Computing competing risks based on family history in genetic diseases with variable age at onset

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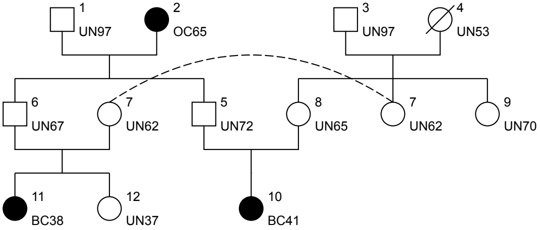
Introduction : Context

- The breast cancer
  - 1st cancer in women. 55,000 women in the UK each year
  - Complex disease due to an accumulation of mutations (ie. : BRCA 1/2 and/or PALB2 and/or RAD51 and/or, etc.)
  - 10 to 15% cases : inherited mutation.
- The genetic counseling



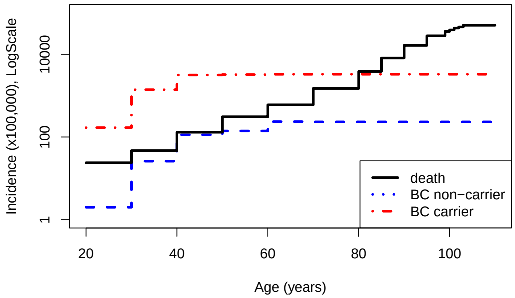
Genetic testing
$\mathbb{P}(\text{genetic predisposition} \mid \mathrm{FH})$
Individual risk of the disease $\mid \mathrm{FH}$
$\Big\}$ → recommendations

Introduction : existing models

- Empirical : The GAIL model (logistic regression)
- Mendelian : Claus-Easton, BRCAPro, BOADICEA, etc.

The Claus-Easton model [Claus et al., 1991, Easton et al., 1993]

- Autosomal, biallelic, dominant, estimated allele frequency f=0.33%
- The hazard functions per genotype (piecewise constant) :



Objectives : Impl. sum/product algorithm + competing risk of death

The model : the likelihood and the genotypes

$$\mathbb{P}(X, \mathrm{FH}) = \underbrace{\prod_i \mathbb{P}\left(X_i | X_{\mathrm{pat}_i}, X_{\mathrm{mat}_i}\right)}_{\text{genotypes}} \times \underbrace{\prod_i \mathbb{P}\left(\mathrm{PH}_i | X_i\right)}_{\text{phenotypes}}, \quad \mathrm{FH} = \{\mathrm{PH}_i\}_i$$

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

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

The model : the phenotypes

With T_i, the age at disease onset for individual i

Survival data : $\mathrm{PH}_i = \begin{cases} \{T_i > \tau_i\} & \text{if } i \text{ is censored at age } \tau_i \\ \{T_i = \tau_i\} & \text{if } i \text{ is affected at age } \tau_i \end{cases}$

Dominant model of disease :

$$\lambda(t|X_i) = \begin{cases} \lambda_0(t) & \text{if } X = 00 \\ \lambda_1(t) & \text{if } X \neq 00 \text{ i.e. } \in \{10, 01, 11\} \end{cases}$$

