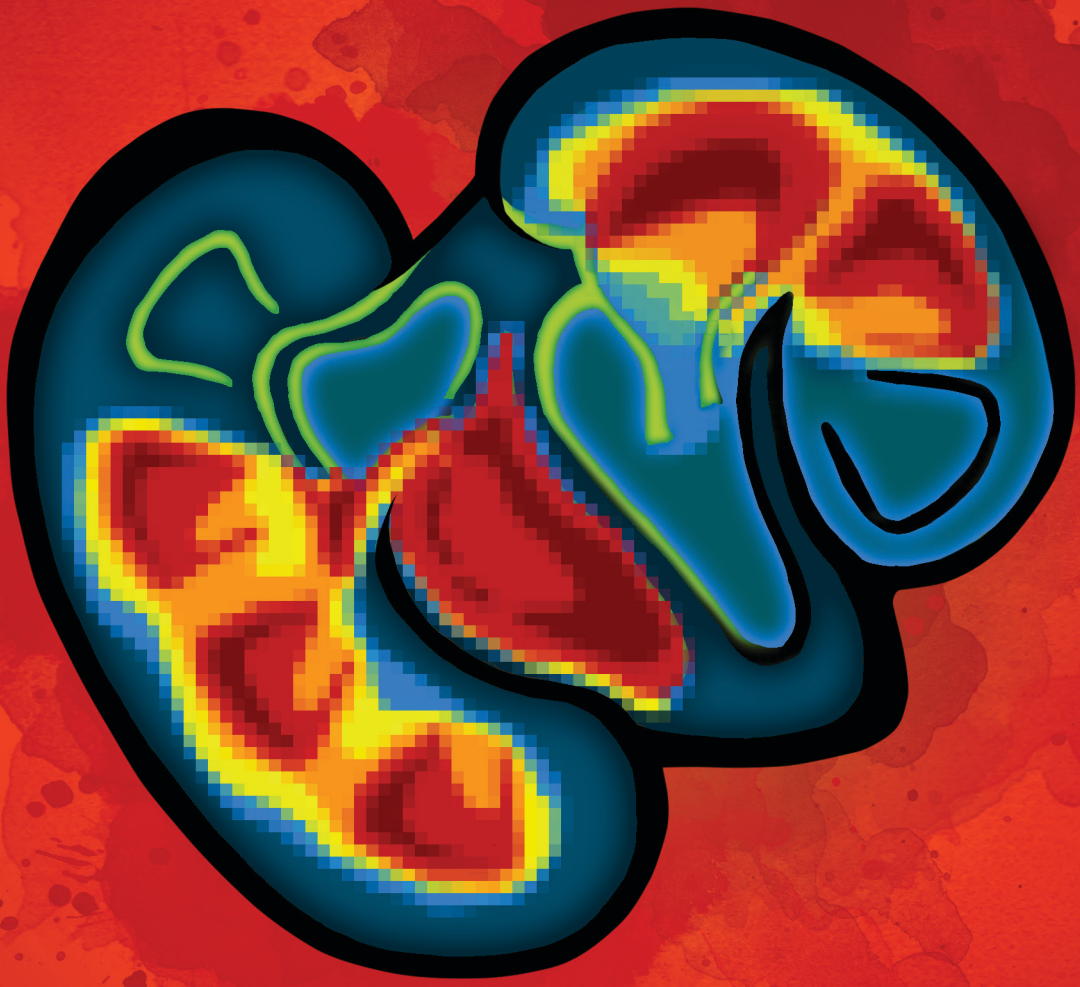

FLUIDAL CONNECTION

Part I

METHODOLOGICAL CONCEPTS

CHAPTER 2

Personalized Dynamic Risk Assessment – the Next Step in Prognostic Research

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ABSTRACT

In medicine, repeated measures are frequently available (glomerular filtration rate or proteinuria) and linked to adverse outcomes. However, several features of these longitudinal data should be considered before making such inferences. These considerations are discussed and we describe how joint modeling of repeatedly measured and time-to-event data may help to assess disease dynamics and to derive personalized prognosis. Joint modeling combines linear mixed-effects models and Cox regression model to relate patient-specific trajectory to their prognosis. We describe several aspects of the relationship between time-varying markers and the endpoint of interest that are assessed with real examples to illustrate the aforementioned aspects of the longitudinal data provided. Thus, joint models are valuable statistical tools for study purposes, but also may help healthcare providers in making well-informed dynamic medical decisions.

