SAMPLING OF PARAMETER UNCERTAINTY IN CAMPSIS

Nicolas Luyckx, Andreas Lindauer, Emilie Hénin

Calvagone, Chazay-d'Azergues, France

INTRODUCTION

Campsis (**www.campsis.org**) is an open-source PK/PD simulation suite running R, freely available on CRAN [1] and GitHub [2], designed to facilitate the simulation of population PK/PD models, and by extension, the simulation of clinical trials. This poster presents a revised way of simulating with parameter uncertainty, including random sampling from the scaled inverse Chi-squared or Wishart distributions for the OMEGA and SIGMA matrix.

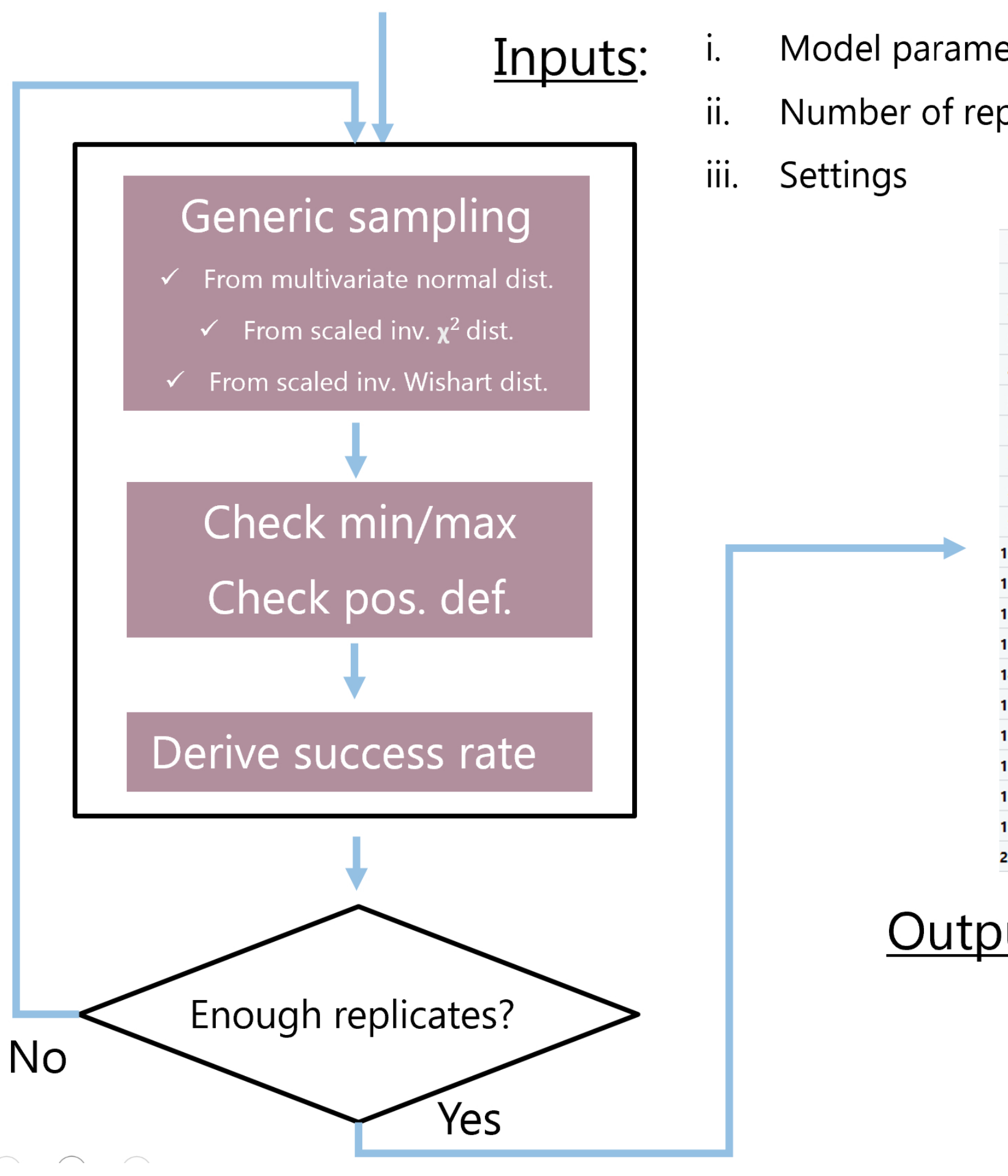
Objectives

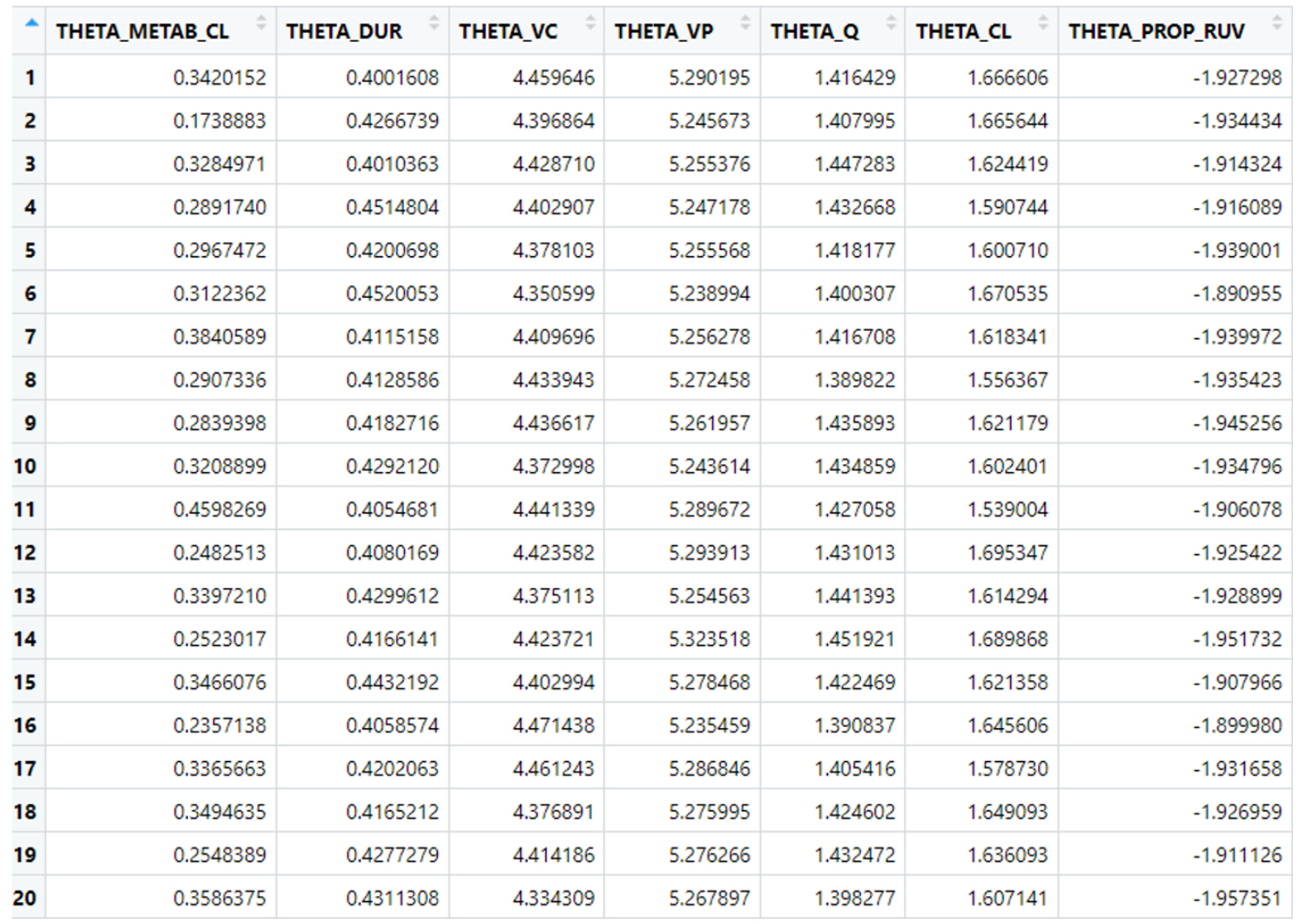
- Revisit the previous process of simulating with parameter uncertainty in Campsis.
- Sample parameters from various sources based on user choice:
  - ➢ **Variance-covariance matrix** (THETAs, OMEGAs and SIGMAs)
  - ➢ **Scaled inverse Chi-squared distribution** (for single OMEGA or SIGMA)
  - ➢ **Scaled inverse Wishard distribution** (for block(s) of OMEGAs or SIGMAs)
  - ➢ **External source** (e.g., manual data frame, CIR file, etc.)
- Allow the users to enter min and max values for each parameter and check these limits during parameter sampling
- When parameters are sampled from the variance-covariance matrix, check the OMEGA or SIGMA matrix is positive definite

DESIGN

The sampling of parameters with uncertainty was implemented in the package *Campsismod* [3] [4] as a generic iterative process (see diagram). First, the model parameters are sampled for each replicate . Second, the model parameters are checked based on the minimal and maximal values provided by the user and based on the positive definiteness of the OMEGA or SIGMA matrices. If the parameters are not valid, the process is repeated until valid parameters are found.

