Chapter 9
Marginal Structural Models

Michael Rosenblum

In many applications, one would like to estimate the effect of a treatment or exposure on various subpopulations. For example, one may be interested in these questions:

- What is the effect of an antidepressant medication on Hamilton Depression Rating Scale (HAM-D) score for those who enter a study with severe depression, and for those who enter with moderate depression?
- What is the effect of a cancer therapy for those who test positive for overexpression of a particular gene and for those who test negative for overexpression of that gene?
- What is the impact of low adherence to antiretroviral therapy on viral load for HIV-positive individuals who have just achieved viral suppression and for those who have maintained continuous viral suppression for 1 year?

In this chapter, we present a method for estimating the effect of a treatment or exposure in various subpopulations in an HIV treatment application. We first present an analysis in which there are only two subpopulations of interest. Then we present an analysis with 12 subpopulations of interest, where we use a marginal structural model as a working model. Marginal structural models, an important class of causal models and target parameters, were introduced by Robins (1998).

9.1 Impact of Missing Doses on Virologic Failure

For HIV-positive individuals taking antiretroviral medication, a danger in missing doses is that the HIV virus may increase replication. A measure of the amount of circulating virus is called “viral load.” It is of interest to understand how different levels of missed doses (e.g., missing 20% of doses in a month or 40% of doses in a month) are related to the probability of subsequent increases in viral load. Furthermore, we’d like to understand how the impact of missed doses on viral load may
differ depending on patient history of viral suppression. The aspect of patient history of viral suppression we focus on is the number of consecutive months in the past, starting just before the current month, that a subject has had viral load below 50 copies/ml (which we refer to as “duration of continuous suppression”). As an example, we’d like to understand the impact of low adherence to antiretroviral therapy on viral load for HIV-positive individuals who have just achieved viral suppression and for those who have maintained continuous viral suppression for 1 year. We describe a particular data analysis that aimed to answer this question, which is fully described in Rosenblum et al. (2009).

The population we consider is HIV-positive individuals in the Research in Access to Care for the Homeless (REACH) cohort; subjects in the study consist of a systematic, community-based sample of HIV-positive urban poor individuals in San Francisco (Moss et al. 2004). Adherence to antiretroviral therapy was assessed based on unannounced pill counts, as described in Bangsberg et al. (2001).

We consider four levels of percent adherence to therapy in a given month: 0–49%, 50–74%, 75–89%, and 90–100%. The outcome we consider is whether a patient’s viral load is less than 50 copies/ml in a given month. We say a patient experiences virologic failure if her viral load is at least 50 copies/ml.

Three hundred and fifty-seven subjects were monitored monthly for medication adherence. Each subject who had a viral load of less than 50 copies/ml over 2 consecutive months (which is an indicator of successful suppression of the HIV virus) was included in the study; a total of 221 subjects met this criterion. For each included subject, we found the earliest occurrence of 2 consecutive months with viral load less than 50 copies/ml; we let “month 0” denote the first of these two consecutive months.

The goal is to produce estimates of the risk of virologic failure at the end of a given month, under each of the four adherence levels, controlling for variables measured prior to that month. We will get such estimates for each of the following 12 groups:

1. Risk of virologic failure at the end of month 2 among subjects who remained continuously suppressed through month 1;
2. Risk of virologic failure at the end of month 3 among subjects who remained continuously suppressed through month 2;
   
12. Risk of virologic failure at the end of month 13 among subjects who remained continuously suppressed through month 12.

We point out that all 221 subjects included in the study contribute data to the estimate in group 1 above (since the inclusion criterion described above requires that subjects be suppressed during month 1). Fewer subjects directly contribute data to the estimates in the latter groups. We also used a nonsaturated marginal structural