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Mixed effects survival models

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Outline

Introduction

About me

Currently a 2nd year PhD student within the Biostatistics Research Group, Department of Health Sciences, University of Leicester, UK. My PhD project covers:

- Mixed effects survival models
- Joint models for longitudinal and survival data
- Use of joint models with healthcare "big data"

Supervisors: Dr. Michael Crowther, Prof. Keith Abrams

Previously:

1. BSc in Statistics and Computing Technologies, Università degli Studi di Padova, Italy (October 2012)
2. MSc in Biostatistics and Experimental Statistics, Università degli Studi di Milano-Bicocca, Italy (March 2015)
3. Karolinska Institutet, Stockholm, Sweden (August 2014 - October 2016)

Milano-Bicocca & Karolinska Institutet

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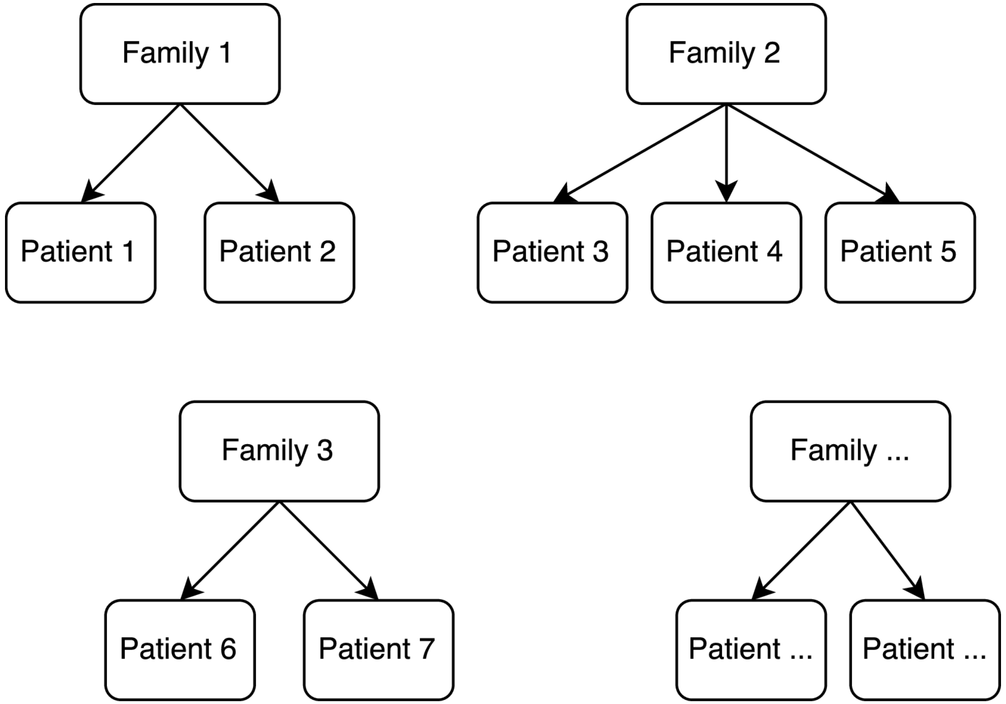
Motivating examples

Survival data is commonly analysed by using parametric survival models or the Cox model.

But:

1. Subjects may be exposed to different baseline risk levels
2. Subjects may be clustered (clinical trials, geographical clusters, paired organs, twin studies, ...)
3. Subjects may experience repeated events (infections, cancer recurrence, ...)

Example of clustered survival data:



Notation

- i indexes the individuals, and j indexes the clusters
- T is the true survival time, C is the censoring time, and $Y = \min(T, C)$ is the observed survival time
- $d = I(T \leq C)$ is the event indicator variable: equals to 1 when the event of interest is observed, 0 otherwise

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- $d = I(T \leq C)$ is the event indicator variable: equals to 1 when the event of interest is observed, 0 otherwise
- Survival function: $S(t) = 1 - F_T(t) = 1 - P(T \leq t) = P(T > t)$
- Hazard function: $h(t) = \lim_{\Delta_t \to 0} \frac{P(t \leq T \leq t + \Delta_t | T \geq t)}{\Delta_t}$
- $S(t) = \exp\left[- \int_0^t h(u)\, du\right]$
- Cumulative hazard function: $H(t) = \int_0^t h(u)\, du = -\log S(t)$

Survival models

The most popular survival model is the Cox model (Cox, 1972):

$$h(t) = h_0(t) \exp(X\beta)$$

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Alternatively, specify a form for $h_0(t)$:

1. Fully parametric distributions: exponential, Weibull, Gompertz, ...

2. Flexible spline-based formulations (Royston and Parmar, 2002; Liu *et al.*, 2016)

Specifying $h_0(t)$ has advantages in terms of predictions and extrapolation.

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Survival models with frailties

Univariate frailty survival models

Say we have survival data with heterogeneity. Heterogeneity is modelled by including a random effect in the model, named *frailty*:

$$h(t|u) = uh_0(t)$$

The model is conditional on the non-observed frailty effect u.

Introducing covariates and inducing proportional hazards:

$$h(t_i|X_i, u) = uh_0(t_i)\exp(X_i\beta)$$

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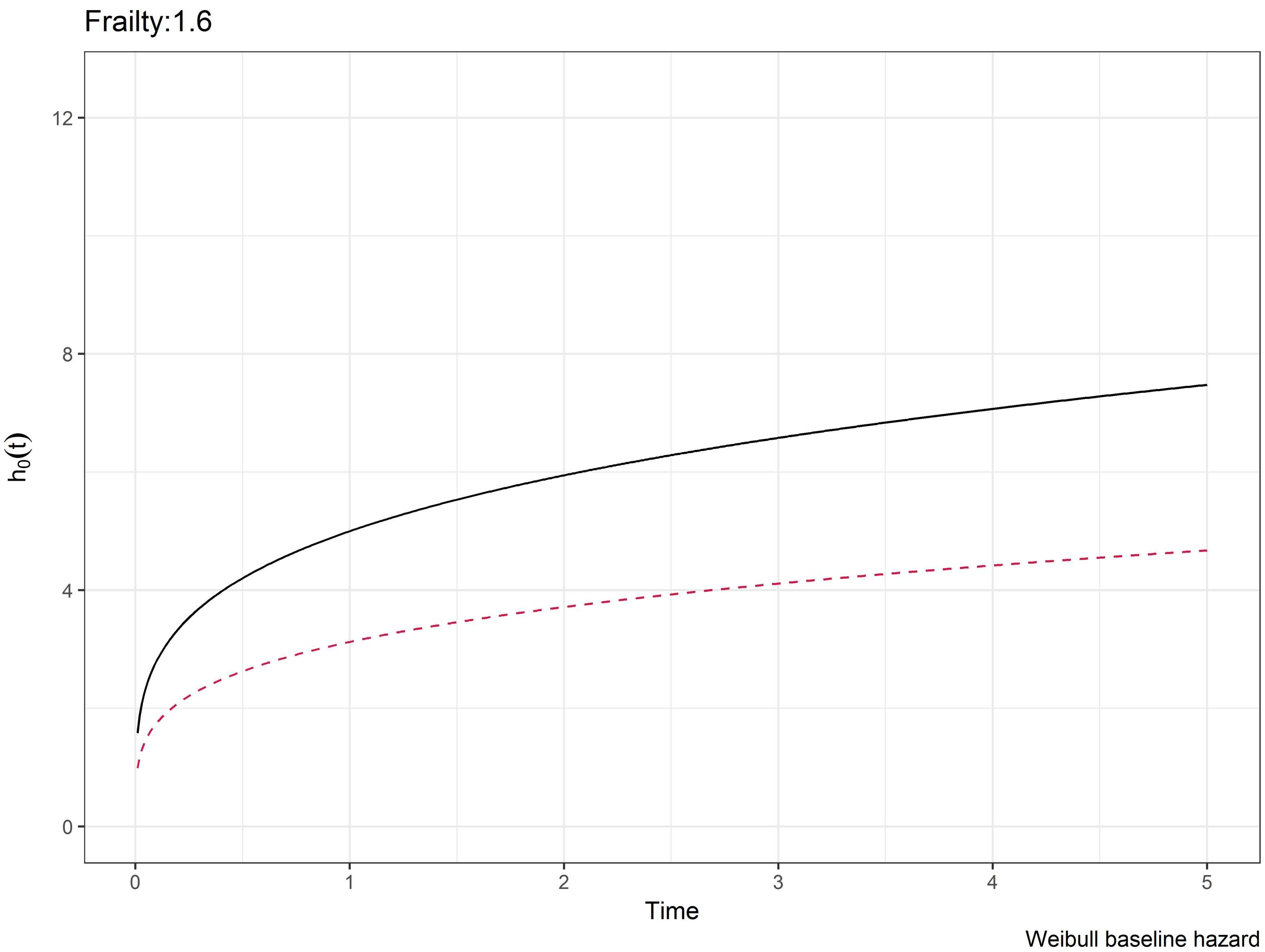
- Individuals with $u > 1$ are *more frail* for reasons left unexplained by the covariates included in the model and will have an increased hazard
- Individuals with $u < 1$ are *less frail* and will survive longer (all else being equal)

Impact of frailty



Shared frailty models

It is possible for the frailty effect u to be shared between clusters of study subjects:

$$h_{ij}(t|u_j) = u_j h(t|X_{ij})$$

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The corresponding marginal (i.e. population-level) survival function is:

$$S_{ij}(t) = \int_U S_{ij}(t)^{u_j} f(u) \, du,$$

with $f(u)$ the distribution of the frailty.

Likelihood

The cluster-specific contribution to the likelihood is obtained by calculating the cluster-specific likelihood conditional on the frailty, consequently integrating out the frailty itself:

$$L_j = \int_U L_j(u_j) f(u) \, du$$

with $f(u)$ the distribution of the frailty, U its domain, and $L_j(u_j)$ the cluster-specific contribution to the likelihood, conditional on the frailty:

$$L_j(u_j) = u_j^D \prod_{i=1}^{n_j} S_{ij}(t)^{u_j} h_{ij}(t)^{d_{ij}},$$

with $D = \sum_{i=1}^{n_j} d_{ij}$

More details in Gutierrez (2002).

Frailty distribution (1)

u is chosen to have a distribution $f(u)$ with expectation $E(u) = 1$ and finite variance $V(u) = \sigma^2$.

$V(u)$ is interpretable as a measure of heterogeneity across the population in baseline risk: as σ^2 increases the values of u are more dispersed, with greater heterogeneity in $uh_0(t)$.

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Assuming that the frailty u has a Gamma distribution with shape parameter a and scale parameter b:

$$f(u) = \frac{u^{a-1} \exp(-u/b)}{\Gamma(a) b^a}$$

Choosing $a = 1/\theta$ and $b = \theta$ the resulting distribution has expectation 1 and finite variance θ. In these settings, the model is analytically tractable:

$$\begin{aligned} S(t) &= \int_0^{+\infty} S(t)^u f(u) \, du \\ &= \left[1 - \theta \log(S(t))\right]^{-1/\theta} \end{aligned}$$

Frailty distribution (2)

Together with the Gamma distribution, the log-normal distribution is the most commonly used frailty distribution.

The the resulting model has a frailty whose expectation is finite, but it cannot be integrated out of the survival function analytically to obtain the population survival function or the likelihood. Numerical methods to approximate the integral are then required (more on that later).

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Other possible distributions for the frailty distribution include: inverse Gaussian, inverse Gamma, positive stable distribution (Hougaard, 1984).

Mixed effects survival models

Mixed effects survival models

Extending proportional hazards survival models to accommodate mixed effects, using the mixed effects modelling framework (Diggle, 2013; Crowther, 2014):

$$h_{ij}(t) = h_0(t) \exp(X_{ij}\beta + Z_j b_j)$$

Mixed effects survival models

Extending proportional hazards survival models to accommodate mixed effects, using the mixed effects modelling framework (Diggle, 2013; Crowther, 2014):

$$h_{ij}(t) = h_0(t) \exp(X_{ij}\beta + Z_j b_j)$$

- β is an unknown vector of fixed effects
- b is an unknown vector of random effects, with mean $E(b) = 0$ and variance-covariance matrix $\text{var}(b) = G$
- $b \sim N(0, G)$
- X and Z are design matrices for fixed and random effects, respectively

Frailty models vs mixed effects models

If $Z = 1$, then we have a random intercept model:

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Frailty models vs mixed effects models

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Frailty models vs mixed effects models

If $Z = 1$, then we have a random intercept model:

$$h_{ij}(t) = h_0(t)\exp(X_{ij}\beta + b_j)$$

$$u_j = \exp(b_j)$$

Then we can write the random intercept model as:

$$\begin{aligned} h_{ij}(t) &= h_0(t)\exp(X_{ij}\beta)\exp(b_j) \\ &= h_0(t)\exp(X_{ij}\beta)u_j \end{aligned}$$

This is a shared frailty model with a log-normal frailty distribution!

Computational challenges

The cluster-specific likelihood of a mixed effects survival model has the form:

$$L_j = \int_{-\infty}^{+\infty} \left[\prod_{i=1}^{n_j} p(t_{ij}, d_{ij} | b_j) \right] \; p(b_j) \; db_j \qquad (*)$$

where

$$p(t_{ij}, d_{ij} | b_j) = h(t_{ij} | b_j)^{d_{ij}} \exp\left[- \int_0^{t_{ij}} h(t_{ij} | b_j) \right]$$

and

$$p(b_j) \sim N(0, G)$$

Equation ***** has no analytical form, and requires numerical integration to solve.

Numerical integration

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Say we have a definite integral that we want to approximate to a given degree of accuracy:

$$\int_a^b f(x)\,dx$$

A method commonly used is *Gaussian quadrature*, that is, an approximation of the definite integral of a function stated as a weighted sum of function values at specified points within the domain of integration:

$$\int_{-1}^{+1} f(x)\,dx = \int_{-1}^{+1} w(x)g(x)\,dx \approx \sum_{i=1}^{k} w_i g(z_i)$$

I will focus on *Gauss-Hermite* quadrature, which is used to approximate integrals over the infinite domain.

