# Bayesian models for physical and virtual patients

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## Summary

Standard statistical models are proposed for the endpoints of the clinical trial. A proportional hazards model for time to conversion and a generalised linear model for incidence of recurrence, and it is proposed that different survival and link functions should be explored for model fitting and information criteria used for their selection. Three different prior structures are proposed for benchmarking, variable selection and the inclusion of expert opinion, respectively. We outline s mechanism for combining the information from the *in silico* and *in vivo* data capable of accommodating varying degrees of agreement between these two sources.

# 1 Modelling approach

Focusing on the main objective of the project, we entertain models for the main endpoints of the STriTuVaD clinical trails, with the aim of making them amenable to sharing information with the data from the UISS-TB computer experiments. We complete the Bayesian models with three alternative prior structures which can help to benchmark the ensuing inferences, select relevant features and include expert opinions from the consortium members. We then propose a methodology for combining both sources of information, capable of allowing varying degrees of influence of the *in silico* data over the clinical trails.

According to the clinical dossier, the two (main) endpoints of the trial are

- time to inactivation, and
- incidence of recurrence,

hence we propose to use industry standard models for each endpoint (Lesaffre and Lawson, 2012; McCullagh and Nelder, 1989), *i.e.*

- proportional hazards, and
- generalised linear model (with logit link),

respectively. These models have been used successfully in related scenarios (see *e.g.* Akinsola *et al.*, 2018; Javaid *et al.*, 2018; Liu *et al.*, 2018; Svensson and Karlsson, 2017; Tierney *et al.*, 2014) and thus seem appropriate as starting points for developing our methodology.

## 1.1 Formal models

In order to formalise our approach, let $t_i$ represent the *time to sputum conversion* for each patient $i = 1, \ldots, m$; and $\boldsymbol{x}_i = \{x_{i1}, \ldots, x_{ip}\}$ the corresponding *vector of features* or characteristics. We model the hazard function,

$$h(t_i) = \frac{f(t_i)}{S(t_i)}$$

where $f(t_i)$ is the density of the endpoint and $S(t_i) = 1 - F(t_i)$ its survival function, with

$$F(t_i) = \int_0^{t_i} f(z)\, \mathrm{d}z,$$

the CDF of the endpoint. We assume the hazard function depends on a linear combination of the features, $h(t_i) = g(\boldsymbol{\beta}\boldsymbol{x}_i')$, with $\boldsymbol{\beta} = \{\beta_1, \ldots, \beta_p\}$ a *vector of coefficients* associated with the patient features. The choice of $f(\cdot)$ will determine the shape of $g(\cdot)$, the most common choice being a Weibull distribution,

$$f(t_i \mid \boldsymbol{\beta}, \boldsymbol{x}_i) = \mu_i \lambda t_i^{\lambda-1} \exp\left[-\mu_i t_i^{\lambda}\right],$$

with $\mu_i = \boldsymbol{\beta}\boldsymbol{x}_i'$. As mentioned above, we will fit the model with different choices of $f(\cdot)$ in order to assess the robustness of the hazard estimates to its choice and eventually decide on the most suitable choice, informed by a suitable information criterion (Casellas, 2016; Guyot *et al.*, 2016; Wang *et al.*, 2017).

Regarding *recurrence*, let

$$r_i = \begin{cases} 1 & \text{the } i\text{-th patient has relapsed} \\ 0 & \text{otherwise} \end{cases},$$

with $\mathrm{P}[r_i = 1] = \theta_i$. We model, $g(\theta_i) = \boldsymbol{\beta}\boldsymbol{x}_i'$ and define

$$g(\theta_i) = \log \frac{\theta_i}{1 - \theta_i};$$

*i.e.* a generalised linear model (GLM) with logit link. Here we will also explore the appropriateness of alternative link functions, using model comparison techniques (Czado and Raftery, 2006; Yunusbaeva *et al.*, 2019).

## 1.2 Prior structure

To complete the Bayesian model, we should specify a prior distribution for all unknown parameters. In order to investigate different aspects of model fit and carry out a sensitivity

analysis, we will entertain three options on the coefficients, $\boldsymbol{\beta}$:

- A conventional Gaussian prior, $\pi(\beta) = \mathrm{N}_p\left(\boldsymbol{x} \mid 0, \Omega^{-1}\right)$, with $\Omega = \omega \mathrm{I}_p$, where $\mathrm{I}_p$ is the identity matrix of size $p$ and $\pi(\omega) = \mathrm{Ga}(\omega \mid a, b)$, a Gamma distribution with parameters $(a, b)$ fixed to reflect relative little prior information.
- A shrinkage prior to perform variable selection on the vector of features (Alenazi *et al.*, 2019)
- An informative prior, using expert information elicited from the members of the consortium.

