Estimating penetrance curves according to mutation in familial genetic studies in the presence of incomplete genotypes

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Outline

1. Introduction
   - Some Recalls
   - A Fictional Genetic Study
   - Estimations from Known Genotypes
2. Expectation-Maximization
   - Principle
   - Posterior in Pedigree
   - Estimations from Unknown Genotypes
3. Advanced Stuff
   - Ascertainment Issues
   - Advanced Models
   - Sophisticated Posteriors

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Binary Disease

Definition:

- $Y \in \{0, 1\}$ a binary disease phenotype,
- $X \in \{\mathtt{DD} = 0, \mathtt{Dd} = 1, \mathtt{dd} = 2\}$ a bi-allelic genotype
- for all $x \in \{0, 1, 2\}$, the *penetrance* $F_x = \mathbb{P}(Y = 1|X = x)$

Mode of Inheritance:

- dominant: $F_0 < F_1 = F_2$
- recessive: $F_0 = F_1 < F_2$
- additive: $F_1 = F_0 + R$ and $F_2 = F_0 + 2R$
- multiplicative: $F_1 = F_0 \times R$ and $F_2 = F_0 \times R^2$

Time-to-event Disease

- T time before disease onset, the *hazard rate* is defined by

$$\lambda_x(t) = \lim_{\Delta \to 0} \frac{1}{\Delta} \mathbb{P}(T \in]t, t+\Delta] | T > t, X = x)$$

- phenotype is $Y = \text{UN}t = \{T > t\}$ or $Y = \text{AF}t = \{T = t\}$
- for all $x \in \{0, 1, 2\}$, the *penetrance* is now:

$$F_x(t) = \mathbb{P}(T \leqslant t | X = x) = 1 - \underbrace{\exp\left(-\int_0^t \lambda_x(s) ds\right)}_{S_x(t)}$$

- the *relative hazards* are

$$\text{RH}_1(t) = \frac{\lambda_1(t)}{\lambda_0(t)} \quad \text{and} \quad \text{RH}_2(t) = \frac{\lambda_2(t)}{\lambda_0(t)}$$

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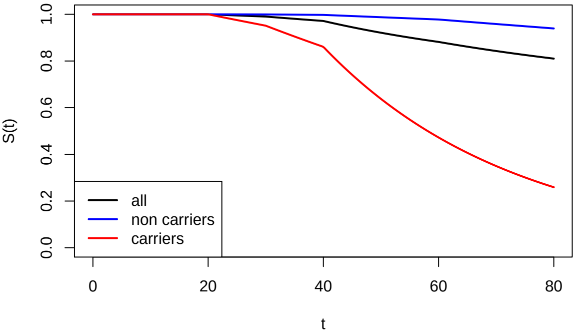
Autosomal Dominant Model

MAF $f = 0.10$ $\pi_0 = (1-f)^2$ $\pi_1 = 1-\pi_0$ $\lambda_1(t) = \lambda_2(t) = \lambda_0(t)\mathrm{RH}(t)$

$$S(t) = \pi_0 \exp\left(\int_0^t \lambda_0(u)du\right) + \pi_1 \exp\left(\int_0^t \lambda_0(u)\mathrm{RH}(u)du\right)$$

known parameter

unknown parameter



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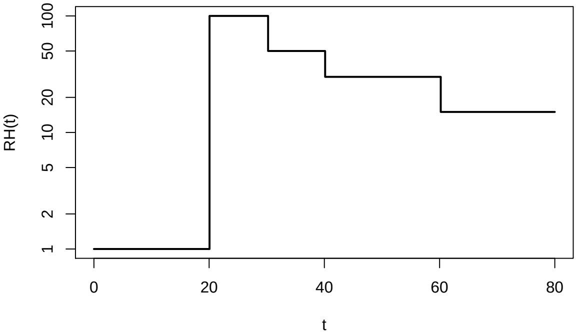
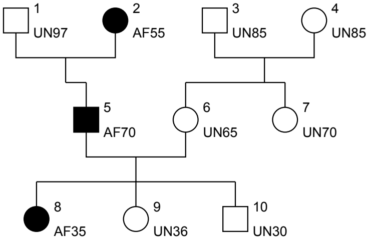
known parameter unknown parameter



Simulated Dataset



Design

- same structure for all families
- Hardy-Weinberg for founders
- uniform censoring $\mathcal{U}([0, 80])$
- $N = 500$ families
- $n = 5000$ individuals

	unaffected	affected	total
non carrier	3985	56	4041
carrier	703	256	959
total	4688	312	5000

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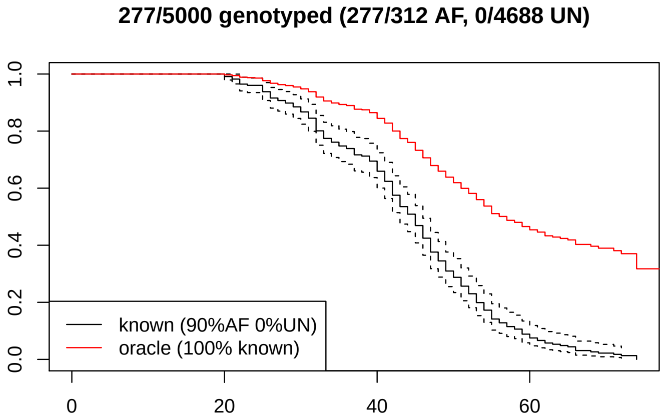
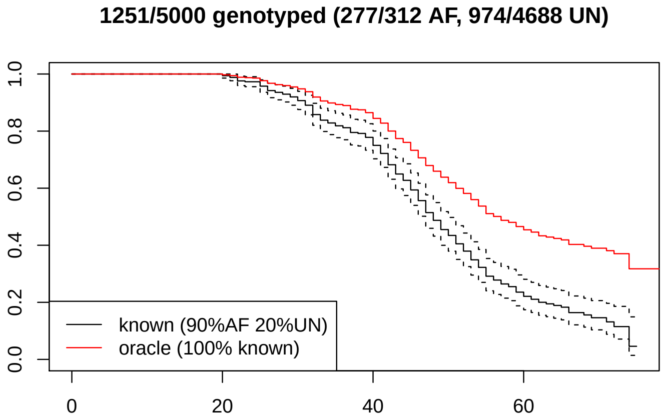
Unbalanced Genotyping Scheme



more affected genotyped than unaffected ⇒ risk of bias

Unbalanced Genotyping Scheme



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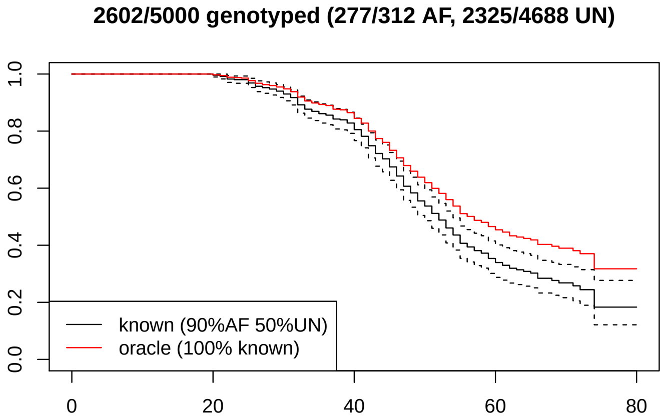

