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R ALGORITHM FOR BAYESIAN POWER MODEL OF CONTINUAL REASSESSMENT METHOD TO DETERMINE ED95

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INTRODUCTION: Continual Reassessment Method (CRM) was originally designed for dose-finding phase I cancer drug trials. The primary goal of CRM is to identify maximum tolerated dose of a new drug which is typically defined as the dose with a dose-limiting toxicity probability that is closest to the target toxicity rate. A 'bcrm' package suitable for R is available on Comprehensive R Archive Network (CRAN) http://cran.r-project.org/

However, the package is not readily suitable to determine ED95, as it requires modifications in data entry and data output to yield the required results. This abstract presents a straightforward R algorithm developed for the purpose. An application of the methodology could be to determine MAC-ED95 of inhalational agents since the traditional up-down study design (Dixon method) determines the concentration to produce an effect in half the subjects, not the clinically relevant ED95.

METHODS: R algorithm was developed using the standard formulas for Bayesian one parameter power model of CRM (Figure 1).[1] The ED95 is defined as the 5th percentile of dose-failure relationship which is modelled as $P\alpha$, where α is the parameter of interest which is continually updated based on observed data in each cohort. As negative values are not compatible with the power model, two types of distributions for α are applicable. They are lognormal (mean = 0 and SD = 2) and gamma (shape=1 and scale=1). The algorithm permits the user to choose the type of distribution. Data input requires entry of initial guess of failure probabilities for a dose level and corresponding values related to size of cohort and number of subject exhibiting failure of a defined clinical response. Updated failure probability closest to the 0.05 target yielded by the output of algorithm is chosen as the current ED95 and given to the next cohort. The algorithm was validated with different datasets using bcrm package as standard.

Figure 1: Formulas used in the algorithm

The dose-failure (probabilities of failure at each dose) model is of the form

$$\pi_j(\alpha) = p_j^{\alpha},$$

Where P_j s are prior guesses of failure at each dose and α is the unkown parameter
We use Bayesian approach and so density of prior distribution is

$$f(\alpha) = \frac{1}{\alpha\sigma\sqrt{2\pi}} e^{-\frac{(\ln(\alpha)-\mu)^2}{2\sigma^2}},$$

$\mu = 0$ and $\sigma = 2$, when one uses lognormal distribution

OR

$$f(\alpha = x) = \begin{cases} \exp(-x) & X > 0 \\ 0 & X \leq 0 \end{cases}$$

Shape = 1 and scale = 1, when one uses gamma distribution

Assuming observed data D = {(n_j y_j), j=1,.....j)} and nj patients treated at dose level j, y_j patients experienced failure, the posterior distribution of α is

$$f(\alpha|D) = \frac{f(\alpha)L(\alpha; D)}{\int_0^{\infty} f(\beta)L(\beta; D)d\beta},$$

Where the likelihood is

$$L(\alpha; D) = \prod_{j=1}^{J} \pi_j(\alpha)^{y_j}(1 - \pi_j(\alpha))^{n_j - y_j}.$$

The failure probabilities (plug-in mean) can be estimated by

$$\widehat{\pi}_{j1} = \pi_j \left(\int_0^{\infty} \alpha f(\alpha|D)d\alpha \right)$$

RESULTS: The present algorithm is simple in terms of data entry and interpretation of output. The output of datasets by the present algorithm was comparable with those obtained by the bcrm package.

DISCUSSION: Power model of CRM is a model-based dose finding approach that uses a single unknown parameter to link true probabilities with pre-specified probabilities corresponding to the prior mean probability set. The probabilities are related to 'toxicity' in phase I trials, whereas they are related to 'failure' in trials to determine ED95. Recently, the method was employed to determine ED95 of a standard drug for an established technique.2 While the authors used R software version [2].10#(R CRAN, Vienna, Austria) for analysis, the exact R algorithm was not described. After presentation of this abstract, the algorithm along with detailed documentation for computations will be made available through a web source. This presentation is intended to encourage future researchers, including those novices to the subject, to use the methodology with better understanding of the scheme.

1. Yin G, Yuan Y. Journal of the American Statistical Association 2009;104:954-68.
2. Kant A, Gupta PK, Zohar S, Chevret S, Hopkins PM. Anesthesiology. 2013; 119:29-35.

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Abstract

Introduction: Continual Reassessment Method (CRM) was originally designed for dose-finding phase I cancer drug trials. The primary goal of CRM is to identify maximum tolerated dose of a new drug which is typically defined as the dose with a dose-limiting toxicity probability that is closest to the target toxicity rate. A 'bcrm' package suitable for R is available on Comprehensive R Archive Network (CRAN) http://cran.r-project.org/
However, the package is not readily suitable to determine ED95, as it requires modifications in data entry and data output to yield the required results. This abstract presents a straightforward R algorithm developed for the purpose. An application of the methodology could be to determine MAC-ED95 of inhalational agents since the traditional up-down study design (Dixon method) determines the concentration to produce an effect in half the subjects, not the clinically relevant ED95.