INTRODUCTION

Application of longitudinal study designs to assess dynamics of medical conditions is currently gaining interest in general medical community and particularly in the fields of cardiology and nephrology.[1-5] Such study designs entail repeated measurements of biological markers (e.g., proteins in the blood or urine) over the time-course of the disease to infer patient prognosis.

As an illustrative example we will consider a study by Brankovic et al. who investigated how longitudinal trajectories of several glomerular and tubular markers in patients with chronic heart failure (HF) relate to their prognosis.[6] Samples were measured at fixed 3-month intervals during 2-year follow-up. Compared to studies that measured these markers at baseline only and related them to patient prognosis, the repeated-measures design utilized by Brankovic et al. carries several advantages.[7] Most importantly, it reflects disease dynamics better than the single-baseline assessment. However, when analyzing repeatedly measured biomarkers, the question arises how to properly relate them to prognosis.[7] To do this, several approaches can be utilized including time-dependent Cox model (TDCM).[8] Alternatively, joint models (JMs) of repeatedly measured and time-to-event data can be performed.

Reasons for choosing JMs over TDCM for estimating prognosis using time-varying markers are discussed below including data-collection, data-analysis, as well as the methodological concept behind JMs.

Data-collection

First, if repeated measurements are not collected at equally spaced time-points or not all patients have the same number of measurements, the longitudinal data are unbalanced.[9] This is often seen when treating physicians determine how often study-visits should take place for data to be taken. For example, Breidthardt[4] et al. studied whether worsening renal function (WRF) predicts mortality in patients admitted for acute HF. They defined WRF as in-hospital increase in serum creatinine ≥0.3mg/dl, and treating physicians determined the timing of serum creatinine sampling. Here, the sicker patients were likely to be monitored more closely (i.e., have more measurements taken) than the less sick patients. Consequently, the likelihood of finding WRF would increase in sicker patients. This unbalanced data-collection would falsely strengthen the association between WRF and mortality if this relation is modeled improperly.

Second, even when patient-visits occur at fixed time-points by a pre-specified study protocol, longitudinal data may become unbalanced. This occurs in three situations: when patients' measurements are not performed in the beginning but start later during follow-up ("late entry"), when patients skip some of the scheduled visits ("intermittent missing"), or when patients withdraw before the study ends ("early dropout").[7] In all situations, the longitudinal data become unbalanced because of missing values. Importantly, if the reason for the missing values is related to patients' survival (e.g., patient misses visits because of deteriorating condition), TDCM becomes inadequate because it assumes that missing values are independent of survival.[7] For example, Li et al. studied longitudinal creatinine-based glomerular filtration rate (GFR_{Cr}) trajectory in the African American Study of Kidney Disease in Hypertension (AASK) trial.[10] Here, 23% of patients were excluded because they withdrew before collecting a sufficient number of measurements. In the majority, the reasons for withdrawal were related to their time-to-event as they died or were started on renal replacement therapy (RRT) before obtaining sufficient serum creatinine measurements.

Data-analysis

Covariates measured (or collected) on patients are internal (i.e., endogenous) predictors. This is important to note because for any internal predictor (i.e., biomarker) future measurements potentially depend on the patient's survival which should be considered when analyzing such covariates.[11,12] This is due to two reasons: patients have to be alive and present at study-visits for markers to be measured, and markers' values might be affected by his/her condition up to that visit.[7] Additionally, internal predictors are biologically subjected to variability and can be measured with error.[7] Examples of such predictors are serum creatinine, body mass index, echocardiography measurements, or proteinuria.