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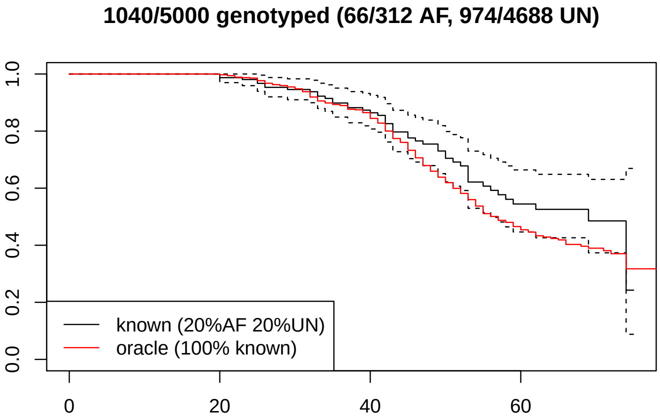
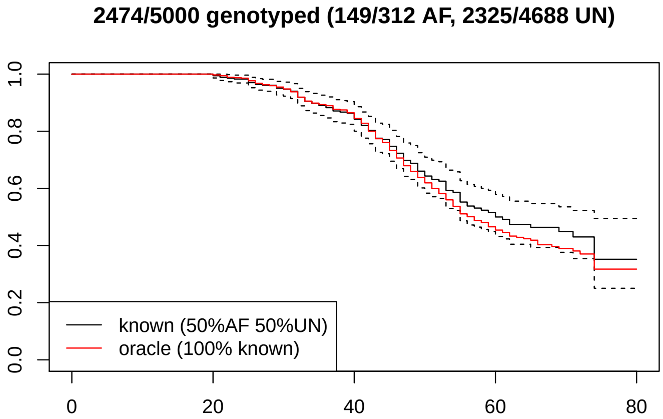


balanced genotyping scheme ⇒ no bias but unrealistic

Balanced Genotyping Scheme



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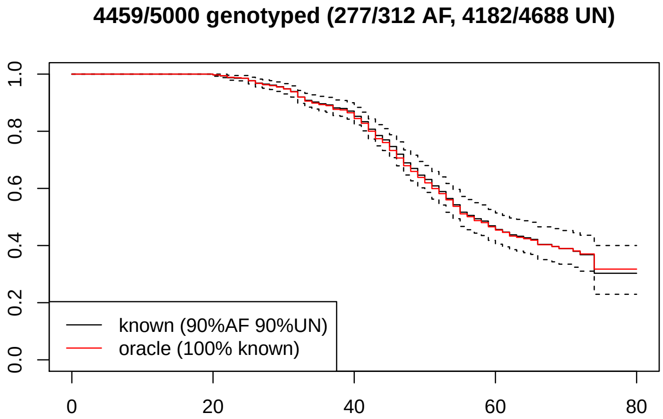
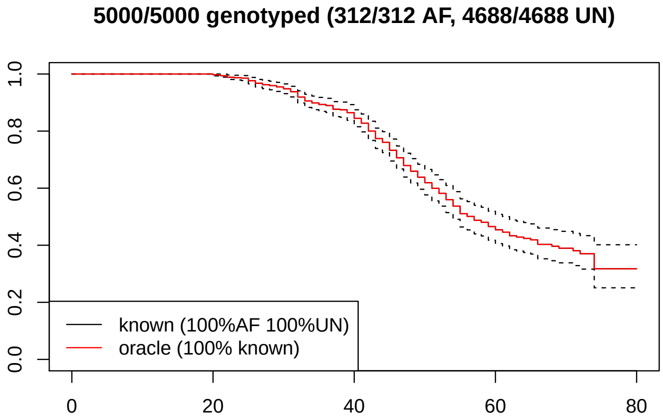
Balanced Genotyping Scheme



balanced genotyping scheme ⇒ no bias but unrealistic

Balanced Genotyping Scheme



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EM Algorithm (Dempster *et al.*, 1977)

Context: X latent variable (*e.g.* unobserved genotypes), Y observed variables (*e.g.* censored time at onset, genetic tests, etc.), θ parameter to estimate (*e.g.* penetrances, hazard rates)

$$\hat{\theta} = \arg\max_{\theta} \log \sum_{X} \mathbb{P}(X, Y|\theta)$$

EM solution: multiple imputation $X^1, \ldots, X^N \sim \mathbb{P}(X|Y; \theta_{\text{old}})$

$$\frac{1}{N}\sum_{j=1}^{N} \log \mathbb{P}(X^j, Y|\theta) \xrightarrow[N\to\infty]{} Q(\theta|\theta_{\text{old}}) = \sum_{X} \mathbb{P}(X|Y; \theta_{\text{old}}) \log \mathbb{P}(X, Y|\theta)$$

$$\theta^{(\text{iter}+1)} = \arg\max_{\theta} Q\left(\theta|\theta^{(\text{iter})}\right) \quad \text{and} \quad \theta^{(\text{iter})} \xrightarrow[\text{iter}\to\infty]{} \hat{\theta}$$

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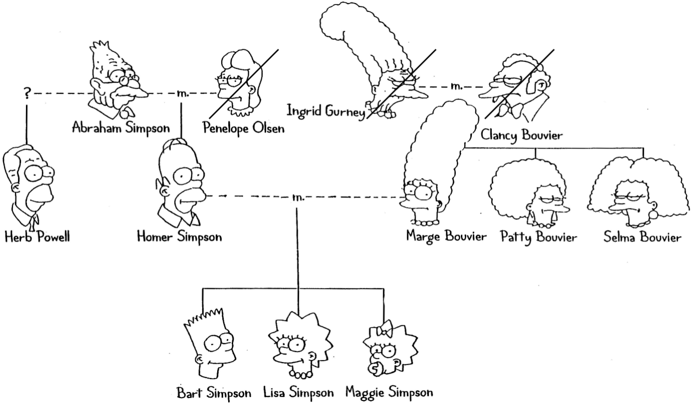
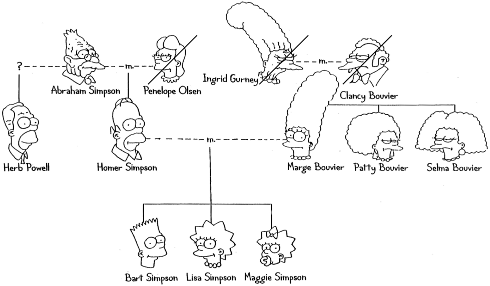
Simpsons' Pedigree and Bayesian Network



1: Herb's mother, **2**: Abraham, **3**: Penelope, **4**: Ingrid, **5**: Clancy, **6**: Herb, **7**: Homer, **8**: Marge, **9**: Patty, **10**: Selma, **11**: Bart, **12**: Lisa, **13**: Maggie

Simpsons’ Pedigree and Bayesian Network



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11: Bart, **12**: Lisa, **13**: Maggie

$$\mathbb{P}(X) = \mathbb{P}(X_1)\mathbb{P}(X_2)\mathbb{P}(X_3)\mathbb{P}(X_4)\mathbb{P}(X_5)$$
$$\mathbb{P}(X_6|\, X_{1,2})\mathbb{P}(X_7|\, X_{2,3})\mathbb{P}(X_8|\, X_{4,5})\mathbb{P}(X_9|\, X_{4,5})\mathbb{P}(X_{10}|\, X_{4,5})$$
$$\mathbb{P}(X_{11}|\, X_{7,8})\mathbb{P}(X_{12}|\, X_{7,8})\mathbb{P}(X_{13}|\, X_{7,8})$$

Blood Type Genetics

- ABO gene $\Rightarrow p_O = 0.60, p_A = 0.30, p_B = 0.10$
- RHD gene $\Rightarrow q_D = 0.60, q_d = 0.39, q_w = 0.01$
- This leads to a total of 12 blood phenotypes:
  A+, B+, AB+, O+, A-, B-, AB-, O-,Aw, Bw, ABw, Ow

