Canvas-stretching: An iterated curve-fitting approach to modelling and extrapolating sequential time-to-event phenomena using aggregate data

Jon Minton

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# Introduction

A number of disease areas are generally recognized as degenerative in nature, and modeled as a sequence of locally absorbing and intransitive states, forming a unidirectional sequence. The simplest example of such phenomena are two-state phenomena, in which an individual begins in state A, and over a unit of time has a probability of transitioning to state B. Once in state B, the individual stays in that state: the archetypal example of this is an alive-to-dead transition, but very different situations, such as time to first birth, can be modeled in exactly the same way. State B is an ‘event’, and a range of techniques exist for estimating and extrapolating time-to-event even given right-censored data.

The three state extension of two-state time-to-event is illustrated in figure [X], in which an individual begins in state A, and has a probability of transitioning over a given unit of time to state B. Once in state B, the individual has a probability of transitioning over a given unit of time to state C.

[Figure here]

A typical example of this phenomena in health technology assessment involves modeling cancer disease progression, where an individual begins with a less virulent, non-progressed cancer (A), and in each time unit there is a given probability that the cancer will move to a progressed state (B). The disease is assumed to be irreversible, so that the probability of transitioning from B to A is zero, but the probability of transitioning from B to C (death) is non-zero. Once dead, the probability of transitioning back to a non-dead state is assumed to be zero.

Given IPD, it would be possible to populate the transition probabilities directly. However, such data are not always available, or are very right-censored. More commonly, aggregate data, in the form of Kaplan-Meier curves (1- the empirical cumulative density function plotted against time) are used instead.

Where the KM curves are taken from a single trial, and are of a single cohort who begin at the same time, the curves should not cross for non…