Methods: R algorithm was developed using the standard formulas for Bayesian one parameter power model of CRM (The Power Mdoel) .[1] The ED95 is defined as the 5th percentile of dose-failure relationship which is modelled as P^{α}, where α is the parameter of interest which is continually updated based on observed data in each cohort. As negative values are not compatible with the power model, two types of distributions for α are applicable. They are lognormal (mean = 0 and SD = 2) and gamma (shape=1 and scale=1). The algorithm permits the user to choose the type of distribution. Data input requires entry of initial guess of failure probabilities for a dose level and corresponding values related to size of cohort and number of subject exhibiting failure of a defined clinical response. Updated failure probability closest to the 0.05 target yielded by the output of algorithm is chosen as the current ED95 and given to the next cohort. The algorithm was validated with different datasets using bcrm package as standard.

Results: The present algorithm is simple in terms of data entry and interpretation of output. The output of datasets by the present algorithm was comparable with those obtained by the bcrm package.

Discussion: : Power model of CRM is a model-based dose finding approach that uses a single unknown parameter to link true probabilities with pre-specified probabilities corresponding to the prior mean probability set. The probabilities are related to 'toxicity' in phase I trials, whereas they are related to 'failure' in trials to determine ED95. Recently, the method was employed to determine ED95 of a standard drug for an established technique.[2] While the authors used R software version 2.10#(R CRAN, Vienna, Austria) for analysis, the exact R algorithm was not described. After presentation of this abstract, the algorithm along with detailed documentation for computations will be made available through a web source. This presentation is intended to encourage future researchers, including those novices to the subject, to use the methodology with better understanding of the scheme.

References:
1. Yin G, Yuan Y. Journal of the American Statistical Association 2009;104:954-68.
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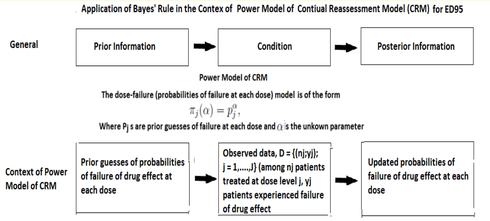
Introduction and Methods

Introduction: Continuous Reassessment Method (CRM) was originally designed for dose-finding phase I cancer drug trials.[1] Several versions and modifications of CRM with different models have evolved over the past two decades. A tutorial is also available on the subject.[2] Primary goal of CRM is to identify maximum tolerated dose of a new drug which is typically defined as the dose with a dose-limiting toxicity probability that is closest to the target toxicity rate. A 'bcrm' package suitable for R is available on Comprehensive R Archive Network (CRAN) http://cran.r-project.org/

However, the package is not readily suitable to determine ED95, as it requires modifications in data entry and data output to yield the required results. This abstract presents a straightforward R algorithm developed for the purpose. An application of the methodology could be to determine MAC-ED95 of inhalational agents since the traditional up-down study design (Dixon method) determines the concentration to produce an effect in half the subjects, not the clinically relevant ED95.

Methods (Model)

1. Fundamental assumption is that increasing dose levels will lead to increased probability of success ful drug effect
2. Actual doses are irrelevant as far as model computations are concerned
3. The ED95 is defined as the 5th percentile of dose-failure relationship which is modelled as P^{α}, where α is the parameter of interest which is continually updated based on observed data in each cohort.
4. As negative values are not compatible with the power model, two types of distributions for α are applicable. They are lognormal (mean = 0 and SD = 2) and gamma (shape=1 and scale=1).



Methods (Example)

Model: Failure vs Success Data

1. As opposed to "dose-failure" data, we usually have in hand "dose-success" data
2. The R algorithm presented in this abstract permits one to use either of the data

Hypothetical example for MAC-ED95 inhalational agent for a particular effect

1. Assume that we have in hand curve constructed on the basis of a logistic model obtained from data on MAC derived from Dixon's method
2. Hence one should use "dose-success" in the working model
3. Prior guesses of probabilities of success are thus incorporated
4. Start the study with a total sample size of 40
5. Size of each cohort should be small (e.g.2) and kept constant through out study

Cohort 1:

1. Start the study at a dose level 5 i.e. the level closest to probability of 0.95
2. Perform the study in 2 patients and obtain the responses
3. Assume both patients exhibited success of drug effect
4. Run the algorithm and obtain the posterior probabilities "plug-in" probabilities to decide the next dose level

Data	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
ET-Conc.	1%	1.5%	2%	2.5%	3%	3.5
Prior Prob	0.18	0.38	0.64	0.84	0.93	0.98
nj	0	0	0	0	2	0
yj	0	0	0	0	2	0
Posterior Prob	0.10	0.28	0.55	0.79	0.90	0.97

