Modeling Time to Alzheimer's Disease with an Immune Model

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Outline

- Cure model in cancer research
- Immune model in dementia research
- Simulation Study

Cure-Rate Model in Cancer Research

- For a heterogeneous population of patients receiving cancer treatment:
  - some patients will respond favorably to the treatment and subsequently become immune or insusceptible to the disease and are said to be cured.
  - The other group will not respond to the treatment and remain uncured. As a result, they are at risk for the development of disease.

Goals in Cure-Rate Model

- Determine the proportion of patients cured.
- Identify patient's factors associated with the cured group.
- Study the failure of the treatment in the uncured group of patients.
- Estimate the time to develop the disease again in the uncured group using a survival model.

Assumption of Standard Survival Models

- The observed outcome may be time to death due to cancer, so survival models will be used.
- However, an implicit assumption of standard survival models is that every subject will experience the event eventually.
- In the presence of a cured subgroup, standard survival techniques may give misleading results.
- A cure model is appropriate in this case.

Standard Survival Curve and Cure Model Curve

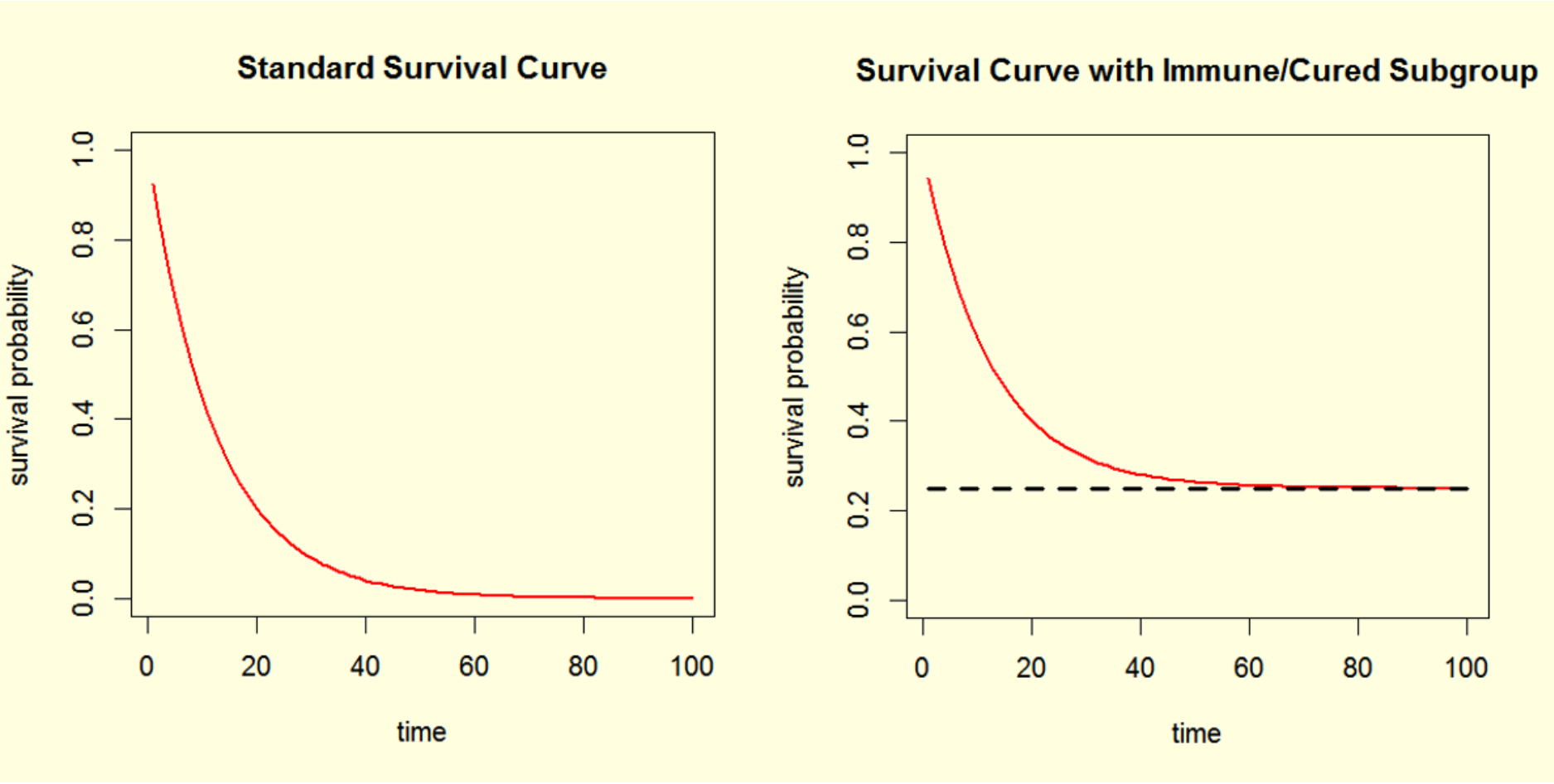

Figure: Comparison of survival curves given by standard survival models and survival models with a cured subgroup.

Are Some People Immune to Alzheimer Disease

- We hypothesize that some people may be immune to AD.
- immune: A patient is called immune to AD if the patient will never develop AD features, according to the current definition, using both biomarker, imaging, and pathology information.

Interpretation of Immune to AD

- An immune person can be viewed as "cured from birth"
- This assumption can not be empirically tested because a person cannot live forever.

Assumption of an Immune to AD Subgroup

- To our best knowledge, this assumption has not been studied carefully.
