Dynamic Prediction of Disease Progression Using Longitudinal Biomarker Data

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Outline

1. What is Dynamic Prediction?
2. A Motivating Example: Chronic Myelogenous Leukemia (CML)
3. Current Methods
   - Joint Modelling of Longitudinal and Survival Data: Not well-suited for prediction
   - Landmark Analysis: Separate unrelated predictions on discrete time points
4. Proposal: An Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)
5. Dynamic Predictive Analysis for CML

Dynamic Prediction

- Keep making updated predictions as time goes by and more data are observed
- After treatment, we need prediction of future disease prognosis at all the time points during a patient's follow-up visits.
- To decide whether or not to initiate extra treatments or interventions.
- Need use not only the baseline information, but also all the information up to the time point of prediction.

Chronic Myelogenous Leukemia (CML)

- The first human cancer that was linked to a single, acquired abnormal gene, the BCR-ABL gene.
- Tyrosine kinase inhibitors (TKIs) can inhibit the BCR-ABL gene.
- Frontline treatment trial of TKIs was usually successful: motivating data set for this talk.
- TKIs are not chemotherapy, have no severe side effects.
- The disease residual can be measured by the expression level of the BCR-ABL gene.

Chronic Myelogenous Leukemia (CML)

- Patients have their BCR-ABL expression levels measured roughly every three months, but in reality can be any time.
- Current practice is to wait until disease relapse (with clinical symptoms) to initiate other treatments
- Question: Can we use BCR-ABL levels to predict future disease relapse and initiate other treatments for early prevention?

Chronic Myelogenous Leukemia (CML)

- **Note: An increasing of BCR-ABL during prolonged remissions does not automatically constitute relapse on its own. Reasons:**
  - **Patient's failure to comply (the pills are expensive, need to take everyday)**
  - **BCR-ABL trajectories have cyclic oscillations**
- **Initiating other treatments too early is not good either, because they are toxic and risky chemotherapies / stem cell transplant**
- **Need a good dynamic prediction model**

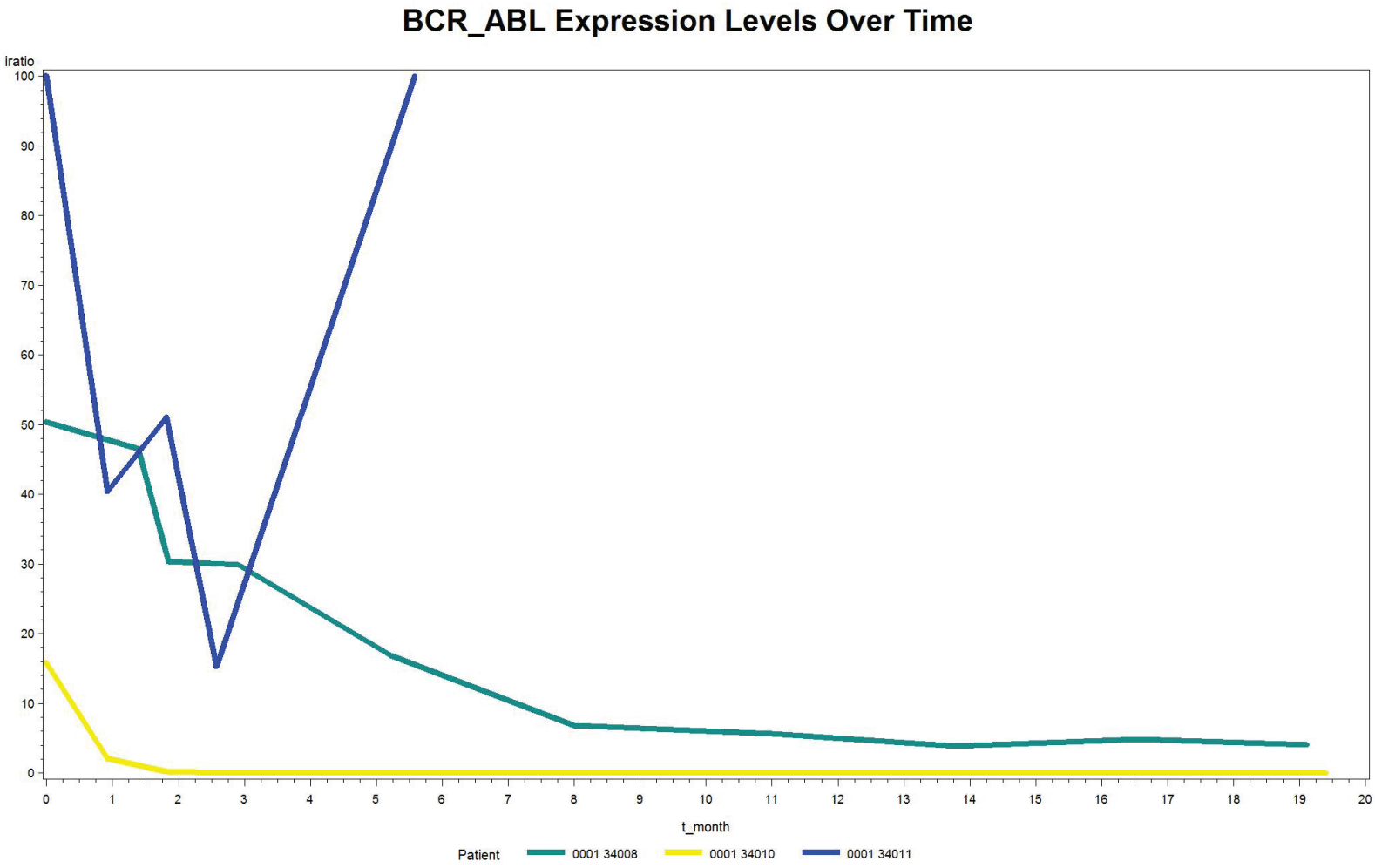


Figure 1: Biomarker Trajectories for Three Patients

Chronic Myelogenous Leukemia (CML)