	ABO	OO	OA	OB	AA	AB	BB
RHD		0.36	0.36	0.12	0.09	0.06	0.01
DD	0.3600	O+	A+	B+	A+	AB+	B+
Dd	0.4680	O+	A+	B+	A+	AB+	B+
Dw	0.0120	O+	A+	B+	A+	AB+	B+
dd	0.1521	O-	A-	B-	A-	AB-	B-
dw	0.0078	Ow	Aw	Bw	Aw	ABw	Bw
ww	0.0001	Ow	Aw	Bw	Aw	ABw	Bw

Simpsons' Pedigree and Bayesian Network

$$\mathbb{P}(X) = \mathbb{P}(X_1)\mathbb{P}(X_2)\mathbb{P}(X_3)\mathbb{P}(X_4)\mathbb{P}(X_5)$$
$$\mathbb{P}(X_6|\ X_{1,2})\mathbb{P}(X_7|\ X_{2,3})\mathbb{P}(X_8|\ X_{4,6})\mathbb{P}(X_9|\ X_{4,6})\mathbb{P}(X_{10}|\ X_{4,6})$$
$$\mathbb{P}(X_{11}|\ X_{7,8})\mathbb{P}(X_{12}|\ X_{7,8})\mathbb{P}(X_{13}|\ X_{7,8})$$

$$X_i \in \mathcal{G} = \{\mathrm{O},\mathrm{A},\mathrm{B}\}^2 \times \{\mathrm{D},\mathrm{d},\mathrm{w}\}^2 \quad |\mathcal{G}| = 3^2 \times 3^2 = 81$$

$$\mathrm{ev} = \{\text{Homer A+ and Bart Ow}\} \quad \mathbb{P}(X|\mathrm{ev}) = \frac{\mathbb{P}(X,\mathrm{ev})}{\sum_{X'}\mathbb{P}(X',\mathrm{ev})}$$

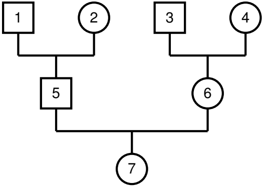
- $X = (X_1, X_2, \dots, X_{13})$ is the family genotype
- in order to compute $\mathbb{P}(\mathrm{ev}) = \sum_{X'}\mathbb{P}(X',\mathrm{ev})$
- we *just* have to sum over 81^{13} configurations

$$\mathbf{81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176}$$

$\Rightarrow$ simply impossible !

Local computations in a simple pedigree

Idea: we consider a smaller (but similar) family, ev (evidence) still represents the available information.



- for *founders* $(1, 2, 3, 4)$ i:

$$\varphi_i(X_i) = \mathbb{P}(X_i \cap \mathrm{ev})$$

- for *offsprings* $(5, 6, 7)$
  k with parents i, j:

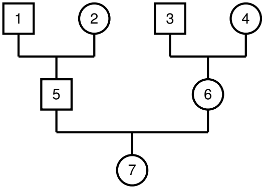
$$\varphi_j(X_i, X_j, X_k) = \mathbb{P}(X_k \cap \mathrm{ev} | X_i, X_j)$$

$$\mathbb{P}(\mathrm{ev}) = \sum_{X_1}\sum_{X_2}\sum_{X_3}\sum_{X_4}\sum_{X_5}\sum_{X_6}\sum_{X_7} \varphi_1(X_1)\varphi_2(X_2)\varphi_3(X_3)\varphi_4(X_4)$$
$$\varphi_5(X_1, X_2, X_5)\varphi_6(X_3, X_4, X_6)\varphi_7(X_5, X_6, X_7)$$

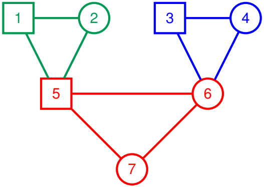
$\Rightarrow 81^7 = 22\,876\,792\,454\,961$ still too large !!

Local computations in a simple pedigree

Pedigree



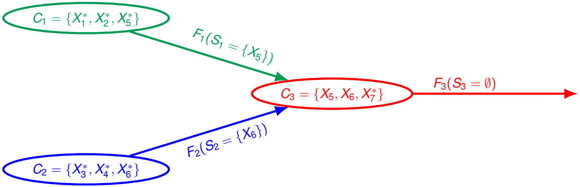
Clique decomposition



$$\mathbb{P}(\mathrm{ev}) = \sum_{X_5}\sum_{X_6}\sum_{X_7}\left\{\left(\overbrace{\sum_{X_1}\sum_{X_2}\varphi_1(X_1)\varphi_2(X_2)\varphi_5(X_1,X_2,X_5)}^{F_1(X_5)}\right)\right.$$

$$\left.\left(\overbrace{\sum_{X_3}\sum_{X_4}\varphi_3(X_3)\varphi_4(X_4)\varphi_6(X_3,X_4,X_6)}^{F_2(X_6)}\right)\varphi_7(X_5,X_6,X_7)\right\}$$

Local computations in a simple pedigree



$C_1 = \{X_1^*, X_2^*, X_5^*\}$

$F_1(S_1 = \{X_5\})$

$C_3 = \{X_5, X_6, X_7^*\}$

$F_3(S_3 = \emptyset)$

$F_2(S_2 = \{X_6\})$

$C_2 = \{X_3^*, X_4^*, X_6^*\}$

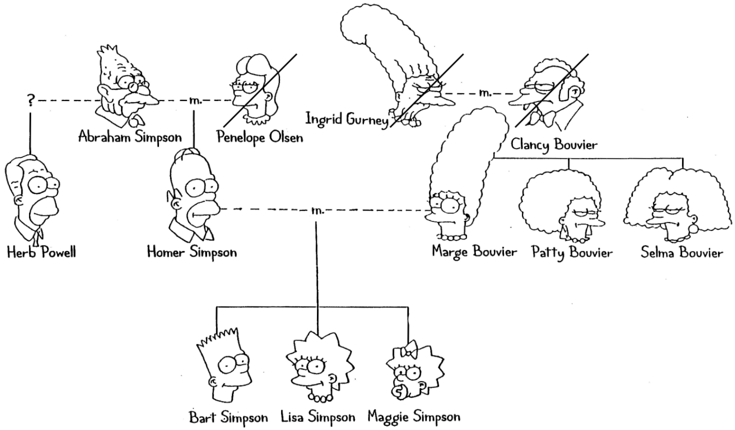
$$F_j(S_j) = \sum_{C_j \setminus S_j} \left(\prod_{i \in \mathrm{from}_j} F_i(S_i) \right) \times \prod_{X_u \in C_j{}^*} \varphi_u(X_{\mathrm{pa}_u}, X_u) \qquad F_3(\emptyset) = \mathbb{P}(\mathrm{ev})$$

Complexity:

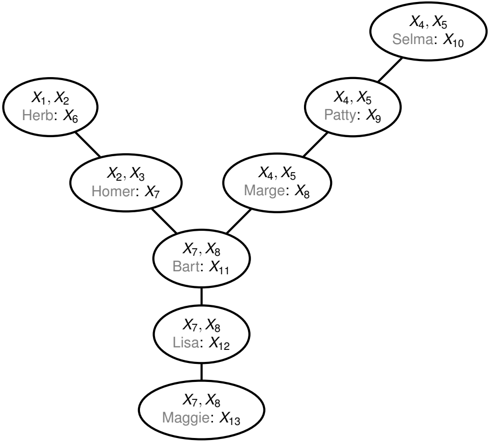
- from $81^7 = 22\,876\,792\,454\,961$
- to $3 \times 81^3 = 1\,594\,323$

