An R Package for Automated Generation of Item Response Theory Model NONMEM Control File

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INTRODUCTION

Pharmacometric item response theory (IRT) models have been recognized as a valuable modeling approach for analyzing healthcare-related composite assessments; it provides a natural framework to combine different outcomes from the same disease into a joint disease model. However, the implementation of pharmacometric IRT presents several technical challenges, eg, IRT models contain many components increasing the risk of coding errors, large number of parameters that require initial estimates, many contributing data types, and require elaborate model diagnostics.[1] These challenges are especially hampering in a drug development setting where analysts need to be skilled in a wide area of techniques. The *piraid* R package can simplify working with IRT models within the nonlinear mixed effects software NONMEM. This work is a result of a collaboration between MSD and Uppsala University.

OBJECTIVES

The objectives of this work are to 1) describe the overall workflow of the package, 2) provide description of key functionalities of the package, and 3) showcase the usage of *piraid* using a theoretical health risk assessment (HRA) composite assessment scale with a simulated dataset.

Capabilities of *piraid* Package

- Generation of NONMEM model code for a longitudinal item response theory models
- Estimation of item characteristic curve (ICC) parameters
- Production of diagnostics based on NONMEM output
- Preparation of a direct latent variable analysis in NONMEM

The key inputs required for use in *piraid* are knowledge of the scale and the IRT dataset. These aspects are described in **Table 1**. A complete list of available functions are further detailed in the package vignettes.

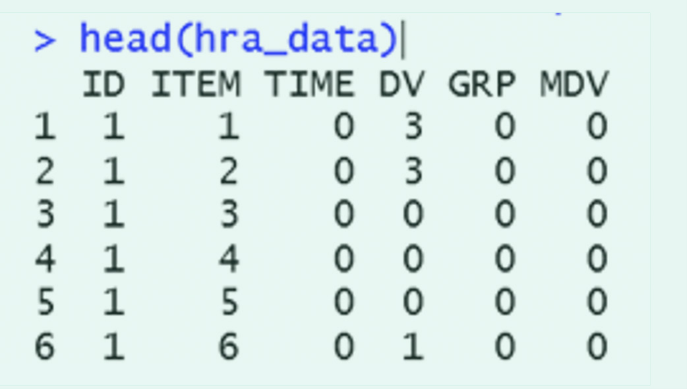
Table 1. The *piraid* Workflow

Steps	Description	How To	Note
1. Scale creation	Required to define the items together with their types and range of levels. Currently ordered categorical and binary items are supported. There are multiple ways to create a scale as illustrated to the right.	• For Parkinson Disease, one can use a predefined scale in *piraid*. In this case, there is no need to use a NONMEM dataset to define the scale.[2] **scale <- load_predefined_scale("MDS-UPDRS")** • Use an input NONMEM IRT dataset **scale <- create_scale_from_csv("mydata.csv")** • User defined scale definition "yaml" file **scale <- load_scale("myscale.yaml")**	• There are options to modify a scale by removing items or selecting subscales (ie, motor vs tremor items) **subscale <- create_subscale(scale, c("motor"))** **new_scale <- remove_items(scale, 1:14)** • One can cross-check data against a particular scale to identify missing items or categories (ie, levels) between the two **check_data(dataset, scale)**
2. Generate NONMEM IRT core base model	Once a scale is created a skeleton NONMEM model control file can be generated.	• Create model **model <- irt_model(scale)** • Set run number **model <- set_run_number(model, 28)** • Add dataset **model <- set_dataset(model, "my.dta", use_path=FALSE)** • Add base latent variable model **model <- add_lv_model(model, lv_model_type = "linear")** • Print corresponding NONMEM code **print_model_code(model)**	It is also possible to add a simulation task and additional estimation options.
3. Set initial estimates	There are multiple ways of setting the initial estimates for the item parameters in a NONMEM IRT model. The order of priority of how the initial estimates are determined is shown here.	• Use the mirt[3] R package **item_prms <- estimate_item_parameters(model)** **model <- set_initial_estimates_table(model, item_prms)** • User defined manually **model <- set_initial_estimates(model, 1:13, c("DIF2", "DIF3", "DIF4"), 0.1)** • Taken from a published model if the predefined scale selected (ie, MDS-UPDRS predefined scale) • If none of the above actions are taken, default values are generated	Consolidation options exist to modify item parameter estimates when responses in higher categories are few. Options also exist to FIX parameter to a large value (ie, 50) if the parameter was consolidated.
4. Save the model	Save the NONMEM model in a text file.	**save_model_code(model, "Run1.mod")**	After this step the user can transfer the model file to any modeling and simulation platform and run with NONMEM.
5. Model diagnostic	Diagnostic plots to evaluate model fit can be created using the output files from successful IRT model runs in NONMEM as input.	Available model diagnostics are: • Mirror plot **plots <- mirror_plots(origdata, scale, simdata, nrow=4, ncol=5)** • Item characteristic curve **plots <- icc_plots(df, scale, items_per_page=6)** • Correlation plot **plot <- correlation_plot(psi.estimates)**	