- Biomarker changing patterns vary greatly from patient to patient
- It is difficult to use parametric models to fit such longitudinal data
- No, I am not going to use non-parametric models
- I will try to avoid using a longitudinal model for biomarker data
- Still, I need to use longitudinal biomarker data to predict survival

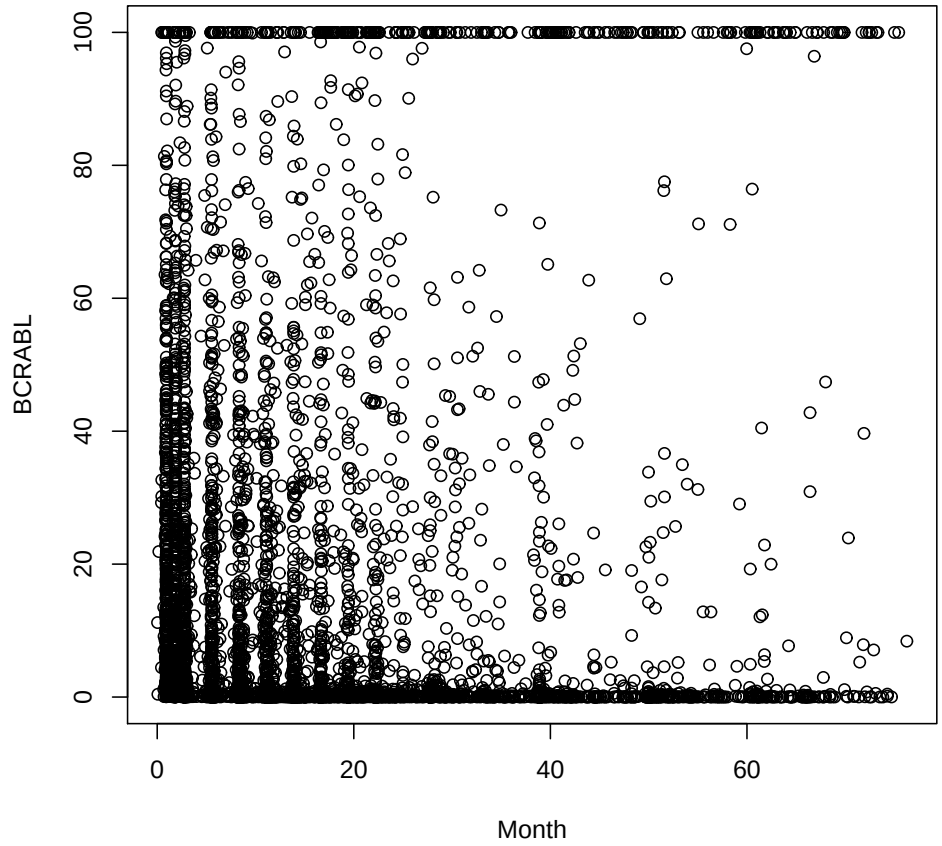


Figure 2: BCR-ABL Measurements for All Patients

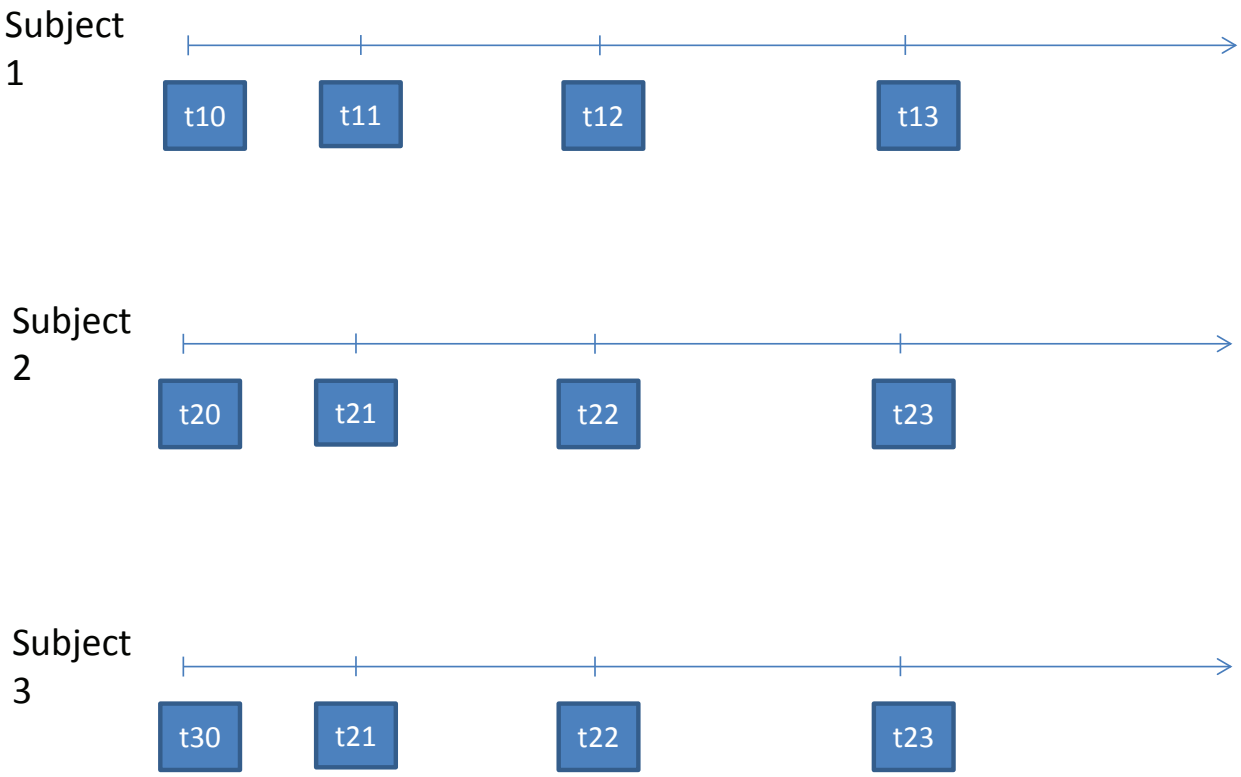


Figure 3: Regular repeated measurements for biomarkers

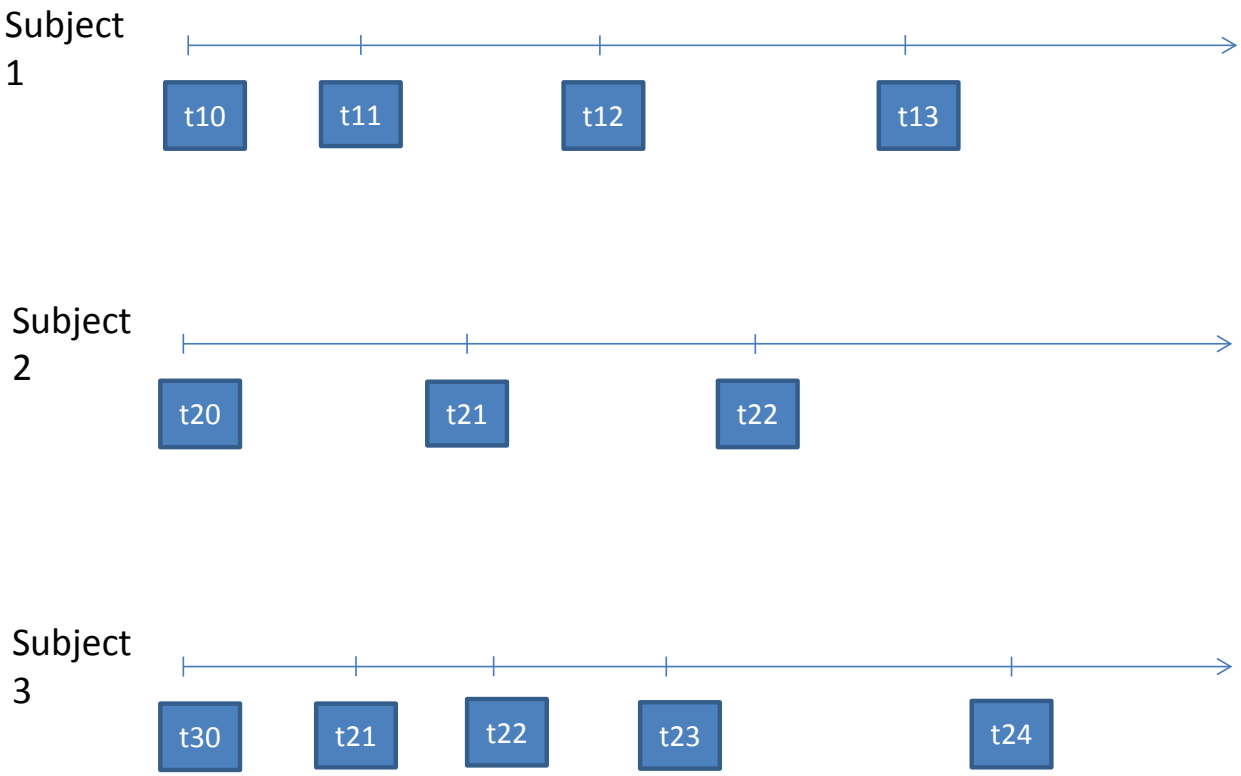


Figure 4: Irregular repeated measurements for biomarkers

Chronic Myelogenous Leukemia (CML)

- Need use BCR-ABL expression level to predict future disease relapse
- Patients may visit any time between the scheduled visits, so need do prediction at any time, not just some specific time points
- Prediction model should be able to use biomarker measurements from irregular time intervals

Notation

T_i: Time to disease relapse, or simply survival time

C_i: Censoring time

$X_i = \min(T_i, C_i)$, $\Delta_i = T_i \leq C_i$