UISS-TB produces *in silico* data for a number of biological entities (*e.g.* cytokines, chemokines, etc), for each virtual patient identified through a vector of features (*e.g.* bacterial load, immunological profile, BMI, etc.), of length $p = 26$—for details see the consortium report (D2.3). The clinical trials will not produce such detailed characterisation and thus we will adapt our modelling accordingly. In any case, the models will be formally identical for both sources of data.

## 2 Combining both sources of information

Our modelling approach for combining the information from the *in silico* and *in vivo* data is to treat the former as a prior in our Bayesian model for the latter. For time to conversion, let

$$f(\boldsymbol{t} \mid \boldsymbol{\beta}, \mathrm{X}) = \prod_{i=1}^{m} f(t_i \mid \boldsymbol{\beta}, \boldsymbol{x}_i),$$

denote the joint distribution of the time to conversion from the *in silico* experiment, where the matrix of features is gathered in $\mathrm{X} = [\boldsymbol{x}_1, \ldots, \boldsymbol{x}_m]$ and $\pi(\boldsymbol{\theta})$ the prior as in Section 1.2, then

$$\pi(\boldsymbol{\beta} \mid \mathrm{D}_s) \propto f(\boldsymbol{t} \mid \boldsymbol{\beta}, \mathrm{X})\ \pi(\boldsymbol{\beta}),$$

with $\mathrm{D}_s$ representing the data from the *in silico* experiment, will be used as the prior for the model used for the *in vivo* data. Now, assume $\mathrm{L}(\boldsymbol{\beta}\ ;\ \mathrm{D}_v)$ is the likelihood from the clinical

trial, then the posterior distribution for the coefficients is

$$\pi(\boldsymbol{\beta} \mid \mathrm{D}) \propto \mathrm{L}(\boldsymbol{\beta}\,;\, \mathrm{D}_v)\, \pi(\boldsymbol{\beta} \mid \mathrm{D}_s),$$

with $\mathrm{D} = \mathrm{D}_s \cup \mathrm{D}_v$. This in turn will be used to derive the posterior distribution of the hazard ratios, providing not only point estimates, but naturally propagating the uncertainty from the computer and physical experiments onto the hazard functions.

Likewise for incidence of recurrence, if we denote the joint distribution for the synthetic data by

$$f(\boldsymbol{r} \mid \boldsymbol{\beta}, \mathrm{X}) = \prod_{i=1}^{m} f(r_i \mid \boldsymbol{\beta}, \boldsymbol{x}_i),$$

we will get the corresponding posterior in a similar fashion.

## 2.1 Weights and information

As it stands, $\pi(\boldsymbol{\beta} \mid \mathrm{D})$ takes the information "at face value"; *i.e.* the same weight is assigned to the information from the computer experiment and the clinical trial. To address this issue, we will use

$$\pi(\boldsymbol{\beta} \mid \mathrm{D}) \propto \mathrm{L}(\boldsymbol{\beta}\,;\, \mathrm{D}_v)\, \pi(\boldsymbol{\beta} \mid \mathrm{D}_s)^{\alpha},$$

with $0 < \alpha < 1$, with $\alpha$ acting as a weight for the information from the *in silico* data (O'Hagan, 1995, 1997). We plan to follow Haddad *et al.* (2017) and express $\alpha = m/M$, with $M$ the size of the virtual patient cohort and $0 < m < M$ the *effective size* of the *in silico* trial, so larger values of $m$ can be interpreted as better agreement of the computer simulations with the physical patients. To provide a measure of agreement, assume $\phi$ is the endpoint of the trial—*i.e.* the context of use of the computer model— and let $\pi(\phi_s \mid D_s)$ and $\pi(\phi_c \mid D_v)$ be the posterior distribution from the virtual cohort and the physical with the conventional prior, respectively. One would expect $p = \mathrm{P}[\phi_c < \phi_s]$ to be close to 0 or 1 if the virtual cohort provided dissimilar information to the physical, thus $p$ can be treated as a measure of disagreement. We can construct a penalty function, $m = h(p) \times m_{\max}$, based on $p$, in such a way that $m \to 0$ if $p \to 0, 1$ and $m \to m_{\max}$ if $p \to 1/2$, with $m_{\max}$ is the number of

maximum virtual patients allowed. Formally,

$$h(p) = \begin{cases} 1 - \exp\left[-(p/\lambda)^k\right] & p < 0.5 \\ 1 - \exp\left[-((1-p)/\lambda)^k\right] & p \geq 0.5 \end{cases},$$

with $\lambda < 1$.

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