Computing risks based on family history in genetic diseases

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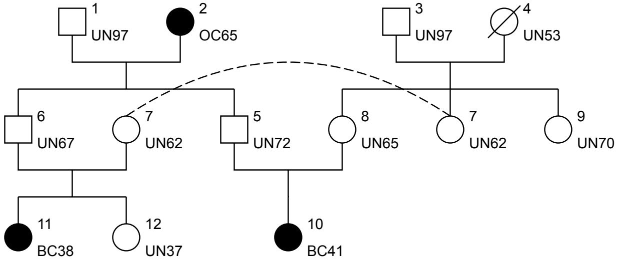
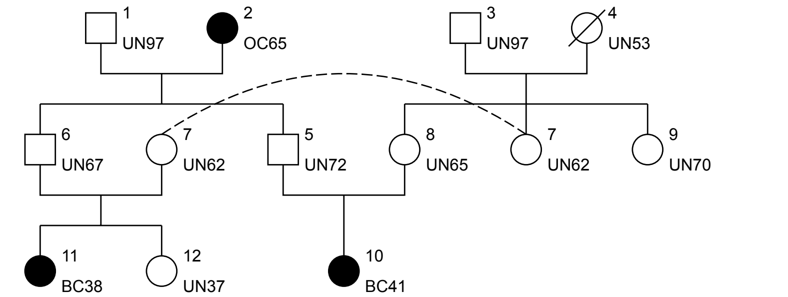
Context of the breast cancer

- 1st cancer in women. 54,000 women in France each year
- Complex disease due to an accumulation of mutations (BRCA 1/2, PALB2, RAD51, etc.)
- **Inherited mutation** in 10 to 15% of the cases



Family History (FH) : Pedigree + Sequencing (seq) + Survival (Y)



Variant data (var)

- Known variant or VUS
- Database
- Functional tests
- Molecular dynamics

Cancer pathology (patho)

- MSI status (Lynch)
- BRAF mutation (Lynch)
- ER, PR, HER2 status (Breast)
- invasive/in situ (Breast)

compute $\Rightarrow$ posterior **variant status** **carrier risk** **tumoral risk**

V : the set of variant status
var : the set of variant data
X : the set of genotypes

$$\left.\begin{array}{l}\text{seq : the set of sequencing data}\\ Y \text{ : the set of phenotypes (survival data)}\end{array}\right\} \rightarrow \mathrm{FH} = \{seq, Y\}$$

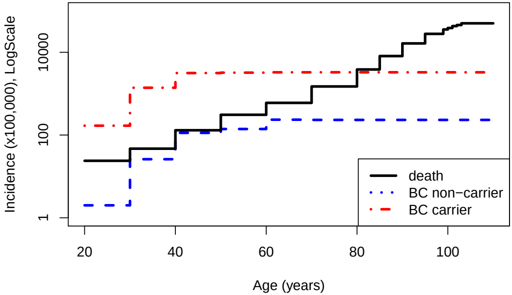
patho : the set of pathology reports

$$\mathbb{P}(\text{var}, V, X, \text{seq}, Y, \text{patho}) = \prod_j \mathbb{P}(\text{var}_j | V_j)\, \mathbb{P}(V_j)$$
$$\prod_i \mathbb{P}\left(X_i | X_{\text{pat}_i}, X_{\text{mat}_i}\right) \mathbb{P}(\text{seq}_i | X_i)\, \mathbb{P}(Y_i | X_i)$$
$$\prod_{i, Y_i \neq \text{UN}} \mathbb{P}(\text{patho}_i | X_i)$$

Our first objective : modelling efficiently the quantity
$$\prod_i \mathbb{P}\left(X_i | X_{\text{pat}_i}, X_{\text{mat}_i}\right) \mathbb{P}(Y_i | X_i)$$
Illustrated with a mendelian model and parameters taken from the breast cancer literature [Claus et al., 1991, Easton et al., 1993].

The Claus-Easton model [Claus et al., 1991]

- Autosomal, biallelic, dominant, estimated allele frequency f=0.33%
- The hazard functions per genotype (λ_0 and λ_1) estimated from the densities in [Easton et al., 1993]:



$$\frac{\lambda_1(t)}{\lambda_0(t)} \in [20 - 80]$$

Objective : Implement the Claus-Easton model in a Bayesian network (sum/product algorithm) combined with survival data.

