Frailty Models: Theory & Practice

Univariate Frailty Models

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Definitions

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With a $p \times 1$ covariate vector x_i and frailty Z_i, the hazard is given by

$$h_i(t|Z_i) = Z_i h_0(t) \exp(\beta^\top x_i)$$

where $h_0(t)$ is the *baseline hazard*, β a $p \times 1$ vector of regression coefficients.

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Because it is conditional on Z_i, $h_i(t|Z_i)$ is called the **conditional hazard**.

Definitions

In an equivalent formulation,

$$h_i(t|Z_i) = h_0(t)\exp(\beta^\top x_i + \log Z_i)$$

$\log Z_i$ is interpreted as the effect of unobserved covariates in a proportional hazards model (or *unobserved heterogeneity*).

Also...

- we assume that censoring is non-informative on the frailty (i.e. censoring does not involve Z)
- $Z > 0$ follows a distribution with density $f(z)$, but we have to scale it somehow (so it does not get absorbed into h_0)

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And the interesting question...

- What are the **marginal** covariate effects and survival (i.e. unconditional on Z) from a frailty model?

The gamma frailty

The gamma distribution

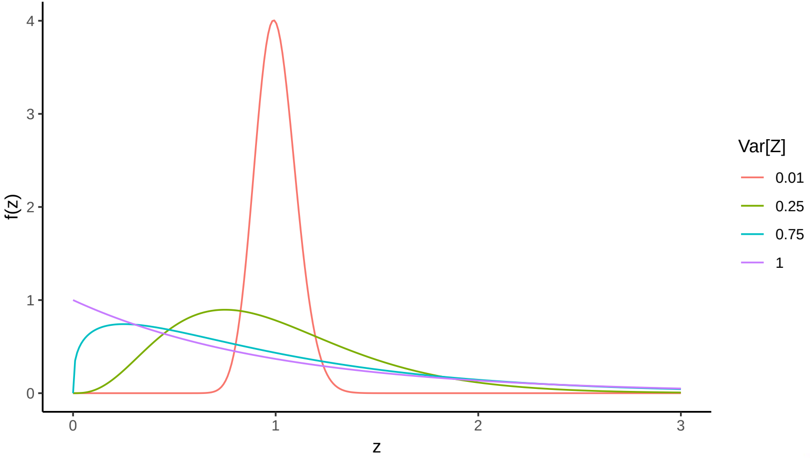
- Traditionally, the gamma distribution was the first one to be proposed in the context of frailty models (Vaupel et al, 1979)
- The gamma distribution with shape α and rate γ has density

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

- We scale it so that $E[Z] = 1$, with $\alpha = \gamma = \theta$. This implies that $Var[Z] = \theta^{-1}$ and

$$f(z) = \frac{\theta^\theta}{\Gamma(\theta)} z^{\theta-1} \exp(-\theta z)$$

The gamma distribution



The marginal hazard

We specified the **conditional** hazard as

$$h_i(t|Z_i) = Z_i \, h_0(t) \, \exp(\beta^\top x_i)$$

The **marginal** (or observed) hazard of an individual with given covariate vector $\mathbf{x}_i$ is then given by

$$h_i(t) = E[Z_i | T \geq t] \, h_0(t) \, \exp(\beta^\top x_i)$$

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$Z|T \geq t$ is the frailty distribution of the survivors at time t.

Updating the frailty distribution

- What is the frailty distribution of an individual that survived up to time t? $(Z|T \geq t)$?
- Denote $H_i(t) = \int_0^t h_0(s) \exp(\beta^\top x_i) ds$

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 z^{\alpha-1} e^{-(\gamma + H_i(t))z}
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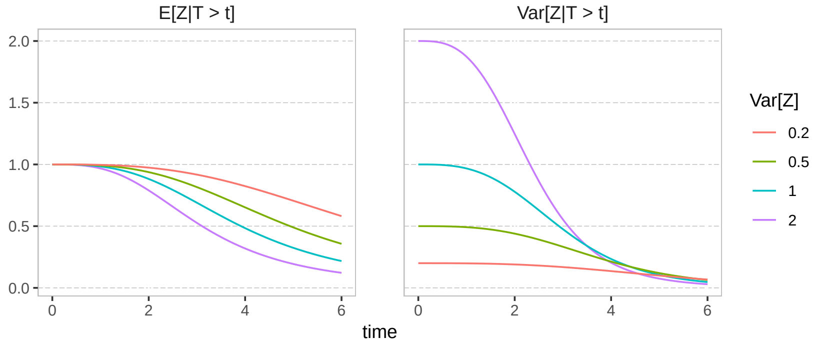
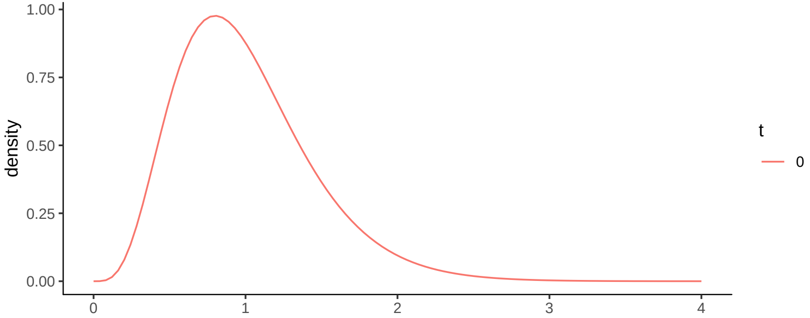
A gamma distribution where $\gamma \to \gamma + H(t)$