TDCM cannot properly handle internal predictors[12] since it assumes that their future values are independent of patient's survival and measured without error.[7] Importantly, it also assumes that the predictor has the same constant value between study-visits, until it suddenly changes when the next measurement is obtained (Figure 1A).[12] This assumption is unrealistic as we expect that biomarkers continuously change, and not only when measured. Consequently, TDCM would produce biased estimates of biomarkers' effect masking their true predictive ability. For example, Asar et al. studied whether repeatedly measured GFR_{Cr} predict initiation of RRT in 1611 patients from Chronic Renal Insufficiency Standards Implementation Study (CRISIS). They showed that the hazard ratios (HRs) for RRT were considerably underestimated by TDCM as compared to JMs (HRs per log-unit GFR_{Cr} decrease: 12.3 versus 38.7).[5] This advantage of JMs over TDCM has been demonstrated by

theoretical work and other simulation studies.[7,11-13]

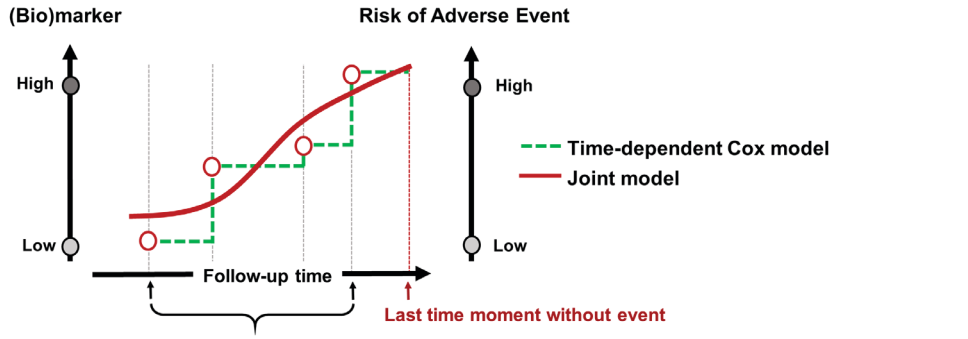
Methodological concept

The JMs combine two models: linear mixed-effects (LME) models and basic Cox model.[9] The LME models estimate a marker's trajectory using repeated measurements; Cox model estimates patients' time-to-event.

The LME models use the 2-component equation. The first "fixed-effect" component estimates a marker's average trajectory over all patients. The second "random-effect" component estimates by how much an individual patient deviates from this average trajectory (Figure 1B). By using these two components of information the patient-specific trajectory is constructed. Through the "random-effects" component they allow repeated measurements taken on the same patient to be correlated, and work well with unbalanced data.[12] Notably, the functional form of time is an important aspect of LME models. That is, in case the patient-specific trajectories are nonlinear, care should be given in the specification of the fixed- and random-effects components; polynomials or splines could be used to model such nonlinear profiles. Altogether, this allows a longitudinal trajectory estimated by LME models to correspond more naturally to the marker's biological evolution than the "jerkily" trajectory assumed by TDCM (Figure 1A).

Subsequently, JMs combine LME and Cox models to relate patient-specific trajectory to his/her prognosis (Figure S1). By doing this, JMs handles marker's missing data and measurement error that can occur during follow-up.[14] JMs are also advantageous when extreme values are observed because they postulate that the underlying rather than the observed value of the longitudinal biomarker is associated with the risk of an adverse endpoint (Figure 1A).

The basic assumptions behind LME and Cox models are the same as when they are separately analyzed. For continuous longitudinal data, we assume normally distributed error terms. The LME models also assume that discontinuation of the data-collection process for reasons other than the occurrence of the adverse endpoint are missing at random, i.e., these reasons can depend on covariates and past observed longitudinal values. For the endpoint a relative risk model is used with the proportional hazards assumption. Further reading on methodology[9], sample size and power determination[15] is provided elsewhere. Finally, JMs have been successfully applied for several medical conditions including HF, aortic aneurisms, aortic stenosis, heart, lung and kidney transplantation.[6,16-20]



