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# Event time analysis of longitudinal neuroimage data

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ABSTRACT

This paper presents a method for the statistical analysis of the associations between longitudinal neuroimaging measurements, e.g., of cortical thickness, and the timing of a clinical event of interest, e.g., disease onset. The proposed approach consists of two steps, the first of which employs a linear mixed effects (LME) model to capture temporal variation in serial imaging data. The second step utilizes the extended Cox regression model to examine the relationship between *time-dependent* imaging measurements and the timing of the event of interest. We demonstrate the proposed method both for the univariate analysis of image-derived biomarkers, e.g., the volume of a structure of interest, and the exploratory mass-univariate analysis of measurements contained in maps, such as cortical thickness and gray matter density. The mass-univariate method employs a recently developed spatial extension of the LME model. We applied our method to analyze structural measurements computed using FreeSurfer, a widely used brain Magnetic Resonance Image (MRI) analysis software package. We provide a quantitative and objective empirical evaluation of the statistical performance of the proposed method on longitudinal data from subjects suffering from Mild Cognitive Impairment (MCI) at baseline.
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## Introduction

Medical events, such as the onset of disease, represent major landmarks in the course of a patient's clinical history. A significant portion of biomedical research is dedicated to studying the risk factors associated with these events, aiming to predict, delay and ultimately prevent their occurrence.

In recent decades, neuroimaging has accelerated the study of brain-related clinical conditions. A classical neuroimaging approach has been to contrast measurements obtained from those who have experienced the event (i.e., cases) with measurements from those who have not (i.e., controls). This methodology has yielded reliable markers of disease, e.g., (Jack et al., 2012), while providing insights about underlying biological mechanisms, e.g. (Buckner et al., 2005; Sabuncu et al., 2012).

Yet, the classical case–control approach treats the two groups as distinct entities and assumes a certain amount of within-group homogeneity. This approach can therefore be limited when the control group is a high-risk cohort, that is, when a significant proportion of subjects have not yet experienced the event of interest but are likely to do so in the not-too-distant future. Such "pre-event" cases, which, in the absence of other information will be treated as controls, typically fall in the gray area between a pure case and a pure control. Thus the within-group homogeneity assumption is violated, which will in turn impact statistical inference. Common examples for this are longitudinal studies of populations that are at high risk for disease, based on their genetic make-up (e.g., carriers of a faulty allele of the *Huntingtin* gene in a Huntington's study (Albin et al., 1990)), familial history (e.g., subjects who have a first-degree relative with schizophrenia (Whitfield-Gabrieli et al., 2009)) or clinical presentation (e.g., subjects with Mild Cognitive Impairment, or MCI, in an Alzheimer's study (Forsberg et al., 2008)). These examples are particularly relevant to drug trials focused on the pre-clinical or early phases of a disease and thus target high-risk populations. In such scenarios, an inappropriate statistical treatment of the group of subjects who have not been observed to experience the event (diagnosis or conversion to disease) during the follow-up period (sometimes referred to as "non-converters") can introduce bias into the analysis and/or reduce efficiency.

An alternative strategy that addresses this issue, directly models the timing of the event of interest, while accounting for finite follow-up or censoring. This is the event time (or survival) analysis approach (Kleinbaum and Klein, 2012), which includes classical models such as Cox proportional hazards regression (Cox, 1972). Standard event time

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[2] Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available at http://tinyurl.com/ADNI-main.

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analysis models have been applied in prior neuroimaging studies (Desikan et al., 2009, 2010; Devanand et al., 2007; Geerlings et al., 2008; Marcus et al., 2007; Sabuncu, 2013; Stoub et al., 2005; Tintore et al., 2008; Vemuri et al., 2011) and have yielded novel insights about various clinical conditions. Most of these prior studies have analyzed associations between imaging measurements from a *single* baseline visit and the timing of the event of interest identified via follow-up clinical assessments. These analyses typically rely on survival models (e.g., the standard Cox model) that assume the explanatory variables are independent of time (gender, genetic marker, birth place, etc.). The employed models are useful for constructing individualized survival curves and making predictions about the timing of a future event. Furthermore, they offer insights about the relationships between independent variables and the event time. As such, survival models have been used to draw conclusions about associations between neuroimaging measurements (e.g., volume of a structure) and the clinical event (e.g., disease onset). This type of inference, however, suffers from two problems. Firstly, imaging measurements typically vary over time (e.g., due to anatomical changes). Yet, interpretation of the standard Cox model, for example, has to be done with respect to the baseline imaging measurements only and not with respect to the dynamically changing measurements. Secondly, in longitudinal designs that span an extended time period, imaging measurements are likely to vary substantially over time, making it harder to detect associations between baseline imaging markers and the clinical event.