Implementation : genotypes

$$\mathbb{P}(X,Y) = \prod_i \underbrace{\mathbb{P}\left(X_i | X_{\text{pat}_i}, X_{\text{mat}_i}\right)}_{\text{genotype}} \underbrace{\mathbb{P}\left(Y_i | X_i\right)}_{\text{phenotypes}}$$

Mode of inheritance : 1 autosomal biallelic gene, f = 0.33%

Founders (**Hardy-Weinberg**) :

$$\begin{cases} \mathbb{P}(X_i = 00) = (1-f)^2 \\ \mathbb{P}(X_i = 10) = \mathbb{P}(X_i = 01) = f(1-f) \\ \mathbb{P}(X_i = 11) = f^2 \end{cases}$$

Offsprings (**Mendel**):

$$\begin{cases} \mathbb{P}(X_i = 00) = (1-\Theta(X_{\text{pat}})) \times (1-\Theta(X_{\text{mat}})) \\ \mathbb{P}(X_i = 10) = \Theta(X_{\text{pat}}) \times (1-\Theta(X_{\text{mat}})) \\ \mathbb{P}(X_i = 01) = (1-\Theta(X_{\text{pat}})) \times \Theta(X_{\text{mat}}) \\ \mathbb{P}(X_i = 11) = \Theta(X_{\text{pat}}) \times \Theta(X_{\text{mat}}) \end{cases}$$

with $\Theta(00) = 0, \quad \Theta(10) = \Theta(01) = 0.5, \quad \Theta(11) = 1$

Implementation : phenotypes

with T_i, the age at disease onset for the individual i.

$$Y_i \text{ (Survival data)} = \begin{cases} \{T_i > \tau_i\} & \text{if } i \text{ is censored (UN) at age } \tau_i \\ \{T_i = \tau_i\} & \text{if } i \text{ is affected (BC or OC) at age } \tau_i \end{cases}$$

Dominant model of disease :

Hazard functions of T : $\begin{cases} \lambda_0(t) & \text{for } X = 00 \text{ (non-carrier)} \\ \lambda_1(t) & \text{for } X \neq 00 \text{ (carrier)} \end{cases}$

Survival functions of T : $\begin{cases} S_0(t) = \exp\left(-\int_0^t \lambda_0(t)\right) dt & \text{for non-carrier} \\ S_1(t) = \exp\left(-\int_0^t \lambda_1(t)\right) dt & \text{for carrier} \end{cases}$

conditional probabilities

- For a **censored** individual at age τ_i

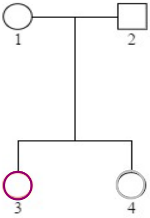
$$\mathbb{P}(Y_i|X_i) = \mathbb{P}(T_i > \tau_i|X_i) = \begin{cases} S_0(\tau_i) & \text{for non-carriers} \\ S_1(\tau_i) & \text{for carriers} \end{cases}$$

- For an **affected** individual at age τ_i

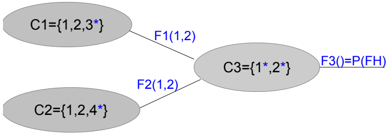
$$\mathbb{P}(Y_i|X_i) = \mathbb{P}(T_i = \tau_i|X_i) = \begin{cases} S_0(\tau_i)\lambda_0(\tau_i) & \text{for non-carriers} \\ S_1(\tau_i)\lambda_1(\tau_i) & \text{for carriers} \end{cases}$$

Impl. in a Bayesian network [1] (sum-product algorithm)

$$\mathbb{P}(X, \mathrm{FH}) = \prod_i \underbrace{\sum_{Y_i \in \mathrm{FH}} \mathbb{P}(X_i | X_{\mathrm{pa}_i}) \mathbb{P}(Y_i | X_i)}_{\mathrm{K}_i(X_i, X_{\mathrm{pa}_i})} \rightarrow \mathbb{P}(\mathrm{FH}) = \sum_X \prod_i \mathrm{K}_i(X_i, X_{\mathrm{pa}_i})$$



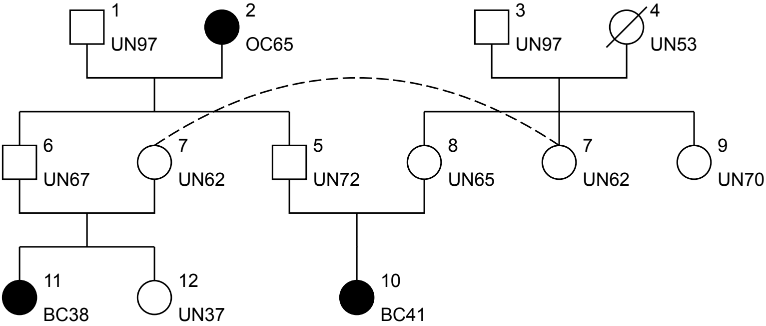
With $X \in \{00, 10, 01, 11\}^n \rightarrow 4^n$configurations