$\lambda_i(t)$: Hazard function of T_i, describing failure risk rate at time t

Y_i: Baseline covariates

$Z_i(t)$: longitudinal biomarker value at time t

t_{ik}: the k^{th} biomarker measurement time for the i^{th} subject, $k = 1, \cdots, n_i$.

Current Approaches for Dynamic Prediction

1. Joint modeling of longitudinal biomarkers and survival data
2. Landmark analysis

Joint Modeling: Current Approach (1) for Dynamic Prediction

Joint modeling of longitudinal biomarkers and survival data

- **Use random effect model for longitudinal data**
- **Cox proportional hazards model for survival, with longitudinal biomarkers as time-dependent covariates**

Current Approach (1) Joint Modeling: Inconvenience for Prediction

Model: $\lambda_i(t) = \lambda_0(t) \exp\{\beta' Z_i(t)\}$,

Prediction at time t, conditional on $T_i \geq t$,

$$\begin{aligned} & \Pr(T_i \geq t+v | T_i \geq t) \\ = \quad & \exp\left[- \int_t^{t+v} \lambda_0(u) \exp\{\beta' Z_i(u)\} \, du \right] . \end{aligned}$$

Inconvenience (1):

Need future values of $Z(u)$ for $u > t$ that are not available yet at the time t.