Gauss-Hermite quadrature

Say we have an integral over the infinite domain:

$$\int_{-\infty}^{+\infty} f(x)\, dx$$

For instance, recall equation *****:

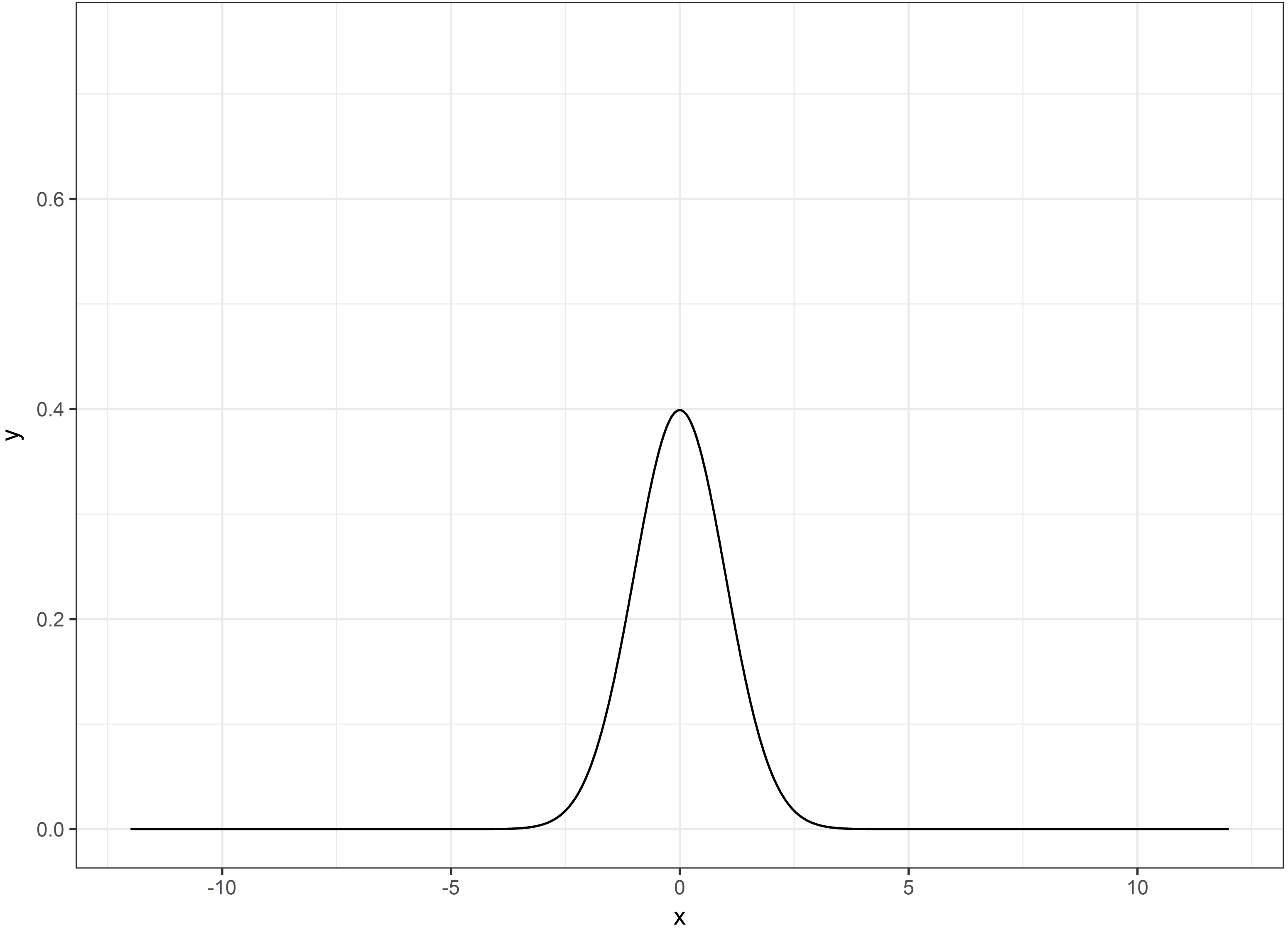
$$L_j = \int_{-\infty}^{+\infty} \left[\prod_{i=1}^{n_j} p(t_{ij}, d_{ij} | b_j) \right] p(b_j)\, db_j$$

Using the normal density with mean μ and variance σ^2 of $p(b_j|\theta)$ as weighting kernel $w(\cdot)$, the integral can be approximated as

$$\int_{-\infty}^{+\infty} f(x)\, dx \approx \sum_{i=1}^{k} \frac{w_i}{\sqrt{\pi}} g(\sqrt{2}\sigma z_i + \mu)$$

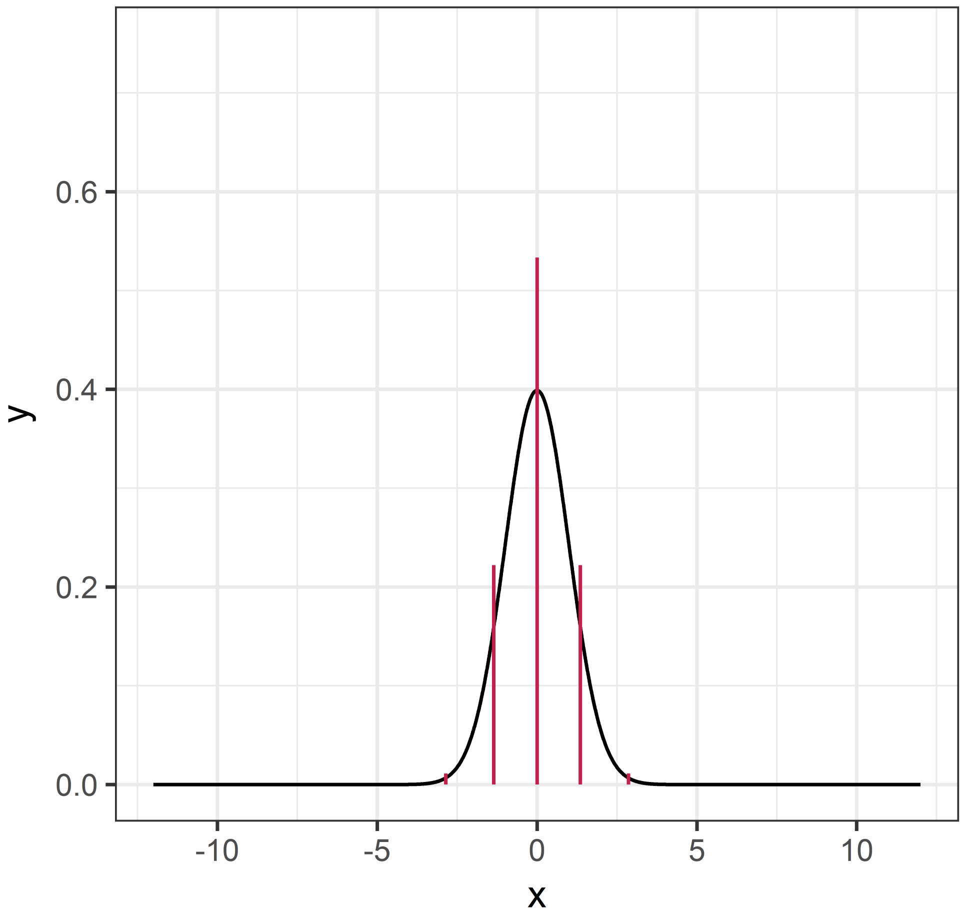
with w_i and z_i weights and nodes from ordinary Gauss-Hermite quadrature. With clustered data, an appealing option to increase accuracy is given by adaptive Gauss-Hermite quadrature (Pinheiro and Bates, 1995).

Gauss-Hermite quadrature

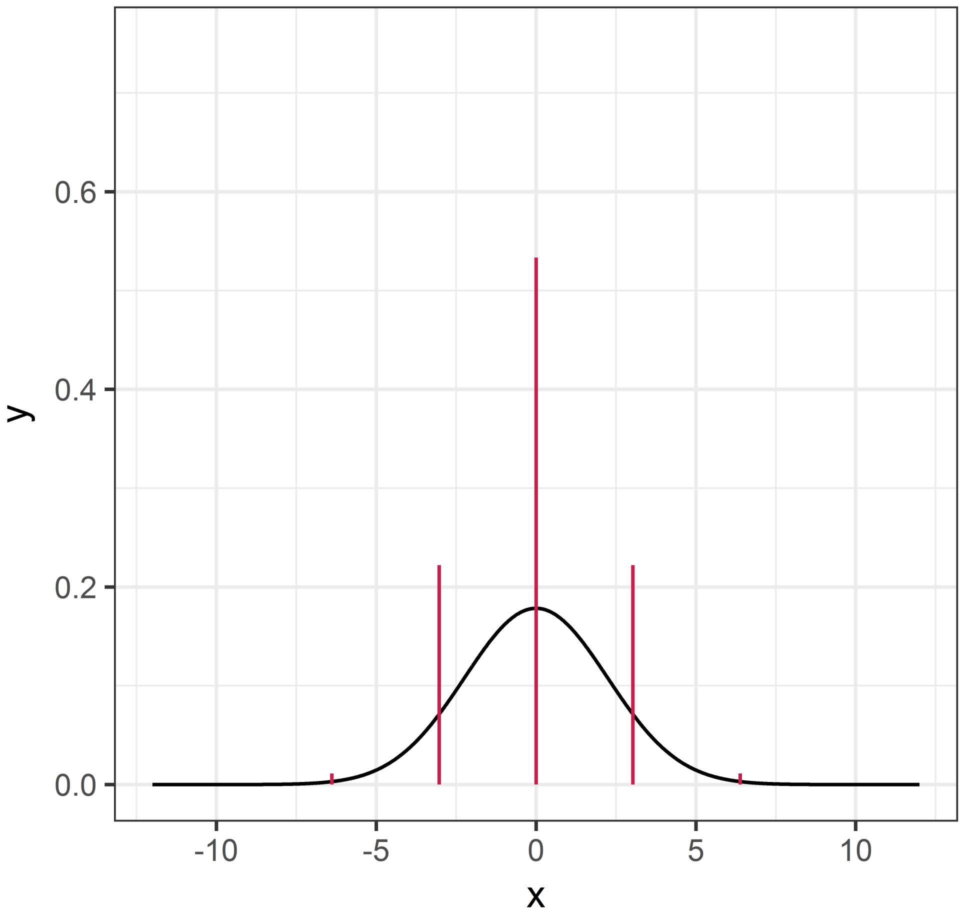


Standard normal density

Gauss-Hermite quadrature

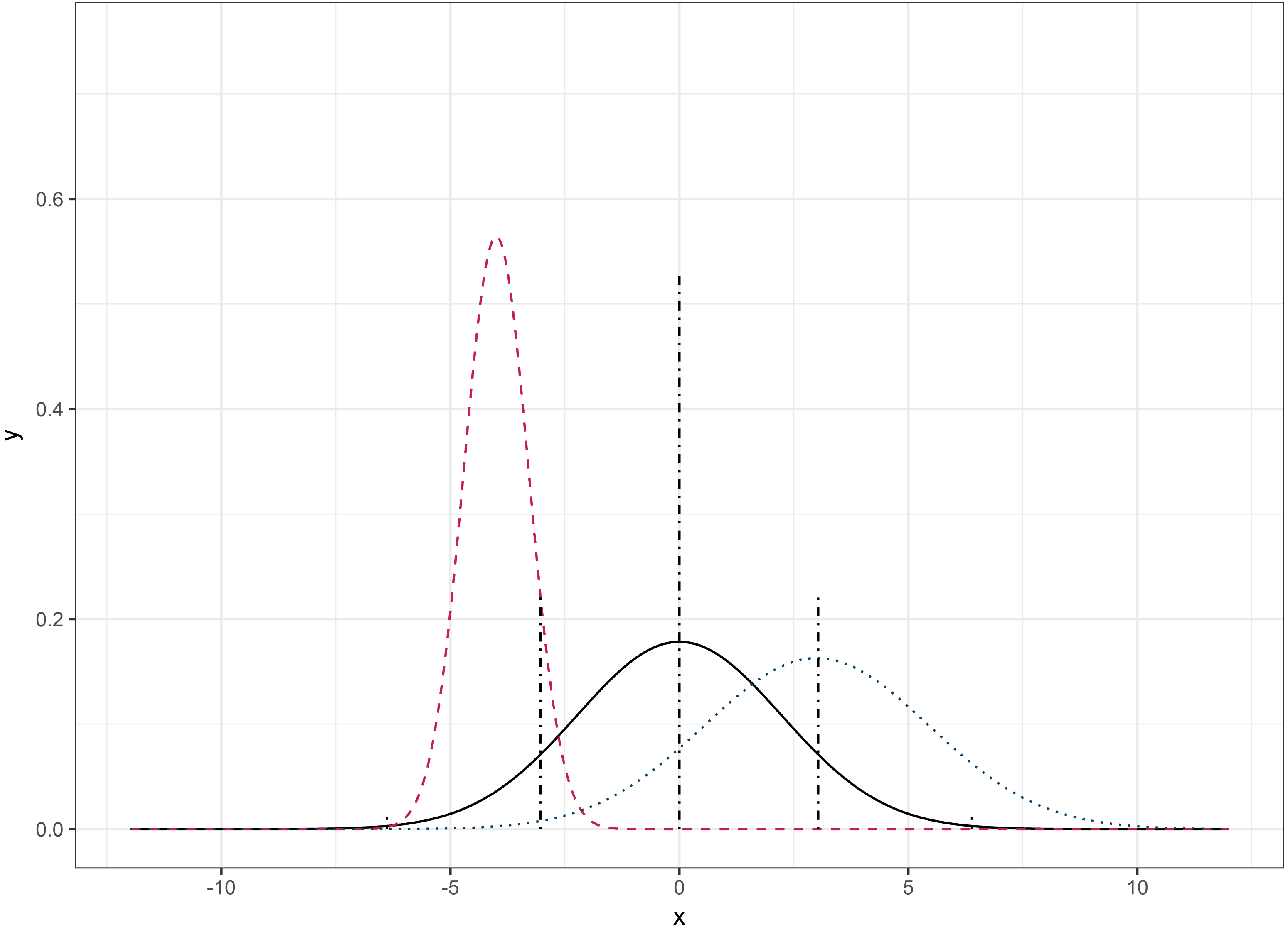


N(μ = 0, σ = 1) density, quadrature with 5 nodes



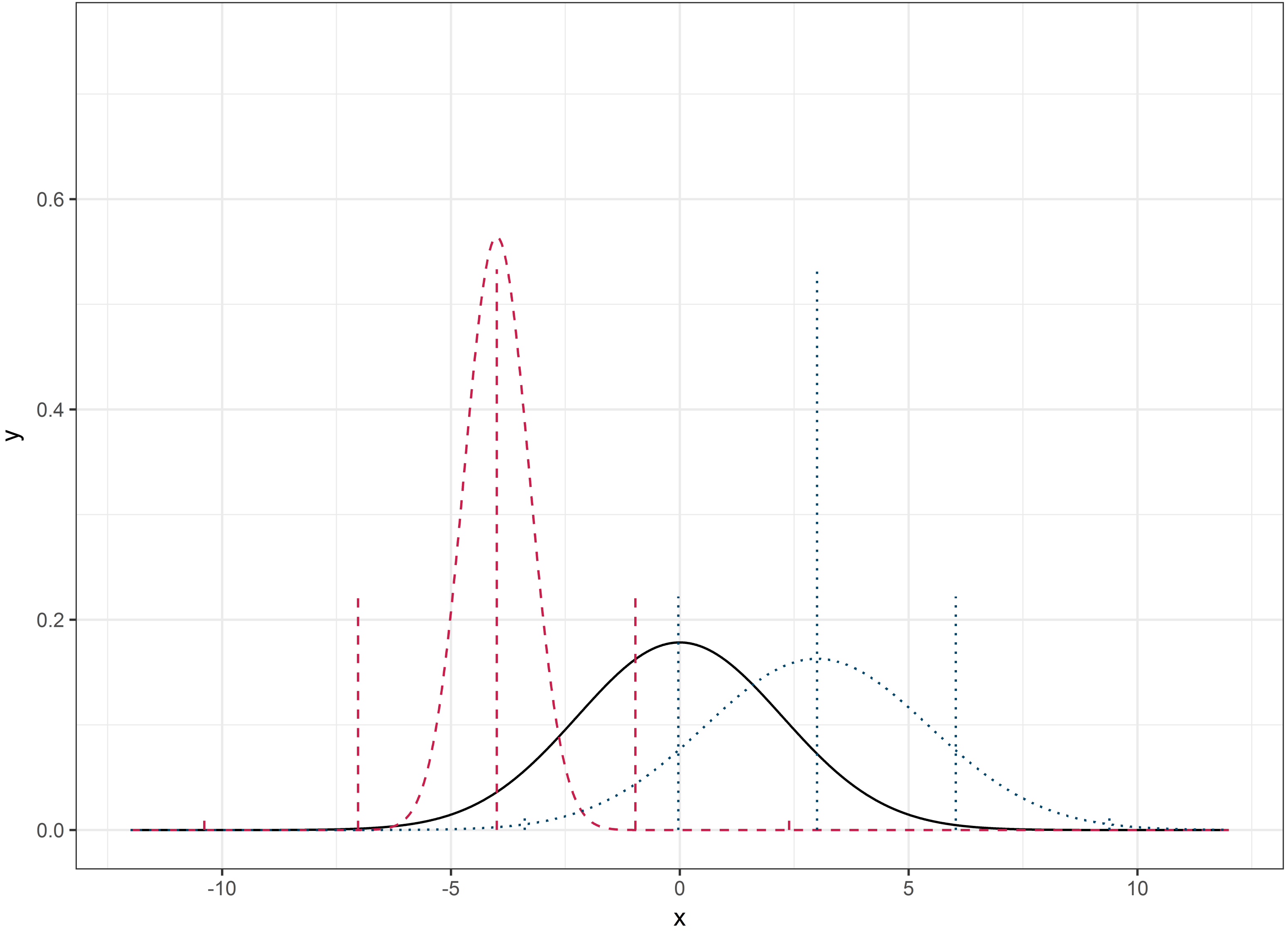
N(μ = 0, σ = 5) density, quadrature with 5 nodes

