# Personalized Dosing Decisions Using a Bayesian Exposure-Hazard Multistate Model

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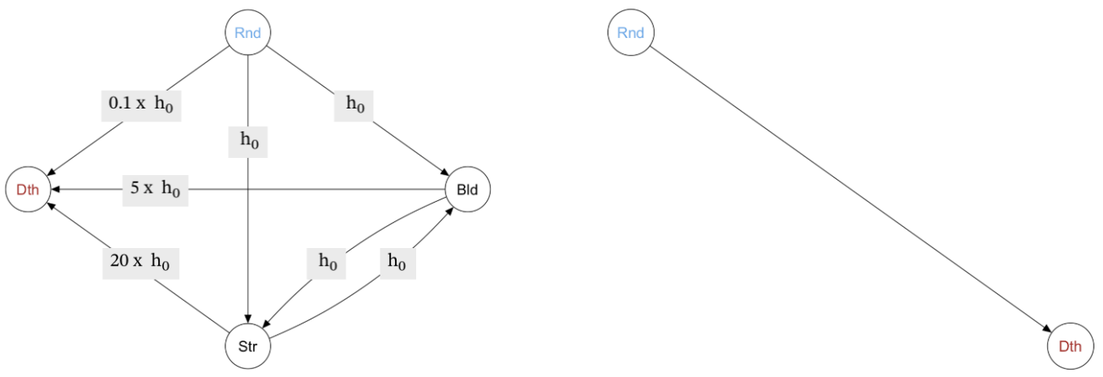
## Introduction

- For anticoagulant drugs, higher drug exposure reduces the risk of thromboembolic events but increases the risk of hemorrhagic events [1]
- Standard time-to-event analysis treats each event independently and ignores how prior events affect future risk
- Pharmacokinetic modeling to estimate drug exposure is computationally demanding under long dosing periods, limiting real-time clinical decision support

## Objectives

- Build a Bayesian multistate model incorporating competing risks and previous event information for improved event risk prediction and personalized dosing
- Develop a computationally efficient strategy to integrate exposure estimation with hazard prediction




*(a) Multistate model* *(b) Time-to-event model*

Figure 1. Multistate model illustration. **a)** A graph of a multistate model with states Randomization (Rnd), Bleed (Bld), Stroke (Str), and Death (Dth). **b)** A multistate model with just two states and one possible transition, equivalent to a standard survival model.

## Bayesian Nonparametric Multistate Modeling

### Time-to-event Model (TTE)

For each subject $i = 1, \ldots, N_{\text{sub}}$, a sequence of **events** occurred during a follow-up period, and a vector of time-independent covariates $\mathbf{x}_i$ is measured, which can include, for example, age, weight or creatinine clearance. The drug dose or estimated drug exposure can also be included in this vector. The Cox proportional hazards model assumes that the hazard function for subject $i$ can be modelled as

$$\lambda_i(t) = b(t) \exp\left(\beta^\top \mathbf{x}_i\right)$$

where $b(t)$ is the baseline hazard function and $\beta$ are regression coefficients. When there are multiple events of interest, we can use this model for each one separately, but this does not take into account the competing risk nature of the events and the dependence of their rates on previous events.

### Multistate Model (MSM)

In MSMs, the observed sequence of events is viewed as a path among **states**. The possible **transitions** can be represented using directed edges of a graph, as in Figure 1a. To model the sequence of events, we use a Bayesian non-parametric MSM with competing risks [2], where the hazard rates $\lambda_i^{(h)}(t)$, $h = 1, \ldots, H$ are taken as

$$\lambda_i^{(h)}(t) = b^{(h)}(t) \exp\left(\beta_{E_h}^\top \mathbf{x}_i\right)$$

where $b^{(h)}(t)$ is the baseline hazard for transition $h$, $E_h$ is an integer indexing which event the transition $h$ ends with, and $\beta_{E_h}$ is the regression coefficient for event $E_h$. We model log baseline hazards $\log b^{(h)}(t)$ nonparametrically using B-splines with priors that are partially pooled among the transitions.

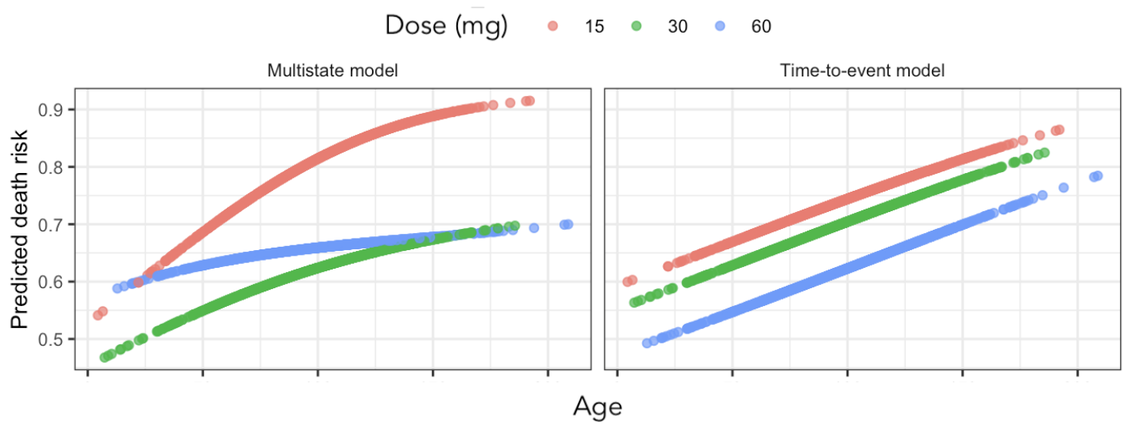



Figure 2. Predicted probability of death during a 3-year follow-up, as a function of covariates $\mathbf{x}_i$ (dose and age), in an experiment with simulated data. The multistate model (left) can capture more elaborate predictor-risk relationships than the standard time-to-event model (right).

