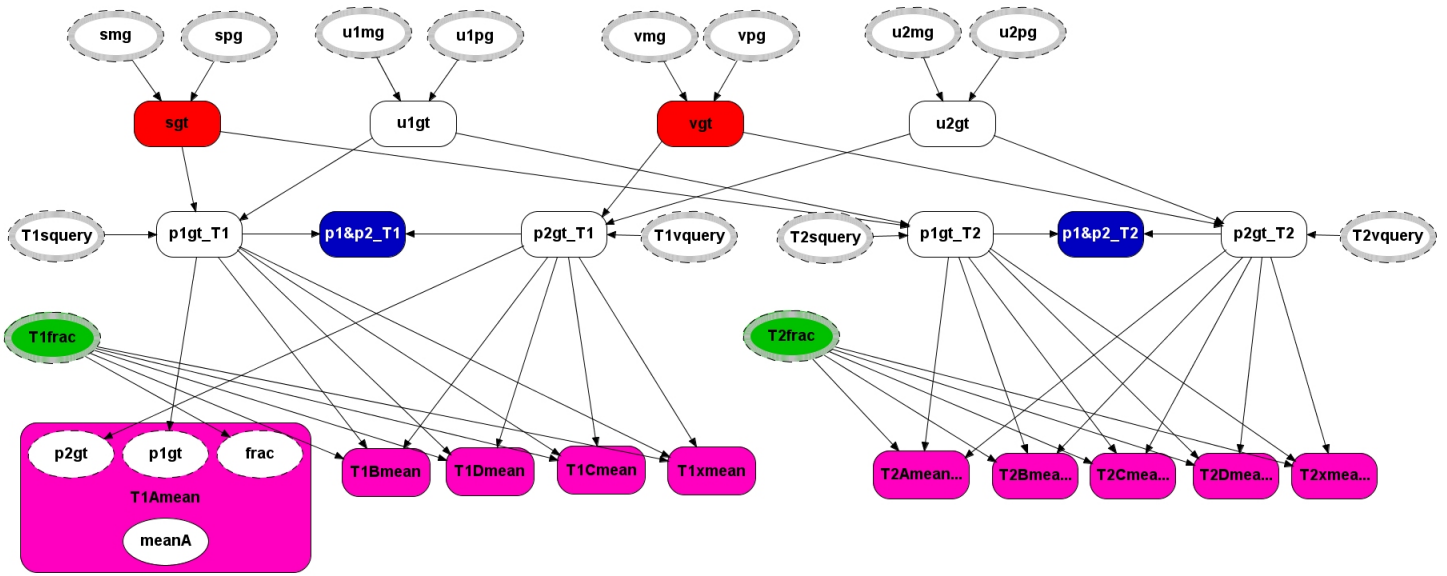
OOBN Master network for DNA mixture



Master network for two DNA traces



Marker network for two DNA traces



Representation of evidence in peak areas

Data on peak areas are thus for each marker m of the form

$$R_a = r_a, a \in A.$$

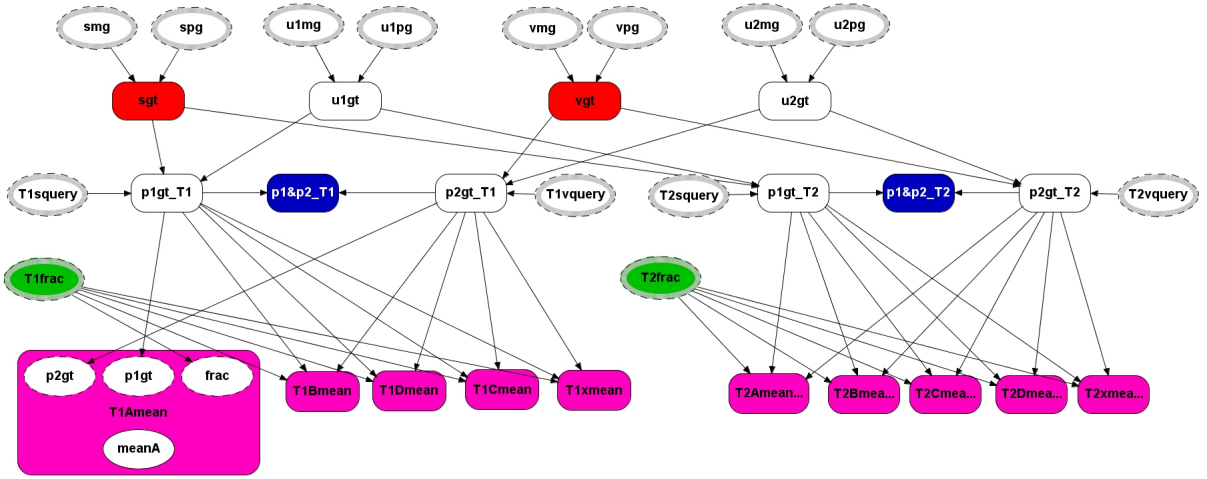
Associated *evidence* is represented in the form of a *likelihood function* on the unknown mean vector $\mu = (\mu_a, a \in A)$ as