Adaptive Gauss-Hermite quadrature



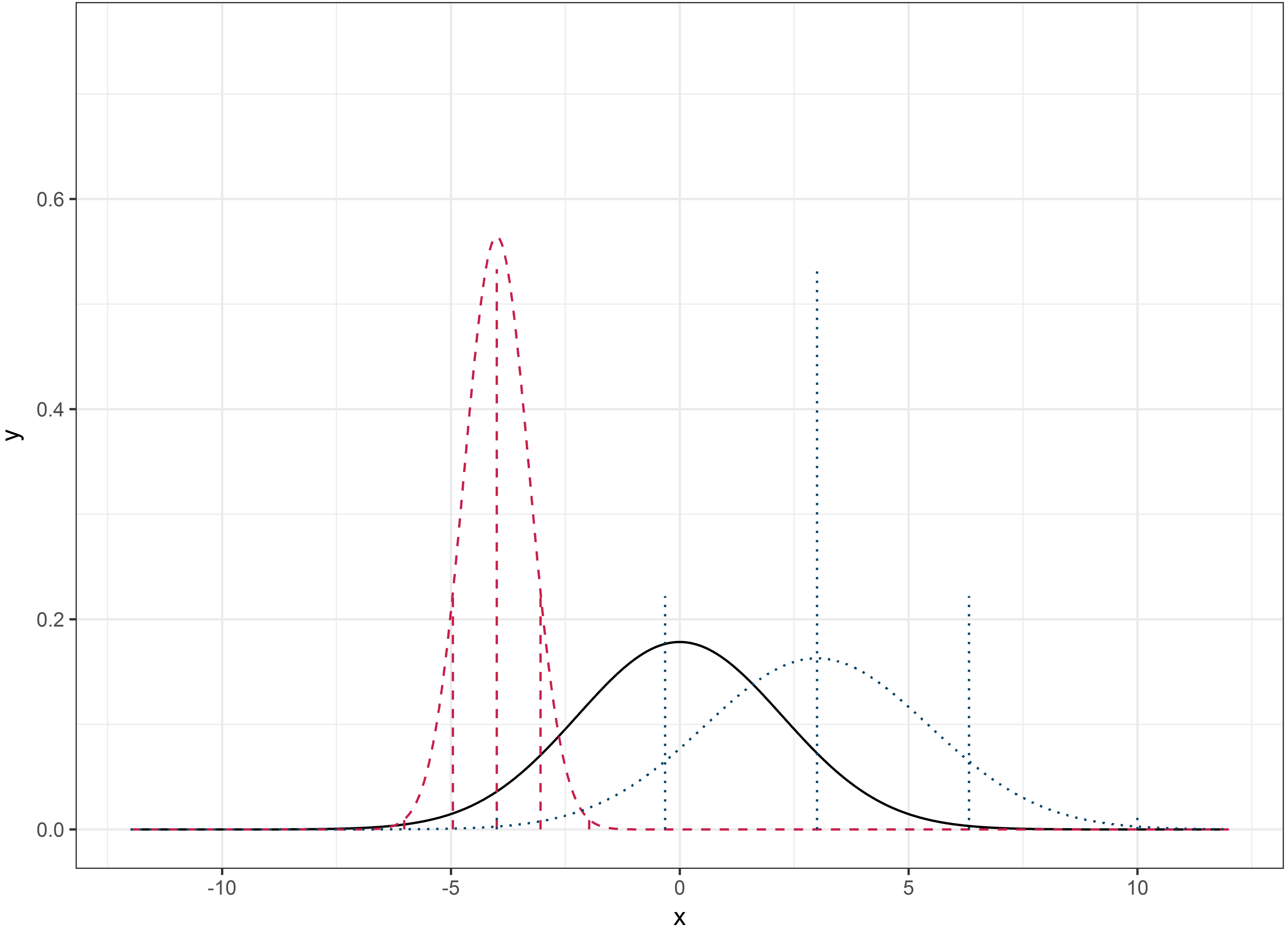
Ordinary Gauss-Hermite quadrature with 5 nodes

Adaptive Gauss-Hermite quadrature



Adaptive Gauss-Hermite quadrature with 5 nodes: center nodes

Adaptive Gauss-Hermite quadrature



Adaptive Gauss-Hermite quadrature with 5 nodes: center and scale nodes

Multidimensional quadrature

The quadrature example I just showed approximates an integral in a single dimension. Quadrature can be easily extended to multidimensional integrals:

$$\int_X \int_Y f(x, y) p(x) p(y) \; dx \; dy \approx \sum_{i=1}^{n_i} \sum_{j=1}^{n_j} w_i w_j f(z_i, z_j)$$

Problem: a d-dimensional N-points rule requires N^d function evalutations. Computationally expensive and inefficient!

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Solution: multivariate adaptive quadrature (Jäckel, 2005)

1. Rotating the matrix of location nodes, accounting for correlation between the d dimensions
2. Pruning the matrix of location nodes, removing those with extremely low weights that contribute very little to the total integral value

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Alternative methods for numerical integration: Monte Carlo integration and importance sampling.

Software

Software

There are many statistical packages available for fitting mixed effects models.

In R, among others:

- `coxme` and `survival`
- `frailtypack`
- `rstpm2`
- `parfm`, `frailtyEM`, …

In Stata:

- `streg`
- `stmixed` and `mestreg`
- `megenreg`

`megenreg`, acronym for *Mixed Effects GENeralised REGression models*, is an extended framework in which it is possible to model multiple outcomes of any type, potentially repeatedly measured, with any number of levels, and with any number of random effects at each level (Crowther, 2017).

Misspecification in shared frailty models

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When modelling survival data via mixed effects (and frailty) models there are a few assumptions to make:

1. Shape of the baseline hazard
2. Distribution of the frailty

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1. Shape of the baseline hazard
2. Distribution of the frailty

The shape of $h_0(\cdot)$ could be:

- unspecified
- fully parametric
- flexible parametric (Royston and Parmar, 2002)
- ...

The distribution of the frailty u, u_j could be:

- Gamma
- log-normal
- inverse Gamma
- ...

A simulation study

Aims:

1. Does it matter how we model the baseline hazard?
2. Does it matter if we misspecify the frailty distribution?

A simulation study

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1. Does it matter how we model the baseline hazard?
2. Does it matter if we misspecify the frailty distribution?

Outcomes:

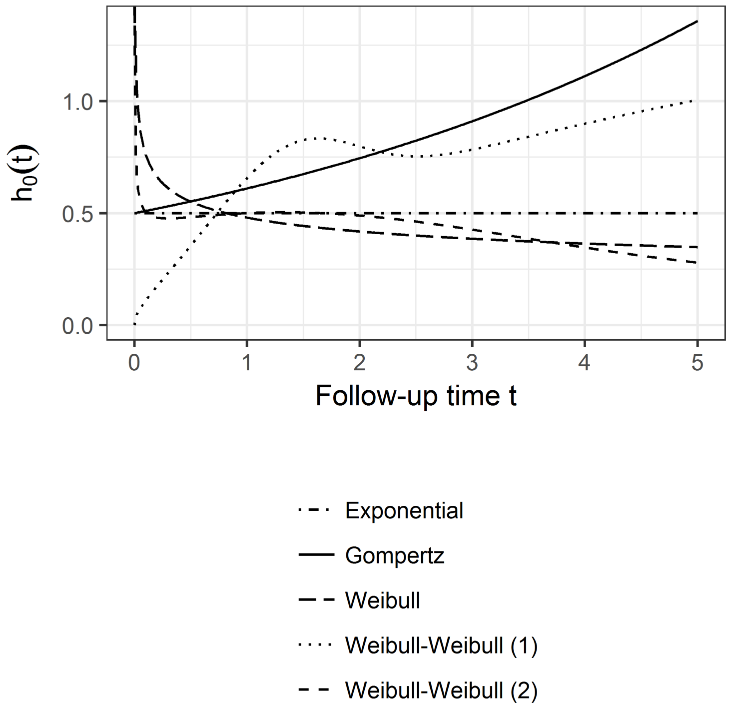
- Relative risk estimates
- Absolute risk estimates
- Measures of heterogeneity

Data-generating mechanisms

Simulating clustered survival data with a binary covariate (e.g. a treatment with two modalities) and frailty term shared between individuals belonging to the same cluster.

Simulation factors:

- Shape of the baseline hazard
  1. Simple parametric functions (exponential, Weibull, Gompertz)
  2. Complex Weibull mixture hazard functions with turning points
- Distribution of the shared frailty term, Gamma or log-normal
- Magnitude of the frailty variance
- Sample size



Models and performance measures

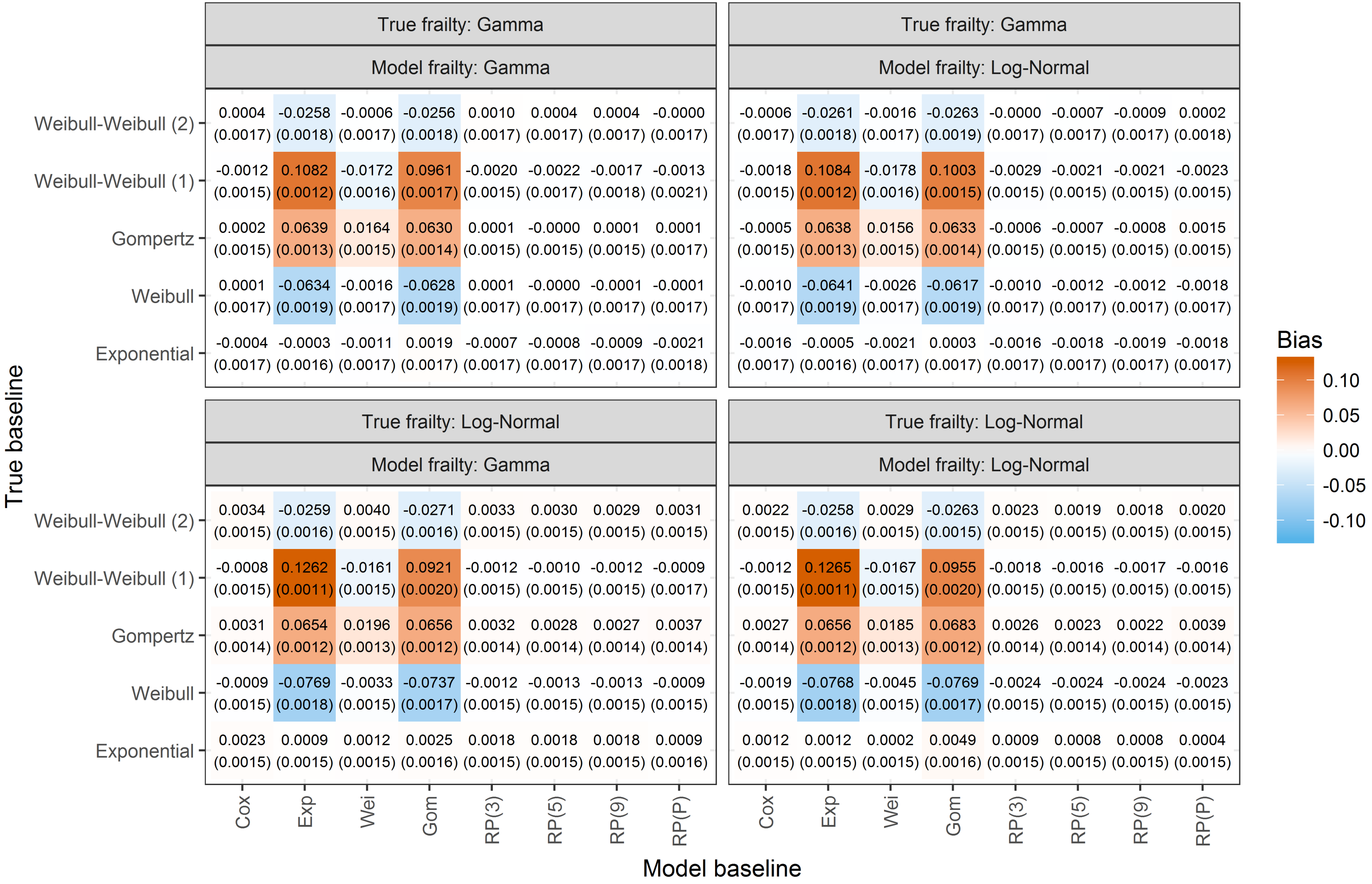
Models:

- Semiparametric
- Fully parametric (exponential, Weibull, Gompertz)
- Flexible spline-based (3, 5, 7, 9 degrees of freedom, full or penalised likelihood; Royston and Parmar, 2002, and Liu *et al.*, 2016)

Performance measures:

- Bias and coverage, percentage bias (when relevant)
- Monte Carlo standard errors are computed as well

Results: bias of regression coefficient



True frailty: Gamma

Model frailty: Gamma

True baseline	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	0.0004 (0.0017)	-0.0258 (0.0018)	-0.0006 (0.0017)	-0.0256 (0.0018)	0.0010 (0.0017)	0.0004 (0.0017)	0.0004 (0.0017)	-0.0000 (0.0017)
Weibull-Weibull (1)	-0.0012 (0.0015)	0.1082 (0.0012)	-0.0172 (0.0016)	0.0961 (0.0017)	-0.0020 (0.0015)	-0.0022 (0.0017)	-0.0017 (0.0018)	-0.0013 (0.0021)
Gompertz	0.0002 (0.0015)	0.0639 (0.0013)	0.0164 (0.0015)	0.0630 (0.0014)	0.0001 (0.0015)	-0.0000 (0.0015)	0.0001 (0.0015)	0.0001 (0.0017)
Weibull	0.0001 (0.0017)	-0.0634 (0.0019)	-0.0016 (0.0017)	-0.0628 (0.0019)	0.0001 (0.0017)	-0.0000 (0.0017)	-0.0001 (0.0017)	-0.0001 (0.0017)
Exponential	-0.0004 (0.0017)	-0.0003 (0.0016)	-0.0011 (0.0017)	0.0019 (0.0017)	-0.0007 (0.0017)	-0.0008 (0.0017)	-0.0009 (0.0017)	-0.0021 (0.0018)

