Univariate Frailty Models

Theodor Balan & Hein Putter

Department of Medical Statistics and Bioinformatics
Leiden University Medical Center

Frailty Models: Theory & Practice
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Definitions

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We assume that censoring is non-informative on the frailty (i.e. censoring does not involve Z).

Useful formulas

The *conditional* survival

$$S_i(t|Z_i) = \exp(-Z_i H_i(t))$$

where $H_i(t) = \int_0^t \exp(\beta^\top x_i) h_0(s) ds$.

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$$\bar{S}_i(t) = \mathrm{E}_{Z_i}[\exp(-Z_i H_i(t))]$$

This is the Laplace transform of Z_i calculated in $H_i(t)$:

$$\mathcal{L}_Z(c) = \mathrm{E}_Z[\exp(-Zc)]$$

Laplace transforms

The Laplace transform

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is another way of expressiong a positive distribution of a random variable.

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Useful formulas

If the marginal survival is

$$\bar{S}(t) = \mathcal{L}_Z\left(H_i(t)\right)$$

then recall that $-\log S(t) = H(t)$ and $d/dt[-\log S(t)] = h(t)$, so the marginal hazard is

$$\bar{h}_i(t) = \frac{\mathcal{L}'_Z(H_i(t))}{\mathcal{L}_Z(H_i(t))} \exp(\beta^\top x_i) h_0(t)$$

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or, in other words:

$$\bar{h}_i(t) = E[Z_i | T \geq t] \exp(\beta^\top x_i) h_0(t)$$

Distributions

General idea

- Technically any positive distribution can be used for Z
- It is common to scale the distribution somehow, usually by fixing $E[Z]$ to 1 and have one parameter that controls the spread of Z
- In practice, there are some desirable properties such as a closed-form Laplace transform

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Infinitely divisible distributions

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Distributions

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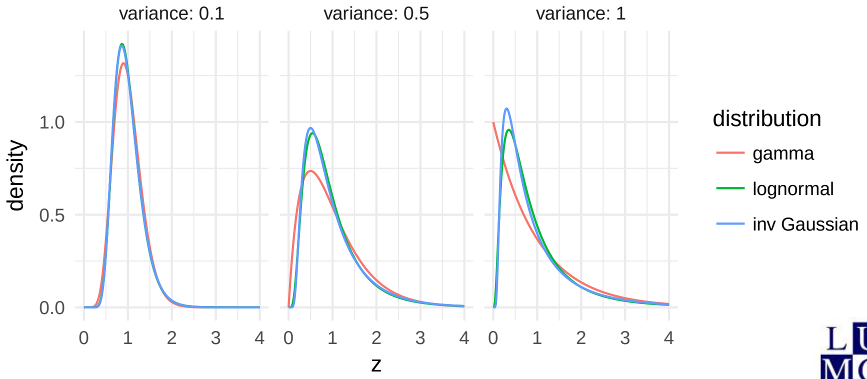
- This includes the gamma, inverse Gaussian, positive stable, compound Poisson and the Power-Variance-Function (PVF) family of distributions
- All calculations such as marginal hazards, frailty distribution of survivors, can be expressed as functions of $\mathcal{L}$ and derivatives of $\mathcal{L}$[1]

[1] Hougaard (2000), Balan & Putter (2017)

Common distributions

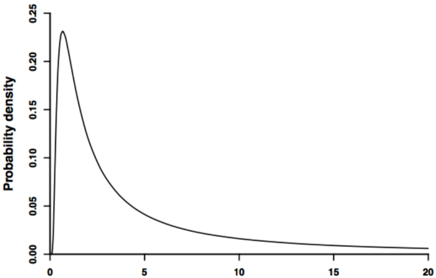
Densities for the gamma, lognormal and inverse Gaussian with $E[Z] = 1$ and matched variance



Less common distributions

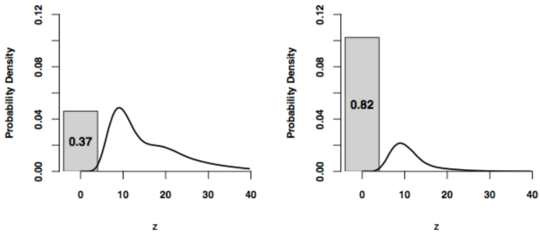
The positive stable distribution has the simplest Laplace transform, $\mathcal{L}(c) = \exp(-c^{\gamma})$), but:

- the expectation is undefined
- the variance is infinite
  - we will refer wrongly to the *variance* in some of the slides, although that will not be rigorous



Less common distributions

The compound Poisson disributions have mass at 0 and are useful when a part of the sample is not susceptible for events[2]:



[2] Figures from Aalen, Borgan & Gjessing (2007)

The odd effects of frailty

Frailty distribution of survivors

- Hein has shown that the individuals that are at a higher risk leave the data set faster, so that at a later time point the low-risk individuals are left
- The same thing happens when the risk is unobserved (i.e. frailty is present)
- For the gamma distribution, everything can be expressed in closed form.