Current Approach (1) Joint Modeling: Inconvenience for Prediction

Assume event times $\{x_i : i = 1, \cdots, n\}$ sorted ascendingly without ties, need maximize $L(\beta)$ to estimate β,

$$L(\beta) = \prod_{i=1}^{n} \left[\frac{\exp\{\beta' Z_i(x_i)\}}{\sum_{j \geq i} \exp\{\beta' Z_j(x_i)\}} \right]^{\Delta_i}$$

Inconvenience (2):

For each event time x_i, need not only $Z_i(x_i)$, but also $Z_j(x_i)$ for all $j \geq i$.

Such $Z_j(x_i)$ are usually not observed.

Current Approach (2)
Landmark Analysis for Dynamic Prediction

- Do predictions at only some selected time points.
- For each selected time point, use a Cox model with only time-independent covariate to summarize biomarker information up to this point.
- Does not use information after this point, i.e., no need to use future biomarker values.

Current Approach (2)
Landmark Analysis: Inconveniences

- **Can be done only at selected time points**

$$\begin{aligned}
\lambda_{i,0}(t) &= \lambda_{0,0}(t)\exp\{\beta_0' Z_i(0)\}\,, \\
\lambda_{i,3}(t) &= \lambda_{0,3}(t)\exp\{\beta_3' Z_i(3)\}\,, \\
\lambda_{i,6}(t) &= \lambda_{0,6}(t)\exp\{\beta_6' Z_i(6)\}\,, \\
&\cdots\cdots
\end{aligned}$$

- **Over-parameterized with $\lambda_{0,0}(t), \lambda_{0,3}(t), \lambda_{0,6}(t), \cdots$ and $\beta_0, \beta_3, \beta_6, \cdots$.**
- **Smoothing techniques have been used to put constraints on the above parameters**

References

- Tsiatis and Davidian (2001): A semiparametric estimator for the proportional hazards model with longitudinal covariates measured with error.
- Zheng and Heagerty (2005): Partly conditional survival models.
- van Houwelingen (2007), van Houwelingen and Putter (2008): Dynamic prediction by landmarking in event history analysis.
- Putter et al (2007): Competing risks and multi-state modeling

A New Approach for Dynamic Prediction

We try to provide a method that

- **does prediction at any time point, not just on pre-specified time points such as $t = 0, 3, 6, \cdots, t_m$.**
- **does not use future value $Z(t + v)$ for prediction at time t**
- **does not need a model for covariates**
- **can use biomarker measurements from irregular time intervals**
- **dose not need to fill biomarker values on other subjects' event time points.**

Proposal: Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

The new approach

- **is modified from landmark analysis**
- **so does not need to use future value $Z(t+v)$ for prediction at time t**
- **Landmark analysis fits m separate models, one for each selected time point.**
- **The new approach uses two-stage modeling,**
  - **1st stage: Fit a Cox model for $t = 0$,**
  - **2nd stage: Add on to the model for $t = 0$ to fit for all $t > 0$.**

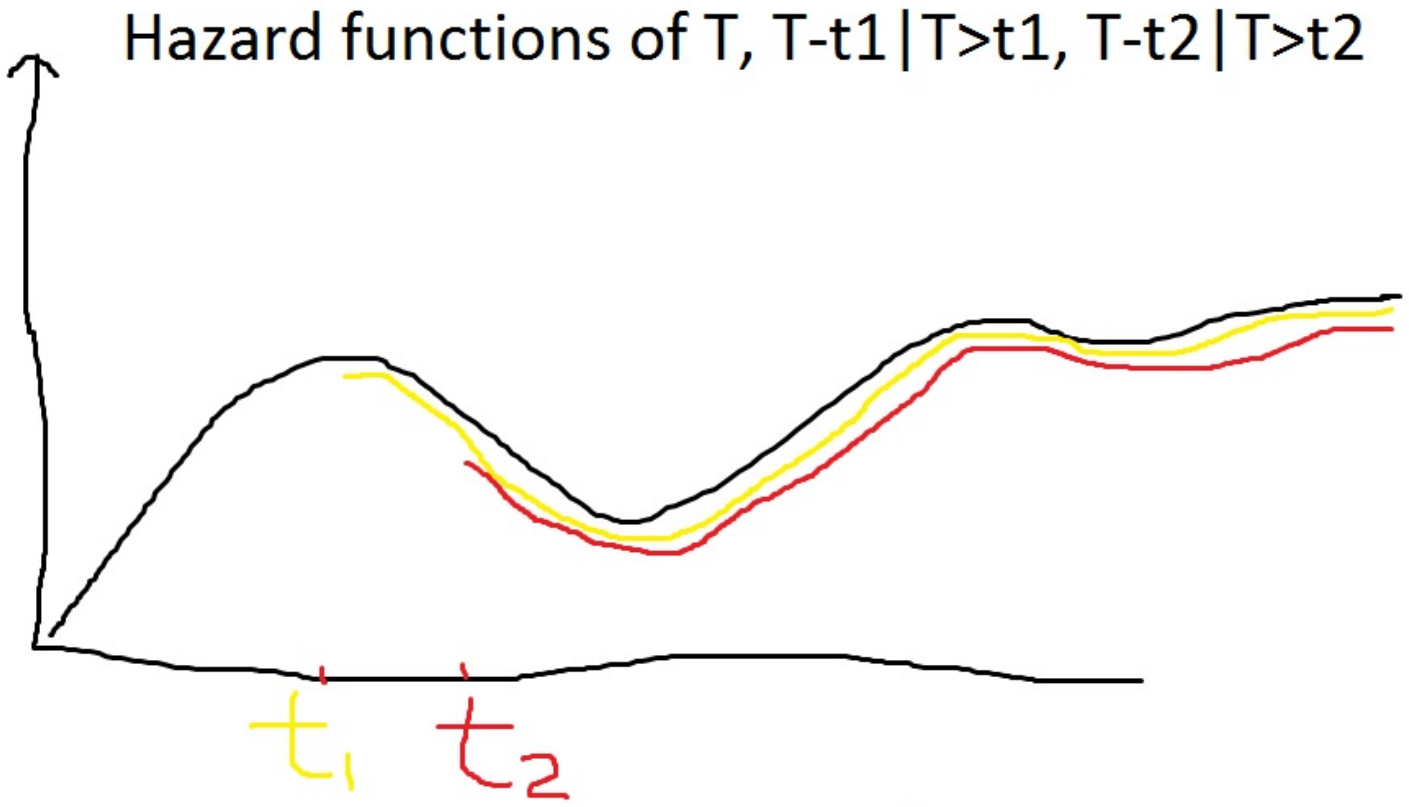
Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