True frailty: Gamma

Model frailty: Log-Normal

True baseline	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	-0.0006 (0.0017)	-0.0261 (0.0018)	-0.0016 (0.0017)	-0.0263 (0.0019)	-0.0000 (0.0017)	-0.0007 (0.0017)	-0.0009 (0.0017)	0.0002 (0.0018)
Weibull-Weibull (1)	-0.0018 (0.0015)	0.1084 (0.0012)	-0.0178 (0.0016)	0.1003 (0.0015)	-0.0029 (0.0015)	-0.0021 (0.0015)	-0.0021 (0.0015)	-0.0023 (0.0015)
Gompertz	-0.0005 (0.0015)	0.0638 (0.0013)	0.0156 (0.0015)	0.0633 (0.0014)	-0.0006 (0.0015)	-0.0007 (0.0015)	-0.0008 (0.0015)	0.0015 (0.0015)
Weibull	-0.0010 (0.0017)	-0.0641 (0.0019)	-0.0026 (0.0017)	-0.0617 (0.0019)	-0.0010 (0.0017)	-0.0012 (0.0017)	-0.0012 (0.0017)	-0.0018 (0.0017)
Exponential	-0.0016 (0.0017)	-0.0005 (0.0016)	-0.0021 (0.0017)	0.0003 (0.0017)	-0.0016 (0.0017)	-0.0018 (0.0017)	-0.0019 (0.0017)	-0.0018 (0.0017)

True frailty: Log-Normal

Model frailty: Gamma

True baseline	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	0.0034 (0.0015)	-0.0259 (0.0016)	0.0040 (0.0015)	-0.0271 (0.0016)	0.0033 (0.0015)	0.0030 (0.0015)	0.0029 (0.0015)	0.0031 (0.0015)
Weibull-Weibull (1)	-0.0008 (0.0015)	0.1262 (0.0011)	-0.0161 (0.0015)	0.0921 (0.0020)	-0.0012 (0.0015)	-0.0010 (0.0015)	-0.0012 (0.0015)	-0.0009 (0.0017)
Gompertz	0.0031 (0.0014)	0.0654 (0.0012)	0.0196 (0.0013)	0.0656 (0.0012)	0.0032 (0.0014)	0.0028 (0.0014)	0.0027 (0.0014)	0.0037 (0.0014)
Weibull	-0.0009 (0.0015)	-0.0769 (0.0018)	-0.0033 (0.0015)	-0.0737 (0.0017)	-0.0012 (0.0015)	-0.0013 (0.0015)	-0.0013 (0.0015)	-0.0009 (0.0015)
Exponential	0.0023 (0.0015)	0.0009 (0.0015)	0.0012 (0.0015)	0.0025 (0.0016)	0.0018 (0.0015)	0.0018 (0.0015)	0.0018 (0.0015)	0.0009 (0.0016)

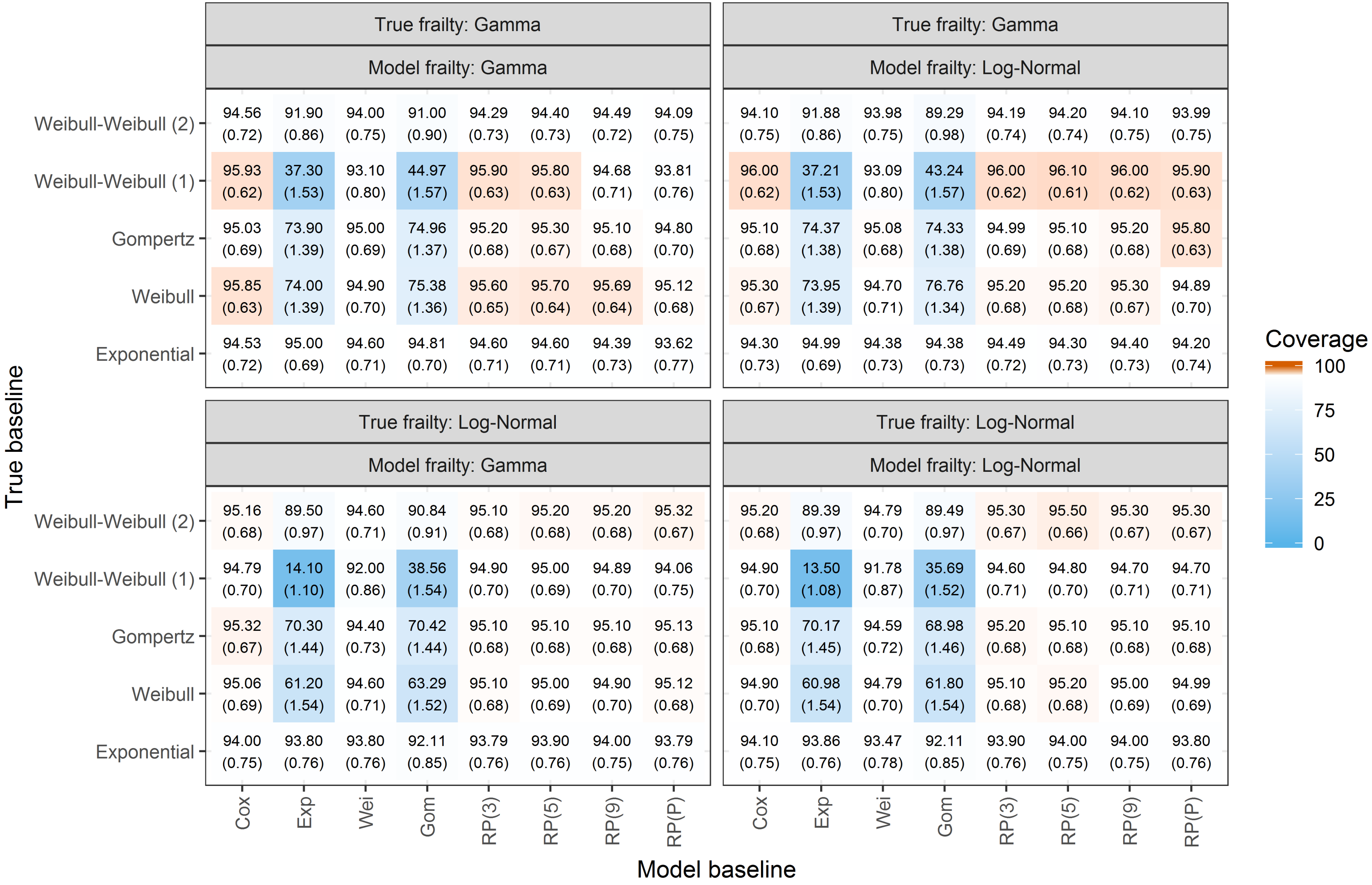
True frailty: Log-Normal

Model frailty: Log-Normal

True baseline	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	0.0022 (0.0015)	-0.0258 (0.0016)	0.0029 (0.0015)	-0.0263 (0.0015)	0.0023 (0.0015)	0.0019 (0.0015)	0.0018 (0.0015)	0.0020 (0.0015)
Weibull-Weibull (1)	-0.0012 (0.0015)	0.1265 (0.0011)	-0.0167 (0.0015)	0.0955 (0.0020)	-0.0018 (0.0015)	-0.0016 (0.0015)	-0.0017 (0.0015)	-0.0016 (0.0015)
Gompertz	0.0027 (0.0014)	0.0656 (0.0012)	0.0185 (0.0013)	0.0683 (0.0012)	0.0026 (0.0014)	0.0023 (0.0014)	0.0022 (0.0014)	0.0039 (0.0014)
Weibull	-0.0019 (0.0015)	-0.0768 (0.0018)	-0.0045 (0.0015)	-0.0769 (0.0017)	-0.0024 (0.0015)	-0.0024 (0.0015)	-0.0024 (0.0015)	-0.0023 (0.0015)
Exponential	0.0012 (0.0015)	0.0012 (0.0015)	0.0002 (0.0015)	0.0049 (0.0016)	0.0009 (0.0015)	0.0008 (0.0015)	0.0008 (0.0015)	0.0004 (0.0015)

Scenario: 50 clusters of 50 individuals each, with a true frailty variance of 1.25

Results: coverage of regression coefficient



True frailty: Gamma — Model frailty: Gamma

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	94.56 (0.72)	91.90 (0.86)	94.00 (0.75)	91.00 (0.90)	94.29 (0.73)	94.40 (0.73)	94.49 (0.72)	94.09 (0.75)
Weibull-Weibull (1)	95.93 (0.62)	37.30 (1.53)	93.10 (0.80)	44.97 (1.57)	95.90 (0.63)	95.80 (0.63)	94.68 (0.71)	93.81 (0.76)
Gompertz	95.03 (0.69)	73.90 (1.39)	95.00 (0.69)	74.96 (1.37)	95.20 (0.68)	95.30 (0.67)	95.10 (0.68)	94.80 (0.70)
Weibull	95.85 (0.63)	74.00 (1.39)	94.90 (0.70)	75.38 (1.36)	95.60 (0.65)	95.70 (0.64)	95.69 (0.64)	95.12 (0.68)
Exponential	94.53 (0.72)	95.00 (0.69)	94.60 (0.71)	94.81 (0.70)	94.60 (0.71)	94.60 (0.71)	94.39 (0.73)	93.62 (0.77)

True frailty: Gamma — Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	94.10 (0.75)	91.88 (0.86)	93.98 (0.75)	89.29 (0.98)	94.19 (0.74)	94.20 (0.74)	94.10 (0.75)	93.99 (0.75)
Weibull-Weibull (1)	96.00 (0.62)	37.21 (1.53)	93.09 (0.80)	43.24 (1.57)	96.00 (0.62)	96.10 (0.61)	96.00 (0.62)	95.90 (0.63)
Gompertz	95.10 (0.68)	74.37 (1.38)	95.08 (0.68)	74.33 (1.38)	94.99 (0.69)	95.10 (0.68)	95.20 (0.68)	95.80 (0.63)
Weibull	95.30 (0.67)	73.95 (1.39)	94.70 (0.71)	76.76 (1.34)	95.20 (0.68)	95.20 (0.68)	95.30 (0.67)	94.89 (0.70)
Exponential	94.30 (0.73)	94.99 (0.69)	94.38 (0.73)	94.38 (0.73)	94.49 (0.72)	94.30 (0.73)	94.40 (0.73)	94.20 (0.74)

True frailty: Log-Normal — Model frailty: Gamma

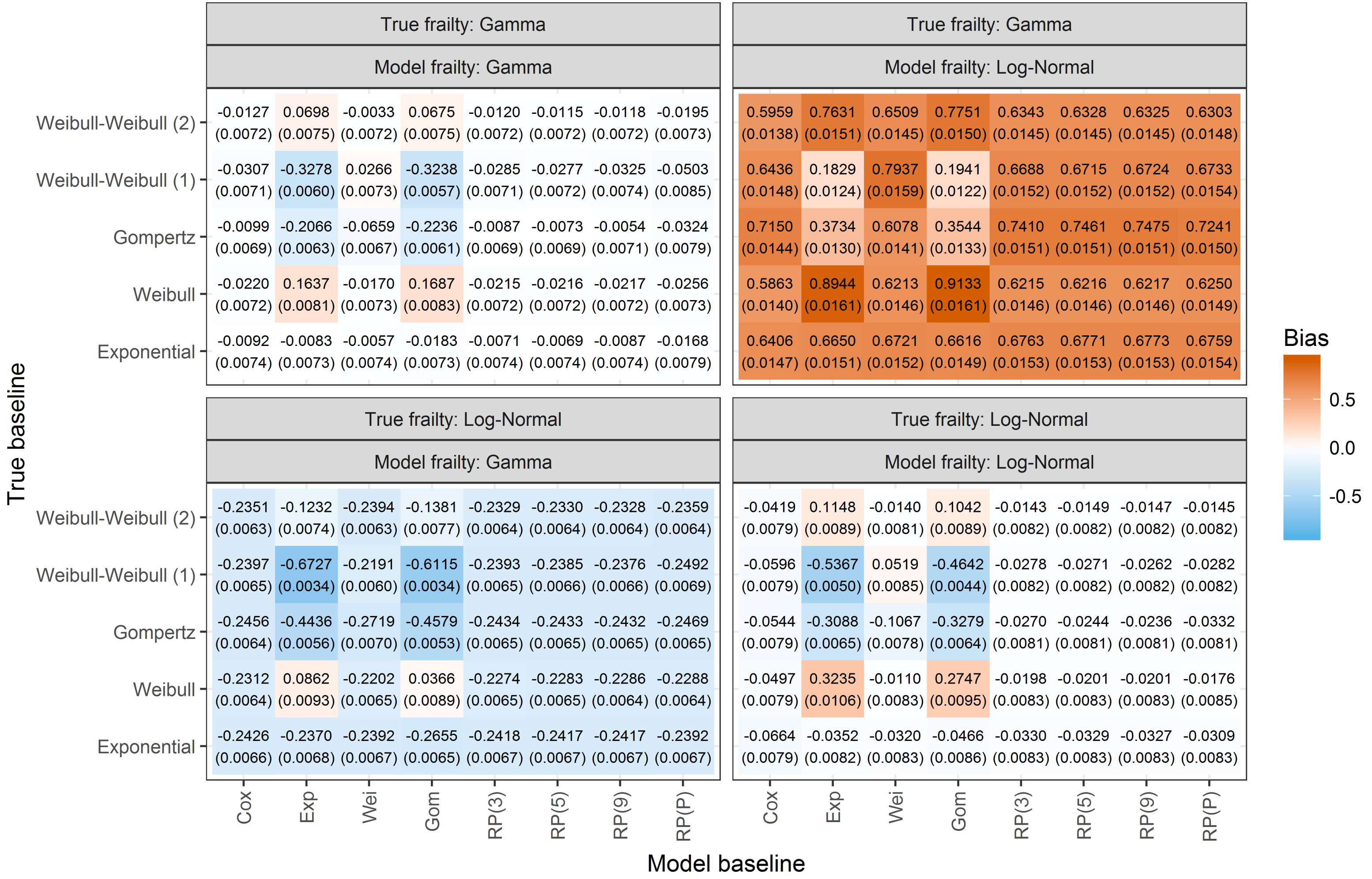
	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	95.16 (0.68)	89.50 (0.97)	94.60 (0.71)	90.84 (0.91)	95.10 (0.68)	95.20 (0.68)	95.20 (0.68)	95.32 (0.67)
Weibull-Weibull (1)	94.79 (0.70)	14.10 (1.10)	92.00 (0.86)	38.56 (1.54)	94.90 (0.70)	95.00 (0.69)	94.89 (0.70)	94.06 (0.75)
Gompertz	95.32 (0.67)	70.30 (1.44)	94.40 (0.73)	70.42 (1.44)	95.10 (0.68)	95.10 (0.68)	95.10 (0.68)	95.13 (0.68)
Weibull	95.06 (0.69)	61.20 (1.54)	94.60 (0.71)	63.29 (1.52)	95.10 (0.68)	95.00 (0.69)	94.90 (0.70)	95.12 (0.68)
Exponential	94.00 (0.75)	93.80 (0.76)	93.80 (0.76)	92.11 (0.85)	93.79 (0.76)	93.90 (0.76)	94.00 (0.75)	93.79 (0.76)

