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First-Hitting-Time Based Threshold Regression

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First-hitting-time (FHT) based threshold regression (TR) model is a relatively new methodology for analyzing ►survival data where the time-to-event is modeled as the first time the stochastic process of interest hits a boundary threshold. FHT models have been applied in analyzing the failure time of engineering systems, the length of hospital stay, the survival time of AIDS patients, and the duration of industrial strikes, etc.

First-Hitting-Time (FHT) Model

A first-hitting-time (FHT) model has two basic components, namely a stochastic process $\{Y(t), t \in \mathcal{T}, y \in \mathcal{Y}\}$ with initial value $Y(0) = y_0$, where $\mathcal{T}$ is the time space and $\mathcal{Y}$ is the state space of the process; and a boundary set $\mathcal{B}$, where $\mathcal{B} \subset \mathcal{Y}$. Assume that the initial value of the process y_0 lies outside the boundary set $\mathcal{B}$, then the first hitting time can be defined by the random variable

$$S = \inf\{t : Y(t) \in \mathcal{B}\},$$

where S is the first time the sample path of the stochastic process reaches the boundary set $\mathcal{B}$. In a medical context, the stochastic process $\{Y(t)\}$ may describe a subject's latent health condition or disease status over time t. The boundary set $\mathcal{B}$ represents a medical end point, such as death, or disease onset. Although the boundary set $\mathcal{B}$ is set to be fixed in time in basic FHT models, it may vary with time in some applications. The stochastic process $\{Y(t)\}$ in the FHT model may take many forms. The most commonly used process is a Wiener diffusion process with a positive initial value and a negative drift parameter. Alternative processes including the gamma process, the Ornstein-Uhlenbeck (OU) process, and the semi-Markov process have also been investigated. For a review, see Lee and Whitmore (2006) and Aalen et al. (2008).

Threshold Regression

Threshold regression (TR) is an extension of the first-hitting-time model by adding regression structures to it so as to accommodate important covariates. The threshold regression model does not required the proportional hazards assumption and hence it provides an alternative model for analyzing time-to-event data. The unknown parameters in the stochastic process $\{Y(t)\}$ and the boundary set $\mathcal{B}$ are connected to covariates using suitable regression link functions. For example, the initial state y_0 and the drift parameter μ of a Wiener diffusion process $\{Y(t)\}$ can be linked to covariates using general link functions of the form

$$y_0 = g_1(\mathbf{x})$$

and

$$\mu = g_2(\mathbf{x}),$$

where $\mathbf{x}$ is the vector of covariates (Lee et al. 2000; Lee and Whitmore 2006). Pennell et al. (2010) proposed a TR model with Bayesian random effects to account for unmeasured covariates in both the initial state and the drift. Yu et al. (2009) incorporated penalized regression and regression splines to TR models to accommodate semi-parametric nonlinear covariate effects.

Analytical Time Scale

In stead of calendar time, in many applications involving time-dependent cumulative effects, an alternative time scale can be better used in describing the stochastic process. Let $r(t|\mathbf{x})$ denote a monotonic transformation of calendar time t to analytical time r (or referred to as process time) with $r(0|\mathbf{x}) = 0$. In a medical context, the analytical time may be some time-dependent measure to describe cumulative toxic exposure or the progression of disease. The process $\{Y(r)\}$ defined in terms of analytical time r can be expressed as a subordinated process $\{Y[r(t)]\}$ in terms of calendar time t. Lee and Whitmore (1993, 2004) examined the connection between subordinated stochastic processes and analytical time.

Whitmore et al. (1998) proposed a bivariate Wiener model in which failure is governed by a latent process while auxiliary readings are available from a correlated marker process. Lee et al. (2000) extended this model to bivariate threshold regression by including CD4 cell counts as a marker process in the context of AIDS clinical trials.

Tong et al. (2008) generalized the bivariate TR model to current status data. Using Markov decomposition methods, Lee et al. (2010) generalized threshold regression to include time-dependent covariates. Lee and Whitmore (2010) discussed the connections between TR and proportional hazard regressions and demonstrated that proportional hazard functions can be generated by TR models.

About the Author

Professor Lee was named the Mosteller Statistician of the Year in 2005 by the American Statistical Association, Boston Chapter. She is Elected member of the International Statistical Institute (1995), and Elected Fellow of: Royal Statistical Society (1998), American Statistical Association (1999) and the Institute of Mathematical Statistics (2005). Professor Lee is the Founding Editor and Editor-in-Chief of the international journal *Lifetime Data Analysis*.

Cross References

►First Exit Time Problem
►Survival Data

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Fisher Exact Test

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The Fisher Exact test was proposed by Fisher (1934) in the fifth edition of *Statistical Methods for Research Workers*. It is a test for independence as opposed to association in 2×2 contingency tables.

A typical situation where such tables arise is where we have counts of individuals categorized by each of two dichotomous attributes, e.g., one attribute may be religious affiliation dichotomized into Christian and non-Christian and the other marital status recorded as married or single.

Another example is that where one of the attributes that are dichotomized corresponds to treatments, e.g., Drug A prescribed, or Drug B prescribed, and the other attribute is the responses to those treatments, e.g., patient condition improves or patient condition does not improve.

In the latter situation if 9 patients are given Drug A and 12 patients are given drug B we might observe the following counts in cells of a 2×2 table:

	Improvement	No improvement	Row total
Drug A	8	1	9
Drug B	3	9	12
Column totals	11	10	21

Fisher pointed out that if we assume row and column totals are fixed then once we know the entry in any cell of the table (e.g., here 8 in the top left cell) then the entries in the remaining three cells are all fixed by the constraint that the marginal totals are fixed. This is usually expressed by saying the table has one degree of freedom. What Fisher noted is that under the hypothesis of independence, if we assume the marginal totals fixed then the distribution of the numbers in the first cell (or any other cell) has a hypergeometric distribution under independence for any of the common models associated with such a table as described, for example in Agresti (2002) or Sprent and Smeeton (2007). These common models are (1) that responses to each drug, for example, are binomially distributed with a common value for the binomial parameter p or (2) have a common Poisson distribution, or (3)

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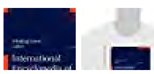

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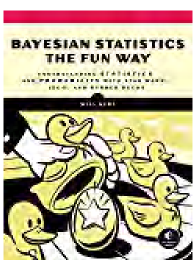

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