Key step: How to add on to the model for $t = 0$ to fit for all $t > 0$?

Answer: Use a fundamental equality for conditional survival.

Suppose $\lambda_0(u)$ is the hazard function for T,
and $\lambda_t(u)$ is the hazard function for $T - t | T > t$ for $T - t = u$.

Then we have $\lambda_t(u) = \lambda_0(t + u)$ for all $t > 0$.


Hazard functions of T, T-t1|T>t1, T-t2|T>t2
t1
t2

Derivation (1)

Let $S_0(t) = \Pr(T \geq t) = \exp(-\int_0^t \lambda_0(v)\, dv)$, then,

$$\Pr(T \geq t+u | T \geq t) = \frac{S_0(t+u)}{S_0(t)}$$

$$\triangleq \quad S_t(u) = \exp(-\int_0^u \lambda_t(v)\, dv)$$

$$= \quad \frac{\exp(-\int_0^{t+u} \lambda_0(v)\, dv)}{\exp(-\int_0^t \lambda_0(v)\, dv)} = \exp(-\int_t^{t+u} \lambda_0(v)\, dv)$$

$$= \quad \exp(-\int_0^u \lambda_0(t+v)\, dv)$$

$\Longrightarrow \lambda_t(v) = \lambda_0(t+v)$, i.e., $\lambda_3(v) = \lambda_0(v+3), \cdots$.

Derivation (2)

$$
\begin{aligned}
\lambda_0(v) &= \frac{-S'(v)}{S(v)}\,, \\
\lambda_t(v) &= \frac{-S_t'(v)}{S_t(v)} \\
&= \frac{\frac{-\partial S(t+v)/S(t)}{\partial v}}{S(t+v)/S(t)} \\
&= \frac{-\frac{\partial S'(t+v)}{\partial v}}{S(t+v)} \\
\Longrightarrow \lambda_t(v) &= \lambda_0(t+v)
\end{aligned}
$$

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

- **Fundamental equality:** $\lambda_t(v) = \lambda_0(t+v)$.
- **Use this inherent constraint for hazard functions of the same survival time** T **at different time origins.**
- **Result in a more parsimonious approach for prediction of** T **at any** $t > 0$ **given** $T \geq t$.

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

- **Stage 1: Using only demographics and biomarker information at baseline ($t = 0$) for prediction**
- **Stage 2: Using longitudinal biomarker information beyond baseline ($t > 0$) to improve prediction obtained from stage 1 (Information-cumulating)**

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

Stage 1: Use a Cox model with only baseline (time-independent) covariates Y_i

$$\lambda_i(t) = \lambda_0(t) \exp\{\alpha' Y_i\} ,$$

This implies, without using any longitudinal data beyond baseline, prediction at time t can be done by

$$\begin{aligned} & S_i(t+u|T_i \geq t, Y_i) \\ = & \frac{S_i(t+u|Z_i)}{S_i(t|Y_i)} = \left\{ \frac{S_0(t+u)}{S_0(t)} \right\}^{\exp(\alpha' Y_i)} . \end{aligned}$$

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

Stage 2: At time t, with longitudinal data $Z_i(t)$, postulate the hazard function of $T_i - t$ as

$$\begin{aligned} \lambda_{i,t}(u) &= \lambda_{0,t}(u)\exp\{\alpha' Y_i + \beta'(t) Z_i(t)\} \\ &= \lambda_0(t+u)\exp\{\alpha' Y_i + \beta'(t) Z_i(t)\}\,. \end{aligned}$$

Notes:

- **Infinite number of reference hazard functions $\lambda_{0,t}(u)$ indexed by $t > 0$ have been expressed by a single reference hazard function $\lambda_0(t+u)$.**
- **Need smoothness assumptions for $\beta(t)$**

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

Then the previous prediction

$$\Pr(t+u|T_i \geq t, Y_i) = \left\{ \frac{S_0(t+u)}{S_0(t)} \right\}^{\exp(\alpha' Y_i)} .$$

can be improved by

$$\begin{aligned} & \Pr(T_i \geq t+u|T_i \geq t, Y_i, Z_i(t)) \\ = & \frac{S_i(t+u|Z_i(t))}{S_i(t|Y_i, Z_i(t))} = \left\{ \frac{S_0(t+u)}{S_0(t)} \right\}^{\exp\{\alpha' Y_i + \beta'(t) Z_i(t)\}} \end{aligned}$$

with improvement achieved by additional information in $Z(t)$.