RESULTS

The ability of the *piraid* package to streamline the implementation of IRT model development is shown using a theoretical HRA composite assessment that has 7 items, 2 binary and 5 categorical (6 levels). In this example, it is assumed that the analyst has a NONMEM dataset for input.

Overview of the NONMEM Dataset

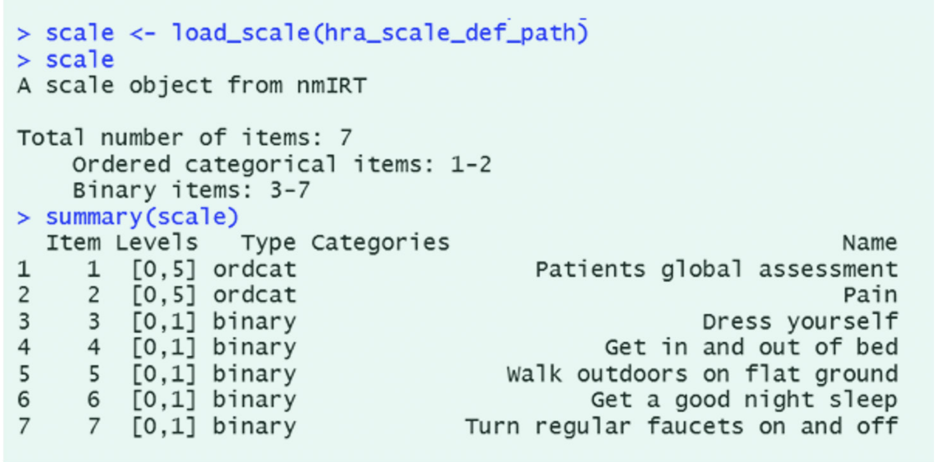


```
> head(hra_data)
  ID ITEM TIME DV GRP MDV
1  1    1    0  3   0   0
2  1    2    0  3   0   0
3  1    3    0  0   0   0
4  1    4    0  0   0   0
5  1    5    0  0   0   0
6  1    6    0  1   0   0
```

Note:

- The minimum required columns are: ID, ITEM, DV
- By default, the item column is called ITEM and the dv column is called DV, but this can be changed with options
- TIME is not required for scale creation; it is however needed for longitudinal IRT

