Library of parametric time-to-event (TTE) models for the MonolixSuite

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Parametric TTE models

Compared to the non-parametric approach or Cox semi-parametric models, parametric models present several advantageous possibilities:

- use of frailty or mixture models
- joint PK-TTE or PD-TTE models
- simulations of new populations or dosing

TTE modeling with the MonolixSuite

With the MonolixSuite, exactly observed, right censored and interval censored data can be modeled, via parametric models.

A library of TTE models is available, which captures the most common survival shapes.

Model definition

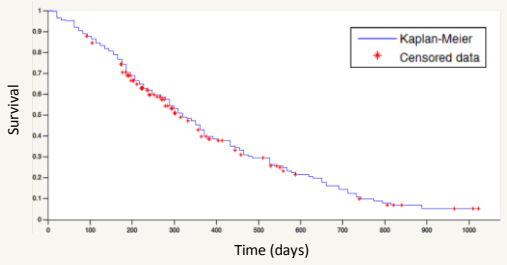
Models are defined via the hazard. The hazard function h(t) is the instantaneous rate of an event, given that it has not already occurred.

Example using the MIxtran language:

```
EQUATION:
h = 1/Te    ; example for an exponential model
DEFINITION:
Event = {type=event, maxEventNumber=1, hazard=h}
```

NCCTG lung cancer study

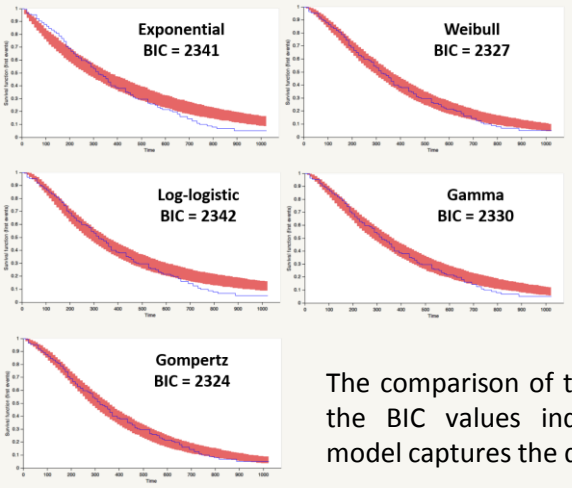
The North Central Cancer Treatment Group (NCCTG) data set records the survival of 228 patients with advanced lung cancer [1]. 63 are right censored.



Choice of a hazard model

We fit each model of the library to find the one that best captures the data.

Below we show empirical Kaplan-Meier curve and the VPC-like 90% prediction interval obtained via simulations in Monolix.



The comparison of these diagnostic plots and of the BIC values indicates that the Gompertz model captures the data set best.

The Monolix statistical tests and diagnostic plots render the model development process straightforward.

Library of models

Exponential model

$$h = \frac{1}{T_e}$$

Weibull model

$$h = \frac{p}{T_e}\left(\frac{t}{T_e}\right)^{p-1}$$

Uniform model

$$h = \frac{1}{T_e - t}$$

Gompertz model

$$h = \frac{k}{T_e'} e^{\frac{t}{T_e'}}$$

with:

$$T_e' = \frac{T_e}{\ln\left(1 + \frac{\ln 2}{k}\right)}$$

Gamma model

$$h = \frac{\frac{\alpha}{T_e}\left(\frac{\alpha t}{T_e}\right)^{\alpha-1} e^{-\frac{\alpha t}{T_e}}}{\Gamma(\alpha) - \gamma(\alpha, \frac{\alpha t}{T_e})}$$

Log-logistic model

$$h = \frac{\frac{s}{T_e}\left(\frac{t}{T_e}\right)^{s-1}}{1 + \left(\frac{t}{T_e}\right)^{s}}$$

Generalized gamma model

$$h = \frac{\frac{p}{T_e'}\left(\frac{t}{T_e'}\right)^{\alpha-1} e^{-\left(\frac{t}{T_e'}\right)^{p}}}{\Gamma\left(\frac{\alpha}{p}\right) - \gamma\left(\frac{\alpha}{p}, \left(\frac{t}{T_e'}\right)^{p}\right)}$$

with: $T_e' = T_e \frac{\Gamma\left(\frac{\alpha}{p}\right)}{\Gamma\left(\frac{\alpha+1}{p}\right)}$

Γ is gamma function

γ is lower incomplete gamma function

Covariate modeling

We next evaluate the prognostic performance of the recorded covariates using a backward strategy based on Wald tests. From the base model with all covariates, covariates are stepwise removed if the beta parameters are not significantly different from zero.

Base model: $T_{e,i} = T_{e,pop} e^{\beta_{sex}[\text{if } sex=M] + \beta_{age}\text{age} + \beta_{ecogPH}\text{ecogPH} + \beta_{karnoPH}\text{karnoPH} + \beta_{karnoPAT}\text{karnoPAT}_e \eta_i}$

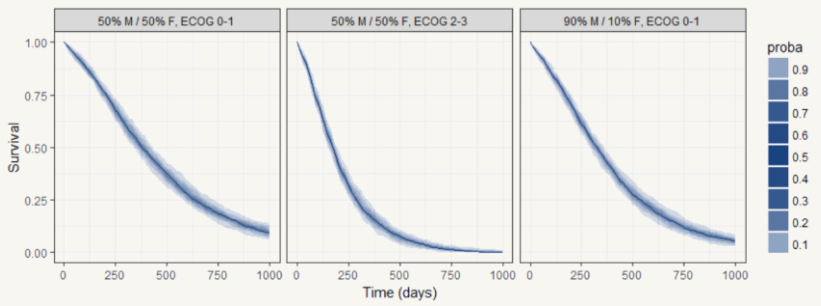
Covariates on Te					Wald test
age	sex	ECOG by patient	karno score by physician	karno score by patient	
x	x	x	x	x	karnoPH can be removed (p=0.41)
x	x	x	-	x	age can be removed (p=0.68)
-	x	x	-	x	karnoPAT can be removed (p=0.043)
-	x	x	-	-	all significant => final model

Predictions

The parametric nature of the model permits to analytically calculate the probability to survive 6, 12 or 24 months depending on the covariates.

		Probability to survive at least		
		6 months	1 year	2 years
Male	ECOG 0	82%	57%	9%
	ECOG 1	71%	31%	≈ 0%
	ECOG 2	53%	5%	≈ 0%
	ECOG 3	26	≈ 0%	≈ 0%
Female	ECOG 0	89%	75%	41%
	ECOG 1	83%	60%	13%
	ECOG 2	73%	35%	0.2%
	ECOG 3	56%	8%	≈ 0%

Using Simulx, the expected survival of populations with complex mixtures of covariates can be simulated and compared. Replicates can be used to calculate prediction intervals.



The survival probability for a typical subject with a given ECOG and sex can easily be calculated, as well as the survival of cohorts with combination of covariates.

[1] Loprinzi et al. (1994), Prospective evaluation of prognostic variables from patient-completed questionnaires, *Journal of Clinical Oncology*, 12(3), 601–607.