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

- Longitudinal data $Z_i(t)$ are used to further distinguish subjects surviving at time t.
- Subjects may have $\beta'(t)Z_i(t) > 0, \ = 0$, or < 0
- Correspond to prediction by using $Z(t)$ being worse, equal or better than prediction without using $Z(t)$.

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

- Note Stage 2 specifies a landmark analysis model for each $t > 0$.
- Recall that landmark analysis does not use future values for prediction.
- This is why the new approach does not need use future biomarker data in prediction.
- Next a few slides show how we avoid using unobserved $Z_j(x_i), j \geq i$.

Two-Stage Parameter Estimation for IMPACT

Stage 1: Estimate α and $S_0(t), t \geq 0$.

- **Only the baseline covariate Y and survival information are used to fit a Cox model (with time-independent covariates).**
- **Maximizing partial likelihood to obtain $\hat{\alpha}$**
- **The Breslow estimator for $S_0(t), t \geq 0$.**

$$\hat{S}_0(t) = \exp\left\{ -\sum_{x_i \leq t} \frac{\delta_i}{\sum_{x_j \geq x_i} \exp(\hat{\alpha}' Y_j)} \right\}$$

Two-Stage Parameter Estimation for IMPACT

Stage 2: Estimate $\beta(t)$

- **From a subject with data Y, $Z(t_1)$, $Z(t_2)$, $\cdots$, $Z(t_m)$ and survival T,**
- **Create m pseudo-subjects with data shown below:**

  Subject 1: Baseline covariates Y and $Z(t_1)$, survival time $T - t_1$;

  $\cdots$

  Subject m: Baseline covariates Y and $Z(t_m)$, survival time $T - t_m$;

- **Each pseudo-subject contributes a likelihood term.**

Two-Stage Parameter Estimation for IMPACT

- **Each pseudo-subject contributes a likelihood term.**

  Subject 1**:** $T - t_1 \sim \left\{ \frac{\hat{S}_0(t_1+t)}{\hat{S}_0(t_1)} \right\}^{\exp\{\hat{\alpha}' Y_i + \beta'(t_1) Z(t_1)\}}$;

  $\ldots$

  Subject m**:** $T - t_m \sim \left\{ \frac{\hat{S}_0(t_m+t)}{\hat{S}_0(t_m)} \right\}^{\exp\{\hat{\alpha}' Y_i + \beta'(t_m) Z(t_m)\}}$.

Two-Stage Parameter Estimation for IMPACT

Stage 2: Estimate $\beta(t)$ (re-parameterized into β)

- **Working independence between pseudo-subjects**
- **Pseudo-likelihood = product of likelihood terms of all pseudo-subjects**
- **Maximize pseudo-likelihood to estimate β,**
- **With $\hat{\alpha}$ and $\hat{S}_0(\cdot)$ being fixed in Stage 2.**
- **Fixed $\hat{S}_0(\cdot)$ eliminates the need to use Cox-type partial likelihood for estimating β, and so eliminates the need to know $Z_j(x_i), j \geq i$.**
- **The only unknown parameter in the pseudo likelihood is β.**

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

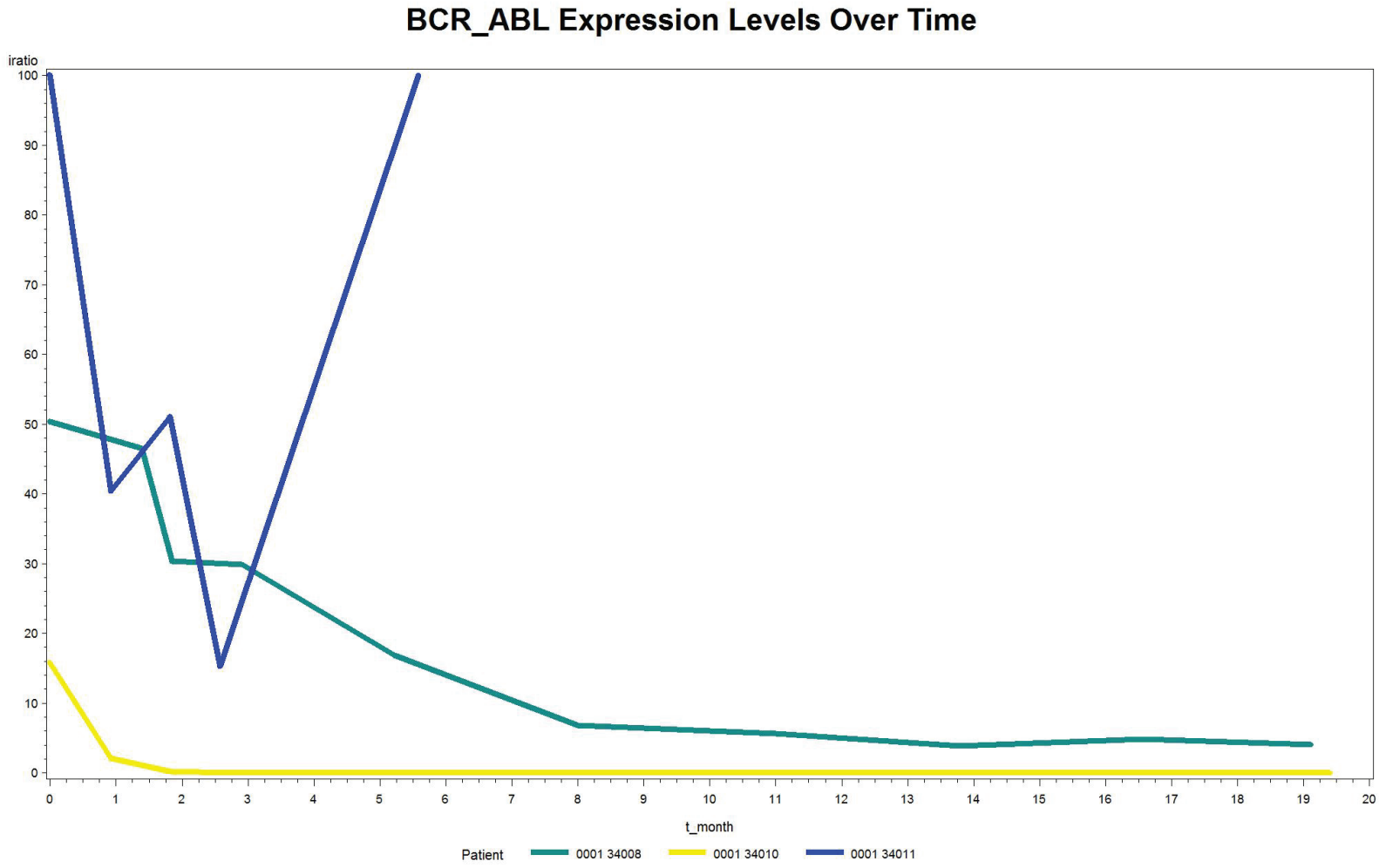
- **Using a training data set, get estimators $\hat{\alpha}$, $\hat{S}_0(t), t \geq 0$ (Stage 1), and $\hat{\beta}(t)$ (Stage 2).**
- **For a new subject, at time t with covariate value $Z_{\text{new}}(t)$, predict his survival distribution as**