- Several findings have reported that individuals exist whose brains are devoid of disease even at the age of 90 years and beyond. This suggests that some people may be immune to dementia.
- Like cure model analysis, standard survival techniques may give misleading results in the presence of an immune subgroup.

Two Part Model for Dealing with Immune Subgroup

- We assume that the population consists of a mixture two parts: subjects immune to AD and subjects at risk for AD.
- Consequently, the survival distribution of the time to AD for a general individual in the study population can be written as

$$S_{pop}(t \mid x, z) = c(x) + (1 - c(x))S(t \mid z)$$

where $c(x)$ is immune probability for subjects with covariate x, and $S(t \mid z)$ is the survival function of AD for susceptible subjects with covariates z. Here x and z may be independent sets of variables.

Two-Part Model

- Similar to Farewell1(1982), we use a logistic-Weibull mixture model to account for the immune fraction.
- We use a logistic regression formula to model the immune probability, and a Weibull distribution to model the survival function for those at risk.
- The two parts are estimated jointly in an immune model.

Mathematical Formula

- "Immune part": the immune rate for subjects with covariates x is modeled as

$$\text{logit}(c(\mathbf{x})) = \beta'\mathbf{x}$$

- "Survival part": the survival function for susceptible subjects with covariates z is modeled as

$$S(t \mid z) = exp(-(\lambda t)^k)$$

, where $\lambda = \lambda(z) = exp(-\beta' z)$

Weibull distribution

- The Weibull model we use here is a popular choice for modeling survival function.
- The hazard function associated this model is $\lambda(t \mid x) = k\lambda^k t^{k-1}$.
- Depending on whether k is greater than 1 or not, it can model hazard function that either increases or decreases over time.
- It is also a special case of the Cox's proportional hazard model, with baseline hazard assumed to be $\lambda_0(t \mid z) = kt^{k-1}$.