Step 1: Scale Creation

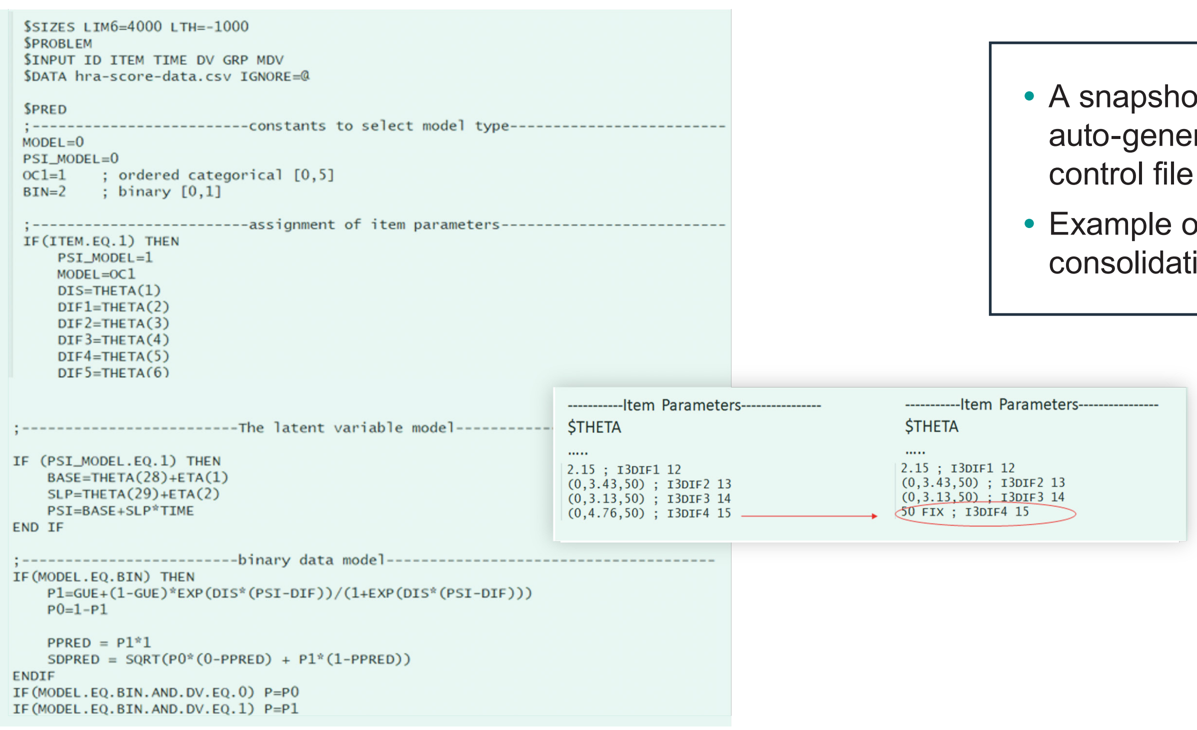


```
> scale <- load_scale(hra_scale_def_path)
> scale
A scale object from nmIRT

Total number of items: 7
    Ordered categorical items: 1-2
    Binary items: 3-7
> summary(scale)
  Item Levels   Type Categories                         Name
1    1  [0,5] ordcat                Patients global assessment
2    2  [0,5] ordcat                                      Pain
3    3  [0,1] binary                            Dress yourself
4    4  [0,1] binary                     Get in and out of bed
5    5  [0,1] binary               Walk outdoors on flat ground
6    6  [0,1] binary                     Get a good night sleep
7    7  [0,1] binary            Turn regular faucets on and off
```

Note:

- Different codes for missing data, ie, DV = -99 needs to be removed prior to creating a scale
- The preferred method of creating a scale is to use a scale definition file (yaml), as it makes it is easier to set item types and names