$$L(\mu) = P(R \mid \mu) \propto \prod_{a \in A} \frac{r_a^{2\rho\gamma\mu_a - 1}}{\Gamma(2\rho\gamma\mu_a)} \propto \prod_{a \in A} \frac{r_a^{\mu_a(\sigma^{-2}-1)}}{\Gamma\{\mu_a(\sigma^{-2}-1)\}} = \prod_a L_a.$$

where we have used that $B_a = 2\gamma\mu_a$ and $\sigma^2 = (\rho B_+ + 1)^{-1}$.

Thus the *joint likelihood evidence factorizes into evidence for each allele a separately.*

Representing evidence from peak areas



The following *likelihood evidence* is inserted in the mean nodes and propagated throughout the network

$$L_a \propto (r_a^{\mu_a(\sigma^{-2}-1)})/\Gamma\left(\mu_a(\sigma^{-2}-1)\right).$$

Prepared mixture in 1:1 ratio which is hard to separate. (Effective fraction $\theta \neq 0.5$)? *Predicted genotypes of p1 and p2 correct on all 11 markers* (excerpt).

Marker	p1 gt	p2 gt	Prob.
D2	17 25	17 23	0.458
D3	14 16	15 15	0.815
D8	8 14	9 13	0.647
D16	9 11	11 11	0.608

Incorrect identifications in red.

Correct on	T1 only 1:1? all	T2 only 1:1 9 out of 11 markers	T1 & T2 all
D2	0.4582	0.3838	0.6956
D3	0.8152	*0.4854*	**0.8531**
D8	0.6471	0.4831	0.7357
D16	0.6078	0.7534	0.7877

Note the *increase in probabilities for D3*, which was *incorrectly* identified when analysing T2 by itself.

Assuming common contributors, using the profile of one contributor in all separations.

Correct on	T1 only 1:1:1 3 out of 14	T2 only 1:2:5 11 out of 14	T1 & T2 all
D2	*0.178*	1.000	1.000
D3	*0.285*	0.768	0.987
D5	*0.432*	*0.190*	**0.883**
D16	*0.171*	*0.299*	**0.967**

Note the *increase in probabilities* for the profiles *on markers D5 and D16*, none of which were correctly identified with a single mixture analysis.

FSS laboratory prepared data (excerpt)

Marker	Alleles	Peak area	Rel. weight	p1	p2
AMELO	X	4716	0.58388	X	X
	Y	3361	0.41612		Y
D19	13	3453	0.43969		13
	14	4086	0.56031	14	14
FGA	20	2913	0.54983	20	20
				23	
	25	1908	0.45017		25
THO1	6	1497	0.46189		6
				7	
	8	1308	0.53811		8

Alleles and relative weights from a 1:10 mixture of two individuals p1 and p2.

Two of $p1$'s alleles have dropped out of the mixture.

Types of artifact

We need to deal with possible artifacts such as:

- *silent alleles*
- *dropout*
- *stutter peaks*

which might be present in a DNA mixture. These are handled all simultaneously in the BN.

Silent alleles

Accounting for the possibility that an *allele is silent* can be incorporated in the network by simply adding to all founder gene nodes and all other gene nodes an extra state representing a silent allele, s.

