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

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Abstract

Detecting familial predisposition to certain diseases (e.g. cancer, diabetes, neurogenerative diseases) is a major challenge in personalized medicine. For such purpose, combining molecular data (e.g. targeted gene sequencing, functional caracterisation of variants, etc.) with personal and familial history of disease is the standard approach. Such investigations highly rely on models combining survival, genetic transmission and genomic data. We specifically focus here on these models and the statistical and computational challenges they arise. When considering a genetic disease with variable age at onset, computing the individual risk of the disease based on family history (FH) is of critical interest both for clinicians and patients. Such a risk is very challenging to compute because: 1) the genotype X of the individual of interest is in general unknown; 2) the posterior distribution P(X — FH,T> t) changes with t (T age at disease onset for the targeted individual); 3) the competing risk of death is not negligible.

In this work, we present a modelization of this problem using a Bayesian network mixed with (right-censored) survival outcomes where hazard rates only depend on the genotype of each individual. We explain how belief propagation can be used to obtain posterior distribution of genotypes given the FH, and how to obtain a time-dependent posterior hazard rate for any individual in the pedigree. Finally, we use this posterior hazard rate to compute individual risk, with or without the competing risk of death.

Our method is illustrated using the Claus-Easton model for breast cancer (BC). This model assumes a autosomal dominant genetic risk factors such as non-carriers (genotype 00) have a BC hazard rate h0(t) while carriers (genotypes 01,10 and 11) have a (much greater) hazard rate h1(t). Both hazard rates are assumed to be piecewise constant with known values (cuts at 20,30,...,80 years). The competing risk of death is derived from the national French registry.

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