Steps 2-4: Generate NONMEM IRT Core Base Model



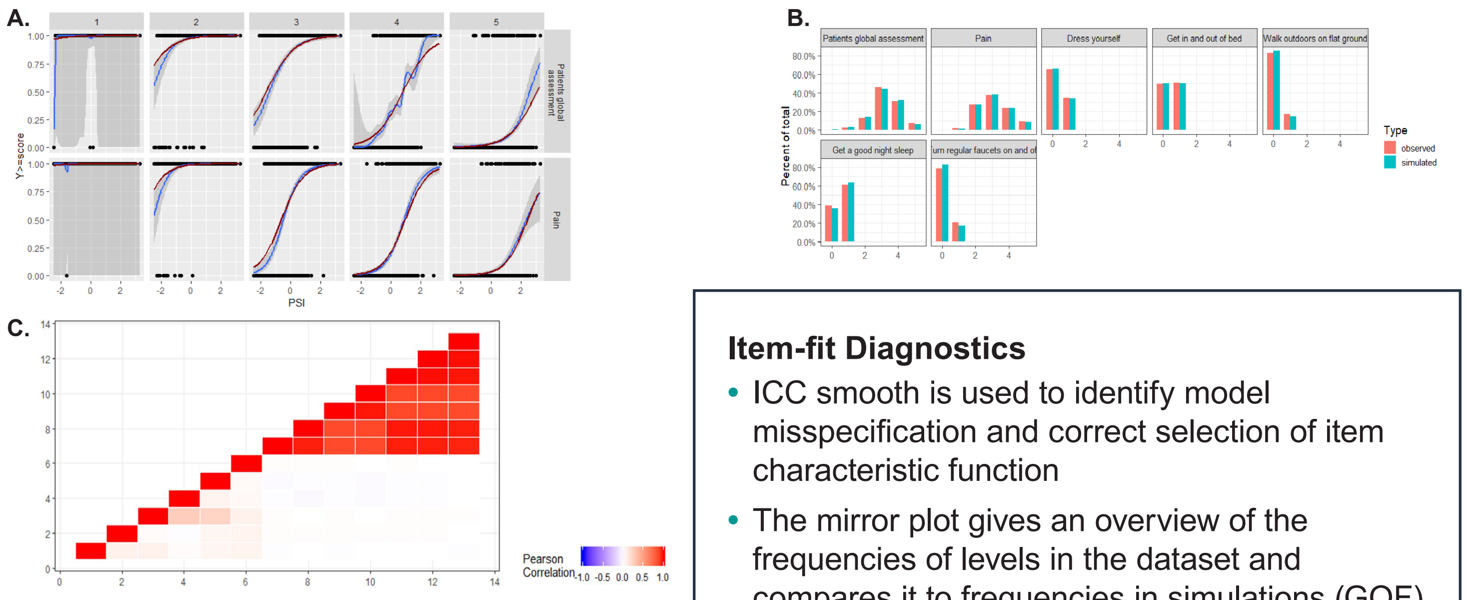
```
$SIZES LIM6=4000 LTH=-1000
$PROBLEM
$INPUT ID ITEM TIME DV GRP MDV
$DATA hra-score-data.csv IGNORE=@

$PRED
;------------------------constants to select model type------------------------
MODEL=0
PSI_MODEL=0
OC1=1    ; ordered categorical [0,5]
BIN=2    ; binary [0,1]

;------------------------assignment of item parameters------------------------
IF(ITEM.EQ.1) THEN
    PSI_MODEL=1
    MODEL=OC1
    DIS=THETA(1)
    DIF1=THETA(2)
    DIF2=THETA(3)
    DIF3=THETA(4)
    DIF4=THETA(5)
    DIF5=THETA(6)


;------------------------The latent variable model-----------

IF (PSI_MODEL.EQ.1) THEN
    BASE=THETA(28)+ETA(1)
    SLP=THETA(29)+ETA(2)
    PSI=BASE+SLP*TIME
END IF

;------------------------binary data model----------------------------------------
IF(MODEL.EQ.BIN) THEN
    P1=GUE+(1-GUE)*EXP(DIS*(PSI-DIF))/(1+EXP(DIS*(PSI-DIF)))
    P0=1-P1

    PPRED = P1*1
    SDPRED = SQRT(P0*(0-PPRED) + P1*(1-PPRED))
ENDIF
IF(MODEL.EQ.BIN.AND.DV.EQ.0) P=P0
IF(MODEL.EQ.BIN.AND.DV.EQ.1) P=P1
```

```
-----------Item Parameters----------------
$THETA
.....
2.15 ; I3DIF1 12
(0,3.43,50) ; I3DIF2 13
(0,3.13,50) ; I3DIF3 14
(0,4.76,50) ; I3DIF4 15
```

```
-----------Item Parameters----------------
$THETA
.....
2.15 ; I3DIF1 12
(0,3.43,50) ; I3DIF2 13
(0,3.13,50) ; I3DIF3 14
50 FIX ; I3DIF4 15
```

- A snapshot example of an auto-generated NONMEM control file
- Example of initial estimates consolidation

Step 5: Model Diagnostic



A. ICC GAM smooth
B. Mirror plot
C. Pearson's correlation plot for residuals

Item-fit Diagnostics

- ICC smooth is used to identify model misspecification and correct selection of item characteristic function
- The mirror plot gives an overview of the frequencies of levels in the dataset and compares it to frequencies in simulations (GOF)
- The correlation plots give a heatmap of correlations between residuals for each item

SUMMARY AND CONCLUSIONS

- The *piraid* IRT model assembler and diagnostics R package is able to expedite the IRT model development process by generating an editable IRT NONMEM control file for a composite scale with input from the user. While the current package contains MDS-UPDRS as the only internal predefined scale, the current package is able to handle datasets from other scales with categorical and binary data, which allows general use for other similar assessments
- The package is available from github at https://github.com/UUPharmacometrics/piraid"

References

1. Ueckert S. *CPT Pharmacometrics Syst Pharmacol.* 2018;7(4):205-218.
2. Gottipati G, Karlsson MO, Plan EL. *AAPS J.* 2017;19(3):837-845.
3. Chalmers RP. *J Stat Soft.* 2012;48(6):1-29. doi: 10.18637/jss.v048.i06.

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