README

Mitchell Aaron Schepps, Jeremy Seurat, France Mentre, and Weng Kee Wong
maschepps@ucla.edu

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Manuscript Introduction

We provide code used to support our findings in the manuscript "Design optimization of longitudinal studies using metaheuristics: application to lithium pharmacokinetics".

Our zip file contains code and data for the designs, tbales, and figures of the optimization of a physician constrained pharmacokinetics pharmacodynamics nonlinear mixed effects model model of sustained-release lithium using flexible metaheuristic algorithms. We provide code used to produce the D-, D_s-, and multiobjective optimal designs based on the Fisher Information Matrix (FIM). Here, we showcase the usage of the the `PFIM` R code and `ppso` and `ecr` R packages for single objective optimization and multiobjective optimization with `ecr`. Plots are created with `ggplot2`.

Table 1 code

- The code to compute the D-optimal designs for different amount of time points in one group by the simplex algorithm implemented in PFIM can be found in the PFIM_analyses.R file.

Table 2 and 3 code

- The code to compute D-optimal designs from the simplex algorithm implemented in PFIM for the one, two, and five group scenarios with and without a genetic covariate can also be found in the table_PFIM.R file.
- File table_ecr.R computes D- and D_s-optimal designs for the one and two group scenarios with and without a genetic covariate for the `ecr` package's single objective optimization functionality.
- File table_ppso.R computes D and D_s-optimal designs for the one, two, and five group scenarios with and without a genetic covariate for the `ppso` package's single objective optimization functionality.

Figure 2 code

- We analyze the convergence properties of the design points. The 100 iteration search will show the long term convergence of the optim_pso function. The code figure_2_code.R uses the data from ppso_long.log to create Figure 2, the convergence of each particle to the respective design point in PSO.

Figure 3 code

- Physicians are interested in best estimating the fixed and random effects for the clearance parameters as well as the genetic covariate in the sustained-release lithium model. We create a multiobjective optimization problem and optimize using the ECR package and ecr() function to simultaneously maximize D_{s3}- and D_{s8}-defficiencies. The "figure_3_code.R" has code to create and analyze the Pareto front for Figure 3.

Supplemental Appendix Table 1 code

The code for Supplementary Table 1, i.e. the five group designs, can be found within each of the table_PFIM.R, table_ecr.R, and table_ppso.R files.

Supplemental Material Figure 1 Code

- We have a single set of nominal values from the earlier lithium study with 17 patients and there were no other sets of nominal values available. In our case, physicians were also not willing to use other sets of nominal values. We implement a hypercube D-optimal design (HCD-optimal design) that optimises a pseudo-Bayesian robust criterion. To find such a design, we usede bootstrapped confidence intervals for each fixed effect as prior information. The criterion uses every combination of the 2.5th and 97.5th percentiles from the intervals and with 5 fixed effects, there are $2^5 = 32$ summands. We optimized the criterion and found that the HCD-optimal designs are similar to our locally D-optimal designs, suggesting that for our problem, the latter designs are relatively robust to misspecifications in the nominal values. Web Figure 1 shows the D-optimal design time points from each of the 32 designs. Provided R code "Supplementary_Figure_1.R" contains code to run the HCD experiment and presents the figure from precalculated results found in the data "HCD_results.csv".

References

- Francke T (2020). ppso: Particle Swarm Optimization and Dynamically Dimensioned Search, optionally using parallel computing based on Rmpi. R package version 0.9-99991. https://github.com/TillF/ppso
- Bossek, J. (2023). ecr: Evolutionary Computation in R. R package version 2.1.1. https://github.com/jakobbossek/ecr2
- Wickahm, H. (2023) ggplot2: Create Elegant Data Visualisations Using the Grammar of Graphics. R package version 3.4.4. https://github.com/cran/ggplot2