Kernel-based visual hazard comparison (kbVHC): a simulation-free diagnostic for parametric repeated time-to-event models

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INTRODUCTION

Commonly used diagnostics for parametric repeated time-to-event models (e.g. Kaplan-Meier VPC) require simulations, which may be difficult to generate in situations with dose titration or informative dropout.

Here, we present a novel simulation-free diagnostic tool for parametric hazard models: the kernel-based visual hazard comparison (kbVHC).

METHODS

kbVHC

Non-parametric kernel estimate of hazard rate [1,2]

- Degree of smoothing determined by bandwidth
- User-defined CV_{target} determines local bandwidth
- Bootstrap to obtain 95% confidence interval

Parametric hazard estimate

- Mean of posthoc individual hazard estimate

The parametric and non-parametric hazardare plotted together and visually compared

Evaluation of kbVHC

We simulated and refitted various scenarios

- Gompertz, Weibull or circadian-varying hazard models
- Number of subjects (50-500)
- CV_{target} (5-40%)

Comparison with Kaplan-Meier VPC [3]

CONCLUSION

- **The kbVHC has good sensitivity for model misspecification in RTTE models**
- **kbVHC outperformed the Kaplan-Meier VPC in scenarios with a rapidly changing hazard rate**
- **The kbVHC can be used when representative simulations cannot be generated**
- **The kernel hazard estimate can be generated prior to model development, to explore the data**

RESULTS

- The kbVHC could distinguish between Gompertz and Weibull models (Figure 1), even when the hazard was relatively low
- Interpretation of the kbVHC depends on the smoothing of the kernel hazard rate. The degree of smoothing can be inspected by plotting the local kernel bandwidth (Figure 2).
- Based on the amount of events in a dataset, we found that the following range of CV_{target} worked well in practice:
  - <250 events; 15-40%
  - 250-1000 events; 10-30%
  - >1000 events; 5-20%
- In scenarios with rapidly changing hazard, kbVHC was more sensitive than Kaplan-Meier VPC to detect model misspecification. (Figure 3)

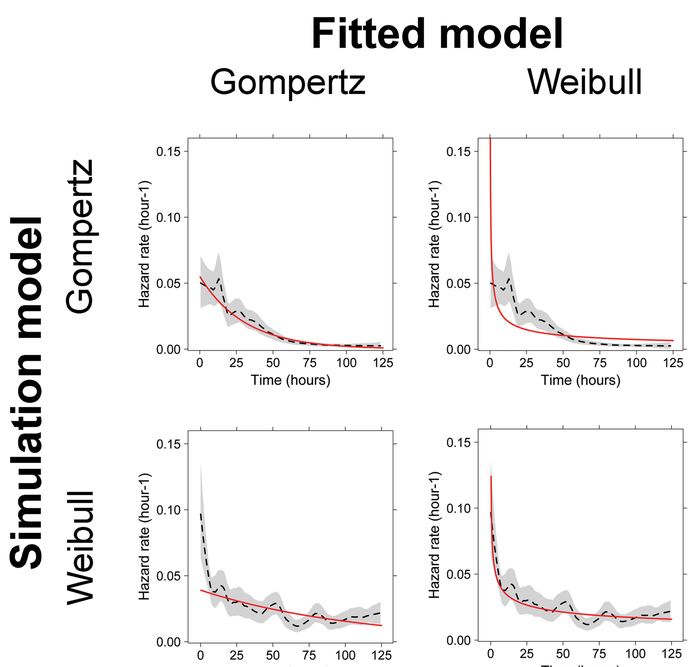

Figure 1. ***KbVHC plots for Gompertz and Weibull scenarios*** *fitted with true and misspecified models. Red line represents parametric hazard estimate, the black dashed line represents the kernel hazard estimate with 95% confidence interval (shaded grey area).*

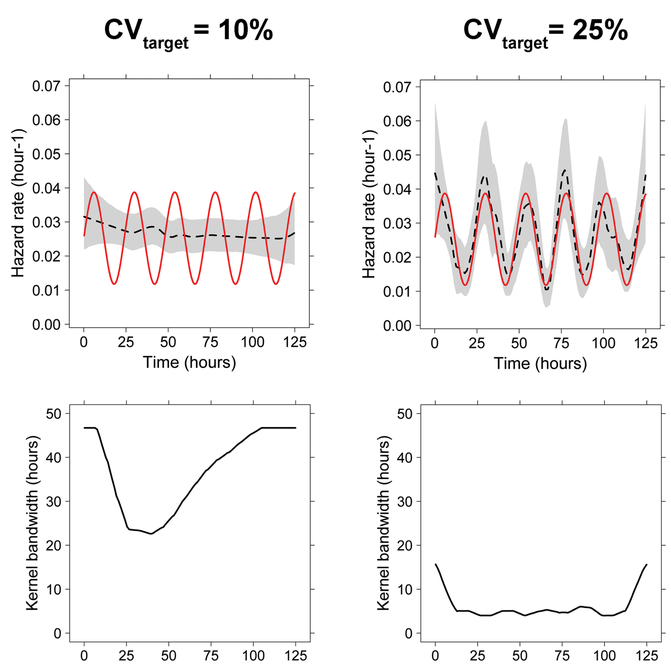

Figure 2. ***Impact of user-defined CVtarget on the kbVHC*** *diagnostic in a simulated dataset with 125 subjects and a circadian-varying hazard (415 events). The upper row shows kbVHC plots, while the lower row shows the local bandwidth of the kernel estimator. Dataset was fitted with the true model.*

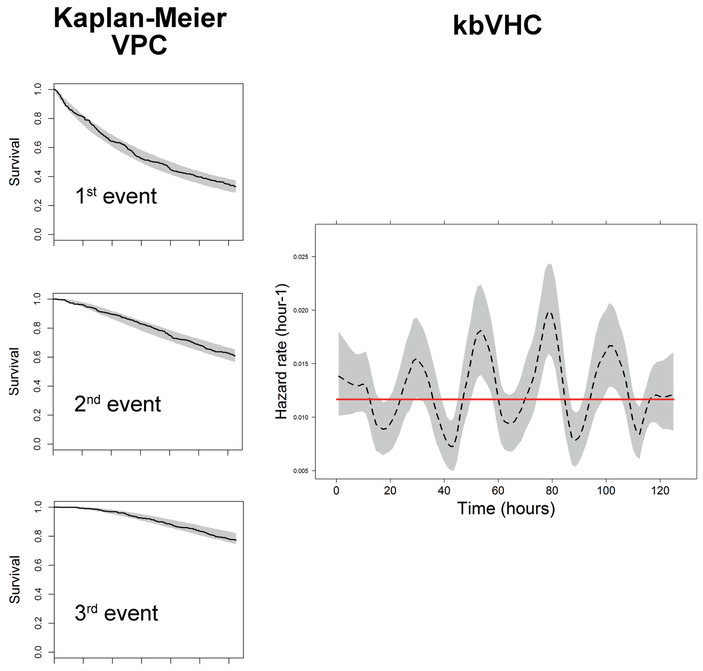

Figure 3. ***Comparison of kbVHC and Kaplan-Meier VPC*** *for a scenario with circadian-varying hazard fitted with a constant hazard model. The simulated dataset contains 500 subjects, 786 events and has a 50% amplitude of the circadian variation of the hazard.*

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