Lisa: *"Much better !"* Homer: *"Woohoo !"*

Clique decomposition for the Simpsons

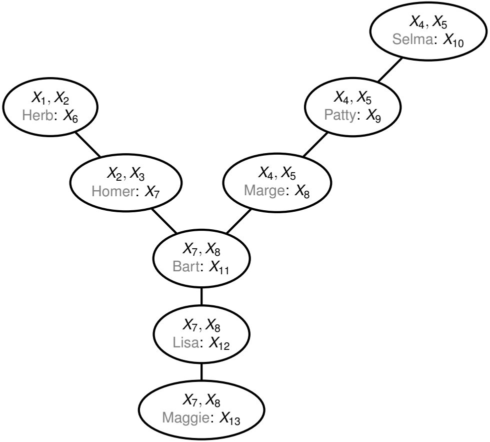


Clique decomposition for the Simpsons


X_4, X_5 Selma: X_{10}
X_1, X_2 Herb: X_6
X_4, X_5 Patty: X_9
X_2, X_3 Homer: X_7
X_4, X_5 Marge: X_8
X_7, X_8 Bart: X_{11}
X_7, X_8 Lisa: X_{12}
X_7, X_8 Maggie: X_{13}

- from $81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176$
- to $8 \times 81^3 = 4\,251\,528$

Clique decomposition for the Simpsons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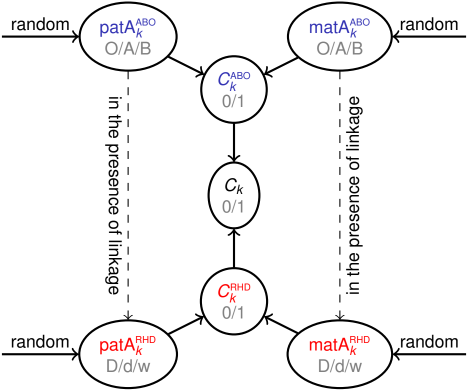
- from $81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176$
- to $8 \times 81^3 = 4\,251\,528$

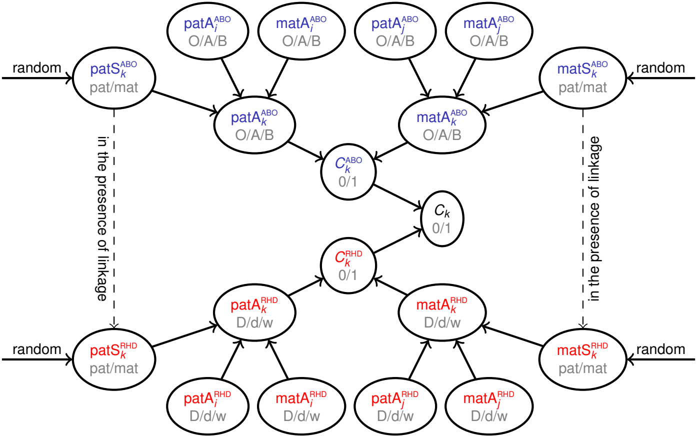
Extended Pedigree: Small Variables

For a *founder i*, instead of $X_i \in \mathcal{G}$ we have:


random
$\text{patA}_k^{\text{ABO}}$
O/A/B
$\text{matA}_k^{\text{ABO}}$
O/A/B
random
C_k^{ABO}
0/1
in the presence of linkage
in the presence of linkage
C_k
0/1
C_k^{RHD}
0/1
random
$\text{patA}_k^{\text{RHD}}$
D/d/w
$\text{matA}_k^{\text{RHD}}$
D/d/w
random

Extended Pedigree: Small Variables

For a *offspring* k (with father i and mother j), instead of $X_k \in \mathcal{G} | X_i, X_j$ we have:


$\text{patA}_i^{\text{ABO}}$ O/A/B
$\text{matA}_i^{\text{ABO}}$ O/A/B
$\text{patA}_j^{\text{ABO}}$ O/A/B
$\text{matA}_j^{\text{ABO}}$ O/A/B
random
$\text{patS}_k^{\text{ABO}}$ pat/mat
$\text{matS}_k^{\text{ABO}}$ pat/mat
random
$\text{patA}_k^{\text{ABO}}$ O/A/B
$\text{matA}_k^{\text{ABO}}$ O/A/B
in the presence of linkage
in the presence of linkage
C_k^{ABO} 0/1
C_k 0/1
C_k^{RHD} 0/1
$\text{patA}_k^{\text{RHD}}$ D/d/w
$\text{matA}_k^{\text{RHD}}$ D/d/w
random
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$\text{matS}_k^{\text{RHD}}$ pat/mat
random
$\text{patA}_i^{\text{RHD}}$ D/d/w
$\text{matA}_i^{\text{RHD}}$ D/d/w
$\text{patA}_j^{\text{RHD}}$ D/d/w
$\text{matA}_j^{\text{RHD}}$ D/d/w

Extended Pedigree: Small Variables

Recall on complexity:

- naive $81^{13} = 6\,461\,081\,889\,226\,672\,446\,898\,176$
- genotypes $8 \times 81^{3} = 4\,251\,528$

Small variables with the three heuristics:

- min-neighbors: the smallest clique
  $\Rightarrow$ 61154 61649 89051
- min-fill: the clique with minimum fill-in
  $\Rightarrow$ 85205 92333 92360
- weighted min-fill: the clique with minimum weighted fill-in
  $\Rightarrow$ 57530 43841 43112

The `bped` Program

`bped` is a C++ program for performing the sum-product algorithm and computing all marginal posterior distribution under the autosomal bi-allelic Mendelian model under HWE.

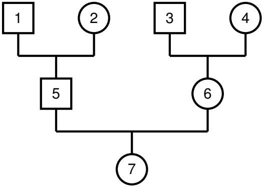
command-line : `bped file.ped file.ev [freq]`

- pedigree file (famID/indID,patID,matID)
- evidence file (famID/indID/`AA`/`Aa`/`aA`/`aa`)
- (option) allelic frequency (default $f = 0.10$)

The **ev. file** contains for each ind. $\propto \mathbb{P}(X_i = \texttt{AA}/\texttt{Aa}/\texttt{aA}/\texttt{aa} | Y_i)$

- $1/1/1/1$ is the neutral evidence (no information)
- $0/1/1/0$ is the evidence for a heterozygous carrier
- $1/0.095/0.095/0.095$ for $T_i = 67, \delta_i = 0$
- $0/0.407/0.407/0.407$ for $T_i = 38, \delta_i = 1$

`bped` Demo 1



- allelic frequency $f = 0.10$
- ev1: full neutral evidence
- ev2: $X_7 \neq \texttt{AA}$
- ev3: $X_7 \neq \texttt{AA}$ and $X_5 = \texttt{AA}$