For example for allele D18:

Allele	12	15	16	x	s
Frequency	0.305	0.166	0.114	0.414	0.001

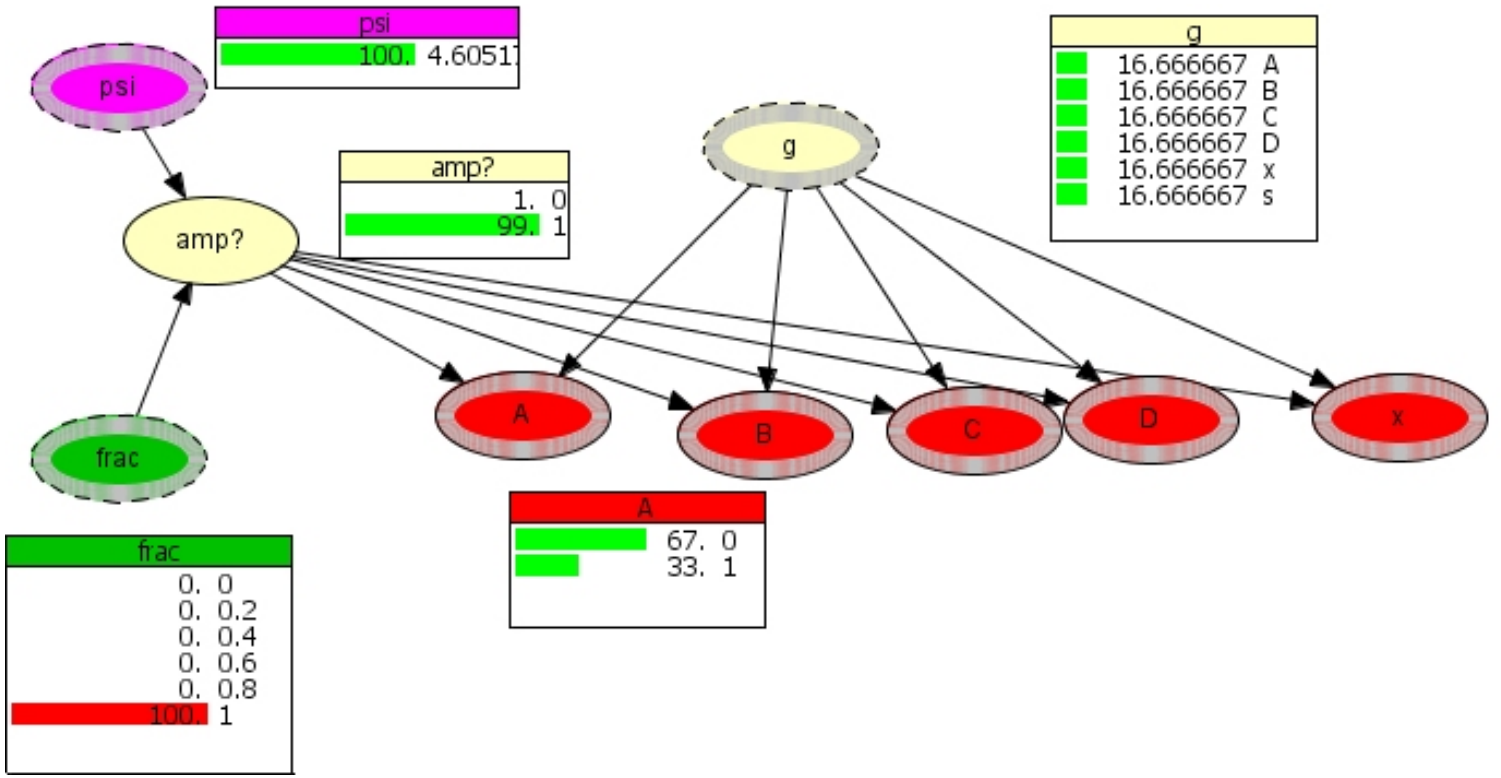
Dropout model

Let n_{ia}^{amp} denote the *alleles amplified*, taking into account dropout D. Assuming an independent allele dropout model yielding a binomial $P(n_{ia}^{amp}|n_{ia},\theta_i)$ depending exponentially on the amount of DNA:

