Vignette for the *DUE* package: The Dose Utility Explorer

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1 Introduction

DUE, the Dose Utility Explorer package for R, is an interactive environment for exploring relationships between priors, utilities, and choice of dose, when toxicity and response are determined by patient-specific thresholds. A user can manupulate inputs describing a hypothetical dose choice scenario. A number of important aspects have been omitted, in order to focus on the factors that are patient-specific. The main output is expected utility as a function of dose. Factors included are:

- The current "prior" or population joint distribution of thresholds for toxicity and for response; the distribution may be multimodal.
- Response-limiting toxicity, representing the case where a patient with a low threshold for toxicity has enough toxicity to require coming off the treatment.
- Refractoriness.
- The combined personal utility of the toxicity and response outcomes.

Not included are:

- The possibility that probabilities of events might be nonmonotonic in dose.
- Priors for the parameters describing the joint distribution.
- Data that might have contributed to the "prior" for the pair of thresholds.
- The scientific, commercial, or prestige-related value of the information to be gained.

- Costs of the drug or of dealing with adverse events, not incurred by the patient.

The package presents a window that includes:

- upper left: a graph of the threshold distribution
- upper right: a graph of the mappings from dose to the expected utility, together with probabilities of events and event combinations,
- lower left: controllers for the threshold distribution
- lower right: controllers for the utility values

2 The threshold distribution inputs

2.1 Threshold distribution parameters

We assume that each patient has a pair of thresholds, θ_R for response and θ_T for toxicity. If the dose exceeds the threshold, then the corresponding event occurs. The model for the joint distribution of toxicity and response thresholds is a mixture of joint lognormals. Each joint lognormal is described by its two means μ_R and μ_T, its two coefficients of variation CV_R and CV_T, and ρ, the correlation between $\log \theta_R$ and $\log \theta_T$. A vector the length of the number of subpopulations describes the probabilities of each component of the mixture distribution. Each of these parameters is controlled by a pair of scale (or slider) objects and text boxes, so that either one can be used to change the parameter value.

To select which subpopulation the parameters refer to, there is a text box labeled "This population". The number of subpopulation is set in the text box "#Pops"; if increased or decreased, reasonable adjustments take place elsewhere. Another text box holds the population fraction for "This population". Because the probabilities of the components must add to one, we provide a box labeled "Which population fraction follows", to select one component that will adjust to accommodate a change in another component's probability.

2.2 Response-limiting toxicity

Response-limiting toxicity represents the case where a patient with a low threshold for toxicity has enough toxicity to prevent response, even if the response threshold is low enough. For example, a toxicity experience might require coming off the treatment or reducing the dose below the threshold. Or, a treatment-caused fatality might occur before a response which otherwise would have happened can occur. This idea is represented by a parameter called "K", with

attendance scale/text pair. It represents the log10 of the ratio between the patient's toxicity threshold and the dose at which toxicity is so severe that response cannot happen. The assumption is that this ratio is the same for all patients. (This works similarly to the relaionship between thresholds for different grades of toxicity introduced in Simon's paper on accelerated titration designs.)

2.3 Refractoriness

Some proportion of patients may have disease which will not respond to the treatment at any dose. Another scale/text input component holds that proportion. This parameter appears to be necessary to better reflect experience in cancer treatment.

2.4 Display of the joint threshold distribution

On the upper left side of the window is the contour plot for the joint threshold distribution. If one clicks on the graph close to one of the modes, then the parameter "This population" should change to refer to the corresponding subpopulation. If the click is too far away, then a "favorite dose" D is selected, corresponding to the closest diagonal point (D, D). When D is selected, it divides the graph into four quadrants, corresponding to four outcomes:

- rtrt: neither response nor toxicity
- rT: only toxicity
- Rt: only response
- RT: both response and toxicity

If the Response-limiting toxicity parameter (K) is small enough, then there also appears an incursion of the rT region towards the left at the bottom, invading the RT region.

3 Probabilities and utilities

3.1 Calculation of probabilities

For each dose in a vector of doses of interest, the probabilities of each of the four regions are computed by integration. Varying the dose gives the mapping from dose to each outcome probability.

3.2 Utility parameters and expected utility

For decision analysis, a necessary input is the utility function which values outcomes.

The scale/text pairs on the lower right specify the utility values for these four outcomes. There are also buttons to set the utilities to specific values: Additive, Simple, Cautios, and Aggressive. All four set $U_{rt} = 0$. The Simple utility assignment values the Rt outcome and sets the other three to zero. It is commonly used in studies of Phase I and II clinical trial designs.

The expected utility, EU, for each dose is calculated as the weighted average of the four utilities, weighted by the four event probabilities.

3.3 Display of the expected utility and probabilities

On the upper right side of the window is a graph showing these probabilities (left-side scale) and expected utilities (right-side scale). The vertical green line corresponds to the "favorite dose" selected in the contour plot. The black dotted vertical line picks out the dose maximizing expected utility.

The seven boxes on the bottom of the graph are three-way toggles, which cycle each of the seven curves through the settings THICK, THIN, and OFF.

4 Applications: Insights from using the DUE [TO-DO]

4.1 Critique of the "Simple" utility

If there are no refractory pts and no Kdeath, claim: "simple" doesn't work well.-dose too high.

4.2 Effect of multimodality

TO DO.

4.3 Insensitivity of expected utility to changes in dose

TO DO.

5 Design considerations

5.1 tcltk and X11

The interface is built using the packages tcltk and tkrplot. On the MacIntosh, the resulting window appears in an X11 device. A desirable improvement would be to adapt DUE for presentation in a web page, to achieve wider use, but this appears to require porting away from tcltk.

5.2 Starting and stopping the DUE; saving and reusing values

The function *DUEstart*() will initialize the window. The first time run, an environment object .DUEenvironment is created in .GlobalEnv, and copied to an object called *DUEenv* which will hold both the working scenario data and the configuration data for the components on the window. One can save a copy of DUEenv under a different name for later re-use, assigning it back to *DUEenv* when one wants to work on that scenario. To stop the interactive DUE window, use *DUEstop*().

5.3 Modifying configurations

Location, size, spacing and other values are stored as *DUEenv$DUEconfig*. Functions that assist in modifying and loading those values include *loadDUEconfig*() . Spacing values are in *DUEenv* itself. These are not documented. With the multiple windowing platforms and screen resolutions, this is a solution, but probably intelligent use of geometry managers would be more elegant and work better.

DUE does not currently provide for changes in the dose range, the dose values, and the slider/scale ranges.

5.4 Lognormal conversions

The choice of lognormal distributions entails conversion between log and native dose scales. The scales for the two means are connected to their corresponding tet boxes differently from the other scale/text pairs because the text is showing the unlogged mean dose while the scale is holding the logged dose. The graph is a log-log graph, so the labeling is on the unlogged scale while the spacing is on the logged scale.