Longitudinal neuroimaging (LNI) studies, where *multiple* serial images are acquired for each participant, provide a means to characterize the temporal trajectories of imaging measurements. Furthermore LNI studies can offer a substantial increase in statistical power for studying imaging markers (Bernal-Rusiel et al., 2013a,b), while opening up the possibility of examining the relationship between the temporal dynamics of imaging markers and clinical variables (Sabuncu et al., 2011). Today, the standard strategy for analyzing the association between LNI data and the occurrence of a clinical event, such as disease onset, is to perform a group comparison based on dichotomizing the subjects into, for example, "converters" versus "non-converters" (Borgwardt et al., 2011; Chetelat et al., 2005; Jack et al., 2008a; Morgan et al., 2011; Sun et al., 2009). However, as we discussed above, this approach can be sub-optimal, since the non-converter group likely includes subjects who might convert beyond the study follow-up.

The core goal of this paper is to propose a powerful method for the statistical analysis of the associations between longitudinal neuroimaging measurements, e.g., of gray matter density or cortical thickness, and the timing of a clinical event of interest, such as disease onset. The proposed approach combines a linear mixed effects (LME) model that captures the spatiotemporal correlation pattern in serial imaging data (Bernal-Rusiel et al., 2013a,b; Verbeke and Molenberghs, 2000) and an extended Cox regression model that allows the examination of associations between the *time-dependent* imaging measurements and the timing of a clinical event (Kleinbaum and Klein, 2012). Recent work showed that such a joint analysis can reduce bias and increase statistical efficiency by exploiting all available information (Tsiatis and Davidian, 2004).

We demonstrate the proposed method both for the univariate and mass-univariate analysis of imaging measurements automatically computed with FreeSurfer, a widely used brain Magnetic Resonance Image (MRI) data analysis software package (Dale et al., 1999; Fischl, 2012; Fischl and Dale, 2000; Fischl et al., 1999a,b). We include a quantitative and objective empirical evaluation of the statistical performance of the proposed method based on publicly available data (the Alzheimer's disease neuroimaging initiative, ADNI[3]) from a group of subjects with Mild Cognitive Impairment (MCI) (Gauthier et al., 2006), a clinically defined condition associated with high-risk incipient dementia. Our experiments revealed that the proposed method offers a substantial increase in statistical efficiency relative to a "two-sample" benchmark method that compares those who convert from MCI to clinical AD against those who remain MCI through follow-up; and a classical Cox regression analysis that employs only baseline scans.

The paper is organized as follows. The Cox proportional hazards model and its extension section and the Linear mixed effects models for longitudinal data section review the Cox proportional hazards and linear mixed effects models, respectively. The Proposed strategy for joint analysis of event time and LNI data section presents the proposed method that unifies these two frameworks. The Alternative methods section describes the alternative analysis strategies that we will use to benchmark our experimental results. The ADNI data section offers a description of the data used in the experiments and the Statistical models section details the statistical analyses conducted on these data. In the Experimental results section, we present experimental results that illustrate the proposed joint modeling approach and compare it against benchmarks. Finally, the Discussion section provides a discussion of the main experimental findings and the Conclusions section closes with concluding remarks.

## Material and methods

### *The Cox proportional hazards model and its extension*

In this section, we provide a brief overview of the classical Cox proportional hazards model (Cox, 1972) and its extension for time-varying explanatory (independent) variables. For a detailed treatment, the reader is referred to dedicated texts, such as Kleinbaum and Klein (2012).

A core component of event time models is the so-called hazard function $h(t)$, which is the instantaneous probability of experiencing the event of interest (e.g., disease onset), given no event up to time $t$. The hazard function is mathematically defined as:

$$h(t) = \lim_{dt \to 0} \frac{P(t \leq T < t + dt | T \geq t)}{dt},$$

where $T$ is the random variable that represents the time of event and $p(.|.)$ denotes conditional probability. The classical Cox model assumes that the hazard function of a sample with $p$ *time-independent* explanatory variables $X = \left(X_1, X_2, \ldots X_p\right)$ can be expressed as:

$$h(t, X) = h_0(t) \exp\left(\sum_{i=1}^{p} \alpha_i X_i\right), \quad (1)$$

where $h_0(t)$ is the so-called baseline hazard function and $\alpha = (\alpha_1, \ldots, \alpha_p)$ is the coefficients associated with the explanatory variables. This model assumes that the hazard function can be written as a product of two factors: one that varies with time but is independent of $X$, and another that is a function of the *time-independent* explanatory variables $X$ and thus is fixed over time. The foundation of the classical Cox model is the proportional hazards assumption, i.e., the proportion of the hazard functions of two samples is constant over time: $\frac{h(t,X^1)}{h(t,X^2)} = \exp\left(\sum_{i=1}^{p} \alpha\left(X_i^1 - X_i^2\right)\right) = \text{const.}$, where $X^j$ is the independent variables of the $j$'th sample.

A popular strategy to estimate the coefficients $\alpha$ is the so-called *partial* likelihood maximization method (Cox, 1972, 1975). In particular, the partial likelihood is expressed as a product of $K$ terms, each corresponding to the likelihood of an observed event computed based on the time of occurrence (i.e., there are $K$ events observed during the

[3] http://tinyurl.com/ADNI-main.

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