Input to run R algorithm

```
#Load the relevant library
# input constant values for the study
prior.prob <- c(0.18, 0.38, 0.64, 0.84, 0.93, 0.98)
target.tox <- 0.95
prior.dist <- "lognormal"
prior.param <- c(0,2)
type <- "success"
method <- "exact"
n.sim <- 100000
# input values related to the cohort and the successful responses
n.cohort <- c(0, 0, 0, 0, 2, 0)
n.success <- c(0, 0, 0, 0, 2, 0)
# Command to run the algorithm
powerBCRM(prior.prob, n.cohort, n.success, target.tox, prior.dist, prior.param)
```

Output R algorithm

Next dose level (from the plug-in means): 6

dose.level	prior.prob	n.cohort	n.outcomes	plugin.mean
1	0.18	0	0	0.1046843
2	0.38	0	0	0.2798743
3	0.64	0	0	0.5557993
4	0.84	0	0	0.7949608
5	0.93	2	2	0.9089105
6	0.98	0	0	**0.9737620**

Follow-up after output of 1st cohort

1. Administer the suggested dose level i.e. 6 in next cohort of 2 patients
2. Observe the response
3. Plug-in the new data and run the algorithm

Methods (Example & Validation)

```
# input values related to the cohort and the successful responses after 2nd cohort
n.cohort <- c(0, 0, 0, 0, 2, 2)
n.success <- c(0, 0, 0, 0, 2, 2)
#Output of the algorithm
```

Next dose level (from the plug-in means): 6

dose.level	prior.prob	n.cohort	n.outcomes	plugin.mean
1	0.18	0	0	0.1389131
2	0.38	0	0	0.3283132
3	0.64	0	0	0.5982649
4	0.84	0	0	0.8181592
5	0.93	2	2	0.9198578
6	0.98	2	2	**0.9770130**

```
# input values related to the cohort and the successful responses after 3rd cohort
n.cohort <- c(0, 0, 0, 0, 2, 4)
n.success <- c(0, 0, 0, 0, 2, 4)
#Output of the algorithm
```

Next dose level (from the plug-in means): 6

dose.level	prior.prob	n.cohort	n.outcomes	plugin.mean
1	0.18	0	0	0.1709011
2	0.38	0	0	0.3690390
3	0.64	0	0	0.6314181
4	0.84	0	0	0.8355814
5	0.93	2	2	**0.9279607**
6	0.98	4	4	0.9794013

Usual stopping rules [3]

1. When planned number of subjects is reached
2. When estimated probability is too low or too high for all dose levels
3. When a suitable estimation of the ED95 is obtained based on predictive gains

Other Features of the algorithm

1. There are two methods of computation: "exact method" or "simulation". The "simulation method" takes the input of number of simulations e.g. 100000
2. Output also includes posterior mean with respective quantiles ranging from 0.05,0.25,0.5,0.75,0.95

The algorithm was validated with different datasets using bcrm package as standard

Results:

1. The present algorithm is simple in terms of data entry and interpretation of output.
2. The output of datasets by the present algorithm was comparable with those obtained by the bcrm package.
3. Validation information is available with the author

Discussion: :

1. Power model of CRM is a model-based dose finding approach that uses a single unknown parameter to link true probabilities with pre-specified probabilities corresponding to the prior mean probability set.
2. The probabilities are related to 'toxicity' in phase I trials, whereas they are related to 'failure' in trials to determine ED95.
3. Recently, the method was employed to determine ED95 of a standard drug for an established technique.[4] While the authors used R software version 2.10#(R CRAN, Vienna, Austria) for analysis, the exact R algorithm was not described.
4. Advantage of R is that it is an open source software and one can view the entire code of any function (algorithm in the present case) by simply typing function name without parenthesis. To run the function one has to type of name of function with arguments in the parenthesis.
5. After presentation of this abstract, the algorithm along with detailed documentation for computations will be made available through a web source.
6. This presentation is intended to encourage future researchers, including those novices to the subject, to use the methodology with better understanding of the scheme.

Formulas & References

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References

1. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics. 1990;46(1):33-48.
2. Garrett-Mayer E. The continual reassessment method for dose-finding studies: a tutorial. Clin Trials. 2006;3(1):57-71.
3. Zohar S, Chevret S. The continual reassessment method: comparison of Bayesian stopping rules for dose-ranging studies. Stat Med. 2001;20(19):2827-43
4. Kant A, Gupta PK, Zohar S, Chevret S, Hopkins PM. Application of the Continual Reassessment Method to Dose-finding Studies in Regional Anesthesia: An Estimate of the ED95 Dose for 0.5% Bupivacaine for Ultrasound-guided Supraclavicular Block. Anesthesiology. 2013;119(1):29-35.

In due course, the compiled algorithm in a package along with detailed documentation for computations will be made available on the personal website of the author: www.srinivasmantha.com