Theta correction, mutations, silent alleles

Thore Egeland[(1),(2)]

(1) Norwegian University of Life Sciences, (2) NIPH

thore.egeland@gmail.com

Beyond standard cases

- Complex pedigrees Large, inbred
- Theta corrrection If e.g. Hardy-Weinberg does not apply
- Mutation If e.g. parent and child share no alleles
- Silent alleles Homozygote or silent allele?
- Drop out Homozygote or drop out?

Dispute laid to rest

nature

SEARCH JOURNAL Go

Journal Home
Current Issue
AOP
Archive

THIS ARTICLE

Download PDF
References

Export citation
Export references

Send to a friend

commentary

Nature **371**, 735 - 738 (27 October 2002); doi:10.1038/371735a0

DNA fingerprinting dispute laid to rest

ERIC S. LANDER & BRUCE BUDOWLE

Whitehead Institute for Biomedical Research, Nine Cambridge Center, Cambridge, Massachu
Forensic Science Research and Training Center, FBI Laboratory, FBI Academy, Quantico, Vi

Hardy Weinberg

Two alleles A, B.

$p_A = 0.4, p_B = 0.6.$

Fraction A/A: $0.4^2 = 0.160$

Fraction A/B: $2*0.4*0.6 = 0.480$

Fraction B/B: $0.6^2 = 0.360$

Sum $= 1.000$

Problem: Above requires HW, not valid if 'unrelated people' are slightly related

Solution: theta-correction

Theta - correction

$$Homozygous \quad A,A: \ \theta p_A + p_A^2(1-\theta),$$

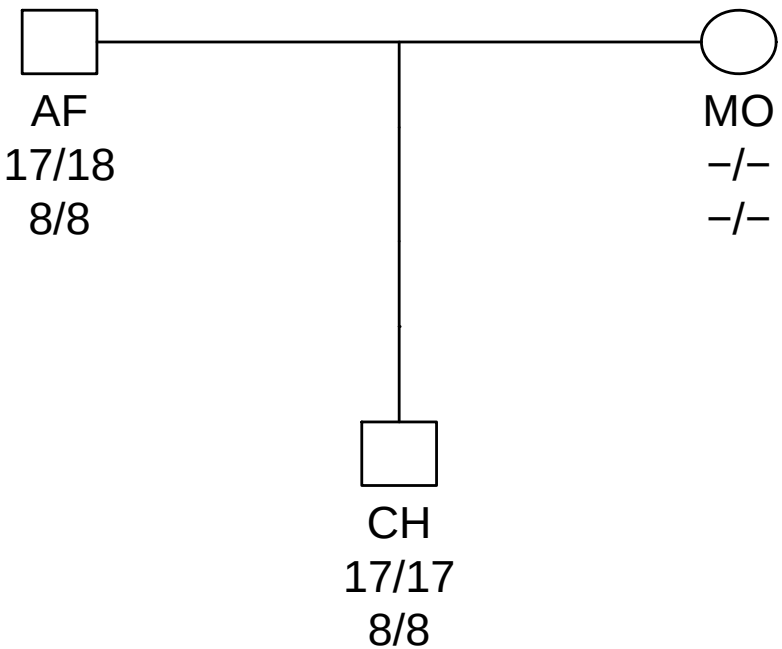
$$Heterozygous \quad A,B: \ 2p_A p_B(1-\theta).$$

$\theta = 0.1$ (extreme case)

Fraction A/A: $0.1*0.4+0.4^2*(1-0.1)$	$=0.184>0.160$	
Fraction A/B: $2*0.4*0.6*(1-0.1)$	$=0.432<0.480$	
Fraction B/B: $0.1*0.6+0.6^2*(1-0.1)$	$=0.384>0.360$	
Sum	1.000	1.000