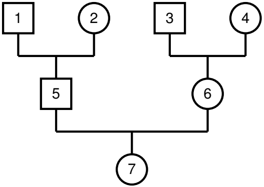
ped file:

```
1 1 0 0
1 2 0 0
1 3 0 0
1 4 0 0
1 5 1 2
1 6 3 4
1 7 5 6
```

ev1 file:

```
1 1 1 1 1 1
1 2 1 1 1 1
1 3 1 1 1 1
1 4 1 1 1 1
1 5 1 1 1 1
1 6 1 1 1 1
1 7 1 1 1 1
```

bped Demo 1

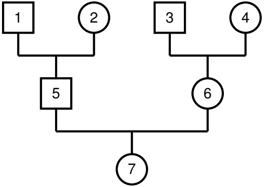


- allelic frequency $f = 0.10$
- ev1: full neutral evidence
- ev2: $X_7 \neq \texttt{AA}$
- ev3: $X_7 \neq \texttt{AA}$ and $X_5 = \texttt{AA}$

bped output for ev1:

```
1:1  0.9801  0.0099  0.0099  0.0001
1:2  0.9801  0.0099  0.0099  0.0001
1:3  0.9801  0.0099  0.0099  0.0001
1:4  0.9801  0.0099  0.0099  0.0001
1:5  0.9801  0.0099  0.0099  0.0001
1:6  0.9801  0.0099  0.0099  0.0001
1:7  0.9801  0.0099  0.0099  0.0001
```

bped Demo 1



- allelic frequency $f = 0.10$
- ev1: full neutral evidence
- ev2: $X_7 \neq \texttt{AA}$
- ev3: $X_7 \neq \texttt{AA}$ and $X_5 = \texttt{AA}$

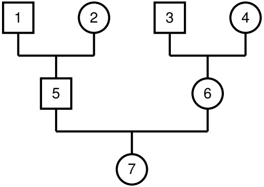
ped file:

1	1	0	0
1	2	0	0
1	3	0	0
1	4	0	0
1	5	1	2
1	6	3	4
1	7	5	6

ev2 file:

1	1	1	1	1	1
1	2	1	1	1	1
1	3	1	1	1	1
1	4	1	1	1	1
1	5	1	1	1	1
1	6	1	1	1	1
1	7	0	1	1	1

`bped` Demo 1

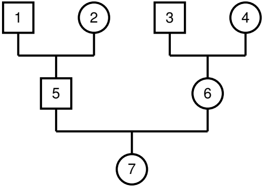


- allelic frequency $f = 0.10$
- ev1: full neutral evidence
- ev2: $X_7 \neq \texttt{AA}$
- ev3: $X_7 \neq \texttt{AA}$ and $X_5 = \texttt{AA}$

`bped` output for ev2:

```
1:1   0.736306   0.130566   0.130566   0.00256256
1:2   0.736306   0.130566   0.130566   0.00256256
1:3   0.736306   0.130566   0.130566   0.00256256
1:4   0.736306   0.130566   0.130566   0.00256256
1:5   0.492513   0.251231   0.251231   0.00502513
1:6   0.492513   0.251231   0.251231   0.00502513
1:7   0.000000   0.497487   0.497487   0.00502513
```

`bped` Demo 1



- allelic frequency $f = 0.10$
- ev1: full neutral evidence
- ev2: $X_7 \neq \texttt{AA}$
- ev3: $X_7 \neq \texttt{AA}$ and $X_5 = \texttt{AA}$

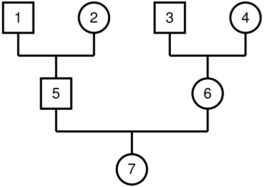
ped file:

```
1 1 0 0
1 2 0 0
1 3 0 0
1 4 0 0
1 5 1 2
1 6 3 4
1 7 5 6
```

ev3 file:

```
1 1 1 1 1 1
1 2 1 1 1 1
1 3 1 1 1 1
1 4 1 1 1 1
1 5 1 0 0 0
1 6 1 1 1 1
1 7 0 1 1 1
```

bped Demo 1

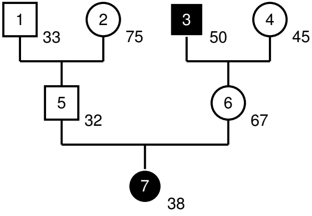


- allelic frequency $f = 0.10$
- ev1: full neutral evidence
- ev2: $X_7 \neq \mathtt{AA}$
- ev3: $X_7 \neq \mathtt{AA}$ and $X_5 = \mathtt{AA}$

bped output for ev3:

```
1:1    0.99      0.005     0.005       0
1:2    0.99      0.005     0.005       0
1:3  0.49005   0.25245   0.25245   0.00505
1:4  0.49005   0.25245   0.25245   0.00505
1:5     1         0         0          0
1:6     0       0.495     0.495      0.01
1:7     0         0         1          0
```

bped Demo 2



$$S(32) = 0.549 \quad S(33) = 0.522$$

$$S(38) = 0.407 \quad S(45) = 0.287$$

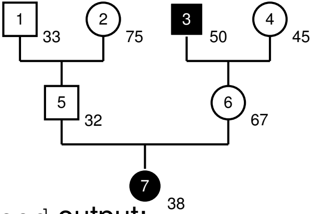
$$S(50) = 0.223 \quad S(67) = 0.095$$

$$S(75) = 0.064$$

	1	1	0	0
	1	2	0	0
	1	3	0	0
ped file:	1	4	0	0
	1	5	1	2
	1	6	3	4
	1	7	5	6

	1	1	1	0.522	"	"
	1	2	1	0.064	"	"
	1	3	0	1	1	1
ev file:	1	4	1	0.287	"	"
	1	5	1	0.549	"	"
	1	6	1	0.095	"	"
	1	7	0	1	1	1

bped Demo 2



$$S(32) = 0.549 \quad S(33) = 0.522$$

$$S(38) = 0.407 \quad S(45) = 0.287$$

$$S(50) = 0.223 \quad S(67) = 0.095$$

$$S(75) = 0.064$$

bped output:

```
1:1   0.961766   0.0189514    0.0189514    0.000331633
1:2   0.995236   0.00236164   0.00236164   4.1211e-05
1:3   0          0.495177     0.495177     0.00964697
1:4   0.988769   0.00557344   0.00557344   8.36409e-05
1:5   0.962757   0.0331219    0.0040797    4.14015e-05
1:6   0.0325306  0.959105     0.0027724    0.00559169
1:7   0          0.034096     0.96433      0.00157444
```

Outline

1. Introduction
   - Some Recalls
   - A Fictional Genetic Study
   - Estimations from Known Genotypes
2. Expectation-Maximization
   - Principle
   - Posterior in Pedigree
   - Estimations from Unknown Genotypes
3. Advanced Stuff
   - Ascertainment Issues
   - Advanced Models
   - Sophisticated Posteriors

The Method

Start from pedigree data, disease status (age, censoring), and possible extra-information (e.g. partial genotyping).

- initialization: random weights w (w_i closer to 1 for affected)
- for iter=$1, 2, 3, \dots$
  - fit a (non-parametric) survival model with weights w

    $$\texttt{fit0} = \texttt{survfit}(\texttt{Surv}(T, \delta) \sim 1, \texttt{weights} = 1 - w)$$

    $$\texttt{fit1} = \texttt{survfit}(\texttt{Surv}(T, \delta) \sim 1, \texttt{weights} = w)$$

  - write the evidence file:

    $$\begin{aligned} \text{affected:}\quad & S_0(T_i)\lambda_0(T_i)\ \text{(AA)},\ S_1(T_i)\lambda_1(T_i)\ \text{(Aa/aA/aa)} \\ \text{unaffected:}\quad & S_0(T_i)\ \text{(AA)},\ S_1(T_i)\ \text{(Aa/aA/aa)} \end{aligned}$$

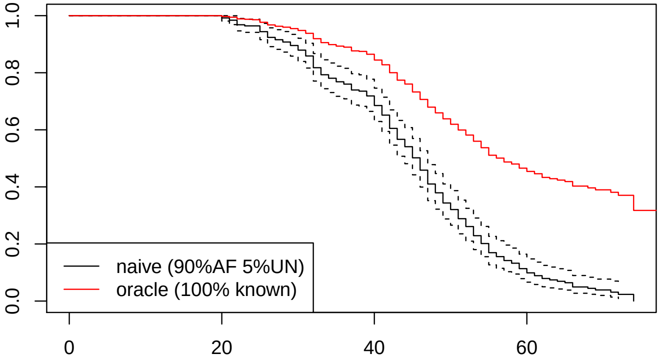
  - use `bped` to update the weights w

    ```
    bped ped ev 0.10
    ```

- output: a fitted survival `fit0`/`fit1` (including survival, confidence intervals, etc.), and post. carrier probabilities w.