Updating the frailty distribution



We chose $h(t) = t^2/20$ and $E[Z] = 1$.

Density of $Z|T \geq t$



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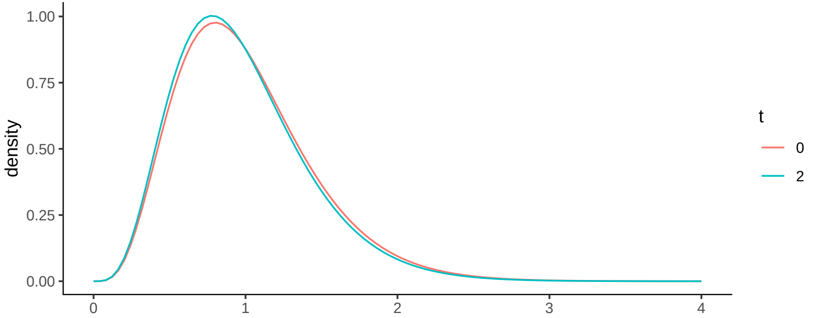
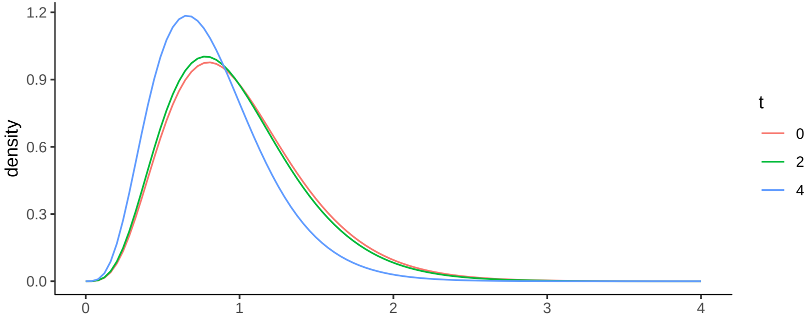
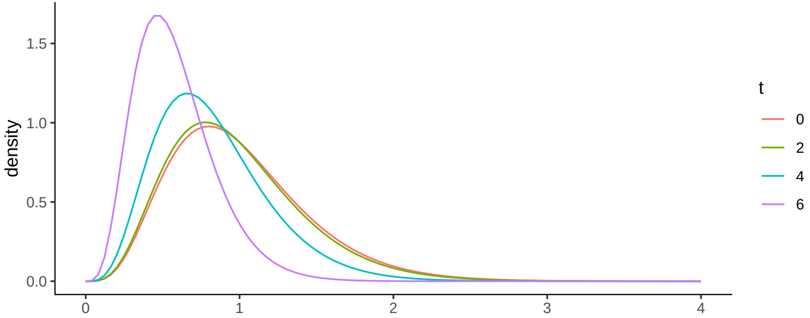


Density of $Z | T \geq t$



Density of $Z|T \geq t$



Message

- The individuals that survive until time t have, on average, lower frailty value and are more homogeneous than the whole sample.
- The population hazard (unconditional on the frailty) may look like a "dragged down" version of the conditional hazard for an individual with frailty 1
- Implication: the population hazard is usually lower than the hazard of an average individual!

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- Implication: the population hazard is usually lower than the hazard of an average individual!

The same ideas carry over to other frailty distributions! (although the formulas get more complicated)

Other distributions

Laplace transforms

The Laplace transform

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

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Properties

$$\mathcal{L}'_Z(c) = -\mathrm{E}_Z[Z\exp(-cZ)] \implies \mathcal{L}'_Z(0) = -\mathrm{E}Z$$

$$\mathcal{L}''_Z(0) = \mathrm{E}_Z[Z^2\exp(-cZ)] \implies \mathcal{L}''_Z(0) = EZ^2$$

The Laplace transform

For example, the survival is defined as

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

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

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

The population survival (for given covariates x_i) is then:

$$S_i(t) = \mathrm{E}_{Z_i}[\exp(-Z_i H_i(t))] = \mathcal{L}(H_i(t))$$

The Laplace transform

The Laplace transform of the frailty distribution of the survivors at time t is then easily obtained from Bayes' theorem:

$$\mathcal{L}_{Z|T\geq t}(c) = \frac{P(T \geq t|Z = z)\mathcal{L}_Z(c)}{P(T \geq t)} = \frac{\mathcal{L}(c + H_i(t))}{\mathcal{L}(H_i(t))}$$

Then the expectation and variance of this distribution can be easily calculated!

