R-Based VPC for Time-To-Event Models with Non-linear Hazard Functions

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Background and Objectives

Parametric survival models with time-varying covariates can readily be implemented in current pharmacometrics non-linear mixed-effects fitting software (e.g., Phoenix NLME, NONMEM, MONOLIX, pmxStan, etc.). The Visual Predictive Check (VPC) technique is an important step in identifying potential model deficiencies. The VPC on survival curves where simulated curves are compared to the original one via Kaplan-Meier estimators is easy to communicate to both technical and non-technical audiences.

We develop a simple way to perform the VPC by simulating event times in R. Compared to current solutions, our proposed method is more efficient, better represents the estimated individual survival function through interpolation, and has the flexibility of working with any non-linear mixed-effects/ODE fitting software.

Methods

- Obtain ***individual survival function values*** at a grid of time points during model fitting or by numerical integration in R using final parameter estimates. The individual survival curves take into account the time since start of trial, time-varying exposures and other time changing biomarkers as appropriate.
- R code uses outputted survival function values to generate event times. For better representation, the survival function is ***interpolated***. Optionally, use a log-linear interpolation which represents a constant hazard between time points.
- Standard or generalized Kaplan-Meier curves can be derived for each replicate and used for VPC against the original data. For repeated time-to-event data, the most common form of between-subject variability (an additive frailty on the log-hazard) can be easily accommodated.

R Code for Simulating Event Times

```
sample.tte <- function(time, survfn, interpolate=c("linear", "log-linear", "none")) {
    interpolate <- match.arg(interpolate)
    cdf <- 1 - survfn
    u <- runif(1)
    if (u > max(cdf)) {
        stime <- max(time)
        status <- 0  # Censored
    } else {
        if (interpolate == "linear") {
            fn <- approxfun(cdf, time, method="linear", rule=2)
            stime <- fn(u)
        } else if (interpolate == "log-linear") {
            fn <- approxfun(log(1 - cdf), time, method="linear", rule=2)
            stime <- fn(log(1 - u))
        } else {
            fn <- approxfun(cdf, time, method="constant", rule=2, f=1)
            stime <- fn(u)
        }
        status <- 1  # Event
    }
    data.frame(time=stime, status=status)
}
```

Simulation Example 1: Proof-of-Concept

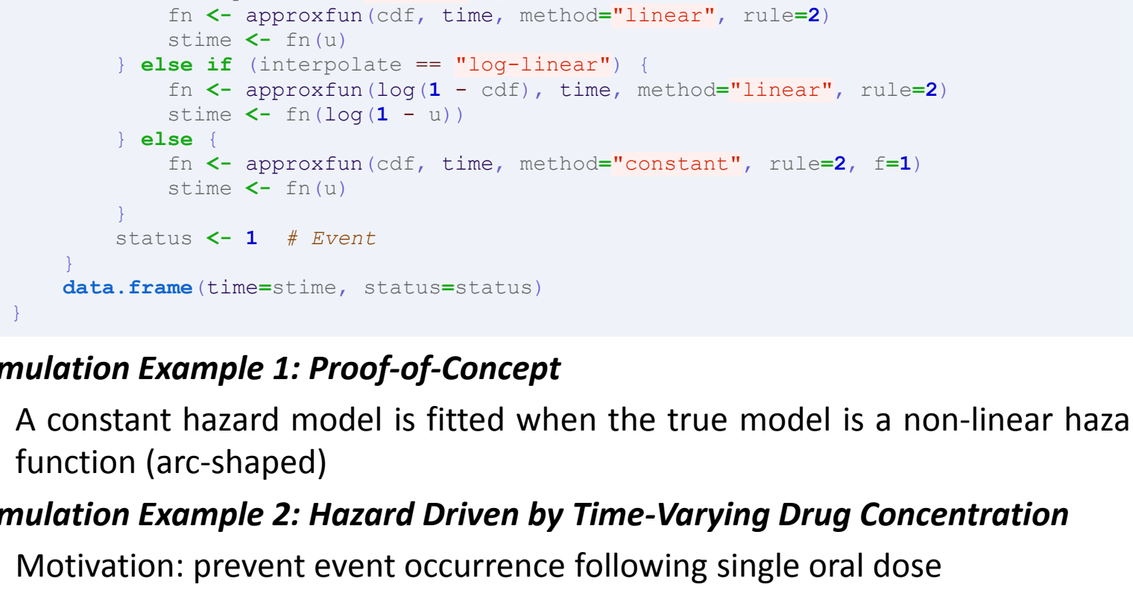
- A constant hazard model is fitted when the true model is a non-linear hazard function (arc-shaped)