True frailty: Log-Normal — Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	95.20 (0.68)	89.39 (0.97)	94.79 (0.70)	89.49 (0.97)	95.30 (0.67)	95.50 (0.66)	95.30 (0.67)	95.30 (0.67)
Weibull-Weibull (1)	94.90 (0.70)	13.50 (1.08)	91.78 (0.87)	35.69 (1.52)	94.60 (0.71)	94.80 (0.70)	94.70 (0.71)	94.70 (0.71)
Gompertz	95.10 (0.68)	70.17 (1.45)	94.59 (0.72)	68.98 (1.46)	95.20 (0.68)	95.10 (0.68)	95.10 (0.68)	95.10 (0.68)
Weibull	94.90 (0.70)	60.98 (1.54)	94.79 (0.70)	61.80 (1.54)	95.10 (0.68)	95.20 (0.68)	95.00 (0.69)	94.99 (0.69)
Exponential	94.10 (0.75)	93.86 (0.76)	93.47 (0.78)	92.11 (0.85)	93.90 (0.76)	94.00 (0.75)	94.00 (0.75)	93.80 (0.76)

Scenario: 50 clusters of 50 individuals each, with a true frailty variance of 1.25

Results: bias of frailty variance



True frailty: Gamma
Model frailty: Gamma

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	-0.0127 (0.0072)	0.0698 (0.0075)	-0.0033 (0.0072)	0.0675 (0.0075)	-0.0120 (0.0072)	-0.0115 (0.0072)	-0.0118 (0.0072)	-0.0195 (0.0073)
Weibull-Weibull (1)	-0.0307 (0.0071)	-0.3278 (0.0060)	0.0266 (0.0073)	-0.3238 (0.0057)	-0.0285 (0.0071)	-0.0277 (0.0072)	-0.0325 (0.0074)	-0.0503 (0.0085)
Gompertz	-0.0099 (0.0069)	-0.2066 (0.0063)	-0.0659 (0.0067)	-0.2236 (0.0061)	-0.0087 (0.0069)	-0.0073 (0.0069)	-0.0054 (0.0071)	-0.0324 (0.0079)
Weibull	-0.0220 (0.0072)	0.1637 (0.0081)	-0.0170 (0.0073)	0.1687 (0.0083)	-0.0215 (0.0072)	-0.0216 (0.0072)	-0.0217 (0.0072)	-0.0256 (0.0073)
Exponential	-0.0092 (0.0074)	-0.0083 (0.0073)	-0.0057 (0.0074)	-0.0183 (0.0073)	-0.0071 (0.0074)	-0.0069 (0.0074)	-0.0087 (0.0074)	-0.0168 (0.0079)

True frailty: Gamma
Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	0.5959 (0.0138)	0.7631 (0.0151)	0.6509 (0.0145)	0.7751 (0.0150)	0.6343 (0.0145)	0.6328 (0.0145)	0.6325 (0.0145)	0.6303 (0.0148)
Weibull-Weibull (1)	0.6436 (0.0148)	0.1829 (0.0124)	0.7937 (0.0159)	0.1941 (0.0122)	0.6688 (0.0152)	0.6715 (0.0152)	0.6724 (0.0152)	0.6733 (0.0154)
Gompertz	0.7150 (0.0144)	0.3734 (0.0130)	0.6078 (0.0141)	0.3544 (0.0133)	0.7410 (0.0151)	0.7461 (0.0151)	0.7475 (0.0151)	0.7241 (0.0150)
Weibull	0.5863 (0.0140)	0.8944 (0.0161)	0.6213 (0.0146)	0.9133 (0.0161)	0.6215 (0.0146)	0.6216 (0.0146)	0.6217 (0.0146)	0.6250 (0.0149)
Exponential	0.6406 (0.0147)	0.6650 (0.0151)	0.6721 (0.0152)	0.6616 (0.0149)	0.6763 (0.0153)	0.6771 (0.0153)	0.6773 (0.0153)	0.6759 (0.0154)

True frailty: Log-Normal
Model frailty: Gamma

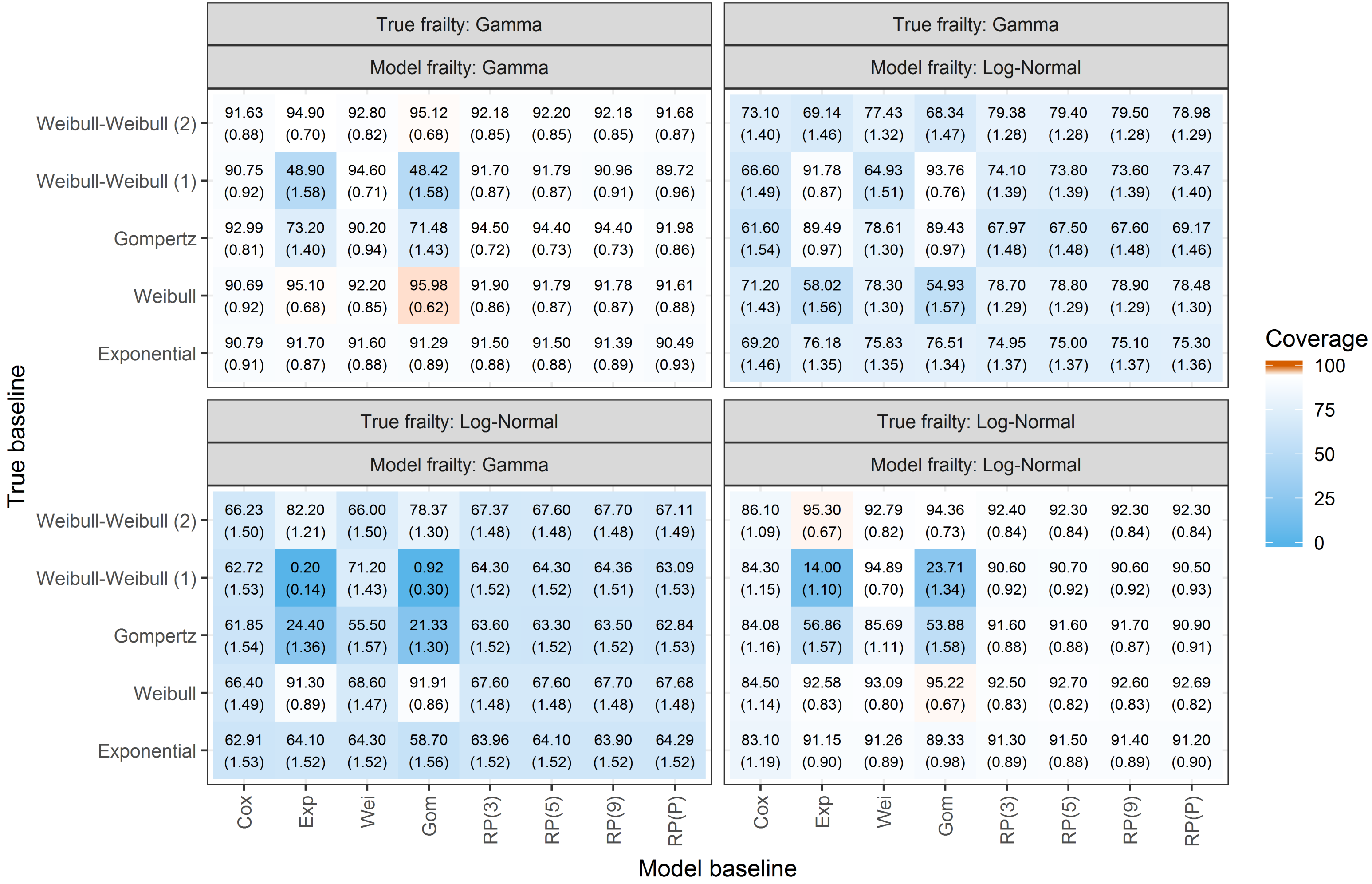
	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	-0.2351 (0.0063)	-0.1232 (0.0074)	-0.2394 (0.0063)	-0.1381 (0.0077)	-0.2329 (0.0064)	-0.2330 (0.0064)	-0.2328 (0.0064)	-0.2359 (0.0064)
Weibull-Weibull (1)	-0.2397 (0.0065)	-0.6727 (0.0034)	-0.2191 (0.0060)	-0.6115 (0.0034)	-0.2393 (0.0065)	-0.2385 (0.0066)	-0.2376 (0.0066)	-0.2492 (0.0069)
Gompertz	-0.2456 (0.0064)	-0.4436 (0.0056)	-0.2719 (0.0070)	-0.4579 (0.0053)	-0.2434 (0.0065)	-0.2433 (0.0065)	-0.2432 (0.0065)	-0.2469 (0.0065)
Weibull	-0.2312 (0.0064)	0.0862 (0.0093)	-0.2202 (0.0065)	0.0366 (0.0089)	-0.2274 (0.0065)	-0.2283 (0.0065)	-0.2286 (0.0064)	-0.2288 (0.0064)
Exponential	-0.2426 (0.0066)	-0.2370 (0.0068)	-0.2392 (0.0067)	-0.2655 (0.0065)	-0.2418 (0.0067)	-0.2417 (0.0067)	-0.2417 (0.0067)	-0.2392 (0.0067)

True frailty: Log-Normal
Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	-0.0419 (0.0079)	0.1148 (0.0089)	-0.0140 (0.0081)	0.1042 (0.0089)	-0.0143 (0.0082)	-0.0149 (0.0082)	-0.0147 (0.0082)	-0.0145 (0.0082)
Weibull-Weibull (1)	-0.0596 (0.0079)	-0.5367 (0.0050)	0.0519 (0.0085)	-0.4642 (0.0044)	-0.0278 (0.0082)	-0.0271 (0.0082)	-0.0262 (0.0082)	-0.0282 (0.0082)
Gompertz	-0.0544 (0.0079)	-0.3088 (0.0065)	-0.1067 (0.0078)	-0.3279 (0.0064)	-0.0270 (0.0081)	-0.0244 (0.0081)	-0.0236 (0.0081)	-0.0332 (0.0081)
Weibull	-0.0497 (0.0079)	0.3235 (0.0106)	-0.0110 (0.0083)	0.2747 (0.0095)	-0.0198 (0.0083)	-0.0201 (0.0083)	-0.0201 (0.0083)	-0.0176 (0.0085)
Exponential	-0.0664 (0.0079)	-0.0352 (0.0082)	-0.0320 (0.0083)	-0.0466 (0.0086)	-0.0330 (0.0083)	-0.0329 (0.0083)	-0.0327 (0.0083)	-0.0309 (0.0083)

Scenario: 50 clusters of 50 individuals each, with a true frailty variance of 1.25

Results: coverage of frailty variance



True frailty: Gamma — Model frailty: Gamma

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	91.63 (0.88)	94.90 (0.70)	92.80 (0.82)	95.12 (0.68)	92.18 (0.85)	92.20 (0.85)	92.18 (0.85)	91.68 (0.87)
Weibull-Weibull (1)	90.75 (0.92)	48.90 (1.58)	94.60 (0.71)	48.42 (1.58)	91.70 (0.87)	91.79 (0.87)	90.96 (0.91)	89.72 (0.96)
Gompertz	92.99 (0.81)	73.20 (1.40)	90.20 (0.94)	71.48 (1.43)	94.50 (0.72)	94.40 (0.73)	94.40 (0.73)	91.98 (0.86)
Weibull	90.69 (0.92)	95.10 (0.68)	92.20 (0.85)	95.98 (0.62)	91.90 (0.86)	91.79 (0.87)	91.78 (0.87)	91.61 (0.88)
Exponential	90.79 (0.91)	91.70 (0.87)	91.60 (0.88)	91.29 (0.89)	91.50 (0.88)	91.50 (0.88)	91.39 (0.89)	90.49 (0.93)

True frailty: Gamma — Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	73.10 (1.40)	69.14 (1.46)	77.43 (1.32)	68.34 (1.47)	79.38 (1.28)	79.40 (1.28)	79.50 (1.28)	78.98 (1.29)
Weibull-Weibull (1)	66.60 (1.49)	91.78 (0.87)	64.93 (1.51)	93.76 (0.76)	74.10 (1.39)	73.80 (1.39)	73.60 (1.39)	73.47 (1.40)
Gompertz	61.60 (1.54)	89.49 (0.97)	78.61 (1.30)	89.43 (0.97)	67.97 (1.48)	67.50 (1.48)	67.60 (1.48)	69.17 (1.46)
Weibull	71.20 (1.43)	58.02 (1.56)	78.30 (1.30)	54.93 (1.57)	78.70 (1.29)	78.80 (1.29)	78.90 (1.29)	78.48 (1.30)
Exponential	69.20 (1.46)	76.18 (1.35)	75.83 (1.35)	76.51 (1.34)	74.95 (1.37)	75.00 (1.37)	75.10 (1.37)	75.30 (1.36)

True frailty: Log-Normal — Model frailty: Gamma

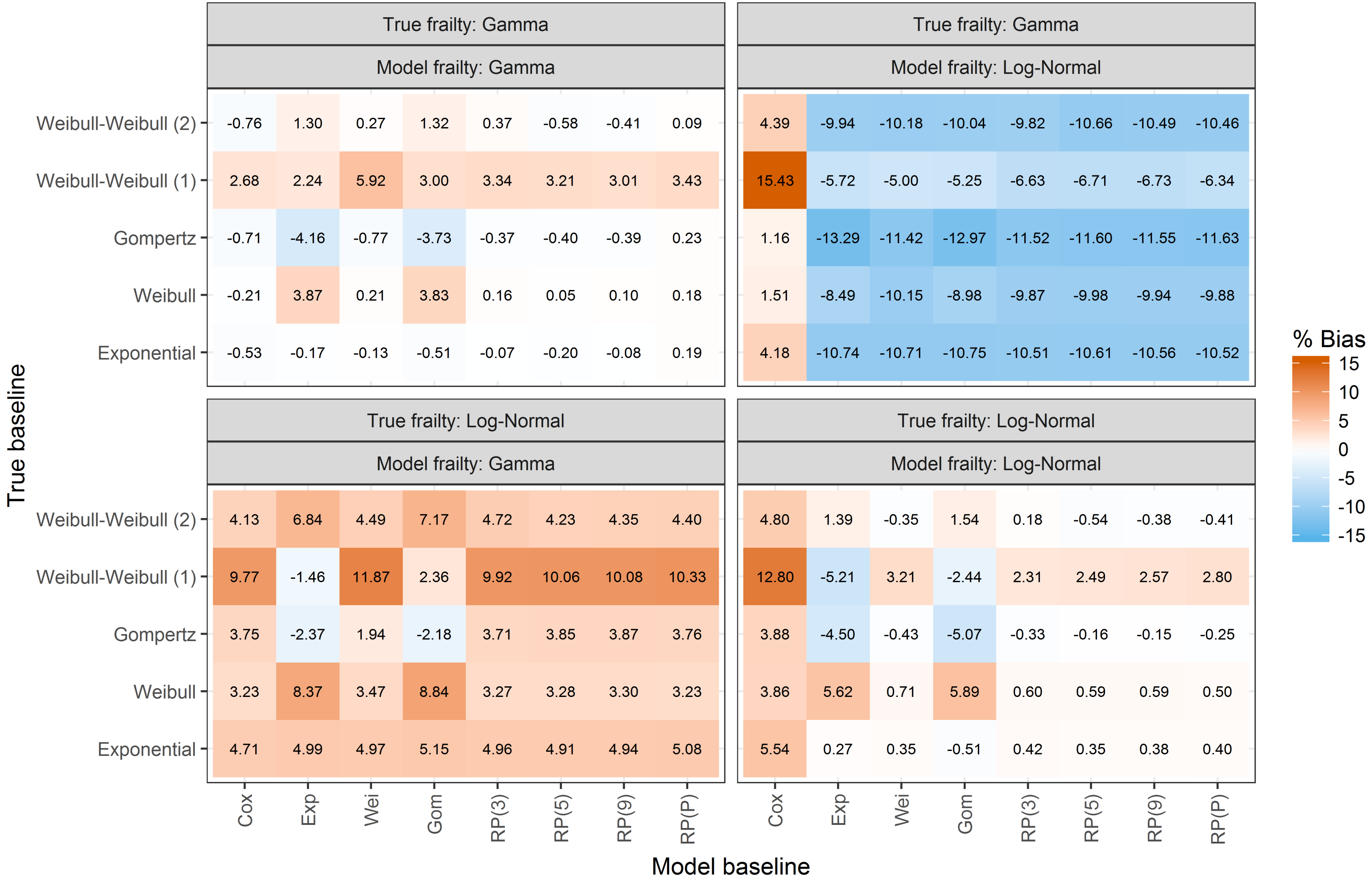
	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	66.23 (1.50)	82.20 (1.21)	66.00 (1.50)	78.37 (1.30)	67.37 (1.48)	67.60 (1.48)	67.70 (1.48)	67.11 (1.49)
Weibull-Weibull (1)	62.72 (1.53)	0.20 (0.14)	71.20 (1.43)	0.92 (0.30)	64.30 (1.52)	64.30 (1.52)	64.36 (1.51)	63.09 (1.53)
Gompertz	61.85 (1.54)	24.40 (1.36)	55.50 (1.57)	21.33 (1.30)	63.60 (1.52)	63.30 (1.52)	63.50 (1.52)	62.84 (1.53)
Weibull	66.40 (1.49)	91.30 (0.89)	68.60 (1.47)	91.91 (0.86)	67.60 (1.48)	67.60 (1.48)	67.70 (1.48)	67.68 (1.48)
Exponential	62.91 (1.53)	64.10 (1.52)	64.30 (1.52)	58.70 (1.56)	63.96 (1.52)	64.10 (1.52)	63.90 (1.52)	64.29 (1.52)