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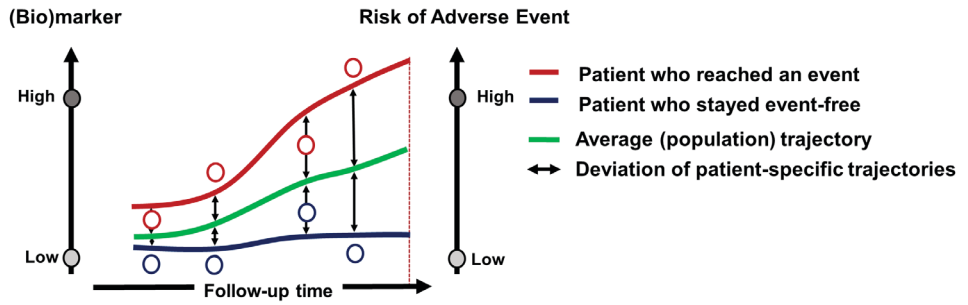

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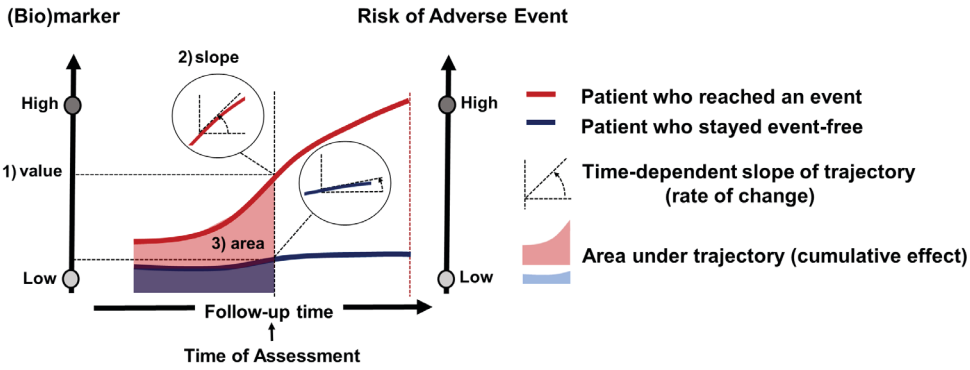

C

FIGURE 1 Graphical depiction of the difference between the marker's trajectory estimated by the time-dependent Cox model and the joint models and of the different aspects of time-varying markers. The X-axis displays follow-up time, the left Y-axis displays the value of a (bio)marker, and the right Y-axis displays a patient's risk prognosis. **Panel A** illustrates the marker's trajectories estimated by the time-dependent Cox model (green dashed line) and by the joint models (smooth red solid line) in the same patient. The panel shows that in the JMs the underlying profile represented by the red solid line is include in the relative risk model, and not the directly observed

value represented by the red circles which is what the Cox model does. In this way, JMs are advantageous because they account for the biological variation that the biomarker exhibits, but also in the settings when extreme values are observed but are not particularly helpful clinically (e.g., extremely low blood pressure). Interpretation of HRs from the JMs is the same as from the Cox model. **Panel B** illustrates how the patient-specific marker trajectory is constructed using linear mixed-effects models. The solid green line depicts the marker's value averaged over all patients at each of the study visits during follow-up (fixed-effect part), and the black arrows depict the deviation of the patient-specific values from the average values at the same study visits. Patient-specific trajectories are depicted for a patient who experienced the event (solid red line) and the one who did not (solid blue line). **Panel C** illustrates different aspects of time-varying markers that can be assessed by joint models: 1) marker's level, 2) slope of the marker's trajectory (rate of change), 3) area under the marker's trajectory (the cumulative effect of the marker's values). The time-dependent slope mathematically corresponds to the first derivative of the trajectory and the cumulative effect to the integral of the trajectory.