- Fraction homozygotes increases with θ

Previous example

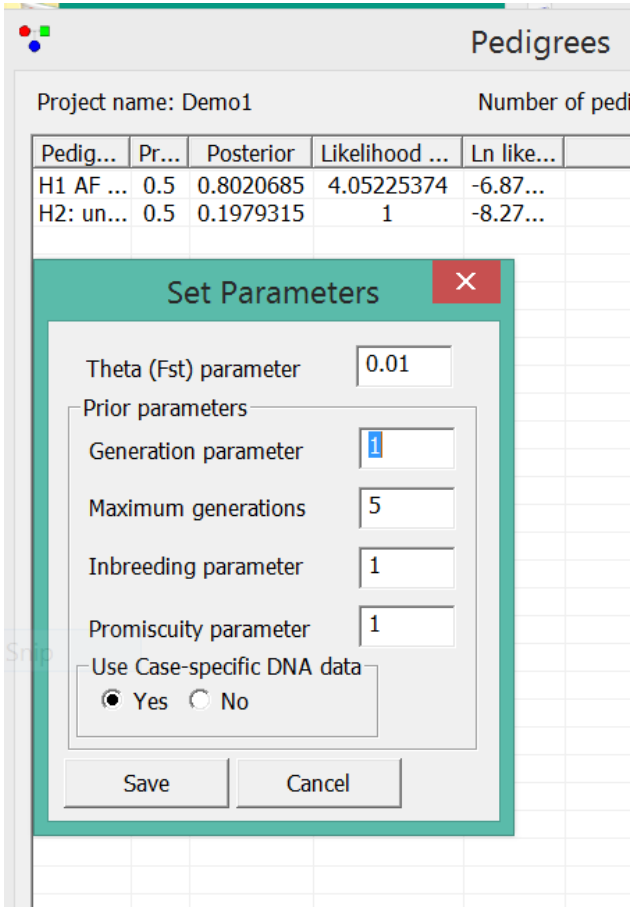


$$LR_1 = \frac{\frac{1}{2}p_{17}}{p_{17}^2} = \frac{1}{2 \times 0.204} = 2.45$$

$$LR_2 = \frac{p_8}{p_8^2} = \frac{1}{0.554} = 1.81$$

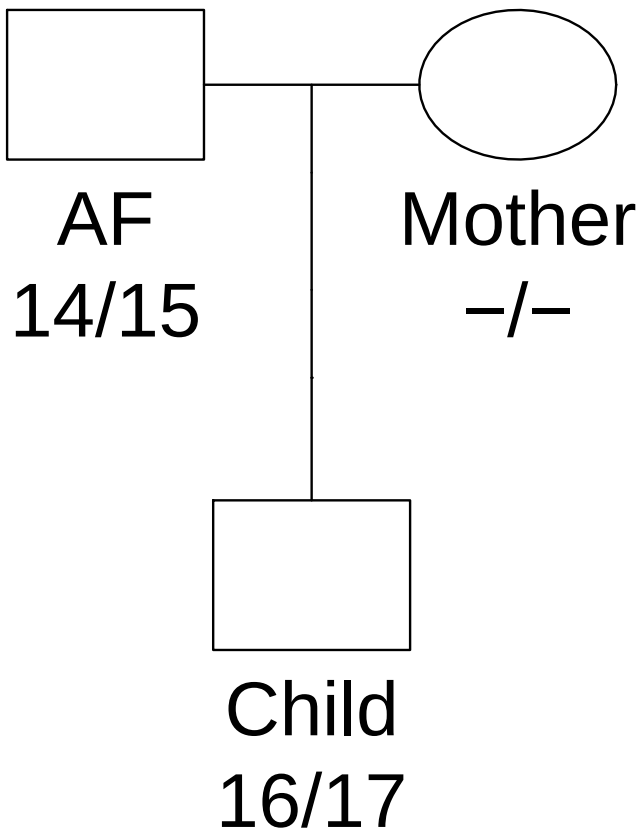
$$LR = LR_1 \times LR_2 = 2.45 \times 1.81 = 4.4.$$

Fst=Theta=0.01. Input: Pedigrees > Parameters



- $LR = 2.298 \cdot 1.764 = 4.1$ when $\theta = 0.01$
- $LR = 2.45 \cdot 1.81 = 4.4$ when $\theta = 0.00$.

Mutation: Exercise 2.2, 2.7



Mutation: Results, simillar to Exercise 2.9

System	Child	AF	LR	LR(mut)
D3S1358	17/17	17/18	2.450	2.449
TPOX	8/8	8/8	1.805	1.804
D6S474	16/17	14/15	0.000	0.001
3 markers			0.000	0.0044
	...	...	...	...
22 (1 mut)			0.000	25070642

Table 1: Genotype data for a Child and alleged father (AF) along with LR-s. The rightmost column is based on a stepwise unstationary mutation model (expained below) with mutation rate 0.001 and range 0.5 for all markers.