The gamma distribution with shape α and rate γ has the density

$$f(z) = \frac{\gamma^\alpha}{\Gamma(\alpha)} z^{\alpha-1} e^{-\gamma z}$$

Frailty distribution of survivors

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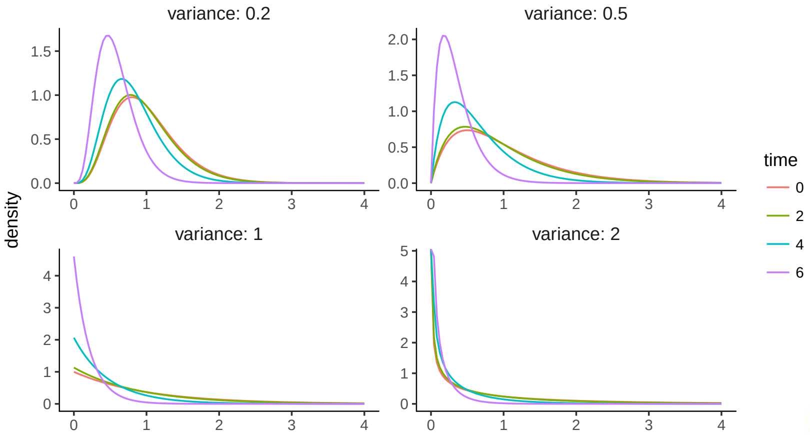
What is the frailty distribution of an individual that survived up to time t? From Bayes' theorem:

$$\begin{aligned} f(z|T \geq t) &= \frac{P(T \geq t|Z = z) f(z)}{P(T \geq t)} \\ &\propto S(t|Z = z) f(z) \\ &= \exp(-zH_i(t)) f(z) \\ &\propto \frac{\gamma^\alpha}{\Gamma(\alpha)} z^{\alpha-1} e^{-(\gamma + H_i(t))z} \end{aligned}$$

Frailty of survivors

Frailty of survivors, gamma frailty, $h(t) = t^2/20$.



Marginal hazard

If the individual hazard is $h_i(t|Z_i) = Z_i h_i(t)$ then the marginal (observed) hazard is $\bar{h}_i(t) = E[Z_i|T \geq t]h_i(t)$.

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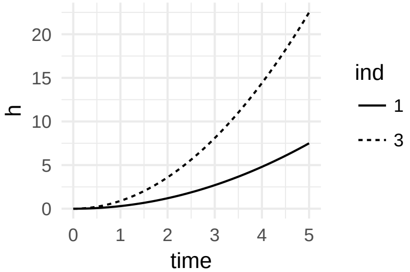
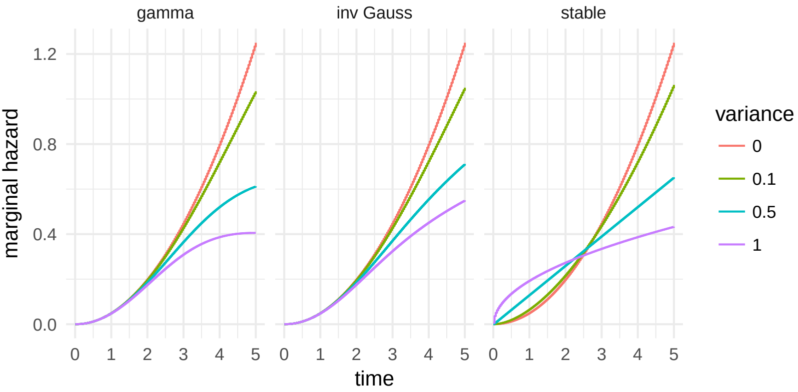
Illustration

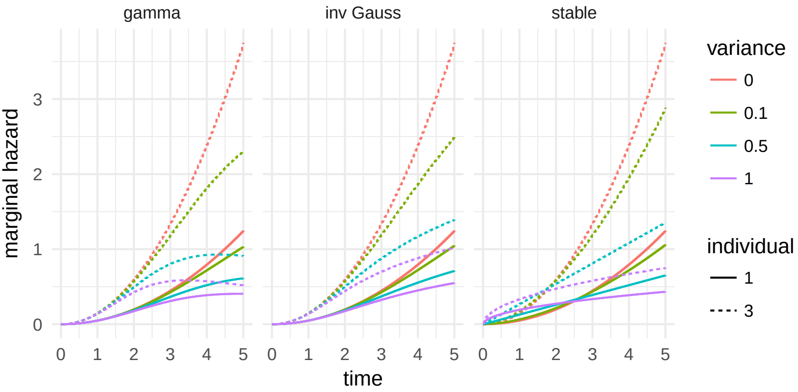
Take two individuals: a low risk with $h_0(t) = t^2/10$ and a high risk with $h_1(t) = 3h_0(t)$:



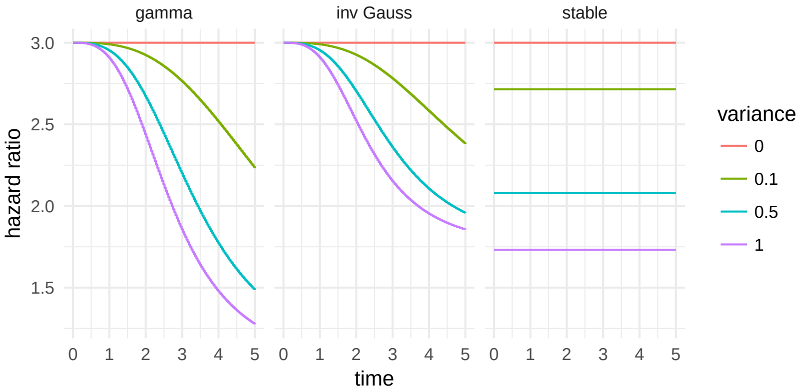
Marginal hazard under frailty



Marginal hazard for two individuals



Marginal hazard ratio of two individuals



Implications

- In general, the frailty has the effect of "dragging down" the hazard, and the hazard ratio is shrunk towards 1
- Can a crossover happen? (the conditional hazard ratio > 1, marginal hazard ratio < 1) Yes, if the frailty has mass at 0, or if the conditional hazard ratio is decreasing.

Implications

- In general, the frailty has the effect of “dragging down” the hazard, and the hazard ratio is shrunk towards 1
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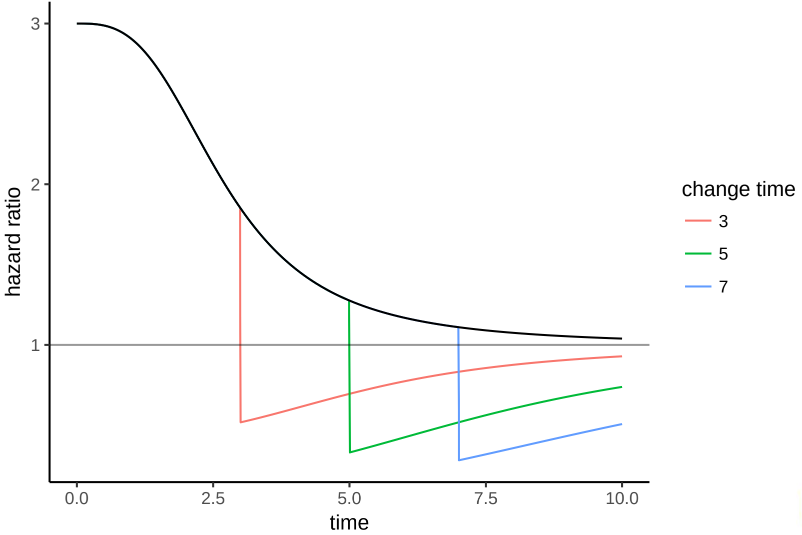
One thing

- Say we have two groups: a low risk one (baseline) with $h_0(t|Z) = Zt^2/20$ and a high risk one with $h_1(t|Z) = 3h_0(t|Z)$.
- We know that $h_1(t)/h_0(t) < 3$ and will be decreasing in time
- What if a high risk individual suddenly switches to the low risk group?

Changing groups



What does this mean?

- Example was simplistic: group switching is unlikely to have an immediate effect
- Still, the marginal hazards don't tell the whole story: it's hard to tell why we observe what we do in a population
- Especially difficult when unobserved heterogeneity is mixed with time-dependent covariates or non-proportional hazards

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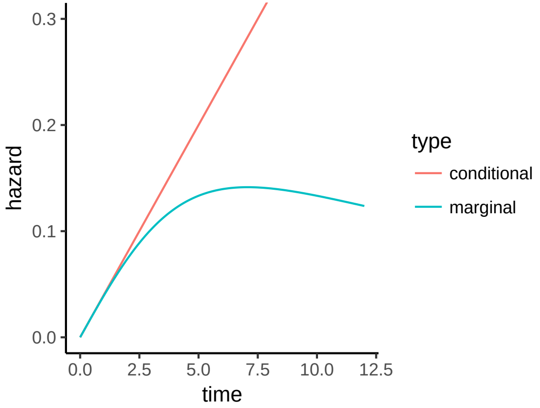
- Elbers & Ridder (1982): The frailty model with covariates is identifiable if proportional hazards are assumed and the frailty has finite expectation. Implication: in practice frailty effects can't be distinguished from marginal non-proportional hazards

7 year itch

Remember the 7 year itch? We can get a similar picture with $h(t|Z) = 0.04t$ and Z gamma frailty with variance 1:



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