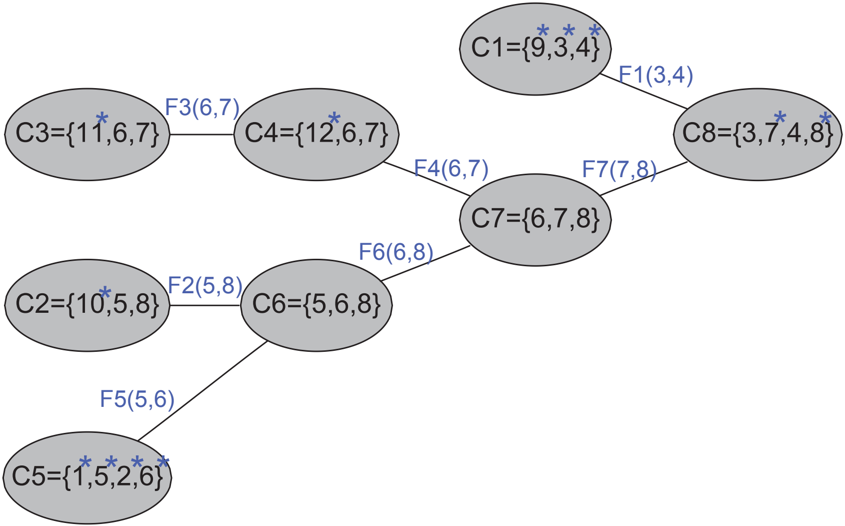


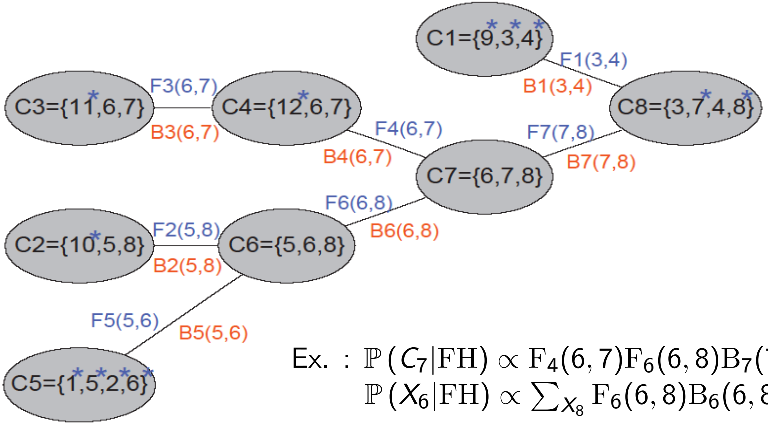
$$\mathbb{P}(\mathrm{FH}) = \sum_{X_1} \mathrm{K}_1(X_1) \sum_{X_2} \mathrm{K}_2(X_2) \overbrace{\sum_{X_3} \mathrm{K}_3(X_3, X_1, X_2)}^{\mathrm{F}_1(X_1, X_2)} \overbrace{\sum_{X_4} \mathrm{K}_4(X_4, X_1, X_2)}^{\mathrm{F}_2(X_1, X_2)}$$

$$\mathbb{P}(\mathrm{FH}) = \mathrm{F}_3(\emptyset) = \sum_{X_1, X_2} \mathrm{K}_1(X_1) \mathrm{K}_2(X_2) \mathrm{F}_1(X_1, X_2) \mathrm{F}_2(X_1, X_2)$$

[1] [Koller and Friedman, 2009]


1
UN97
2
OC65
3
UN97
4
UN53
6
UN67
7
UN62
5
UN72
8
UN65
7
UN62
9
UN70
11
BC38
12
UN37
10
BC41


C1={9,3,4}
F1(3,4)
C3={11,6,7}
F3(6,7)
C4={12,6,7}
C8={3,7,4,8}
F4(6,7)
F7(7,8)
C7={6,7,8}
F6(6,8)
C2={10,5,8}
F2(5,8)
C6={5,6,8}
F5(5,6)
C5={1,5,2,6}

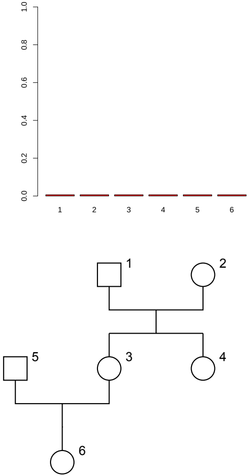


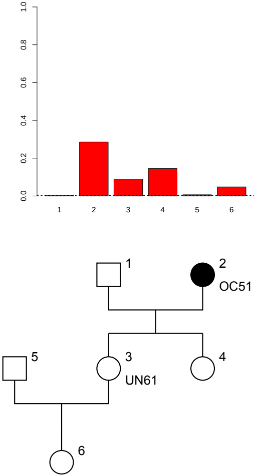
Ex. : $\mathbb{P}(C_7|\mathrm{FH}) \propto \mathrm{F}_4(6,7)\mathrm{F}_6(6,8)\mathrm{B}_7(7,8)$