True frailty: Log-Normal — Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	86.10 (1.09)	95.30 (0.67)	92.79 (0.82)	94.36 (0.73)	92.40 (0.84)	92.30 (0.84)	92.30 (0.84)	92.30 (0.84)
Weibull-Weibull (1)	84.30 (1.15)	14.00 (1.10)	94.89 (0.70)	23.71 (1.34)	90.60 (0.92)	90.70 (0.92)	90.60 (0.92)	90.50 (0.93)
Gompertz	84.08 (1.16)	56.86 (1.57)	85.69 (1.11)	53.88 (1.58)	91.60 (0.88)	91.60 (0.88)	91.70 (0.87)	90.90 (0.91)
Weibull	84.50 (1.14)	92.58 (0.83)	93.09 (0.80)	95.22 (0.67)	92.50 (0.83)	92.70 (0.82)	92.60 (0.83)	92.69 (0.82)
Exponential	83.10 (1.19)	91.15 (0.90)	91.26 (0.89)	89.33 (0.98)	91.30 (0.89)	91.50 (0.88)	91.40 (0.89)	91.20 (0.90)

Scenario: 50 clusters of 50 individuals each, with a true frailty variance of 1.25

Results: % bias of survival difference



True frailty: Gamma
Model frailty: Gamma

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	-0.76	1.30	0.27	1.32	0.37	-0.58	-0.41	0.09
Weibull-Weibull (1)	2.68	2.24	5.92	3.00	3.34	3.21	3.01	3.43
Gompertz	-0.71	-4.16	-0.77	-3.73	-0.37	-0.40	-0.39	0.23
Weibull	-0.21	3.87	0.21	3.83	0.16	0.05	0.10	0.18
Exponential	-0.53	-0.17	-0.13	-0.51	-0.07	-0.20	-0.08	0.19

True frailty: Gamma
Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	4.39	-9.94	-10.18	-10.04	-9.82	-10.66	-10.49	-10.46
Weibull-Weibull (1)	15.43	-5.72	-5.00	-5.25	-6.63	-6.71	-6.73	-6.34
Gompertz	1.16	-13.29	-11.42	-12.97	-11.52	-11.60	-11.55	-11.63
Weibull	1.51	-8.49	-10.15	-8.98	-9.87	-9.98	-9.94	-9.88
Exponential	4.18	-10.74	-10.71	-10.75	-10.51	-10.61	-10.56	-10.52

True frailty: Log-Normal
Model frailty: Gamma

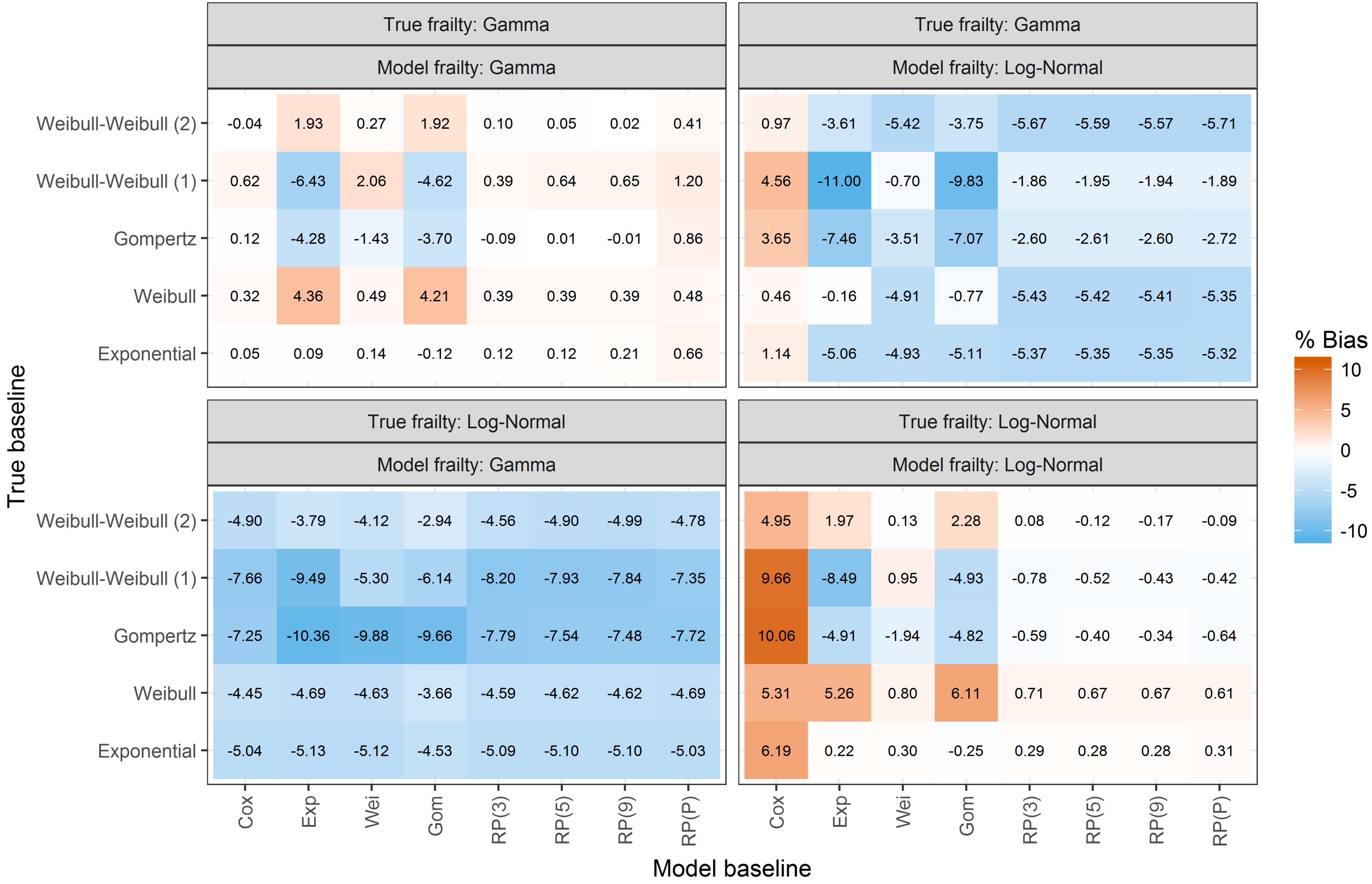
	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	4.13	6.84	4.49	7.17	4.72	4.23	4.35	4.40
Weibull-Weibull (1)	9.77	-1.46	11.87	2.36	9.92	10.06	10.08	10.33
Gompertz	3.75	-2.37	1.94	-2.18	3.71	3.85	3.87	3.76
Weibull	3.23	8.37	3.47	8.84	3.27	3.28	3.30	3.23
Exponential	4.71	4.99	4.97	5.15	4.96	4.91	4.94	5.08

True frailty: Log-Normal
Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	4.80	1.39	-0.35	1.54	0.18	-0.54	-0.38	-0.41
Weibull-Weibull (1)	12.80	-5.21	3.21	-2.44	2.31	2.49	2.57	2.80
Gompertz	3.88	-4.50	-0.43	-5.07	-0.33	-0.16	-0.15	-0.25
Weibull	3.86	5.62	0.71	5.89	0.60	0.59	0.59	0.50
Exponential	5.54	0.27	0.35	-0.51	0.42	0.35	0.38	0.40

Scenario: 50 clusters of 50 individuals each, with a true frailty variance of 1.25

Results: % bias of loss in life expectancy



True frailty: Gamma
Model frailty: Gamma

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	-0.04	1.93	0.27	1.92	0.10	0.05	0.02	0.41
Weibull-Weibull (1)	0.62	-6.43	2.06	-4.62	0.39	0.64	0.65	1.20
Gompertz	0.12	-4.28	-1.43	-3.70	-0.09	0.01	-0.01	0.86
Weibull	0.32	4.36	0.49	4.21	0.39	0.39	0.39	0.48
Exponential	0.05	0.09	0.14	-0.12	0.12	0.12	0.21	0.66

True frailty: Gamma
Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	0.97	-3.61	-5.42	-3.75	-5.67	-5.59	-5.57	-5.71
Weibull-Weibull (1)	4.56	-11.00	-0.70	-9.83	-1.86	-1.95	-1.94	-1.89
Gompertz	3.65	-7.46	-3.51	-7.07	-2.60	-2.61	-2.60	-2.72
Weibull	0.46	-0.16	-4.91	-0.77	-5.43	-5.42	-5.41	-5.35
Exponential	1.14	-5.06	-4.93	-5.11	-5.37	-5.35	-5.35	-5.32

True frailty: Log-Normal
Model frailty: Gamma

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	-4.90	-3.79	-4.12	-2.94	-4.56	-4.90	-4.99	-4.78
Weibull-Weibull (1)	-7.66	-9.49	-5.30	-6.14	-8.20	-7.93	-7.84	-7.35
Gompertz	-7.25	-10.36	-9.88	-9.66	-7.79	-7.54	-7.48	-7.72
Weibull	-4.45	-4.69	-4.63	-3.66	-4.59	-4.62	-4.62	-4.69
Exponential	-5.04	-5.13	-5.12	-4.53	-5.09	-5.10	-5.10	-5.03

True frailty: Log-Normal
Model frailty: Log-Normal

	Cox	Exp	Wei	Gom	RP(3)	RP(5)	RP(9)	RP(P)
Weibull-Weibull (2)	4.95	1.97	0.13	2.28	0.08	-0.12	-0.17	-0.09
Weibull-Weibull (1)	9.66	-8.49	0.95	-4.93	-0.78	-0.52	-0.43	-0.42
Gompertz	10.06	-4.91	-1.94	-4.82	-0.59	-0.40	-0.34	-0.64
Weibull	5.31	5.26	0.80	6.11	0.71	0.67	0.67	0.61
Exponential	6.19	0.22	0.30	-0.25	0.29	0.28	0.28	0.31

Scenario: 50 clusters of 50 individuals each, with a true frailty variance of 1.25

Applications

Kidney data

```
. webuse catheter, clear
(Kidney data, McGilchrist and Aisbett, Biometrics, 1991)

. describe
Contains data from http://www.stata-press.com/data/r15/catheter.dta
  obs:            76                          Kidney data, McGilchrist and Aisbett, Biometrics, 1991
 vars:             9                          1 May 2016 15:58
 size:         1,064
--------------------------------------------------------------------------------
              storage   display    value
variable name   type    format     label      variable label
--------------------------------------------------------------------------------
patient         byte    %7.0g                 Patient ID
time            int     %9.0g                 recurrence times in days
infect          byte    %4.0g                 1=infection; 0=right-censoring
age             float   %6.0g                 Patient age
female          byte    %6.0g                 Patient gender (0=male, 1=female)
[...]
--------------------------------------------------------------------------------


. summarize

    Variable |        Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
     patient |         76        19.5    11.03872          1         38
        time |         76    97.68421    128.3424          2        562
      infect |         76    .7631579    .4279695          0          1
         age |         76    43.69737    14.73795         10         69
      female |         76    .7368421    .4432733          0          1
-------------+---------------------------------------------------------
[...]

. stset time, fail(infect)
```

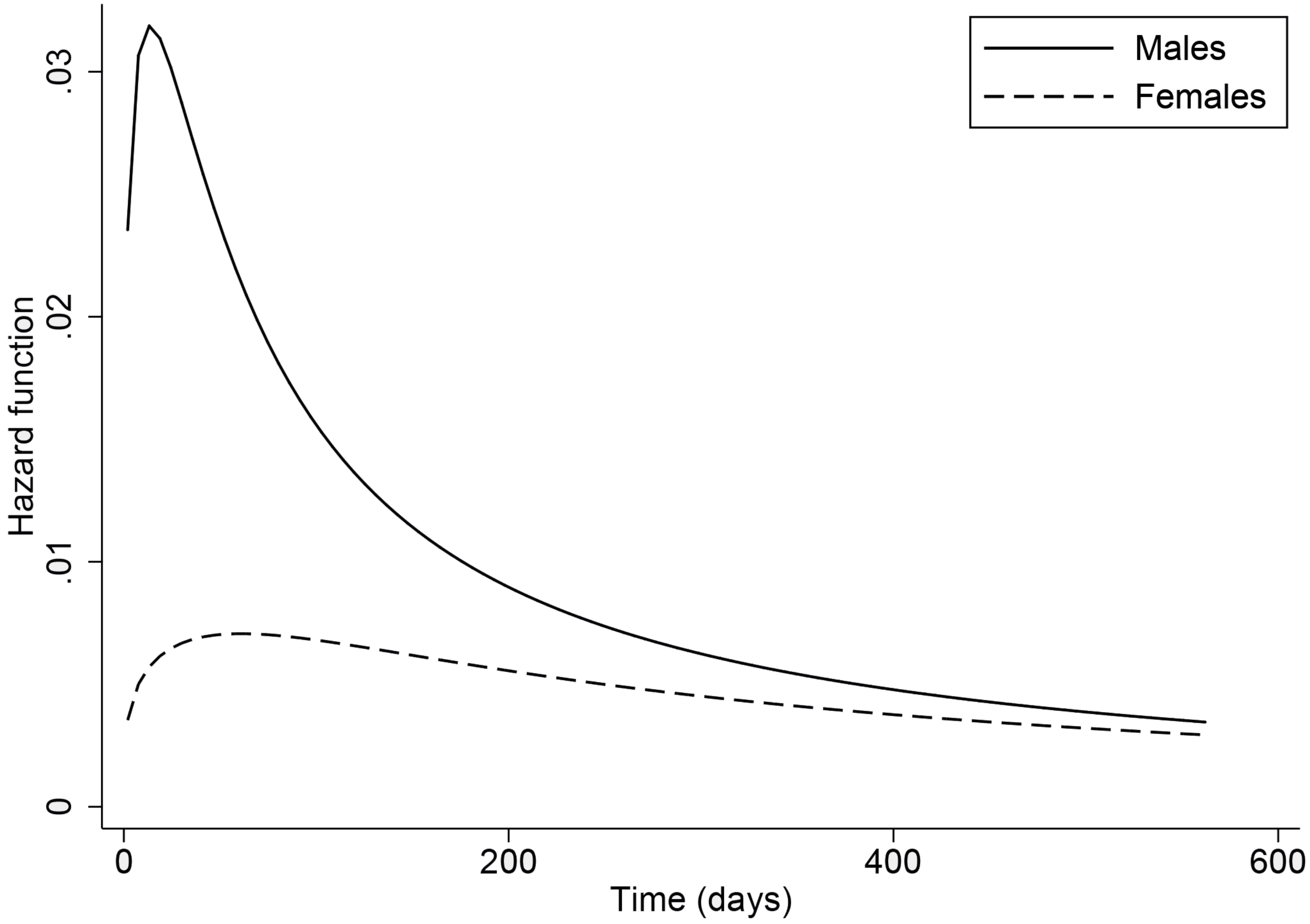
Kidney data: Weibull regression model

```
. streg age female, dist(weibull)

[...]

Weibull PH regression

No. of subjects =           76                  Number of obs    =         76
No. of failures =           58
Time at risk    =         7424
                                                LR chi2(2)       =       8.05
Log likelihood  =   -103.44362                  Prob > chi2      =     0.0179

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.004122   .0092317     0.45   0.655     .9861902     1.02238
      female |   .4361966   .1250348    -2.89   0.004     .2487066     .765028
       _cons |   .0206079   .0136819    -5.85   0.000     .0056093    .0757113
-------------+----------------------------------------------------------------
       /ln_p |  -.1028083   .0935237    -1.10   0.272    -.2861114    .0804949
-------------+----------------------------------------------------------------
           p |      .9023   .0843865                      .7511789    1.083823
         1/p |   1.108279   .1036504                      .9226596    1.331241
------------------------------------------------------------------------------
```