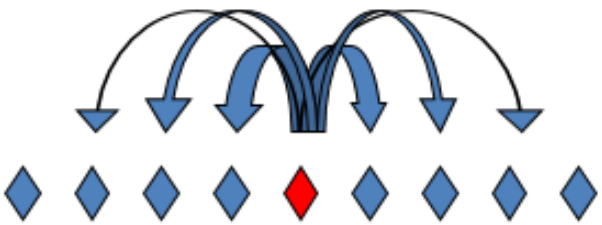
Equal model

	Mutation to					
Al...	13	14	15	16	17	18
13	0.999	0.0002	0.0002	0.0002	0.0002	0.0002
14	0.0002	0.999	0.0002	0.0002	0.0002	0.0002
15	0.0002	0.0002	0.999	0.0002	0.0002	0.0002
16	0.0002	0.0002	0.0002	0.999	0.0002	0.0002
17	0.0002	0.0002	0.0002	0.0002	0.999	0.0002
18	0.0002	0.0002	0.0002	0.0002	0.0002	0.999

- $P(\text{no mutation}) = 0.999$
- Problem: $P(14 \to 17) = P(15 \to 16) = 0.0002$.

Mutation: Biology

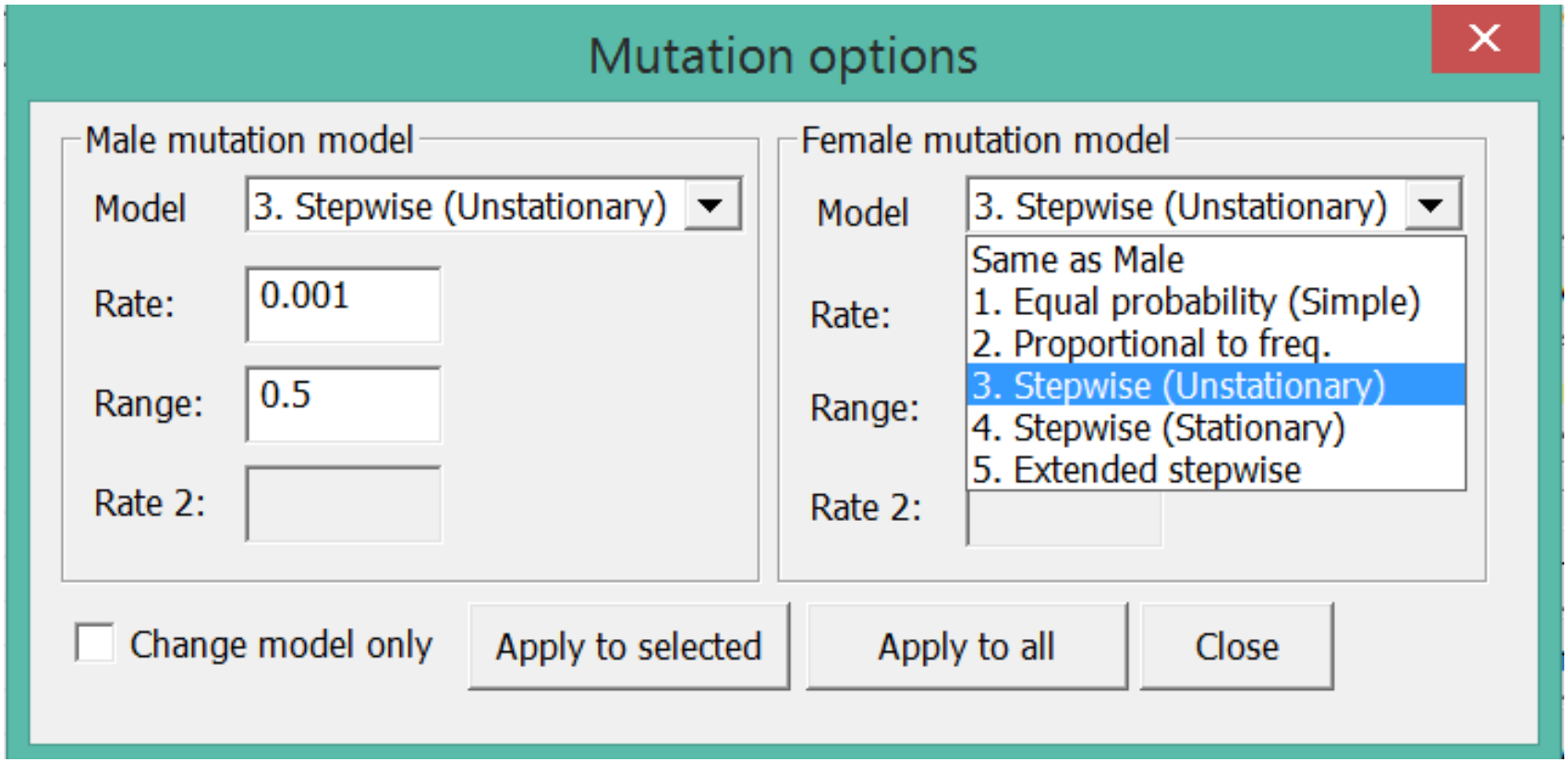
- Mutation rate varies with
  - Sex of parent and locus.
    Alleles tend to mutate to close alleles:



  - Several models

- Mutation rates:
  `http://www.cstl.nist.gov/strbase/mutation.htm`

Mutation: Input

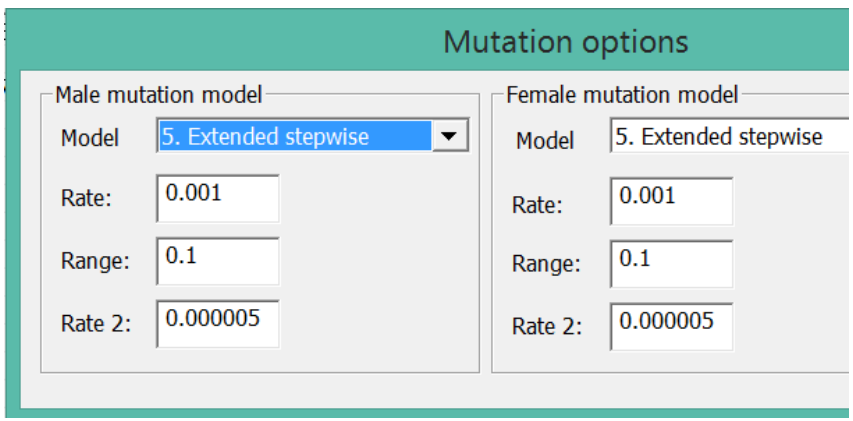


Mutation Matrix. Range

Mutation to						
Al...	13	14	15	16	17	18
13	0.999	0.000...	0.000258...	0.00012903	6.4516e-005	3.2258e-
14	0.0003...	0.999	0.000347...	0.00017391	8.6957e-005	4.3478e-
15	0.0001...	0.000...	0.999	0.00030769	0.00015385	7.6923e-
16	7.6923...	0.000...	0.000307...	0.999	0.00030769	0.00015
17	4.3478...	8.695...	0.000173...	0.00034783	0.999	0.00034
18	3.2258...	6.451...	0.000129...	0.00025806	0.00051613	0.999

$$\text{Range} = \frac{15 \to 17}{15 \to 16} = \frac{0.00015385}{0.00030769} = 0.5$$

Extended stepwise model: Generally recommended, consistent for microvariants



- Rate Integer mutations: $9 \rightarrow 10$, $9.3 \rightarrow 10.3$
- Range: As before. 1 step $1/0.1 = 10$ times more likely than two steps, etc.
- Rate2 Fractional Mutations: $9.3 \rightarrow 10$, $9 \rightarrow 9.3$