- For a censored individual at age τ_i

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

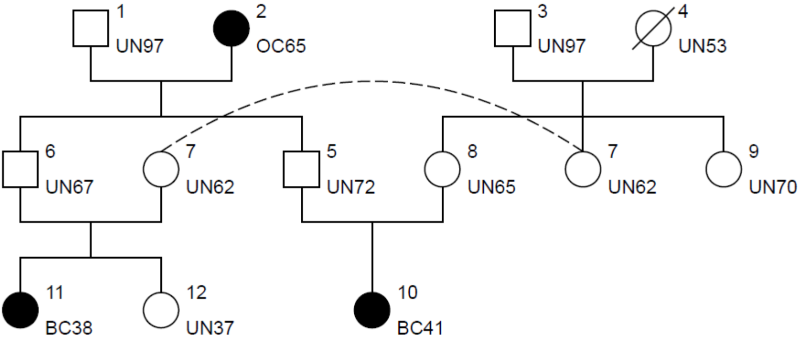
- For an affected individual at age τ_i

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

Model: The bayesian network[1] ; sum-product algorithm

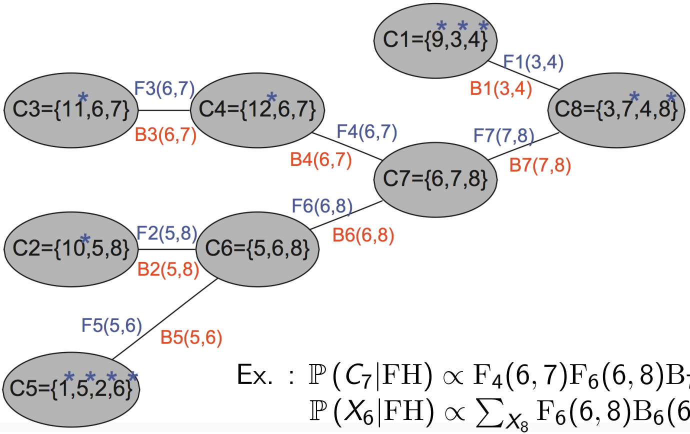
$$\mathbb{P}(X, \mathrm{FH}) = \prod_i \underbrace{\mathbb{P}\left(X_i | X_{\mathrm{pat}_i}, X_{\mathrm{mat}_i}\right) \mathbb{P}\left(\mathrm{FH}_i | X_i\right)}_{\mathrm{K}_i(X_i | X_{\mathrm{pat}_i}, X_{\mathrm{mat}_i})} \rightarrow \mathbb{P}(\mathrm{FH}) = \sum_X \prod_i \mathrm{K}_i(X_i | X_{\mathrm{pat}_i}, X_{\mathrm{mat}_i})$$

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



[1] [Koller and Friedman, 2009]

Belief propagation



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

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

Bayesian network

Complexity $\mathcal{O}(4^n) \to \mathcal{O}(n \times 4^k)$, k:tree-width (ex: k=3 if no loop)

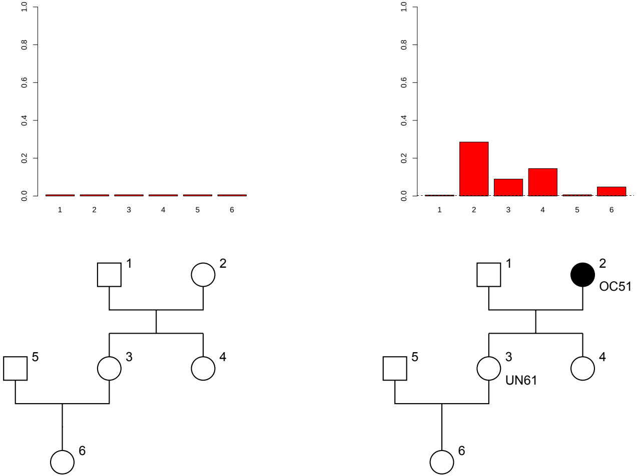
F & B computed once for any later marginal or joint distribution needed

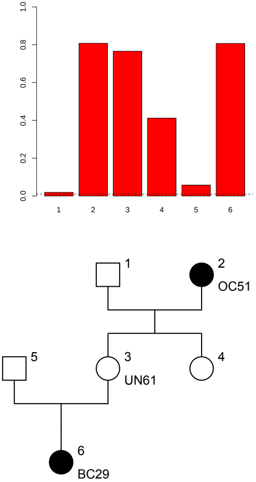
Model : Disease risk prediction for an unaffected individual