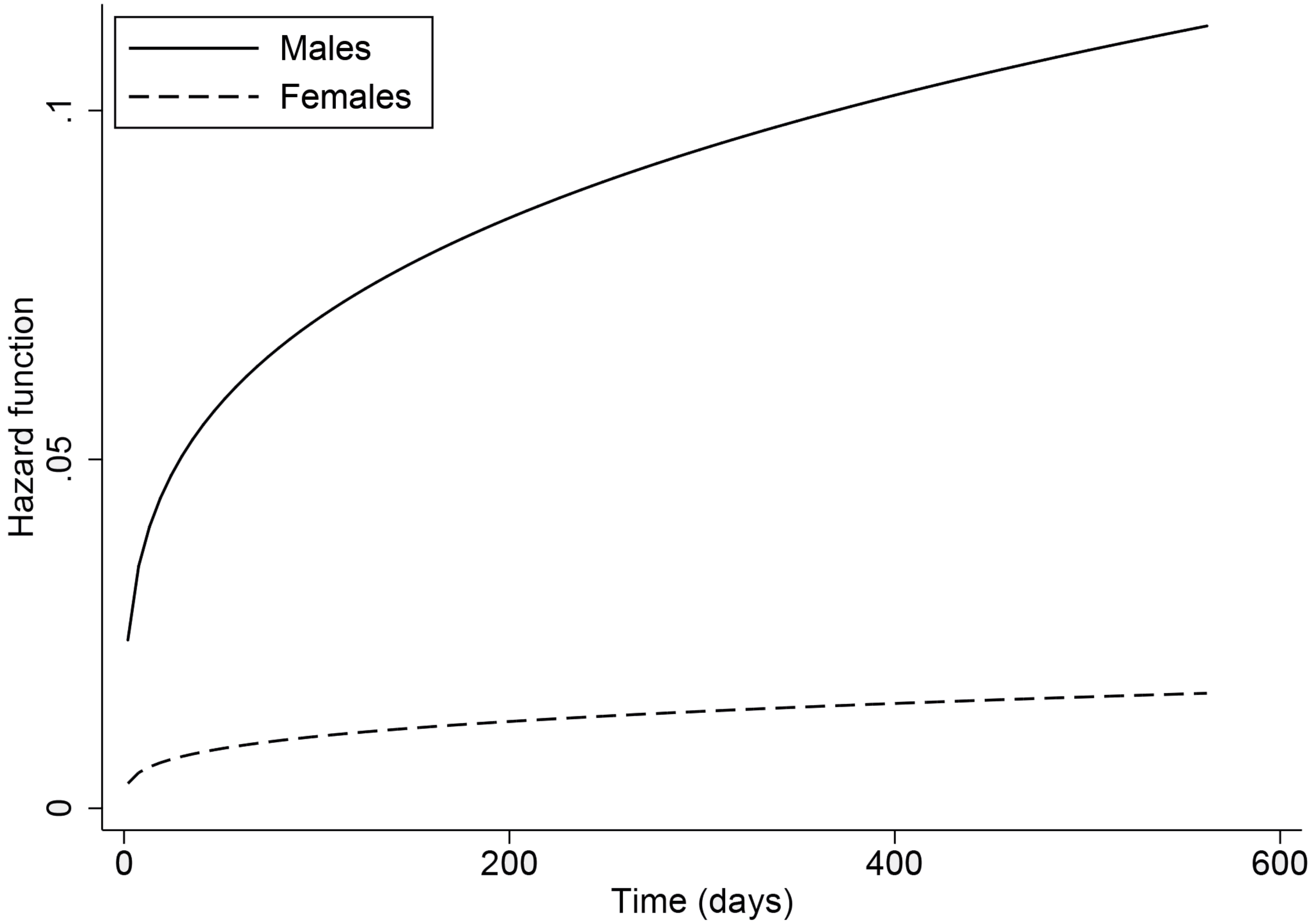
Kidney data: adding a shared Gamma frailty

```
. streg age female, dist(weibull) frailty(gamma) shared(patient)

[...]

Weibull PH regression

Gamma shared frailty                            Number of obs      =         76
Group variable: patient                         Number of groups   =         38
                                                Obs per group:
No. of subjects =           76                                min =          2
No. of failures =           58                                avg =          2
Time at risk    =         7424                                max =          2

                                                LR chi2(2)         =      14.81
Log likelihood  =   -98.006931                  Prob > chi2        =     0.0006

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.008569   .0132847     0.65   0.517      .982865    1.034946
      female |   .1470075   .0807275    -3.49   0.000     .0501086    .4312876
       _cons |   .0108047    .009282    -5.27   0.000     .0020061    .0581915
-------------+----------------------------------------------------------------
       /ln_p |   .2410369   .1336503     1.80   0.071    -.0209129    .5029866
    /lntheta |  -.4546298   .4747326    -0.96   0.338    -1.385089     .475829
-------------+----------------------------------------------------------------
           p |   1.272568   .1700791                      .9793043    1.653653
         1/p |   .7858127   .1050241                      .6047219    1.021133
       theta |   .6346829   .3013047                      .2503016    1.609348
------------------------------------------------------------------------------
LR test of theta=0: chibar2(01) = 10.87                Prob >= chibar2 = 0.000
```

Kidney data: population baseline hazard



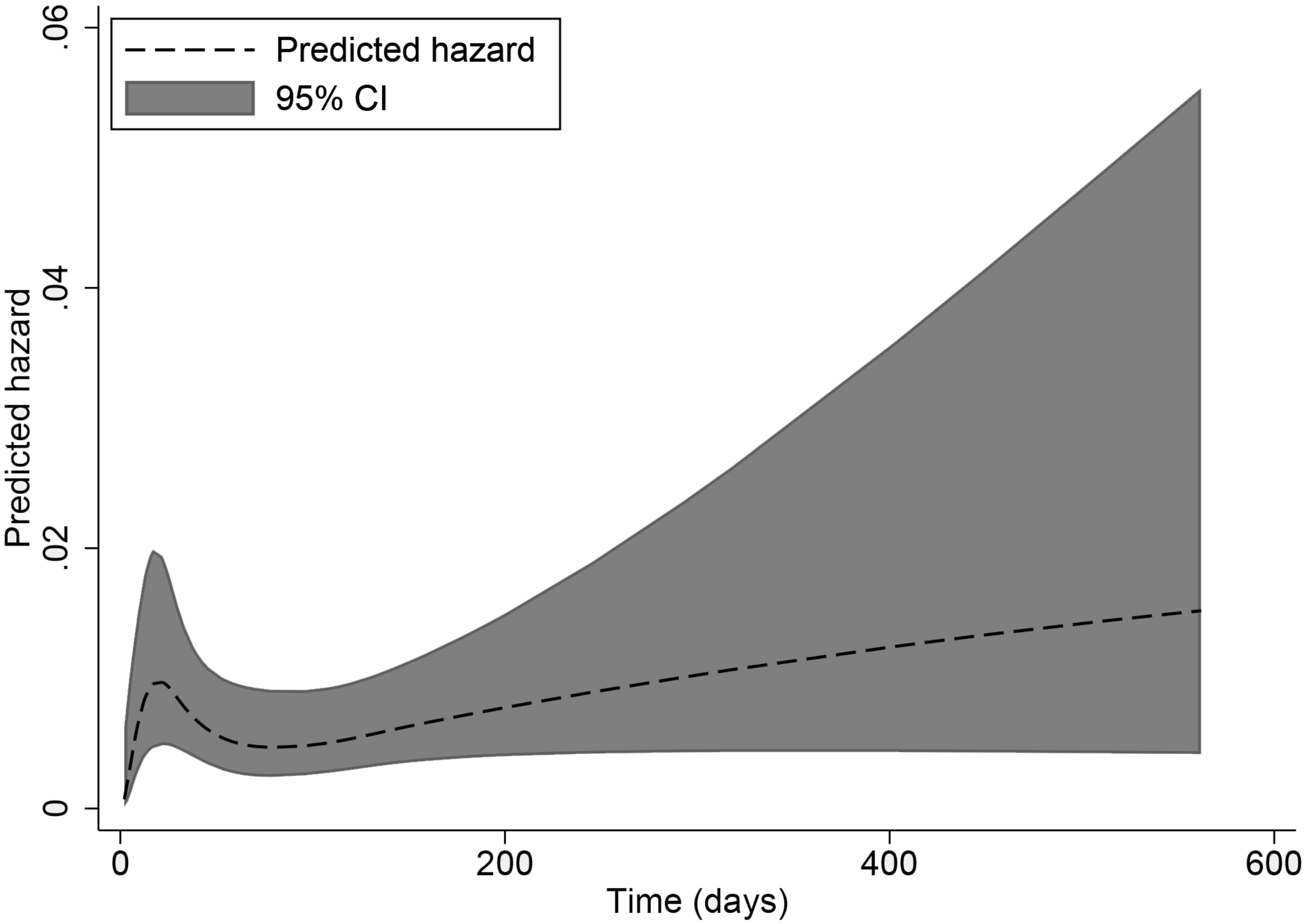
Kidney data: conditional baseline hazard



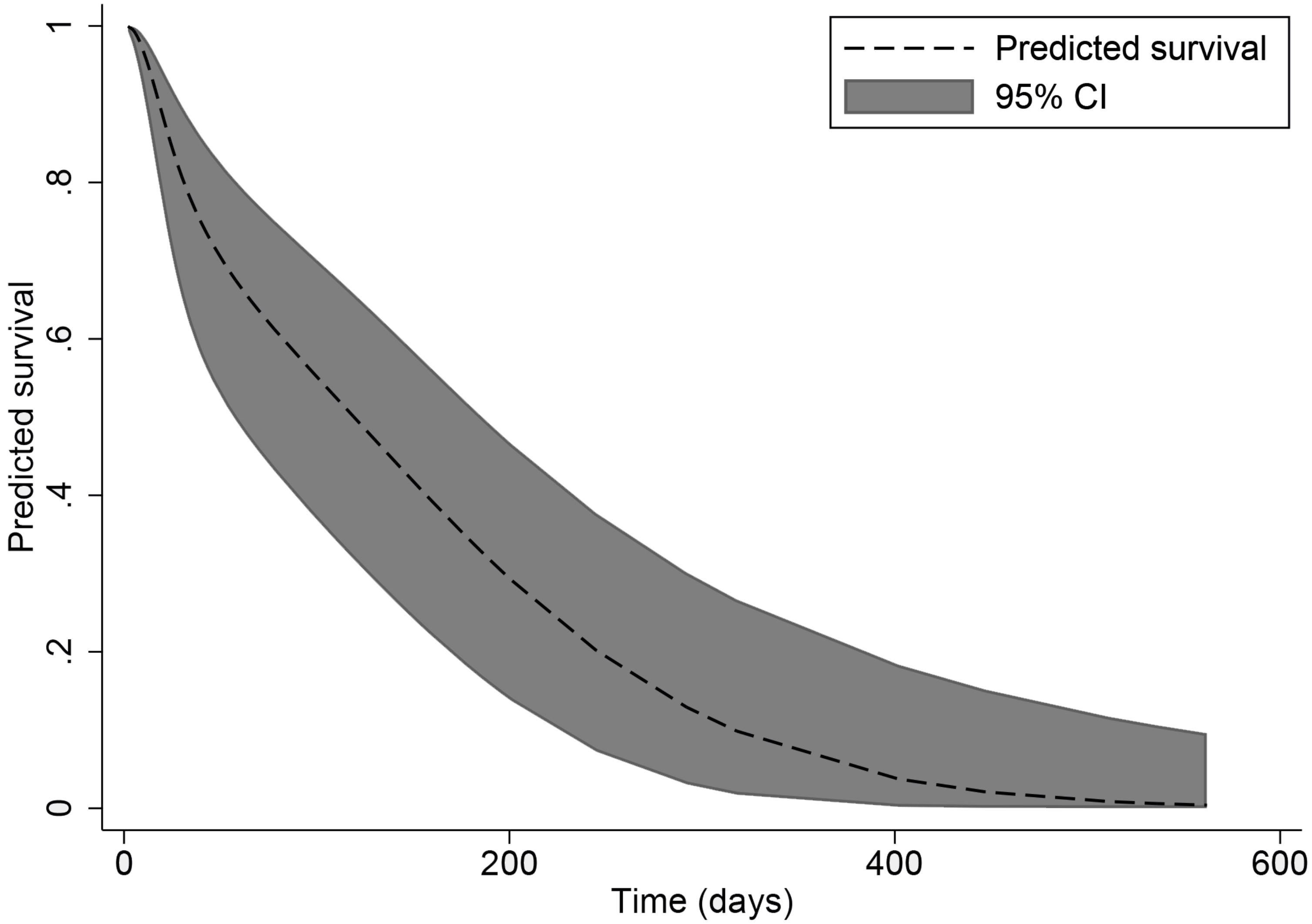
Kidney data: random intercept flexible parametric model

```
. stmixed age female || patient:, dist(fpm) df(3)

[...]

Mixed effects survival regression                Number of obs.    =         76
Panel variable: patient                          Number of panels =         38

Log-likelihood = -94.86354

------------------------------------------------------------------------------
             | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
xb           |
         age |   1.007186   .0130094     0.55   0.579     .9820077    1.033009
      female |   .2309644   .1135461    -2.98   0.003      .088121    .6053556
       _rcs1 |   5.771724   1.389549     7.28   0.000     3.600625     9.25195
       _rcs2 |   1.425724   .2397905     2.11   0.035     1.025353     1.98243
       _rcs3 |   .8005217   .0762482    -2.34   0.019     .6641982    .9648248
       _cons |   .7059908   .4738904    -0.52   0.604      .189425    2.631243
------------------------------------------------------------------------------


------------------------------------------------------------------------------
  Random effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
patient: Identity            |
                   sd(_cons) |   .8000731   .2681015      .4148539    1.542994
------------------------------------------------------------------------------
  Survival submodel: Flexible parametric model
 Integration method: Adaptive Gauss-Hermite quadrature using 9 nodes
```

