A Distribution Function Result

Suppose W, X, and Y are independent exponentials. Let $Z = \gamma W + \beta X + \alpha Y$. Let $F(z, \alpha, \beta, \gamma)$ be the distribution function of $Z = \beta X + \alpha Y + \gamma W$. Then for fixed X and Y, W ranges from zero to $(z - \beta X - \alpha Y)/\gamma$. By definition,

$$P\left[Z \le z\right] = \int_0^{z/\alpha} \int_0^{(z-\alpha y)/\beta} \int_0^{(z-\alpha y-\beta x)/\gamma} \exp(-x - y - w)\ dw\ dx\ dy.$$

Without loss of generality, suppose $\alpha \ge \beta \ge \gamma \ge 0$. Consider the case with $\alpha > \beta > \gamma > 0$. Then

$$\begin{aligned}
P\left[Z \le z\right] &= \int_0^{z/\alpha} \int_0^{(z-\alpha y)/\beta} [\sinh\left(\frac{z - \alpha y - \beta x}{\gamma} + x + y\right) - \cosh\left(\frac{z - \alpha y - \beta x}{\gamma} + x + y\right) \\
&\quad - \sinh(x + y) + \cosh(x + y)]\ dx\ dy \\
&= \int_0^{z/\alpha} \frac{e^{-y}\left(\beta\left(-e^{\frac{\alpha y - z}{\beta}}\right) + \gamma\left(e^{\frac{\alpha y - z}{\gamma}} - 1\right) + \beta\right)}{\beta - \gamma}\ dy \\
&= \frac{\frac{\beta^2\left(e^{-\frac{z}{\alpha}} - e^{-\frac{z}{\beta}}\right)}{\beta - \alpha} - \beta e^{-\frac{z}{\alpha}} - \frac{\gamma\left(\alpha\left(-e^{-\frac{z}{\alpha}}\right) + \alpha + \gamma\left(e^{-\frac{z}{\gamma}} - 1\right)\right)}{\alpha - \gamma} + \beta}{\beta - \gamma}
\end{aligned}$$

Similarly, if $\alpha > \beta > \gamma = 0$,

$$P\left[Z \le z\right] = \int_0^{z/\alpha} \int_0^{(z-\alpha y)/\beta} \exp(-x - y)\ dxdy.$$

The special case with $\alpha = \beta$ and $\beta = \gamma$ might also be calculated, but are omitted here.

Simulations

Simulate related values of efficacy, adverse event severity, and adverse evemt duration. Let K represent the number of types of adverse events. Let J represent the maximal severity score; serverity scores are then $j \in \{0, 1, \ldots, J\}$. Efficacy is represented by E, severities are represented by S_k, and durations are represented by D_k. In all cases, simulated variables are independent.

Choose an efficacy threshold ϵ, duration means μ_k, severity proportions $\pi_0, \ldots, \pi_J$, a coefficient α controling association among efficacy, severity, and duration, and a coefficient γ adding association among severity and duration but not efficacy.

Let $Y \sim \text{Expon}(1)$ and $X \sim \text{Expon}(1)$ and $U \sim \text{Expon}(1)$. Let

$$E = \begin{cases} 0 & \text{if } F(X + \alpha Y, \alpha, 1, \gamma) \le 1 - \epsilon, \\ 1 & \text{if } F(\beta X + \alpha Y, \alpha, 1, \gamma) > 1 - \epsilon. \end{cases}$$

For adverse event type $k \in \{1, \ldots, K\}$, let $T_k \sim \text{Expon}(1)$ and let $V_k \sim \text{Expon}(1)$. Let $D_k = \alpha Y + \gamma U + (\mu_k - \alpha - \gamma)T_k$, and let

$$S_k = \begin{cases} 0 & \text{if } F(\alpha Y + V_k, \alpha, 1, \gamma) < \pi_0, \\ 1 & \text{if } \pi_0 \le F(\alpha Y + \gamma U + V_k, \alpha, 1, \gamma) < \pi_0 + \pi_1, \\ \vdots & \vdots, \\ j - 1 & \text{if } \pi_0 + \ldots + \pi_{j-2} \le F(\alpha Y + \gamma U + V_k, \alpha, 1, \gamma) < \pi_0 + \ldots + \pi_{j-1}, \\ j & \text{if } \pi_0 + \ldots + \pi_{j-1} \le F(\alpha Y + \gamma U + V_k, \alpha, 1, \gamma). \end{cases}$$

Consider various scenarios:

1. All subjects have efficacy, event severity, and event duration related, with duration mean 8 days. One might take $\alpha = 1$ (the default), $\gamma = 0$ (the default), and $\mu_k = 8 \forall k$.
2. All subjects have event severity, and event duration related, with duration mean 8 days. One might take $\alpha = 0$, $\gamma = 1$, and $\mu_k = 8 \forall k$.
3. All subjects have efficacy, event severity, and event duration highly related, with duration mean 8 days. One might take $\alpha = 7$, $\gamma = 0$ (the default), and $\mu_k = 8 \forall k$.
4. No correlation between efficacy and duration or severity, but some correlation between severity and duration. One might take $\alpha = 0$, $\gamma = 2$ and $\mu_k = 8 \forall k$.