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

- Breast cancer specific, no competing risk
  $S(t|\mathrm{FH}) = \sum_{X_i} \mathbb{P}(T > t, X_i|\mathrm{FH}) = \pi(\tau)\frac{S_1(t)}{S_1(\tau)} + (1-\pi(\tau))\frac{S_0(t)}{S_0(\tau)}$
  $\pi(t|\mathrm{FH}) = \dfrac{\pi(\tau)S_1(t)}{S(t|\mathrm{FH})S_1(\tau)}$
  $\boldsymbol{\lambda_{disease}(t|\mathrm{FH})} = \pi(t|\mathrm{FH})\lambda_1(t) + (1-\pi(t|\mathrm{FH}))\lambda_0(t)$
- With competing risk of death : $T^* = \min(T_{\text{disease}}, T_{\text{death}})$
  $\lambda_{\text{both}}(t|\mathrm{FH}) = \boldsymbol{\lambda_{disease}(t|\mathrm{FH})} + \lambda_{\text{death}}(t)$: hazard function of T^*
  $$\begin{aligned}\mathbb{P}(T \le t|\mathrm{FH}) &= \int_\tau^t S_{\text{both}}(u)\lambda_{\text{disease}}(u)du \\ &= \int_\tau^t \exp\left(-\int_\tau^u \lambda_{\text{both}}(v)dv\right)\lambda_{\text{disease}}(u)du\end{aligned}$$
  $\rightarrow$ discretized λ $\rightarrow$ closed form formulas for pch

Results : Carrier risk, posterior marginal carrier distribution




0.0
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OC51
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UN61
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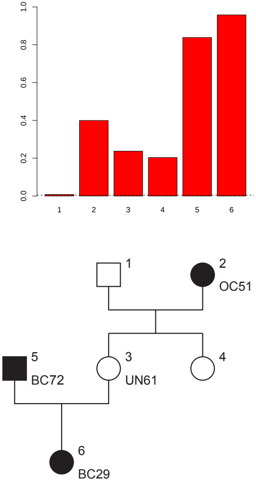
BC29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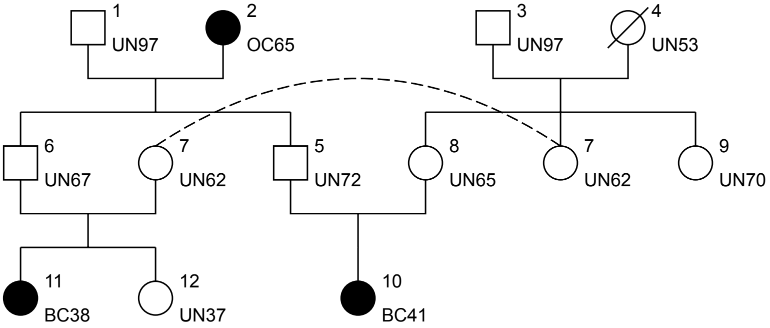
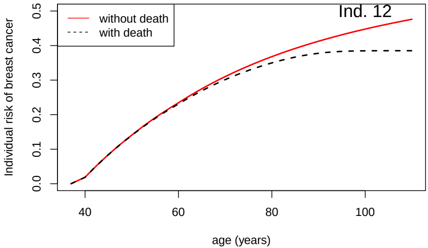
BC29

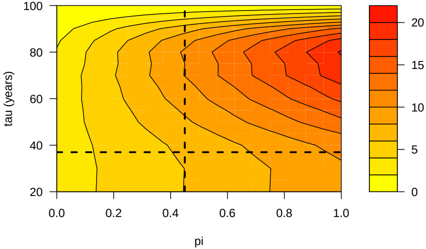
Results, Disease risk, With competing death



Results, Disease risk, With competing death



Ind. risk with vs without competing risk of death



Difference in % of S(100) with vs without competing risk

Conclusion

- The model
  - Adaptable (any genetic disease and model of disease)
  - Fast (bayesian network - sum-product algorithm - belief propagation)
  - Takes into account the competing risk of death

- What's next?
  - Parameters estimations
  - Complex distributions (number of carriers in the family) with generating functions of probabilities (polynomials) $\rightarrow$ familial risk
  - Multi-state and frailty models

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Thank you for your attention