$\mathbb{P}(X_6|\mathrm{FH}) \propto \sum_{X_8} \mathrm{F}_6(6,8)\mathrm{B}_6(6,8)$

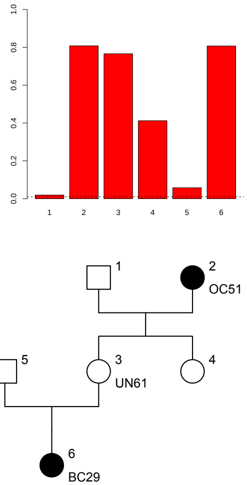
F & B computed once for any later marginal or joint distribution needed
Complexity $\mathcal{O}(4^n) \to \mathcal{O}(n \times 4^k)$, k:tree-width

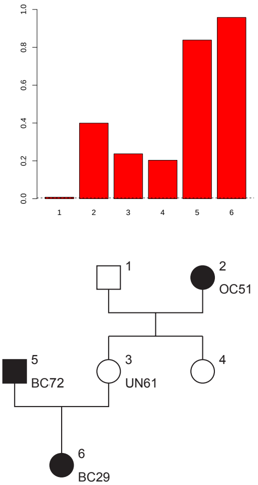
Results : Carrier risk, posterior marginal carrier distribution





Results : Carrier risk, posterior marginal carrier distribution





Implementation : Disease risk prediction

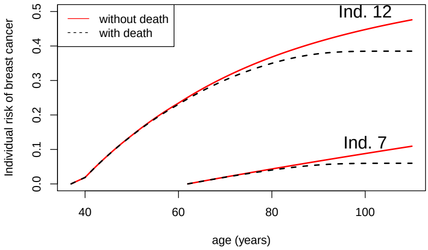
$\pi(\tau) = \mathbb{P}(\text{carrier}|\mathrm{FH})$

- Breast cancer risk with no competing risk of death.
  $\mathbb{P}(T \leq t|\mathrm{FH}) = 1 - S(t|\mathrm{FH})$ with
  $S(t|\mathrm{FH}) = \sum_{X_i} \mathbb{P}(T > t, X_i|\mathrm{FH}) = \pi(\tau)\frac{S_1(t)}{S_1(\tau)} + (1 - \pi(\tau))\frac{S_0(t)}{S_0(\tau)}$

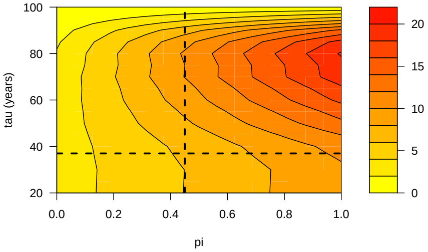
- With competing risk of death.
  $T^* = \min(T_{\text{disease}}, T_{\text{death}})$
  $\lambda_{\text{both}}(t|\mathrm{FH}) = \boldsymbol{\lambda}_{\textbf{disease}}(\boldsymbol{t}|\mathbf{FH}) + \lambda_{\text{death}}(t)$
  $$\begin{aligned}\mathbb{P}(T \leq t|\mathrm{FH}) &= \int_\tau^t S_{\text{both}}(u)\boldsymbol{\lambda}_{\textbf{disease}}(\boldsymbol{u})\boldsymbol{du} \\ &= \int_\tau^t \exp\left(-\int_\tau^u \lambda_{\text{both}}(v)dv\right)\boldsymbol{\lambda}_{\textbf{disease}}(\boldsymbol{u})\boldsymbol{du}\end{aligned}$$

  $\boldsymbol{\lambda}_{\textbf{disease}}(\boldsymbol{t}|\mathbf{FH}) = \pi(t|\mathrm{FH})\lambda_1(t) + (1 - \pi(t|\mathrm{FH}))\lambda_0(t)$
  $\pi(t|\mathrm{FH}) = \frac{\pi(\tau)S_1(t)}{S(t|\mathrm{FH})S_1(\tau)}$

Results : Disease risk



Individual disease risk
with vs without
competing risk of death



Difference in % of disease risk at 100
with vs without
competing risk of death

Perspectives

- Adaptation to Microsatellite Instability (MSI cancer / Lynch syndrome) (A. Duval, Saint-Antoine Hospital)
- Taking into account the sequencing data, the pathology reports, variant data especially to help classify the Variants of Uncertain Significance (VUS).
- Parameters estimations
- Complex distributions (number of carriers in the family) with probability generating functions (polynomials) $\rightarrow$ familial risk
- Multi-state and frailty survival models

Claus, E. B., Risch, N., and Thompson, W. D. (1991).
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Thank you for your attention