Laplace transform

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

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

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For a fixed vector of covariates, the posterior estimates of the frailty at time t $\mathbf{x}_i$, $\mathrm{E}[Z_i|T > t]$, are given by

$$\mathrm{E}[Z_i|T > t] = \frac{\mathcal{L}'_Z(H_i(t))}{\mathcal{L}_Z(H_i(t))}.$$

Distributions

Infinitely divisible distributions

- The Laplace transform of an infinitely divisible distribution is

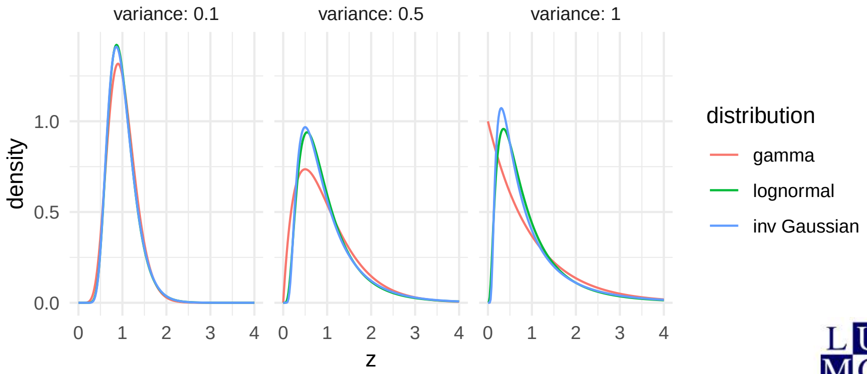
$$\mathcal{L}(c) = \exp\left(-\alpha\psi(c;\gamma)\right)$$

- 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 (2018)

Common distributions

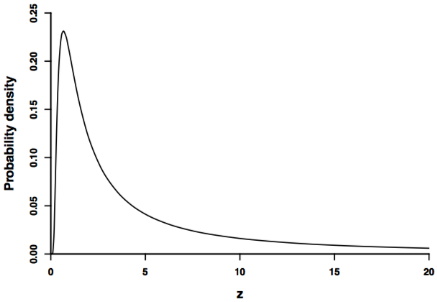
Densities for the gamma, lognormal and inverse Gaussian with $E[Z] = 1$ and matched variance



Less common distributions

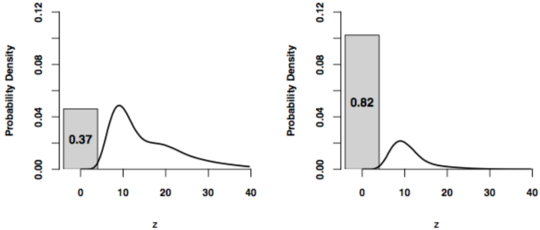
The positive stable distribution has the simplest Laplace transform, $\mathcal{L}(c) = \exp(-c^\gamma))$, but:

- the expectation is undefined
- the variance is infinite



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]:

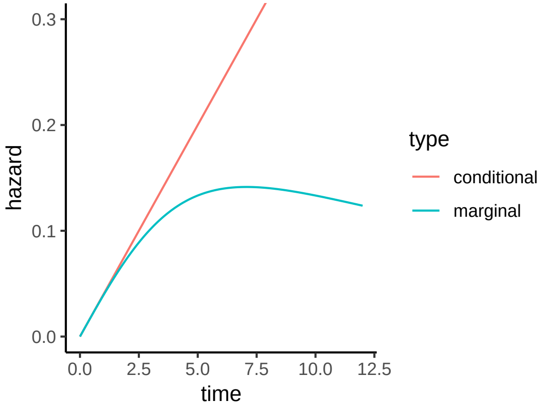


[2] Figures from Aalen, Borgan & Gjessing (2007)

Univariate frailty models in practice

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.