## Multistate vs. Time-to-event Model

We generate simulated data involving three doses that were studied in a randomized trial of edoxaban vs. warfarin in atrial fibrillation [1], with $N_{\text{sub}} = 6000$ subjects using the model in Figure 1a with constant hazards and $h_0 = 5 \times 10^{-4}$. The data is generated such that the dose, used as a proxy for the exposure, increases the risk of transitions leading to bleed but decreases the risk of the ones leading to stroke. Furthermore, age also increases the risk of transitions leading to death.

We fit both models shown in Figure 1 using Bayesian inference, with half of the subjects as training data. The multistate model achieves a **better concordance index** (0.58 vs. 0.56) in predicting the 3-year risk of death for the test subjects. It also achieves **a more accurate** 3-year death **risk prediction** (Figure 2), with values summarized by dose in Table 1. The results were confirmed to be stable by rerunning the experiment multiple times (results shown for only a single run).

| | Predicted P(death) | | Observed P(death) | |
|---|---|---|---|---|
| Dose (mg) | MSM | TTE | Train data | Test data |
| 15 | 0.80 | 0.75 | 0.80 | 0.80 |
| 30 | 0.63 | 0.71 | 0.64 | 0.63 |
| 60 | 0.65 | 0.62 | 0.64 | 0.65 |

Table 1. Predicted 3-year risk of death with different doses for the multistate (MSM) and time-to-event (TTE) models, compared to observed proportions of deaths in training and test data. The multistate model recovers the observed death rates more accurately.

## Partially Steady-State Pharmacokinetic Modeling

- In additional experiments, we use a one-compartment pharmacokinetic (PK) model, where each subject is assumed to reach a steady state where drug concentration follows the same pattern over each dosing interval (Figure 3)
- Effect of missing doses or inexact dose timing needs to be taken into account only during the last dosing intervals before a concentration measurement
- From this model, we can compute the steady-state exposure and use it as a predictor in $\mathbf{x}_i$ instead of dose
- A model for the PK parameters includes covariates such as weight and renal function, informing how well a subject can absorb and clear the drug

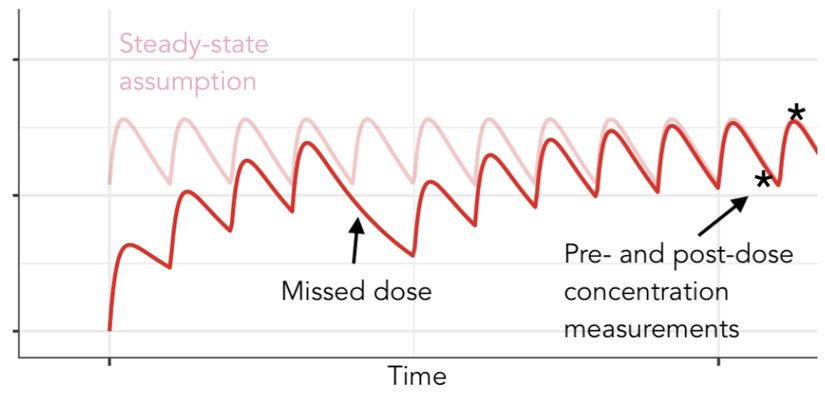



Figure 3. A pharmacokinetic model for drug concentration under a long dosing period where a steady state is reached. Missing a dose or inexact dose timing creates a temporary perturbation, which can be ignored in model fitting if it is not close to the measurement times of interest.

## Conclusions and Remarks

- Multistate modeling is useful for event rate prediction, but requires more data than standard survival modeling to be estimated accurately
- Modeling multiple events of interest can be amended with **utility functions** that depend on risks of different events (death, disability, etc.) to allow personalized dosing recommendations that can take into account patient preferences
- Estimating exposure using the partially steady-state PK model is faster than summing the effect of all doses, and accurate if the dosing schedule is regular enough

## References

[1] Robert P. Giugliano, Christian T. Ruff, Eugene Braunwald, Sabina A. Murphy, Stephen D. Wiviott, Jonathan L. Halperin, Albert L. Waldo, Michael D. Ezekowitz, Jeffrey I. Weitz, Jiri Spinar, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *The New England Journal of Medicine*, 369:2093–2104, 2013.

[2] Thomas Kneib and Andrea Hennerfeind. Bayesian semi parametric multi-state models. *Statistical Modelling*, 8:169–198, 2008.

[3] Jennifer G. Le-Rademacher, Terry M. Therneau, and Fang-Shu Ou. The utility of multistate models: A flexible framework for time-to-event data. *Current Epidemiology Reports*, 9(3):183–189, 2022.