Application to Our Simulated Dataset

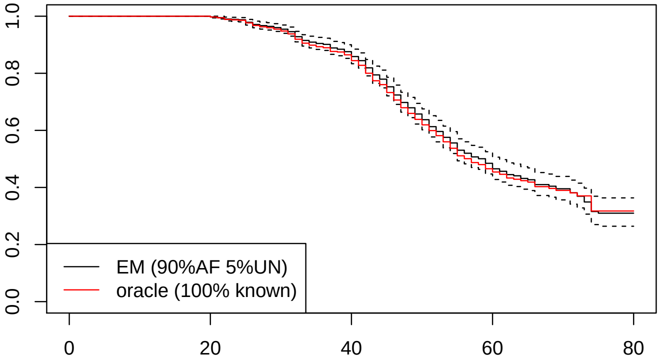
Simulated Dataset: $N = 500$ families, $n = 5000$ individuals, 312 affected, 959 carriers, 75% of affected are carriers.



Naive estimation ⇒ bias

Application to Our Simulated Dataset

Simulated Dataset: $N = 500$ families, $n = 5000$ individuals, 312 affected, 959 carriers, 75% of affected are carriers.



EM ⇒ no bias, and very close to the oracle

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Modified Simulation

- same model than before, but $f = 0.5\%$ instead of 10%
- $\lambda_0(t) \in (5, 200)/100000$ and $\text{RH}(t) \in (15, 100)$
- $N = 10000$ families of 10 individuals (fixed pedigree)
- ascertainement: at least one affected before age 45

	unaffected	affected	total
non carrier	97695	1310	99005
carrier	761	234	995
total	98456	1544	100000

full dataset

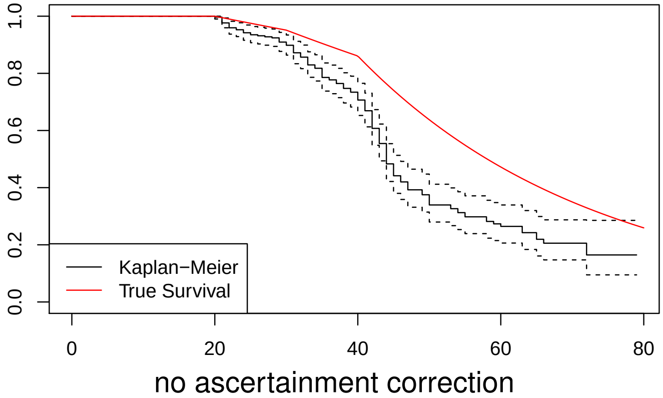
Modified Simulation

- same model than before, but $f = 0.5\%$ instead of 10%
- $\lambda_0(t) \in (5, 200)/100000$ and $\mathrm{RH}(t) \in (15, 100)$
- $N = 10000$ families of 10 individuals (fixed pedigree)
- ascertainement: at least one affected before age 45

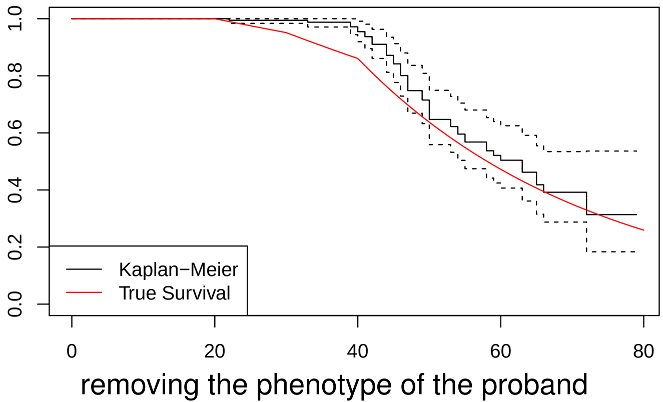
	unaffected	affected	total
non carrier	4301	442	4743
carrier	203	164	367
total	4504	606	5110

after ascertainment

Estimations with 100% Known Genotypes



Estimations with 100% Known Genotypes



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Just in One Slide

polygenic effects (*e.g.* BOADICEA)

- latent or partially observed
- hypergeometric polygenic model
- usually discretized and approximated

familial frailty (*e.g.* Gorfine, 2013)

- Gaussian frailty shared in the family
- sum-product on a grid of frailty values
- posterior frailty distribution available

parent of origin (*e.g.* amyloid neuropathy)

- $\lambda_1^{\text{pat}}(t) = \lambda(t|X = 10)$ $\lambda_1^{\text{mat}}(t) = \lambda(t|X = 01)$
- almost impossible without EM

covariates (*e.g.* mammographic density for BC)

- effect could depend on carrier status
- how to deal with missing data

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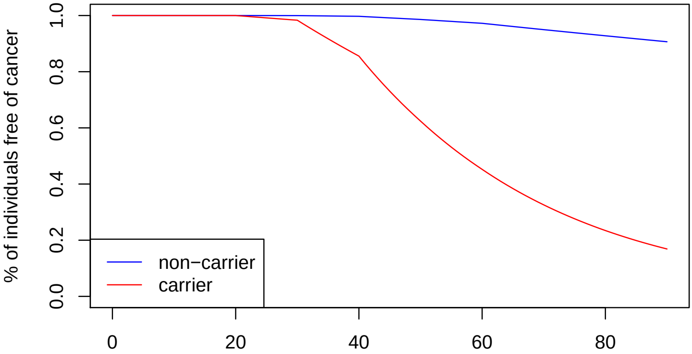
Claus Model for BC/OC (Claus, 1991)

Claus' Model: dominant bi-allelic mutation, freq. $q = 0.33\%$

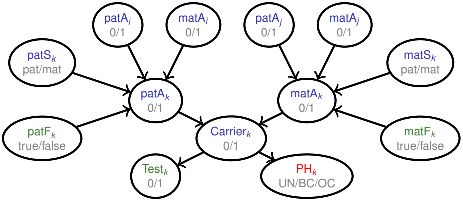
- PCH[1]: non-carrier hazard $\lambda_0(t)$, carrier hazard $\lambda_1(t)$
- male BC → BC25, OC<70 → BC25, OC≥70 → BC35



[1] Piecewise Constant Hazard with cuts in 20,30,40,50,60,70,80.