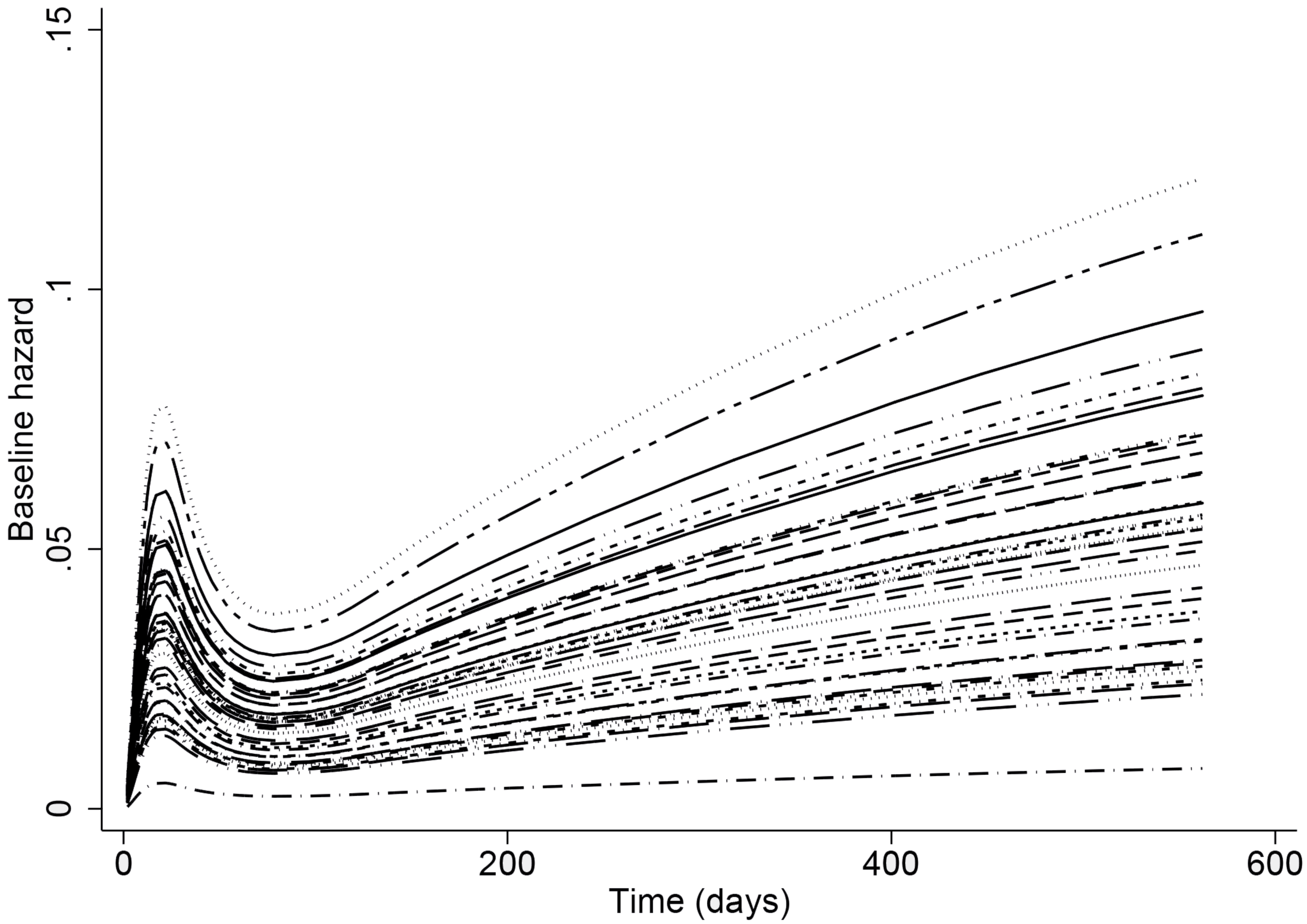
Kidney data: hazard for a 45-years old female



Kidney data: survival for a 45-years old female



Kidney data: patient-specific baseline hazards



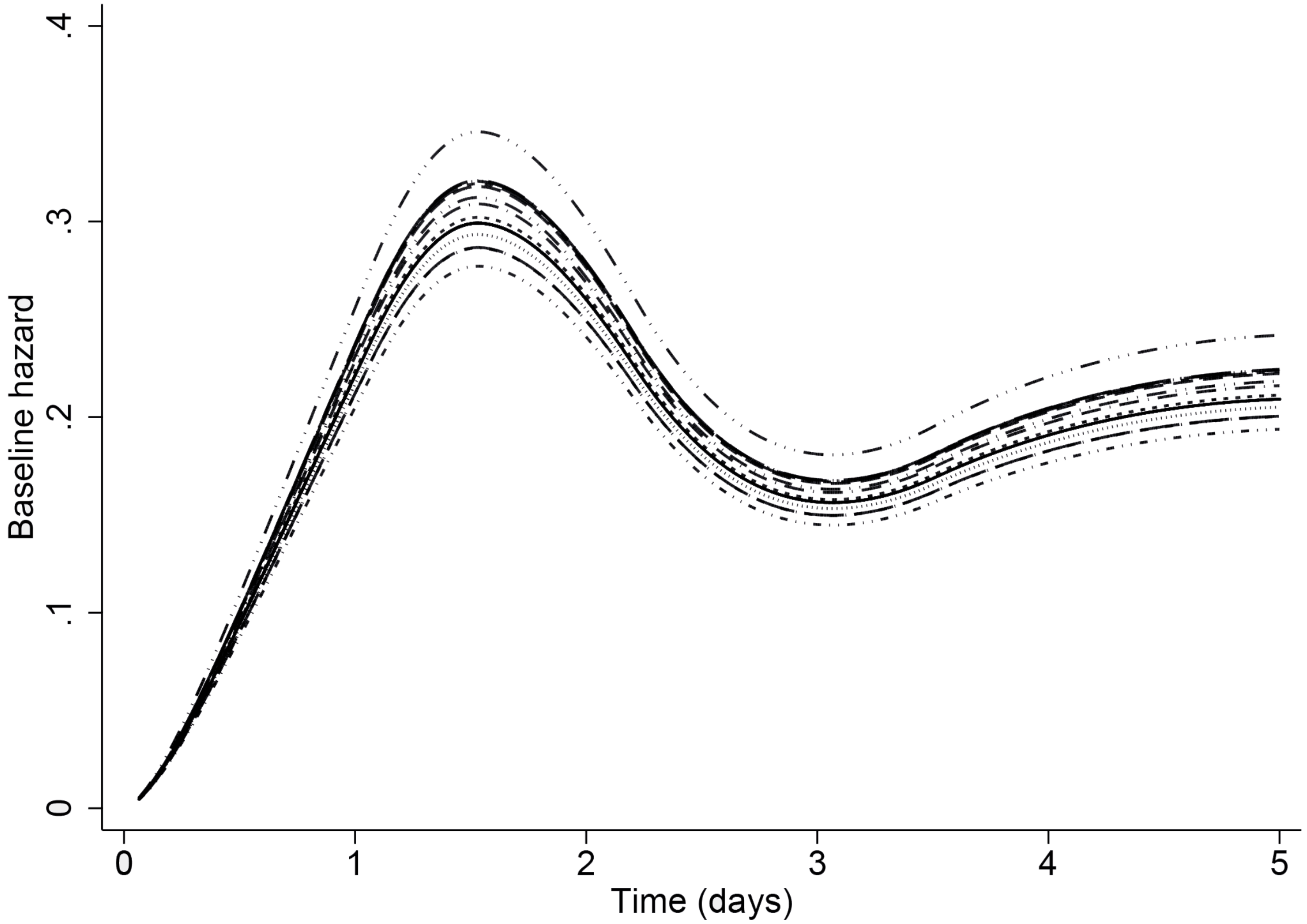
IPD meta-analysis

```
. describe

Contains data
  obs:         7,500
 vars:             7
 size:       217,500
------------------------------------------------------------
              storage   display    value
variable name   type    format     label      variable label
------------------------------------------------------------
trial           float   %9.0g
trteffect       float   %9.0g
trt             float   %9.0g
trteffectsim    float   %9.0g
stime           double  %10.0g
_survsim_rc     float   %9.0g
event           byte    %8.0g
------------------------------------------------------------


. summarize

    Variable |        Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
       trial |      7,500           8    4.320782          1         15
   trteffect |      7,500   -.3520517    1.009164   -2.04969   1.654998
         trt |      7,500       .4888    .4999079          0          1
trteffectsim |      7,500   -.1705032    .7221885   -2.04969   1.654998
       stime |      7,500    3.410759    1.690242   .0640601          5
-------------+---------------------------------------------------------
 _survsim_rc |      7,500      1.3072    1.487657          0          3
       event |      7,500    .5642667    .4958857          0          1
```

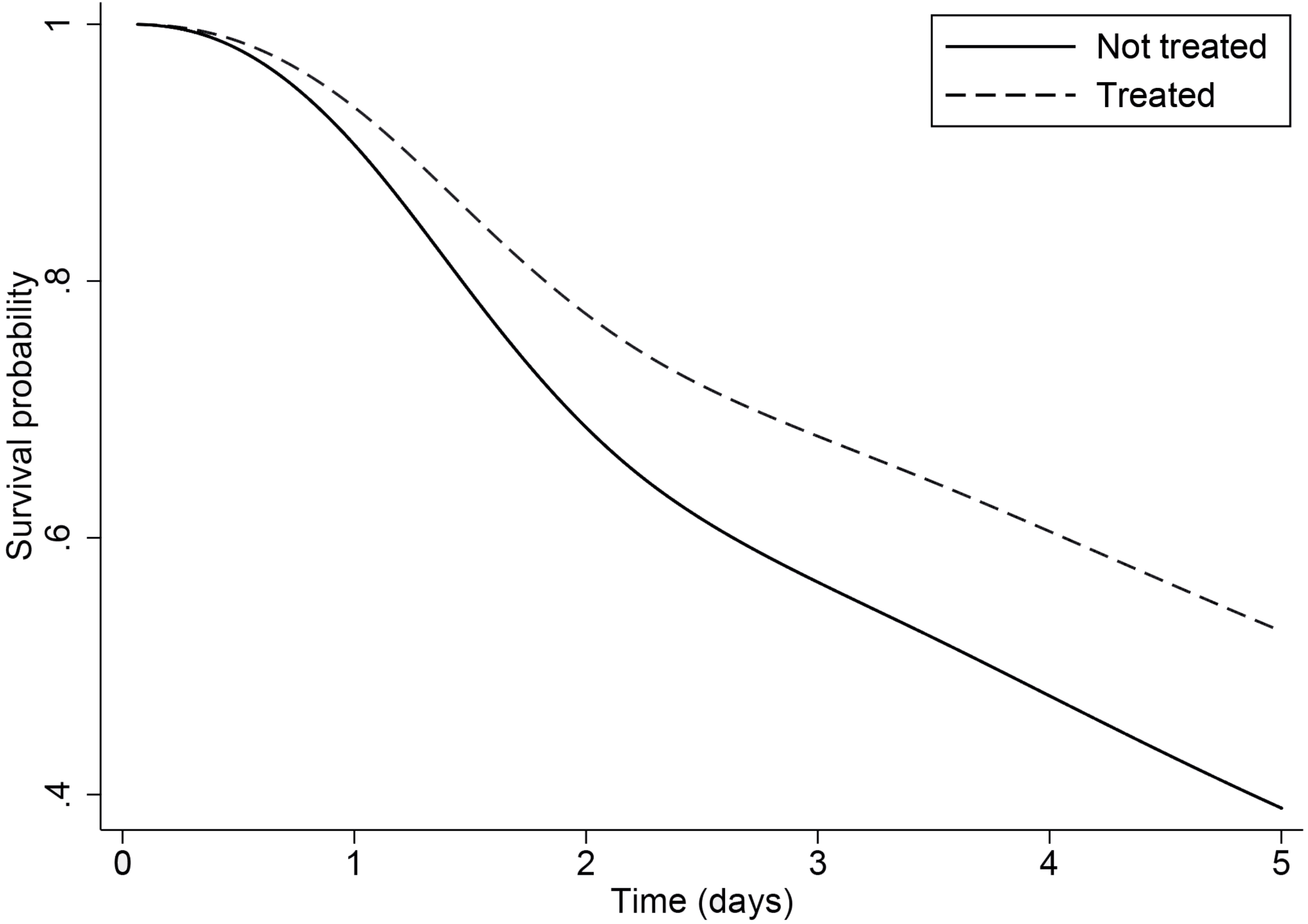
IPD meta-analysis

```
. stmixed trt trialvar2-trialvar15 || trial: trt, nocons dist(fpm) df(5) gh(35)

[...]

Mixed effects survival regression                Number of obs.    =       7500
Panel variable: trial                            Number of panels =          15

Log-likelihood = -8088.0481

------------------------------------------------------------------------------
             | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
xb           |
         trt |   .6787073   .1896202    -1.39   0.165     .3925275    1.173532
   trialvar2 |   1.062548   .1200946     0.54   0.591     .8514152    1.326037
[...]
  trialvar15 |   1.071724   .1208388     0.61   0.539     .8592278    1.336772
       _rcs1 |   2.899527   .0450234    68.56   0.000     2.812612    2.989128
       _rcs2 |   1.253025   .0189086    14.95   0.000     1.216507    1.290638
       _rcs3 |   1.068354   .0097081     7.28   0.000     1.049495    1.087552
       _rcs4 |   .9849881   .0042694    -3.49   0.000     .9766557    .9933916
       _rcs5 |   .9852981   .0021529    -6.78   0.000     .9810876    .9895267
       _cons |   .4441625   .0367203    -9.82   0.000     .3777205    .5222919
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
trial: Identity              |
                     sd(trt) |   1.073018   .2006323      .7437893    1.547976
------------------------------------------------------------------------------
  Survival submodel: Flexible parametric model
 Integration method: Adaptive Gauss-Hermite quadrature using 35 nodes
```

IPD: trial specific baseline hazards



IPD: survival probability



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- I have introduced a family of models that:
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- Bear in mind computational time and accuracy of numerical integration
- It is important to correctly specify the model if using fully parametric distributions; flexible parametric models are a great alternative, with or without mixed effects
- Don't be afraid of using more complex, non standard models if you have complex data!

References

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Simulating IPD data

```
clear
set seed 2139875

* 15 trials
set obs 15
gen trial = _n

* trial specific treatment effect (log hazard ratio)
* from a normal distribution with mean -0.5, and sd 1
gen trteffect = rnormal(-0.5,1)

* 500 patients per trial
expand 500

* patient level treatment group indicator
gen trt = runiform() > 0.5

* patient specific treatment effect to use in simulations
gen trteffectsim = trt * trteffect

* simulate survival times from a mixture Weibull distribution, incorporating the random treatment effect
* and administrative censoring at time t = 5
* if not already installed, install survsim from ssc:
*   ssc install survsim
survsim stime event, mixture lambdas(0.03 0.3) gammas(1.9 2.5) pmix(0.7) maxtime(5) covariates(trteffectsim 1)
```