Simulation Example 2: Hazard Driven by Time-Varying Drug Concentration

- Motivation: prevent event occurrence following single oral dose
- Event intensity (hazard) is higher at the start of the 24h follow-up
- Drug concentration peaks early (no effect past 10 hours)

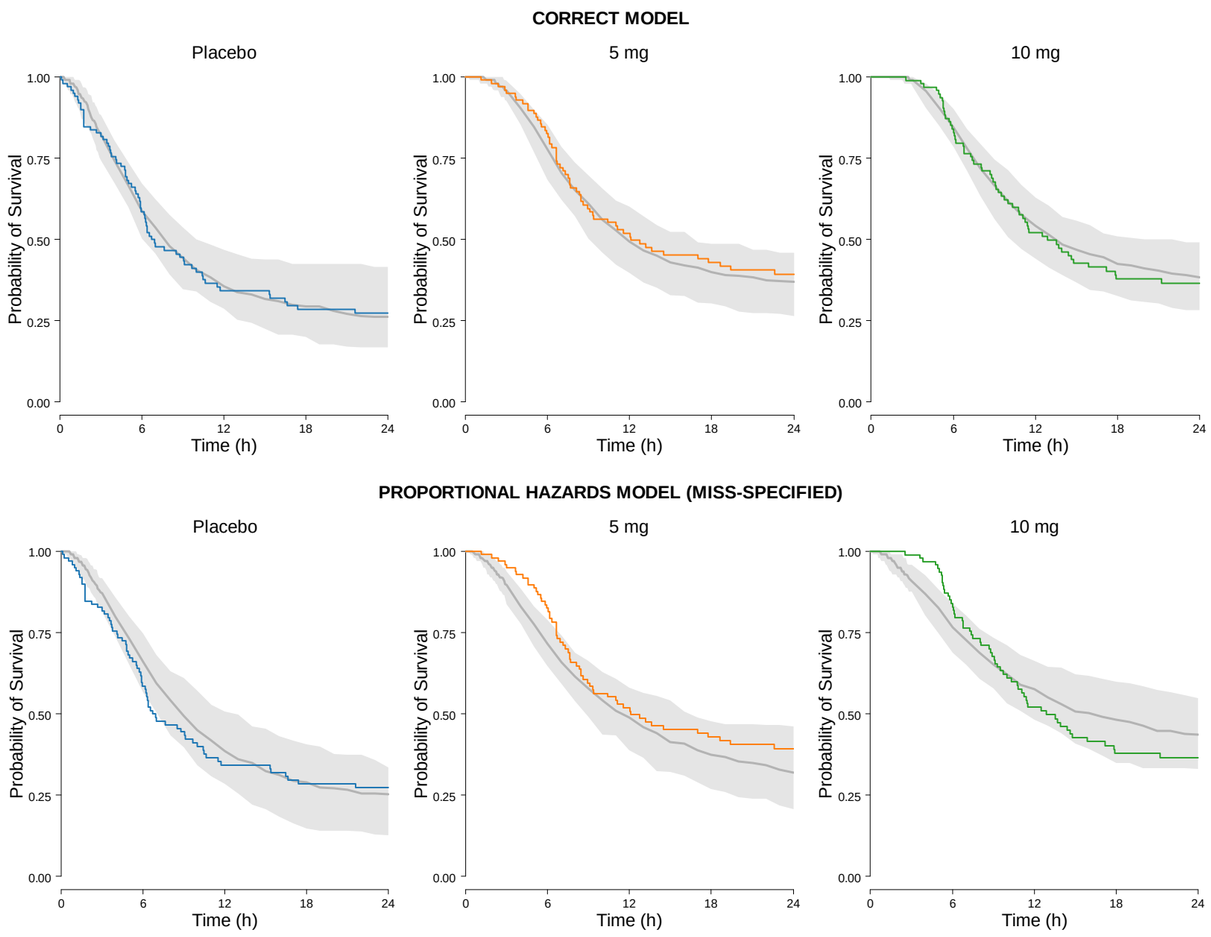
Results

Simulation Example 1

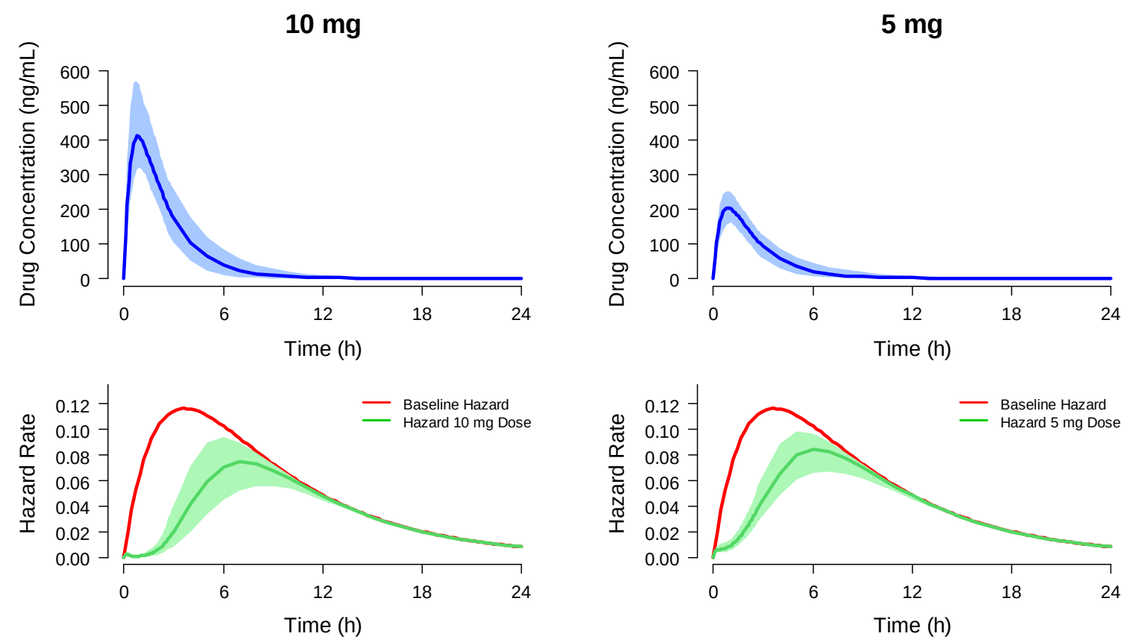


Results (Con't)

Simulation Example 2



VPC shows lack of fit of the miss-specified proportional hazards model because the drug effect is of short duration, not constant over time.



True hazard function: $h(t) = h_0(t)\, e^{-0.01\, C(t)}$, $h_0(t) = 0.3(e^{-0.15t} - e^{-0.45t})$

Conclusions

- A simple, general approach to VPC for time-to-event models is a useful addition to the pharmacometrician's toolbox that will help in quickly evaluating and communicating time-to-event models.
- Two simulation examples demonstrate the VPC can help identify model deficiencies with or without time-varying covariates
- Source code: https://github.com/benjaminrich/RvpcTTE

References

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