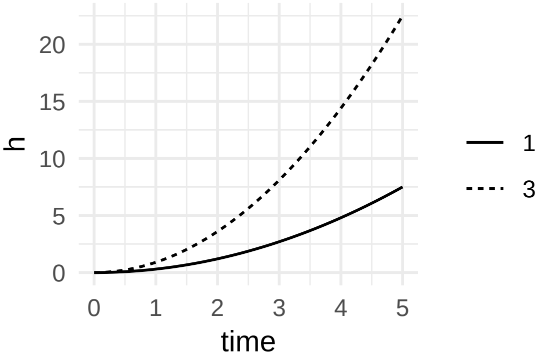


Question

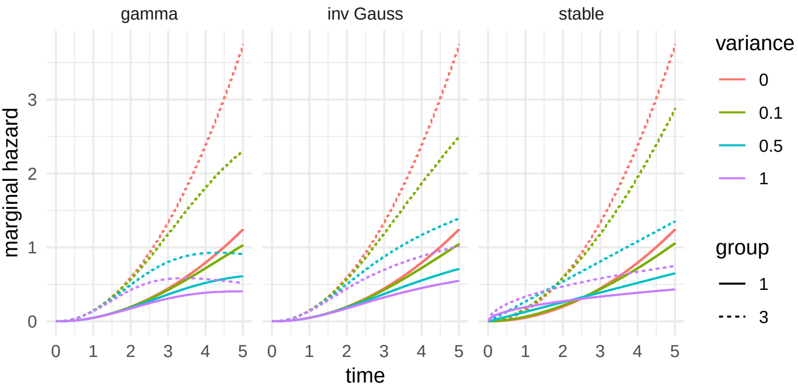
In practice we only observe the *marginal* hazard. Do you think that we can tell if there is a frailty effect from that alone?

Illustration

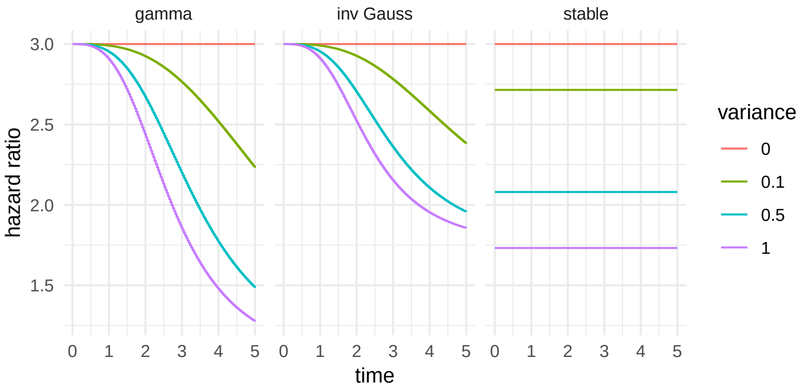
Take two groups of individuals: a low risk with $h_0(t) = t^2/10$ and a high risk with $h_1(t) = 3h_0(t)$:



The marginal hazards for the two groups



Marginal hazard ratio



Implications

- In general, the frailty has the effect of "dragging down" the hazard, and the hazard ratio is shrunk towards 1
- The hazard ratio between the two groups is also 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.

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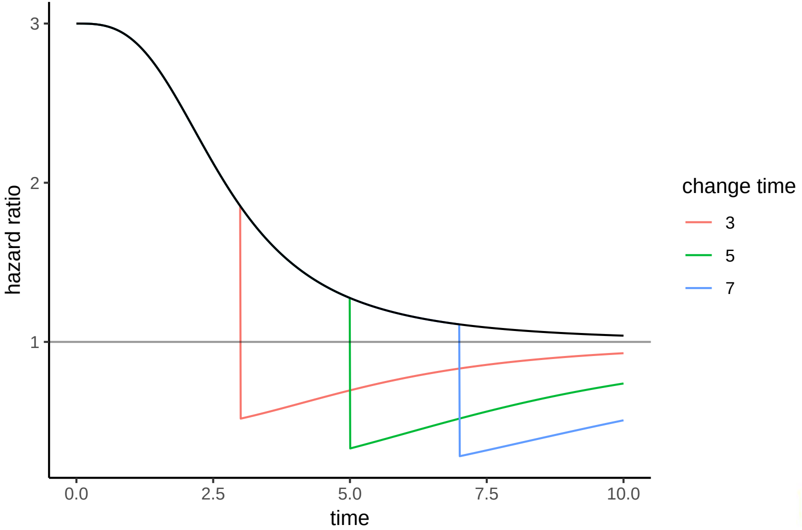
- Can a crossover happen? (the conditional hazard ratio > 1, marginal hazard ratio < 1) Yes, if the frailty has mass at 0, or if the conditional hazard ratio is decreasing.

One thing

- What would happen 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

Conclusions (1)

Is the frailty model *plausible*?

- Testicular cancer incidence reaches a peak at around 30 years, then decreases sharply.
- This may be because high-risk individuals leave the data set early, while individual risk is increasing throughout life (Aalen, Tretli, 1999)
- Idea is that testicular cancer is caused by cellular damage during early life

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Conclusions

- It is usually impossible to distinguish between proportional hazards and frailty, on one hand, and non-proportional hazards, on the other hand (unless we make other untestable assumptions)
- The frailty distribution that "fits best" is the one for which the marginal hazards fit best with the observed hazards
- Limited applications; estimation and more in part 2.

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References

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