Components of time-varying markers

JMs tailor a patient's prognosis based on his/her own marker's values (Figure 1C). However, other components of the longitudinal marker can also be investigated.[7] For example, the rate at which a marker changes can be determined by estimating the instantaneous slope of its trajectory. The slope indicates by how much marker's values have been increasing or decreasing at the certain timepoint.[7] Consequently, disease's progression can be adequately quantified and related to prognosis. JMs can also assess entire history of marker values by estimating the area under its trajectory. The area indicates the cumulative effect of all values that the marker has taken up to the certain timepoint.[12] Altogether, JMs analyse comprehensively disease's dynamics to accurately profile patient's prognosis, wherein the application of TDCM is limited.

Personalized dynamic risk assessment

Patients are often seen in different disease's stages, react differently to treatment, or have other characteristics relevant for their phenotype. Thus, it is clear that a disease can differ both between patients and within the same patient over time. Consequently, a true marker's potential in ascertaining disease's severity in an individual, and its accurate relation to prognosis can only be revealed if individual (i.e., patient-specific) values are considered. For physicians, it is also medically relevant to utilize all available information (baseline and follow-up) to accurately detect disease's progression and profile better individual prognosis. JMs can easily update the patient's prognosis whenever additional information is collected, thereby assessing the risk in real-time.[14]

CONCLUSION

Although attention should be taken when analyzing repeatedly measured data, repeated-measures designs are valuable when assessing the dynamics of medical conditions. The use of JMs may improve patients monitoring by providing personalized dynamic risk predictions.

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SUPPLEMETARY INFORMATION

R code to fit joint model

Joint model will be fit using primary biliary cirrhosis (PBC) data collected at the Mayo Clinic from 1974 to 1984[1] available with the package JMBayes.[2] For the analysis we will consider 312 patients who have been randomized to D-penicillamine treatment and 154 patient randomized to placebo. During follow-up, serum bilirubin was collected on average 6 times per patient with a total of 1945 measurements. To assess how longitudinal trajectory of serum bilirubin relates to a patient-specific prognosis we have to use two datasets.

The first dataset is denoted by "**pbc2"** and contains repeatedly measured data organized in the long format (i.e., contains several rows per each patient; number of rows depends on how many samples the patient had provided). This dataset will be used to estimate longitudinal trajectory of serum bilirubin using linear mixed-effects (LME) models.

The second dataset is denoted by **"pbc2.id"** and contains patients' survival times organized in the wide format (i.e., contains a single row per patient). This dataset will be used to fit basic Cox model.

Full description of R codes provided below is discussed in the paper under reference 2.

```
# R code:
# first load package "JMbayes" and define the indicator "status2" as the
# composite event
# of transplantation or death

library("JMbayes")
pbc2$status2 <- as.numeric(pbc2$status != "alive")
pbc2.id$status2 <- as.numeric(pbc2.id$status != "alive")

# now fit the LME model
# variable "log(serBilir)" denotes logarithmically transformed marker: serum bilirubin
# variable "year" denotes the time from baseline when the marker was collected
# in this example, we used natural splines with two knots to better estimate marker's
# trajectory

lmeFit <- lme(log(serBilir) ~ ns(year, 2), data = pbc2,
random = ~ ns(year, 2) | id)
```

```
# now fit basic Cox model
# variable "years" denotes the time to event or censoring (note: this is different than variable
# "years" used for LME model)
# variable "status2" is event indicator
# variable "drug" denotes if a patient was randomized to D-penicillamine or placebo
# variable "age" denotes a patient's age at baseline
coxFit <- coxph(Surv(years, status2) ~ drug + age, data =
pbc2.id, x = TRUE)
# now fit joint model for the marker's value
jointFit.value <- jointModelBayes(lmeFit, coxFit, timeVar =
"year", n.iter = 30000)
summary(jointFit.value)
# calculate hazard ratio with corresponding 95% confidence interval
exp(confint(jointFit.value, parm = "Event"))
# in the output "Assoct" denotes HR for the value of log(serBilir)
# now fit joint model for marker's value and slope
dForm <- list(fixed = ~ 0 + dns(year, 2), random = ~ 0 +
dns(year, 2), indFixed = 2:3, indRandom = 2:3)
jointFit.value.slope <- update(jointFit.value, param = "td-
both", extraForm = dForm)
summary(jointFit.value.slope)
# calculate hazard ratio with corresponding 95% confidence interval
exp(confint(jointFit.value.slope, parm = "Event"))
# in the output "Assoct" denotes HR for the value of log(serBilir)
# in the output "AssoctE" denotes HR for the slope i.e., delta-log(serBilir)/year)
# the time-dependent slope mathematically corresponds to the first derivative of the
# trajectory
# now fit joint model for marker's cumulative effect
iForm <- list(fixed = ~ 0 + year + ins(year, 2), random = ~
0 + year + ins(year, 2), indFixed = 1:3, indRandom = 1:3)
jointFit.area <- update(jointFit.value, param = "td-extra",
extraForm = iForm)
summary(jointFit.area)
# calculate hazard ratio with corresponding 95% confidence interval
exp(confint(jointFit.area, parm = "Event"))
# in the output "AssoctE" denotes HR for the area under log(serBilir) trajectory
# the area mathematically corresponds to the integral of the trajectory
# Plotting marker's trajectory with corresponding survival probability in an
# individual patient
# in the following example we plotted serum bilirubin for patient number 4 from
# PBC data with survival
```

```
# probability for serum bilirubin value
ND <- pbc2[pbc2$id == 4, ]
sfit <- survfitJM(jointFit.value, newdata = ND)
plot(sfit, estimator = "mean", include.y = TRUE,conf.int =
TRUE, fill.area = TRUE, col.area = "lightgrey")
```