Claus Model for BC/OC

offspring model with allelic variables (inspired by Lauritzen, 2003)



$$\mathbb{P}(\text{patA}_k = a/b|\text{patA}_i = a, \text{matA}_i = b, \text{patS}_k = \text{pat}/\text{mat}, \text{patF}_k = \text{true}) = 1$$

$$\mathbb{P}(\text{patS}_k = \text{pat}) = 0.5 \quad \mathbb{P}(\text{patA}_k = 1|\text{patF}_k = \text{false}) = q$$

$$\mathbb{P}(\text{Carrier}_k = 1|\text{patA}_k = a, \text{matA}_k = b) = (a \neq 00 \text{ or } b \neq 00)$$

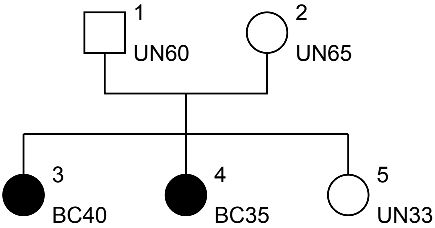
$$\mathbb{P}(\text{patF}_k = \text{false}) = 1\% \quad \mathbb{P}(\text{matF}_k = \text{false}) = 0.01\%$$

$$\mathbb{P}(\text{Test}_k = 1| \text{ Carrier}_k = 1) = 80\% \quad \mathbb{P}(\text{Test}_k = 0| \text{ Carrier}_k = 0) = 98\%$$

$$\mathbb{P}(\text{maleUN}t|\text{C}_k = a) = S_a(25) \quad \mathbb{P}(\text{femaleUN}t|\text{C}_k = a) = S_a(t)$$

$$\mathbb{P}(\text{maleBC}t|\text{C}_k = a) = S_a(25)\lambda_a(25) \quad \mathbb{P}(\text{femaleBC}t|\text{C}_k = a) = S_a(t)\lambda_a(t)$$

Simple Example

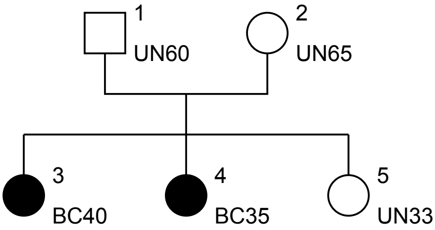


$$\pi(\cdot) = \mathbb{P}(\cdot|\text{FH})$$

Individual i	$\pi(\text{NC})$	1/1	1/2	1/3	1/4	1/5
$\pi(C_i = 1)$	–	52.1	21.2	70.0	71.6	35.4

2 founders, 3 offsprings, 32 variables, 22 cliques, complexity 396

Simple Example

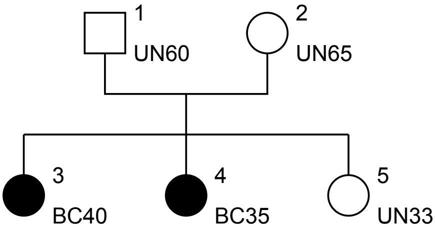


$$\pi(\cdot) = \mathbb{P}(\cdot|\mathrm{FH})$$

1/1	1/2	1/3	1/4	$\pi(\mathrm{C}_{\mathcal{J}})$
1	0	1	1	48.6
0	0	0	0	26.9
0	1	1	1	19.7
1	0	0	1	2.1
1	0	1	0	1.0
0	1	0	1	0.8

Individual *i*	$\pi(\mathrm{NC})$	1/1	1/2	1/3	1/4	1/5
$\pi(\mathrm{C}_i = 1)$	–	52.1	21.2	70.0	71.6	35.4
$\pi(\mathrm{C}_i = 1\|\mathrm{NC} = 3)$	37.4	71.4	28.6	**96.2**	**98.2**	5.6
$\pi(\mathrm{C}_i = 1\|\mathrm{NC} = 4)$	33.1	71.1	29.2	**100.0**	**100.0**	**99.8**
$\pi(\mathrm{C}_i = 1\|\mathrm{NC} = 0)$	26.9	0.0	0.0	0.0	0.0	0.0
$\pi(\mathrm{C}_i = 1\|\mathrm{NC} = 2)$	2.3	71.8	28.2	32.2	66.5	1.3
$\pi(\mathrm{C}_i = 1\|\mathrm{NC} = 5)$	0.2	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Simple Example

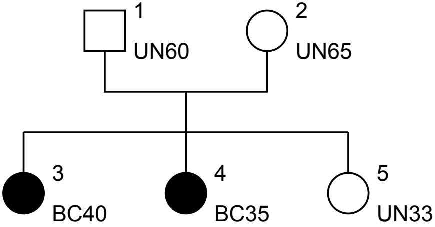


$$\pi(\cdot) = \mathbb{P}(\cdot|\mathrm{FH}, \mathsf{T}_1 = 1)$$

1/1	1/2	1/3	1/4	$\pi(\mathsf{C}_{\mathcal{J}})$
1	0	1	1	91.3
1	0	0	1	3.9
1	0	1	0	1.9
0	0	0	0	1.3
0	1	1	1	0.9
1	1	1	1	0.5

Individual *i*	$\pi(\mathrm{NC})$	1/1	1/2	1/3	1/4	1/5
$\pi(\mathsf{C}_i = 1)$	–	97.8	1.5	94.7	96.7	47.7
$\pi(\mathsf{C}_i = 1|\mathrm{NC} = 3)$	50.6	**99.0**	1.0	**96.2**	**98.2**	5.6
$\pi(\mathsf{C}_i = 1|\mathrm{NC} = 4)$	44.6	**99.0**	1.3	**100.0**	**100.0**	**99.7**
$\pi(\mathsf{C}_i = 1|\mathrm{NC} = 2)$	3.1	**99.0**	1.0	32.2	66.5	1.3
$\pi(\mathsf{C}_i = 1|\mathrm{NC} = 0)$	1.3	0.0	0.0	0.0	0.0	0.0
$\pi(\mathsf{C}_i = 1|\mathrm{NC} = 5)$	0.4	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Simple Example

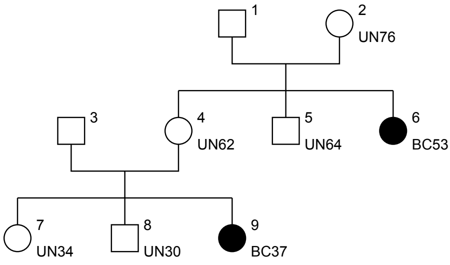


$$\pi(\cdot) = \mathbb{P}(\cdot | \mathrm{FH}, \mathsf{T}_1 = 0)$$

1/1	1/2	1/3	1/4	$\pi(\mathsf{C}_{\mathcal{J}})$
0	0	0	0	46.0
0	1	1	1	33.6
1	0	1	1	17.0
0	1	0	1	1.4
1	0	0	1	0.7
0	1	1	0	0.7

Individual i	$\pi(\mathrm{NC})$	1/1	1/2	1/3	1/4	1/5
$\pi(\mathsf{C}_i = 1)$	–	18.2	35.8	51.7	52.9	26.2
$\pi(\mathsf{C}_i = 1 \| \mathrm{NC} = 0)$	46.0	0.0	0.0	0.0	0.0	0.0
$\pi(\mathsf{C}_i = 1 \| \mathrm{NC} = 3)$	27.5	33.8	66.3	**96.2**	**98.2**	5.6
$\pi(\mathsf{C}_i = 1 \| \mathrm{NC} = 4)$	24.6	33.4	66.7	**100.0**	**100.0**	**99.9**
$\pi(\mathsf{C}_i = 1 \| \mathrm{NC} = 2)$	1.7	34.2	65.8	32.2	66.5	1.3
$\pi(\mathsf{C}_i = 1 \| \mathrm{NC} = 1)$	0.1	5.9	11.1	26.7	55.3	1.1

More Realistic Example

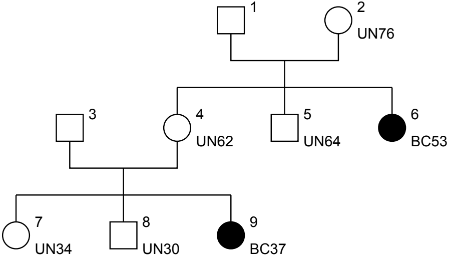


$$\pi(\cdot) = \mathbb{P}(\cdot|\text{FH})$$

Individual i $\pi(\text{NC})$	2/1	2/2	2/3	2/4	2/5	2/6	2/7	2/8	2/9
$\pi(C_i = 1)$ $-$	17.3	5.1	10.7	20.0	11.1	20.8	14.7	15.2	30.0

