DESIGNING PERSONALIZED TREATMENT: AN APPLICATION TO ANTICOAGULATION THERAPY

Technical Appendix

0.1. Proof of Theorem 4.2

Define the objective function $f(d) = e^{2\beta+2\mu_M d+2\sigma_M^2 d^2+2\sigma_\epsilon^2} - 2ce^{\beta+\mu_M d+0.5\sigma_M^2 d^2+0.5\sigma_\epsilon^2}$. By differentiating $f(d)$ and setting its derivative equal to 0, we obtain that:

$$f'(d) = (2\mu_M + 4\sigma_M^2 d)e^{2\beta+2\mu_M d+2\sigma_M^2 d^2+2\sigma_\epsilon^2} - 2c(\mu_M + \sigma_M^2 d)e^{\beta+\mu_M d+0.5\sigma_M^2 d^2+0.5\sigma_\epsilon^2} = 0,$$

which reduces to

$$(2\mu_M + 4\sigma_M^2 d)e^{\beta+\mu_M d+1.5\sigma_M^2 d^2+1.5\sigma_\epsilon^2} - 2c(\mu_M + \sigma_M^2 d) = 0.$$

First, we formulate conditions for the existence of a local minimum of the objective function using the first derivative test. Then, to establish that this will be a unique and global minimum, we impose conditions that guarantee strict convexity of the function. A local minimum for a strictly convex function must be both unique and global.

We begin by establishing a sufficient condition for the existence of a local minimum. In particular, we impose a condition that guarantees the existence of a root d^* such that $f'(d^*) = 0$, and we also impose that $f^{(2)}(d^*) > 0$. We will go further and impose that $f^{(2)}(d) > 0$ for all d (strict convexity). Note that $\lim_{d\to\infty} f'(d) = \infty$. Thus, by the intermediate value theorem, and by the continuity of the function, it suffices to impose that $f'(0) < 0$ i.e., we need to have that $2\mu_M e^{\beta+1.5\sigma_\epsilon^2} - 2c\mu_M < 0$. This reduces to

$$e^{\beta+1.5\sigma_\epsilon^2} < c,$$

where we assume that $\mu_M > 0$ which should also hold since the sensitivity should be non-negative. This yields the upper bound in the theorem. We now impose that:

$$\begin{aligned} f^{(2)}(d) = &\left(4\sigma_M^2 + 4(\mu_M + 2\sigma_M^2 d)^2\right) e^{2\beta+2\mu_M d+2\sigma_M^2 d^2+2\sigma_\epsilon^2} \\ &- 2c\left(\sigma_M^2 + (\mu_M + \sigma_M^2 d)^2\right) e^{\beta+\mu_M d+0.5\sigma_M^2 d^2+0.5\sigma_\epsilon^2} \\ > 0. \end{aligned} \tag{0.1}$$

This is equivalent to showing that

$$\begin{aligned} h(d) = &\left(4\sigma_M^2 + 4(\mu_M + 2\sigma_M^2 d)^2\right) e^{\beta+\mu_M d+1.5\sigma_M^2 d^2+1.5\sigma_\epsilon^2} - 2c\left(\sigma_M^2 + (\mu_M + \sigma_M^2 d)^2\right) \\ > 0. \end{aligned} \tag{0.2}$$

In order for $h(d) > 0$, it suffices to have that h is strictly increasing and $h(0) > 0$. For h to be strictly increasing, we need that $h'(d) > 0$. For $h'(d) > 0$, it suffices to have that $h^{(2)}(d) > 0$ and $h'(0) > 0$. We differentiate $h(\cdot)$ twice and obtain:

$$\begin{aligned} h'(d) = &\left(16\sigma_M^2(\mu_M + 2\sigma_M^2 d)\sigma_M^2 + \left(4\sigma_M^2 + 4(\mu_M + 2\sigma_M^2 d)^2\right)(\mu_M + 3\sigma_M^2 d)\right) e^{\beta+\mu_M d+1.5\sigma_M^2 d^2+1.5\sigma_\epsilon^2} \\ &- 4c(\mu_M + \sigma_M^2 d)\sigma_M^2. \end{aligned} \tag{0.3}$$

$$h^{(2)}(d) = \left(32\sigma_M^4 + 32(\mu_M + 2\sigma_M^2 d)\sigma_M^2(\mu_M + 3\sigma_M^2 d)\right.$$
$$\left. + \left(4\sigma_M^2 + 4(\mu_M + 2\sigma_M^2 d)^2\right)\left(3\sigma_M^2 + (\mu_M + 3\sigma_M d)^2\right)\right) e^{\beta + \mu_M d + 1.5\sigma_M^2 d^2 + 1.5\sigma_\epsilon^2} - 4c\sigma_M^4. \tag{0.4}$$

To guarantee the above conditions, it suffices to impose that

$$\max\{\frac{c}{2}, \frac{c\sigma_M^4}{3\sigma_M^4 + 4\sigma_M^2\mu_M^2 + \mu_M^4}, \frac{2.5\sigma_M^2}{5\sigma_M^2 + \mu_M^2}\} < e^{\beta + 1.5\sigma_\epsilon^2}$$

as in the theorem. ■

0.2. Justification of an Additive Risk Model

Let η_1 and η_2 denote the respective parameters used for weighing the bleeding and stroke risks in our risk function (Figure 2). Also, let p_0 and p_1 denote the benchmark probabilities of bleeding and stroke corresponding to a baseline INR in $(2, 3)$. That is, p_0 and p_1 are constant and independent of time. For ease of exposition in what follows, we assume that there is no discounting (this could be easily incorporated). Under our objective function, we minimize the sum of expected relative risks, i.e., we select dosages $d_1, d_2, \cdots, d_{T-1}$ at epochs $1, 2, \cdots, T-1$ to minimize the following objective:

$$\sum_{t=1}^{T} \mathbb{E}[r_t] = \sum_{t=1}^{T} \mathbb{E}\left[\frac{\eta_1}{p_0} P_S^t + \frac{\eta_2}{p_1} P_B^t\right], \tag{0.5}$$

where r_t is the relative risk at epoch t, P_S^t is the probability of stroke at t, and P_B^t the probability of bleeding at t (P_S^t and P_B^t are *conditional* probabilities, conditional on the underlying INR at t which, in turn, depends on d_{t-1}). Let us define I_S and I_B to be indicator random variables which equal 1 if there is a stroke or a bleeding, respectively. Then, we can rewrite the objective in (0.5) as follows where INR_t is the INR at t:

$$\sum_{t=1}^{T} \mathbb{E}\left[\frac{\eta_1}{p_0}\mathbb{E}[I_S|INR_t] + \frac{\eta_2}{p_1}\mathbb{E}[I_B|INR_t]\right] = \frac{\eta_1}{p_0}\sum_{t=1}^{T}\mathbb{E}[\mathbb{E}[I_S|INR_t]] + \frac{\eta_2}{p_1}\sum_{t=1}^{T}\mathbb{E}[\mathbb{E}[I_B|INR_t]] \tag{0.6}$$
$$= \frac{\eta_1}{p_0}\mathbb{E}[\#\text{ strokes }] + \frac{\eta_2}{p_1}\mathbb{E}[\#\text{ bleeds }].$$

From (0.6), it is readily seen that minimizing our objective function is equivalent to minimizing the weighted sums of expected numbers of strokes and bleeding events over our horizon. Since minimizing our objective is equivalent to minimizing this weighted sum, a cumulative additive risk criterion is justified. ■