Some Extensions

- Instead of Weibull model for $S(t \mid z)$, we can also assume a semi-parametric Cox model for it.
- Yin and Ibrahim (2005) developed a general class of cure models through Box- Cox (1964) transformation on the population survival function:

$$((S_{pop}(t \mid x, z))^{\lambda} - 1)/\lambda = \theta(x, \lambda) S(t \mid z)$$

Simulation Study

- We conducted a simulation study to illustrate why ignoring the immune subgroup may cause problems in survival curve estimation.
- Suppose we have 10000 subjects in our sample. We generated their immune rate and survival time according to an immune-rate model.
- Immune rate model

$$S_{pop}(t \mid z) = c + (1 - c)S(t \mid z)$$

  - c: immune rate
  - $S(t \mid z)$ is supposed to follow a Weibull distribution, a popular choice for modeling survival curve
  - Scale parameter of Weibull distribution λ is set to be greater than 1, representing hazard of getting dementia increases as subject ages.
- Suppose we have a follow-up time of 10 years for each person.

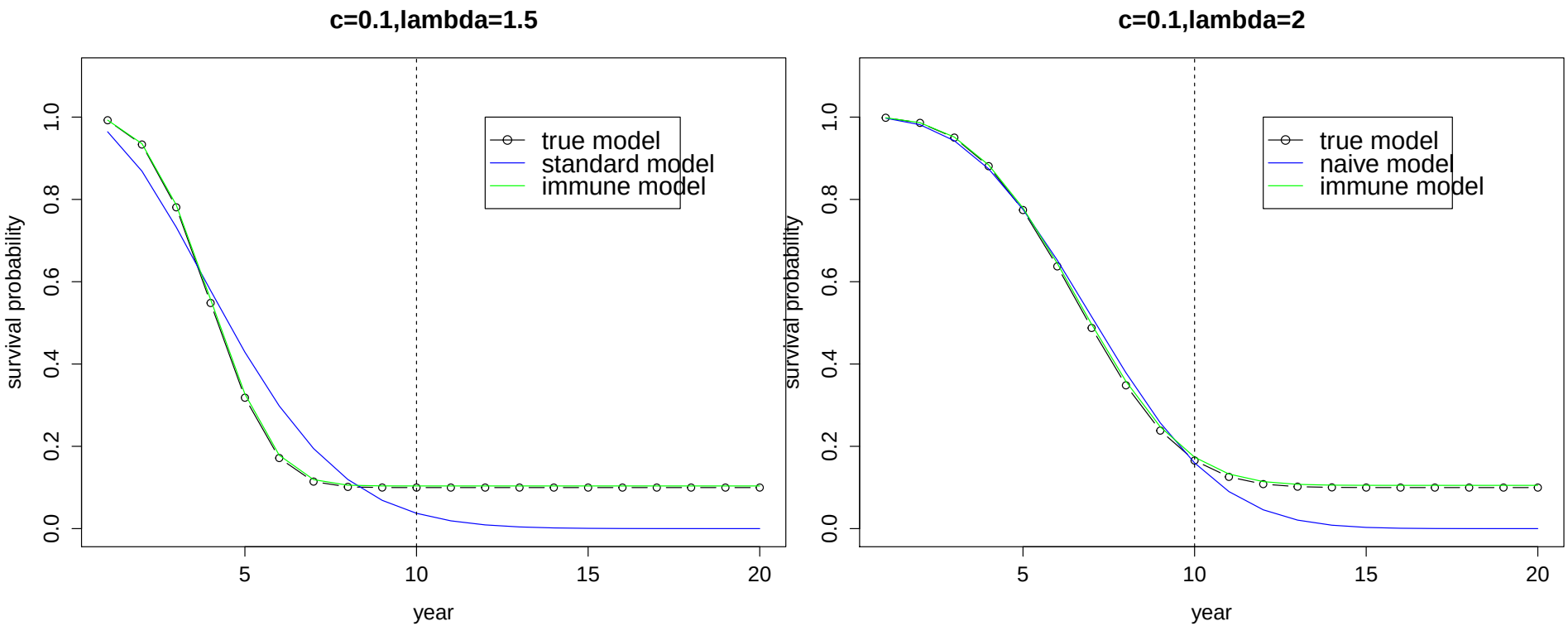

Figure: Comparison of survival curve estimates when 10 percent of subjects are immune.