3 founders, 6 offsprings, 60 variables, 41 cliques, complexity 748

More Realistic Example

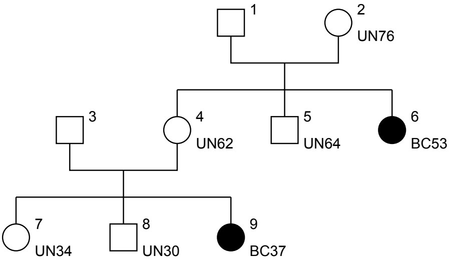


$$\pi(\cdot) = \mathbb{P}(\cdot|\text{FH})$$

2/3	2/4	2/6	2/9	$\pi(C_{\mathcal{J}})$
0	0	0	0	67.5
0	1	1	1	18.0
1	0	0	1	10.0
0	0	1	0	1.9
0	1	0	1	1.4
0	1	1	0	0.4

Individual i	$\pi(\text{NC})$	2/1	2/2	2/3	2/4	2/5	2/6	2/7	2/8	2/9
$\pi(C_i = 1)$	–	17.3	5.1	10.7	20.0	11.1	20.8	14.7	15.2	30.0
$\pi(C_i = 1\|\text{NC} = 0)$	67.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$\pi(C_i = 1\|\text{NC} = 5)$	7.6	**77.6**	22.4	1.6	**98.5**	36.9	**93.1**	34.7	37.0	**98.1**
$\pi(C_i = 1\|\text{NC} = 6)$	7.0	**77.6**	22.6	2.1	**98.5**	68.1	**97.5**	66.0	68.3	**99.3**
$\pi(C_i = 1\|\text{NC} = 3)$	6.2	14.6	4.2	**81.1**	4.1	14.8	15.6	39.7	42.5	**83.5**
$\pi(C_i = 1\|\text{NC} = 4)$	5.5	44.0	12.6	44.2	55.7	4.4	46.6	47.5	47.8	**97.1**

More Realistic Example

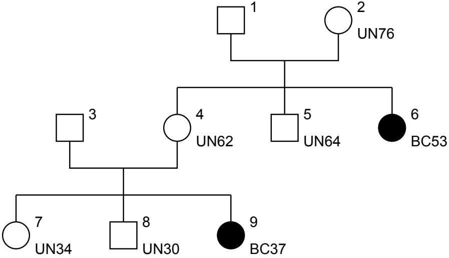


$$\pi(\cdot) = \mathbb{P}(\cdot|\mathrm{FH}, \mathrm{T}_4 = 1)$$

2/3	2/4	2/6	2/9	$\pi(C_{\mathcal{J}})$
0	1	1	1	81.8
0	0	0	0	7.7
0	1	0	1	6.4
0	1	1	0	1.7
1	0	0	1	1.1
1	1	1	1	0.8

Individual *i*	$\pi(\mathrm{NC})$	2/1	2/2	2/3	2/4	2/5	2/6	2/7	2/8	2/9
$\pi(C_i = 1)$	–	70.8	20.7	2.0	**90.9**	45.4	**84.6**	44.6	46.2	**90.2**
$\pi(C_i = 1 \vert \mathrm{NC} = 5)$	34.1	**77.6**	22.4	0.2	**100**	36.9	**93.1**	34.7	37.0	**98.1**
$\pi(C_i = 1 \vert \mathrm{NC} = 6)$	31.3	**77.6**	22.6	0.7	**100**	68.0	**97.5**	66.0	68.3	**99.3**
$\pi(C_i = 1 \vert \mathrm{NC} = 4)$	14.1	**76.2**	21.8	2.0	**98.1**	7.6	**80.5**	9.2	9.7	**95.0**
$\pi(C_i = 1 \vert \mathrm{NC} = 7)$	10.2	**77.7**	23.6	3.8	**100**	**97.4**	**99.8**	**98.9**	**99.0**	**100**
$\pi(C_i = 1 \vert \mathrm{NC} = 0)$	7.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

More Realistic Example



$$\pi(\cdot) = \mathbb{P}(\cdot|\mathrm{FH}, \mathsf{T}_4 = 0)$$

2/3	2/4	2/6	2/9	$\pi(\mathsf{C}_{\mathcal{J}})$
0	0	0	0	80.3
1	0	0	1	11.9
0	1	1	1	4.4
0	0	1	0	2.2
0	1	0	1	0.3
1	0	1	1	0.3

Individual i	$\pi(\mathrm{NC})$	2/1	2/2	2/3	2/4	2/5	2/6	2/7	2/8	2/9
$\pi(\mathsf{C}_i = 1)$	–	5.9	1.7	12.5	4.9	3.8	7.1	8.3	8.6	17.1
$\pi(\mathsf{C}_i = 1\|\mathrm{NC} = 0)$	80.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$\pi(\mathsf{C}_i = 1\|\mathrm{NC} = 3)$	7.1	12.6	3.6	**83.9**	0.9	15.2	15.5	40.9	43.8	**83.7**
$\pi(\mathsf{C}_i = 1\|\mathrm{NC} = 2)$	4.5	20.9	5.9	73.2	0.1	1.9	24.9	1.4	1.5	70.4
$\pi(\mathsf{C}_i = 1\|\mathrm{NC} = 4)$	3.6	17.2	4.9	**79.5**	20.4	1.8	18.2	**79.5**	**79.6**	**98.8**
$\pi(\mathsf{C}_i = 1\|\mathrm{NC} = 5)$	2.0	**77.6**	22.4	7.2	**93.0**	36.9	**93.1**	34.8	37.1	**98.1**

Summary

Take-Home Messages:

- unbalanced genotyping scheme induces bias
- EM for pedigrees efficiently solves the problem
- `bped` program for posterior marginals

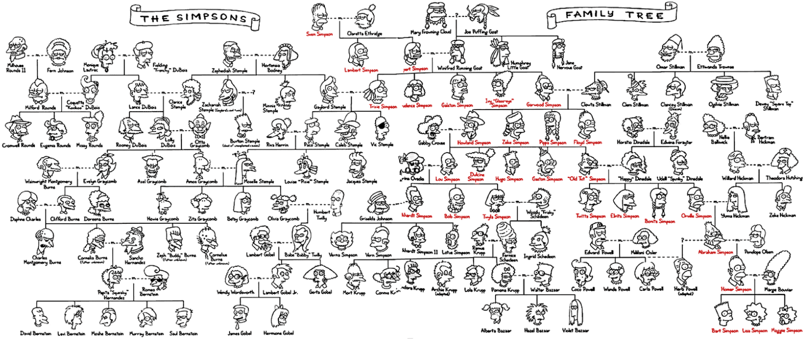
What Next:

- more sophisticated models (frailty, covariates, POO, etc.)
- tackling ascertainement (raking ?)
- clinical relevance of advanced posterior distribution

Many Human Diseases

- Cancers:
  - Breast and Ovarian: *Institut Curie*
  - MSI Cancer and Lynch Syndrome: *Saint-Antoine*
  - Li-Fraumeni: *La Pitié-Salpêtrière*
- Rare Genetic Diseases:
  - Hereditary Amyloid Neuropathy: *Henri Mondor*
  - Pulmonary Arterial HT: *Marie Lannelongue*
  - Huntington Disease: *Hôpital Saint-Anne*
- Common Disease with Genetic Factors:
  - Alzheimer Disease: *CHU Rouen*
  - Diabetes, autism, cardio-vascular, obesity, . . .

Just for Pleasure



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