$$\begin{aligned} & \Pr(T_{\text{new}} \geq t+u | T_{\text{new}} > t, Y_{\text{new}}, Z_{\text{new}}(t)) \\ = & \left\{ \frac{\hat{S}_0(t+u)}{\hat{S}_0(t)} \right\}^{\exp\{\hat{\alpha}' Y_{\text{new}} + \hat{\beta}'(t) Z_{\text{new}}(t)\}} \end{aligned}$$

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

Assume a parametric form or use splines for $\beta(t)$.

- Trade-off between
  - Using parametric models for $Z(t)$ to impute covariate values at time points they are not observed
  - Assuming a parametric form for $\beta(t)$.
- It is reasonable to believe that the true shape of $\beta(t)$ is more smooth than covariate $Z(t)$.
- Covariate $Z(t)$'s are very bumpy, see next.


BCR_ABL Expression Levels Over Time
iratio
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
t_month
Patient
0001 34008
0001 34010
0001 34011

Information-cumulating Model for Predictive Analysis Continuously over Time (IMPACT)

An example of a parametric form $\beta(t)$, after re-parameterizing,

$$
\begin{aligned}
& \Pr(T_i \geq t+u | T_i \geq t, Z_i(t)) \\
= & \frac{S_i(t+u|Z_i(t))}{S_i(t|Z_i(t))} \\
= & \left\{ \frac{S_0(t+u)}{S_0(t)} \right\}^{\exp\{\alpha' Y_i + \beta_0' Z_i(0) + \beta_1' \ln(t+1) Z_i(t)\}}
\end{aligned}
$$

CML Example

The model for dynamic prediction

$$\begin{aligned} & \Pr(T_{\textbf{new}} \geq t+u | T_{\textbf{new}} > t, Z_{\textbf{new}}(t)) \\ = & \left\{ \frac{\hat{S}_0(t+u)}{\hat{S}_0(t)} \right\}^{\exp\{\hat{\alpha}' Y_{\textbf{new}} + \hat{\beta}'(t) Z_{\textbf{new}}(t)\}} \end{aligned}$$

with

$$\begin{aligned} & \hat{\alpha}' Y_{\textbf{new}} + \hat{\beta}'(t) Z_{\textbf{new}}(t) \\ & = 0.458\, I(\textbf{age} > 60) + 0.0185\, \textbf{BCR}(0) \\ & \quad -0.298 \log(t+1) - 0.002\, \textbf{BCR}(t)\ \log(t+1). \end{aligned}$$