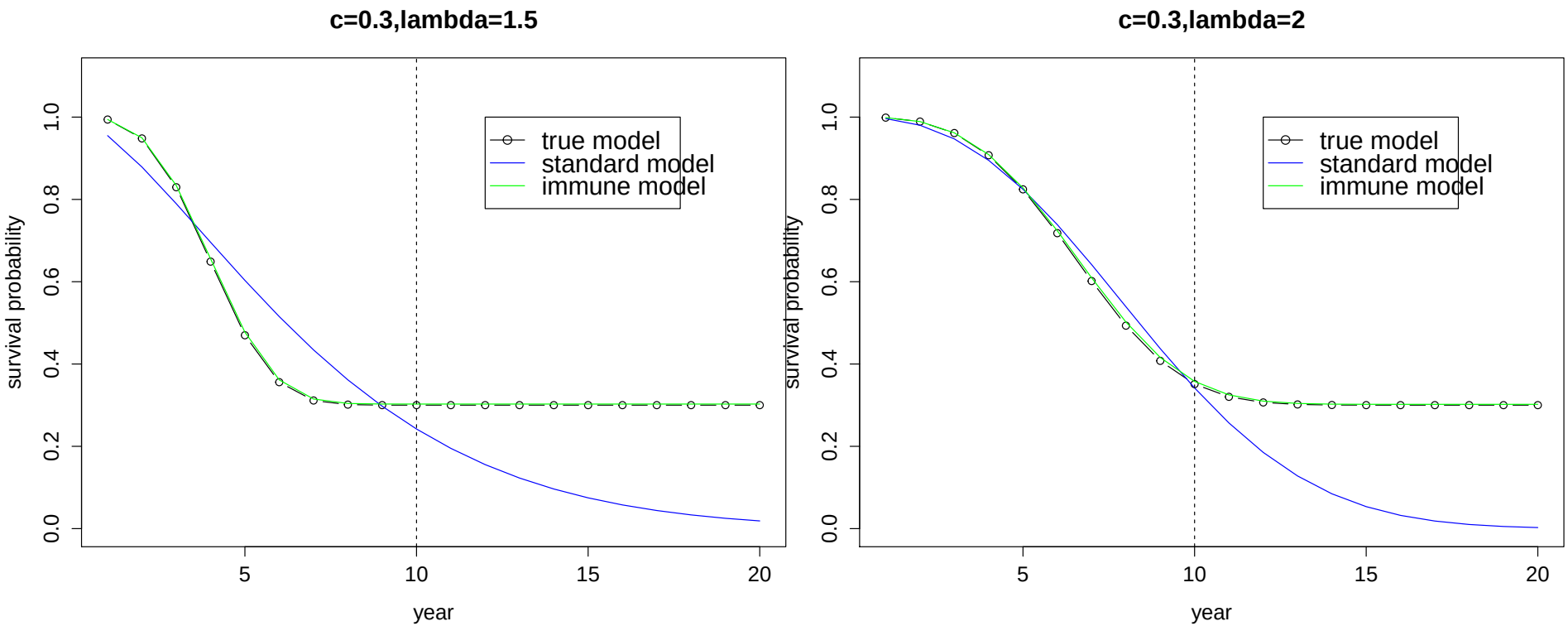

Figure: Comparison of survival curve estimates when 30 percent of subjects are immune.

Summary of Simulation Study

- When the plateau of survival curve is not observed, the standard survival curve may have an okay fit before censoring occurs.
- Otherwise the fit of standard survival curve can be terrible from the start.

Summary

- We introduce the concept of immune subgroup for AD research.
- We illustrate that standard survival models may give misleading results when an immune sub-population exists.
- Currently working on applying the immune models to UDS data set and other data sets.
- Currently working on extensions to new models