Statistical Modeling of Survival Data on Decompression Sickness

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1. Introduction

Humans exposed to low atmospheric pressure environments, such as astronauts during extra-vehicular activity (EVA), typically experience the formation of nitrogen gas bubbles in venous blood, as a result of hypobaric decompression. The reduction in pressure from, for example, the Space Shuttle or a space station, to a pressurized space suit can cause nitrogen gas normally dissolved in body fluids and tissue to escape from solution too rapidly, causing the formation of bubbles in the bloodstream. The presence of these circulating gas bubbles in the blood stream contributes to altitude or hypobaric decompression sickness (DCS).

Prebreathing oxygen helps to eliminate nitrogen from tissues, reducing the density of circulating bubbles while at altitude. Prebreathe procedures are evaluated prior to their use on space missions by using altitude chambers that simulate low gravity conditions. In these simulation chambers, the existence of nitrogen bubbles is typically monitored using Doppler detection, and the extent of bubble signals is measured in grades (from Grade 0 -- absence of bubble signals in cardiac cycles, to Grade IV -- bubble signals are detected continuously throughout the monitoring period, overriding the amplitude of cardiac motion and blood flow signals.

In this paper, we describe a model for predicting the time to onset of grade IV venous gas bubbles. For building and fitting the model, we use a databank from NASA consisting of test results from volunteer subjects undergoing monitoring for venous gas emboli in simulated low pressure conditions. To understand the influence of physiological characteristics on the time to onset of grade IV bubbles, certain explanatory variables, as well as information on the partial pressure of nitrogen prior to exposure, are used in the present study.

2. Description of the Data

We analyzed a set of data taken from NASA's Hypobaric Decompression Sickness Databank (Conkin et al., 1992). This databank contains monitoring test results from human volunteer subjects undergoing denitrogenation test procedures prior to being exposed to a simulated low pressure environment. The exposure records are from 453 males and 96 females that participated in a total of 28 different tests from 1983 to 1998. However, the number of *individuals* tested was 238 (177 male), because many subjects participated in more than one test. The highest number of test results contributed by a single individual was 13. The median was 2.

Each testing session was scheduled to last anywhere between 2 and 6 hours. If grade IV bubbles were detected within a four-minute monitoring interval, the recorded onset time was the interval between the end of the last monitoring period and the beginning of the period in which grade IV bubbles were detected. Thus, these cases were effectively interval-censored. If grade IV bubbles were not detected during the test period, the recorded onset time was right-censored at the end of the session. If the test was stopped for any reason prior to the end of the session, the observation was right-censored at that time.   Of the 548 records, 124 were interval-censored (i.e., grade IV bubbles were detected), leaving over 77% right-censored.

Explanatory variables included experimental variables and physical characteristics of the subjects. These variables include TR360, a measure of decompression stress, NOADYN, an indicator for whether the test subject was ambulatory (NOADYN = 1) or lower body adynamic (NOADYN = 0), ALTTIME, the prescheduled time at altitude (2, 3, 4, 5, or 6 hours), and SEX (male = 1, female = 0).

3. Model Fitting

We initially fit a lognormal model to the interval- and right-censored times. The lognormal model was chosen because the form of its hazard function is consistent with the potential for experiencing grade IV bubbles in the population of interest. The lognormal distribution function is

$$F\left(t \mid \boldsymbol{b}, \boldsymbol{s}, \mathbf{x}\right) = \Phi\left(\frac{\log(t) - \boldsymbol{m}(\mathbf{x})}{\boldsymbol{s}}\right)$$

where

$$\boldsymbol{m}(\mathbf{x}) = \boldsymbol{b}_0 + \sum_{j=1}^{p} x_j \boldsymbol{b}_j , \text{ and } x_j \quad j = 1,.,.p \text{ are values of } p \text{ explanatory variables.}$$

Sometimes it is known or suspected that a subset of the observations will never experience the event, perhaps because they are immune to the event or are cured of the disease, and will never relapse. In these cases, the survival model can be thought of as a mixture model. A traditional mixture model is a model (parametric or nonparametric) for a data set where the data set is suspected of comprising two or more mutually exclusive groups. The Limited Failure Population (LFP) Model is mixture model for survival data consisting of two groups: 1) individuals who will eventually experience the event, and 2) individuals who will never experience the event, sometimes called "immune" individuals.

Several variants of the LFP model were fit. These models varied in their total number of parameters and the constraints made on the values of the parameters. We present two of the final models. The first model (called the Full LFP Model) fits the largest model, estimating 5×1 parameter vectors for both $\boldsymbol{a}$ and $\boldsymbol{b}$, as well as one scale parameter, for a total of 11 parameters. The second model (Trimmed LFP Model) models log survival time as depending on two of the explanatory variables: TR360 and NOADYN, and models the logit of the probability of grade IV bubbles as depending on three explanatory variables: SEX, AGE and ALTTIME (time at altitude). The second model is nested within the Full LFP Model and provided the best fit.

Bibliography

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Summary

We fit a lognormal mixture survival model to the interval- and right-censored data that accounts for the possibility of a subset of subjects who are immune to experiencing the event. Model assessments and validation indicate that this mixture model is an improvement over a model that does not acknowledge an immune fraction.