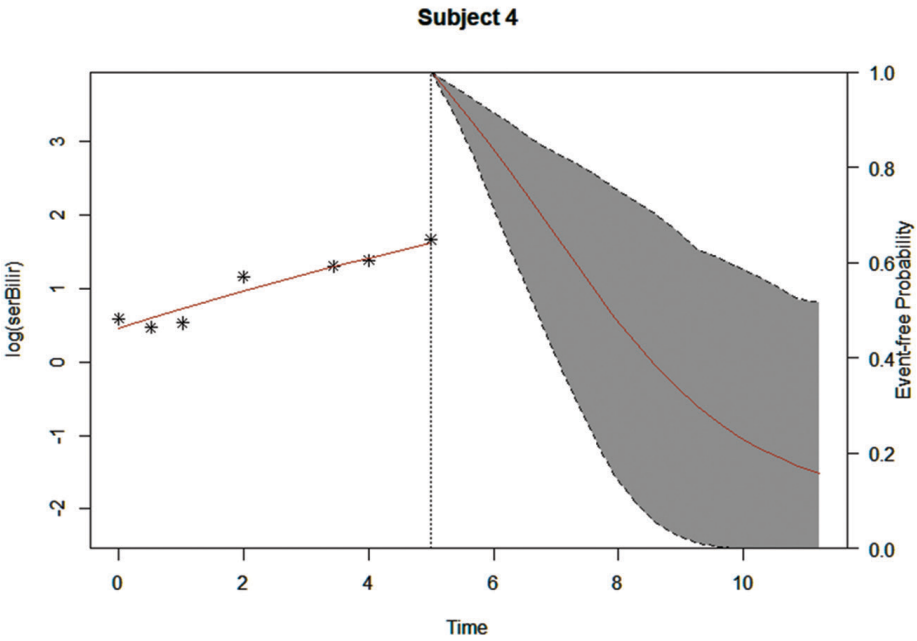

FIGURE S1 Personalized dynamic risk assessment using patient-specific trajectory of serum bilirubin. Serum bilirubin levels (on a log scale) are displayed on the primary (left) Y-axis and survival probability on the secondary (right) Y-axis. Follow-up time (years) is displayed on the X-axis. Patient-specific marker's trajectory (solid red line) with scatter points (asterisks) is displayed left of the vertical dotted black line. To the right of this line, the corresponding conditional survival probability curve (solid red line) is displayed with 95% confidence intervals (grey area).

Supplementary references:

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