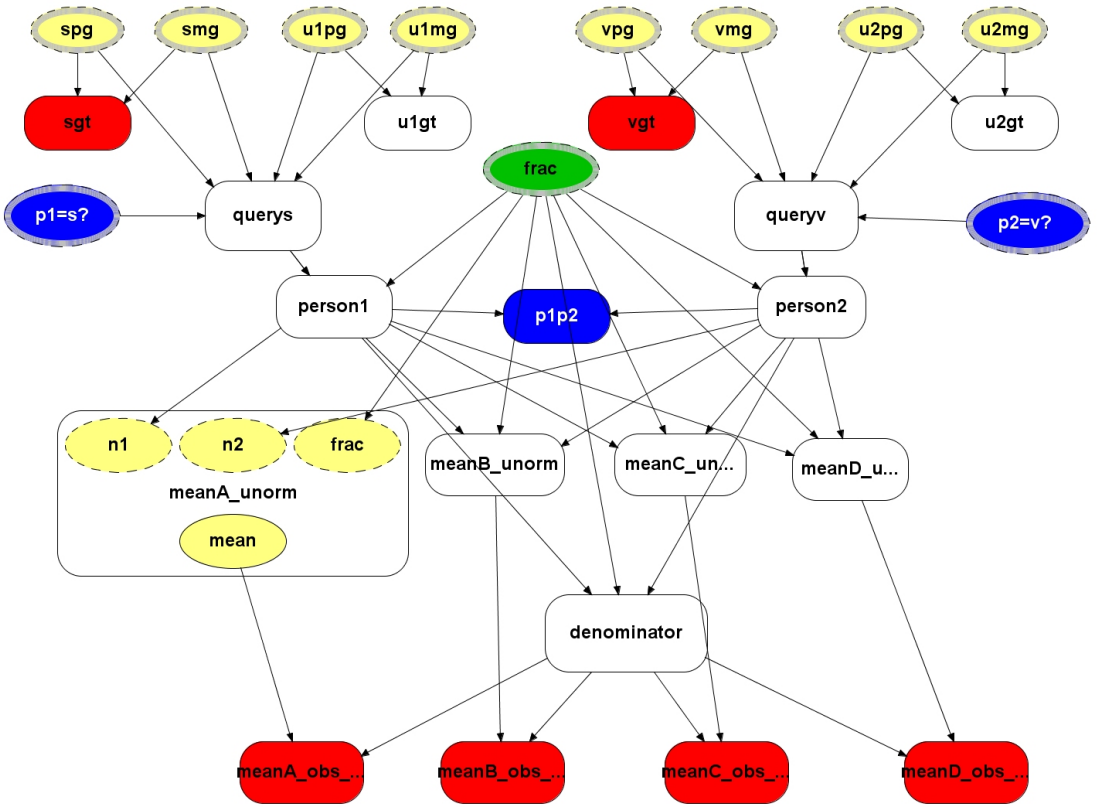
	n_{ia}		
n_{ia}^{amp}	0	1	2
0	1	$\exp(-\psi\theta_i)$	$\exp(-2\psi\theta_i)$
1	0	$1-\exp(-\psi\theta_i)$	$2(1-\exp(-\psi\theta_i))\exp(-\psi\theta_i)$
2	0	0	$(1-\exp(-\psi\theta_i))^2$

We use the estimate $\psi = -\log P(D=1\,|\,\theta=1) = -\log 0.01$.