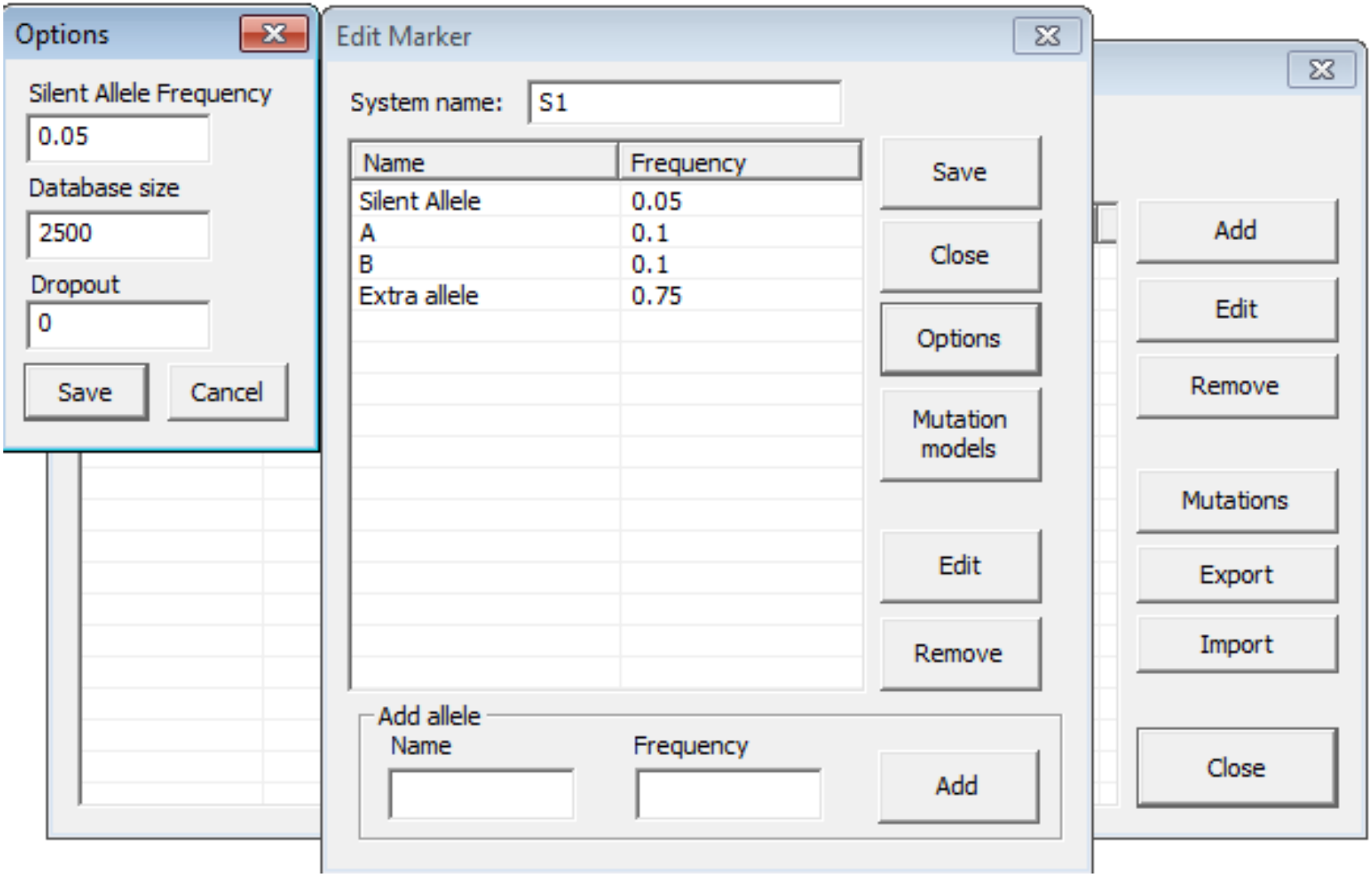
Extended stepwise model: Example

	Mutation to				
A...	9	9.3	10	10.3	11
9	0.998995	2.5e-006	0.0009090909091	2.5e-006	9.090909091e-005
9.3	1.666666667e-006	0.998995	1.666666667e-006	0.001	1.666666667e-006
10	0.0005	2.5e-006	0.998995	2.5e-006	0.0005
10.3	1.666666667e-006	0.001	1.666666667e-006	0.998995	1.666666667e-006
11	9.090909091e-005	2.5e-006	0.0009090909091	2.5e-006	0.998995

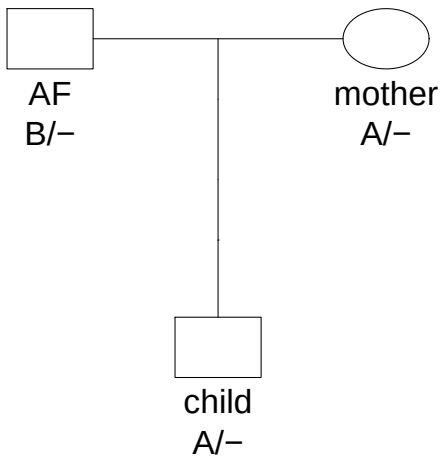
- Recall: Rate $= 0.001$, Range $= 0.1$, Rate2 $= 0.000005$.
- Note: Pr("no mut") $= 1 - (0.001 + 0.000005) = 0.998995$.

$$\Pr(9 \to 10) = 0.0009 >$$
$$\Pr(9 \to 9.3) = 2.5e-006 = 0.0000025$$
$$\frac{\Pr(9 \to 11)}{\Pr(9 \to 10)} = \frac{0.00009}{0.0009} = 0.1$$

Silent alleles. Input: General DNA data > . . . > Options



Exercise 2.11



- Enter genotypes as homozygous.
- $p_B = 0.1,\ p_S = P(\text{“Silent allele”}) = 0.05$. Now e.g.
- $P(B/-) = p_B^2 + 2 \cdot p_B p_S = 0.02$.
- Statistics for silent alleles:
  `http://www.cstl.nist.gov/strbase/NullAlleles.htm`