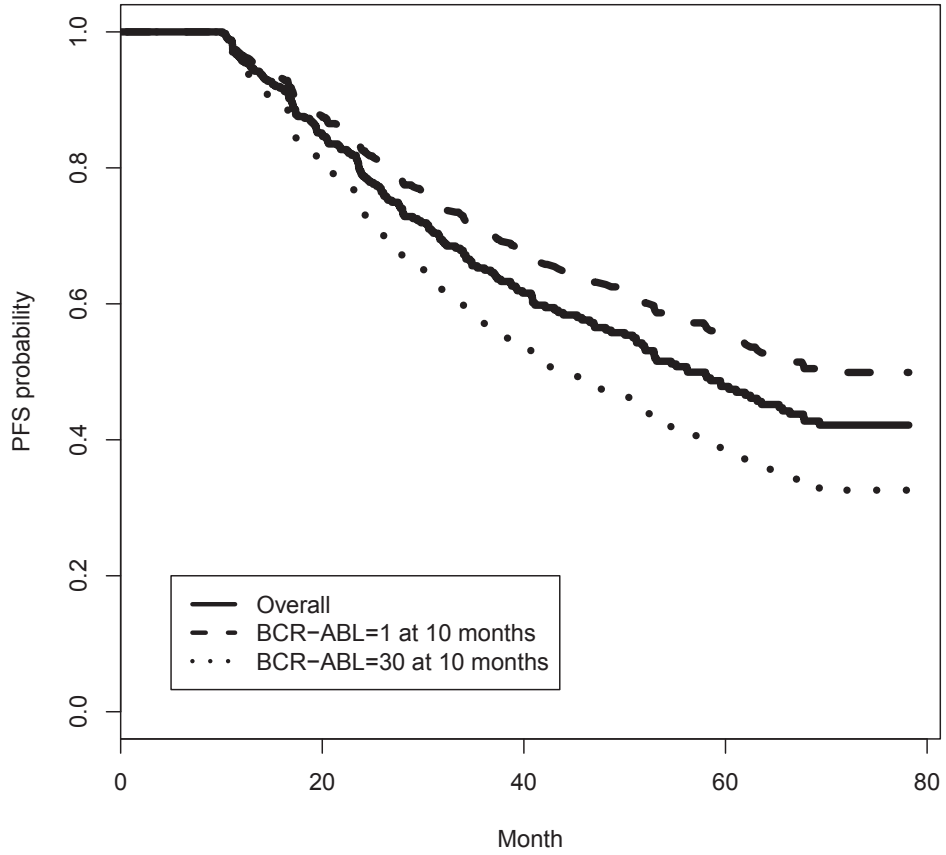


Figure 5: (1) Without using Z(10) (solid line), (2) Z(10)= 1 (dashed line), and (3) Z(10)= 30 (dotted line).

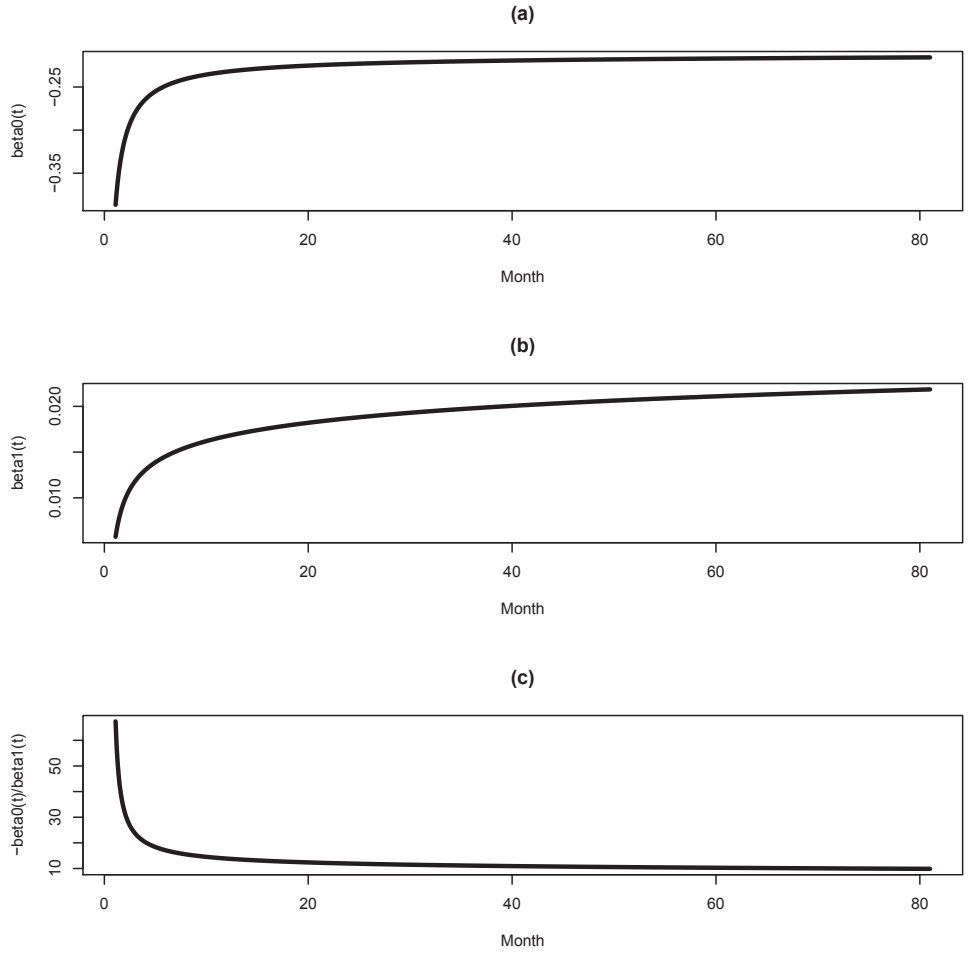


Figure 6: A biomarker trajectory with average (typical) survival

Summary

- Proposed approach uses a series of landmark analysis models over continuous t that are smoothed by using a parametric or spline $\beta(t)$.
- Landmark analysis approach avoids need to use future biomarker values in prediction.
- Two-stage estimation approach
  - avoids need of $Z_j(x_i), j \geq i$ by estimating $\lambda_0(t)$ (and thus $S_0(t)$) from the 1st stage and being fixed at 2nd stage
  - avoids need of model for $Z(t)$.

Discussion

- The estimation and interpretation of α are not distorted by intermediate outcomes reflected in time-dependent covariates $Z(t)$.
- This is usually what we want, i.e., α estimates the marginal population effects of baseline covariates on survival.
- The interpretation of corresponding regression coefficients in joint modeling is awkward.
- Bottom line: Proposed approach is easy and convenient to use.