Network for modelling dropout

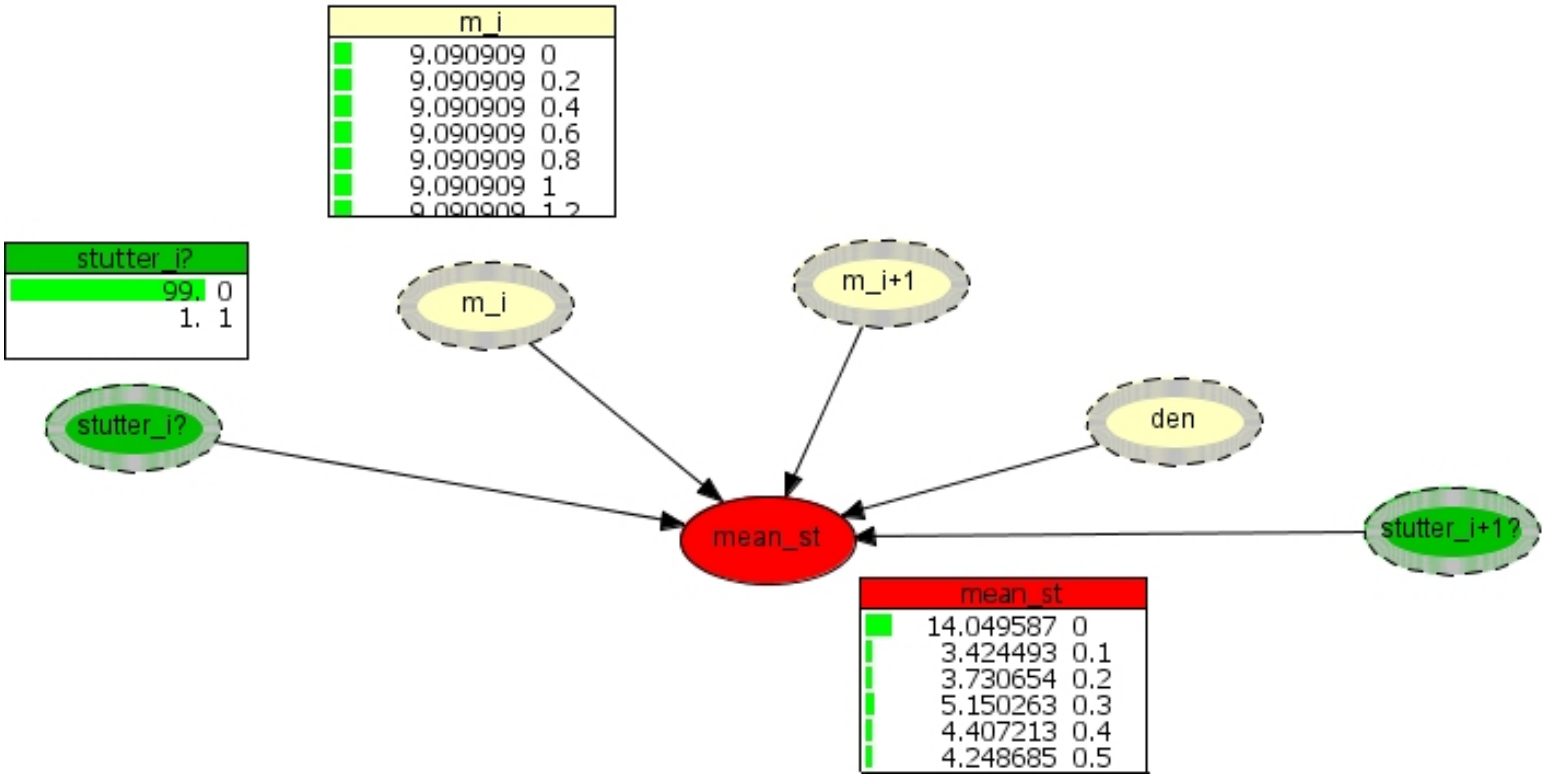


Marker network with dropout

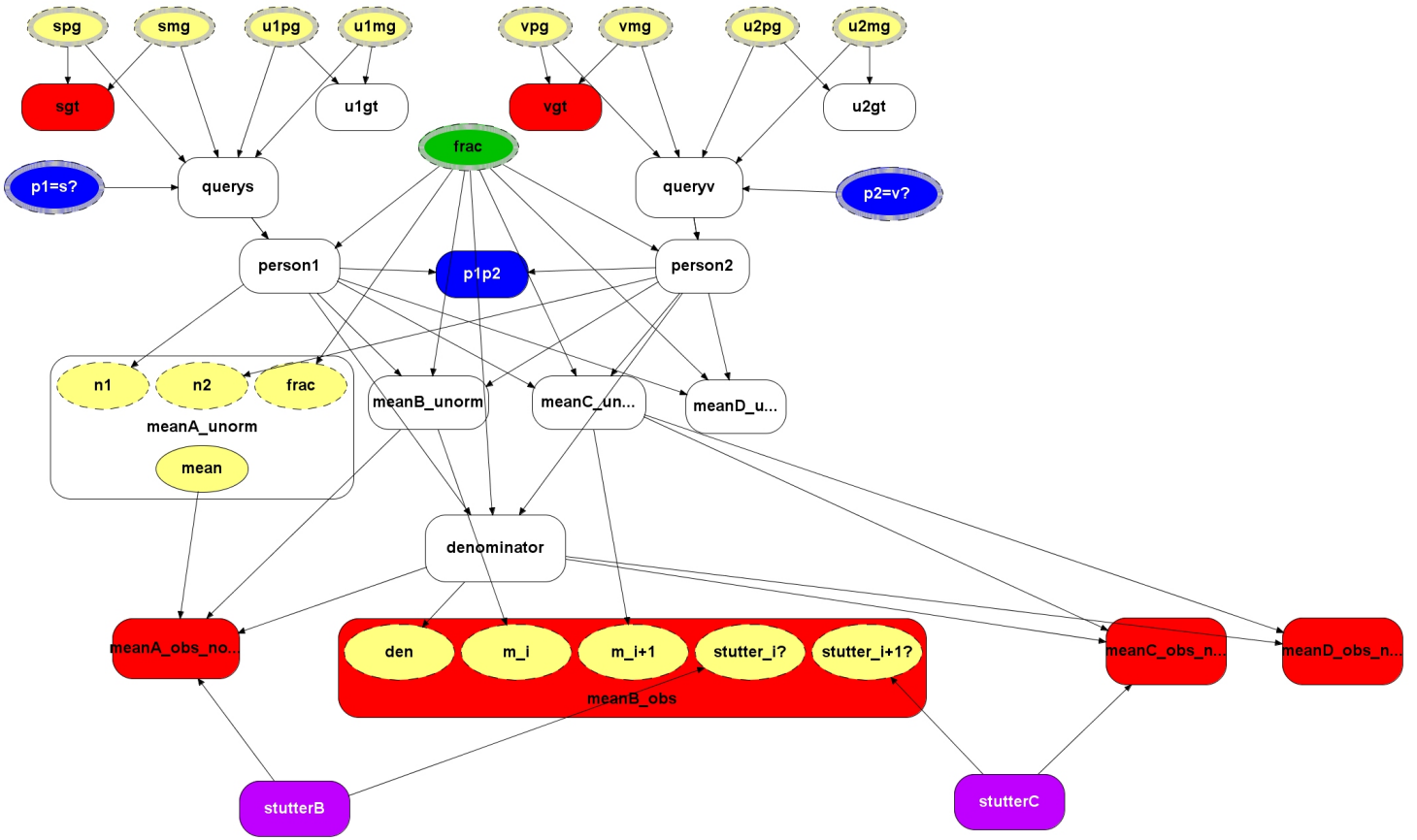


A stutter peak is typically *one repeat unit less than the associated peak*. They tend to be about 15% of the size of the associated allelic peak.
Here we use $Pr(Stutter) = 0.01$

Stutter module



Marker with stutter



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Results for evidence calculation

	$\log_{10}$ LR
s & v vs. v & u	3.89
s & v vs. 2u	10.66

Predicted genotypes: one actor known

			p1 known	p2 known	
	p1	**p2**	**Prob.**	**Prob.**	**rank**
AMELO	X X	X Y	0.9994	0.5448	
D19	14 14	13 14	0.9718	0.3433	2
	13 14	*13 14*		0.4252	
FGA	20 23	20 25	0.9793		
	20 +	20 25		0.8038	
THO	7 9,3	6 8	0.9947		
	+	6 8		0.9999	

Separation both unknown

Marker	p1	p2	Probability	rank
AMELO	X X	X Y	0.5203	1
D19	*13 14*	*13 14*	*0.3723*	
	14 14	13 14	0.3007	2
D21	28 32.2	30 30	0.7896	1
FGA	20 +	20 25	0.4796	
THO	+ +	6 8	0.8852	

Posterior probability of dropout

	p1	p2
D19	0.143130	0.007332
FGA	0.580572	0.001439
THO1	0.999920	3.10E-06

Posterior probability of stutter

Allele	**D18**	**D8**	**D19**
B	0.010821	0.011933	0.131230
C		0.001004	

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- Sensitivity as in Green and Mortera (2009).

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