Inputs:
i. Model parameters (including variance-covariance matrix)
ii. Number of replicates
iii. Settings


Generic sampling
✓ From multivariate normal dist.
✓ From scaled inv. χ² dist.
✓ From scaled inv. Wishart dist.
Check min/max
Check pos. def.
Derive success rate
Enough replicates?
No
Yes

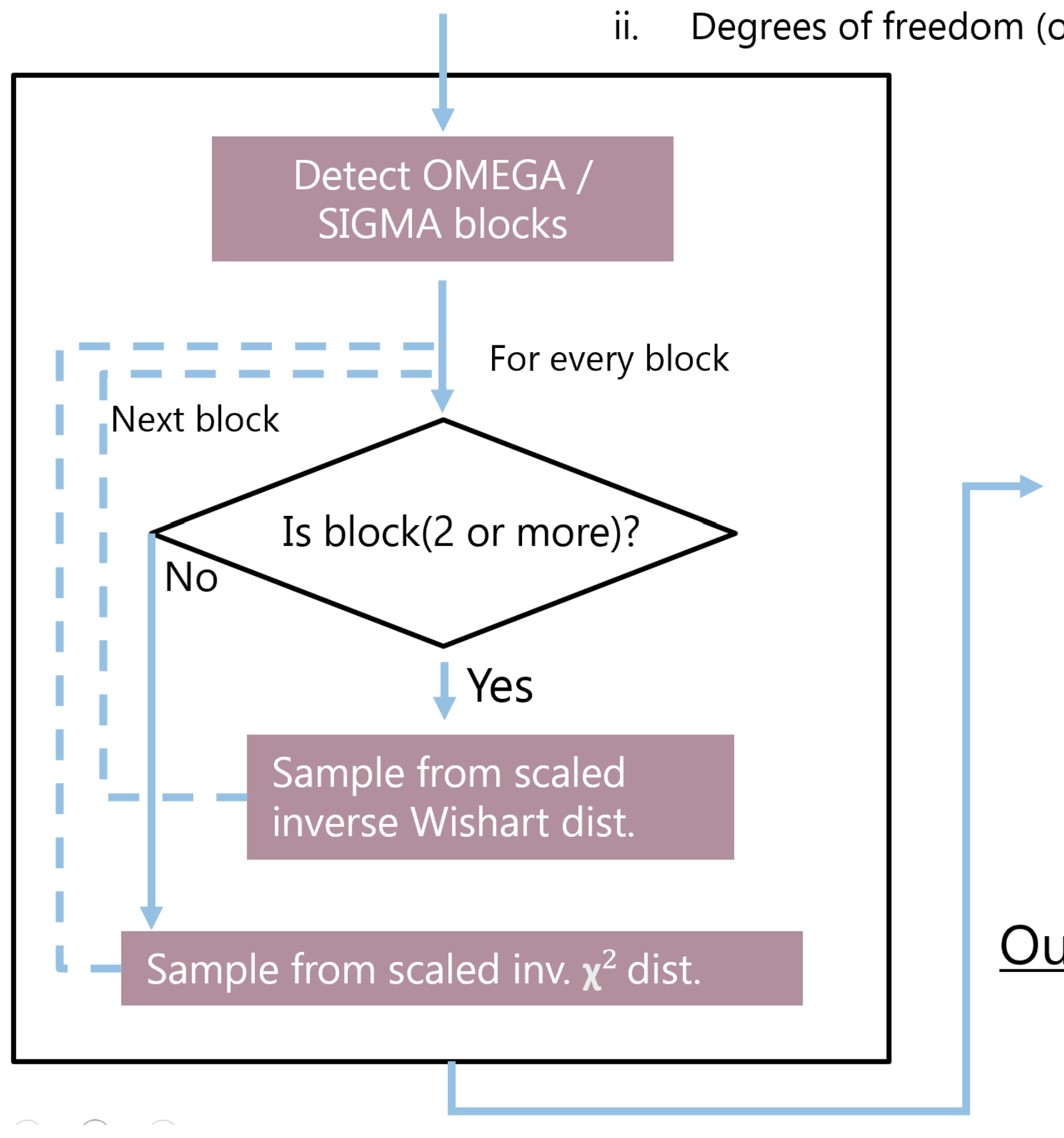


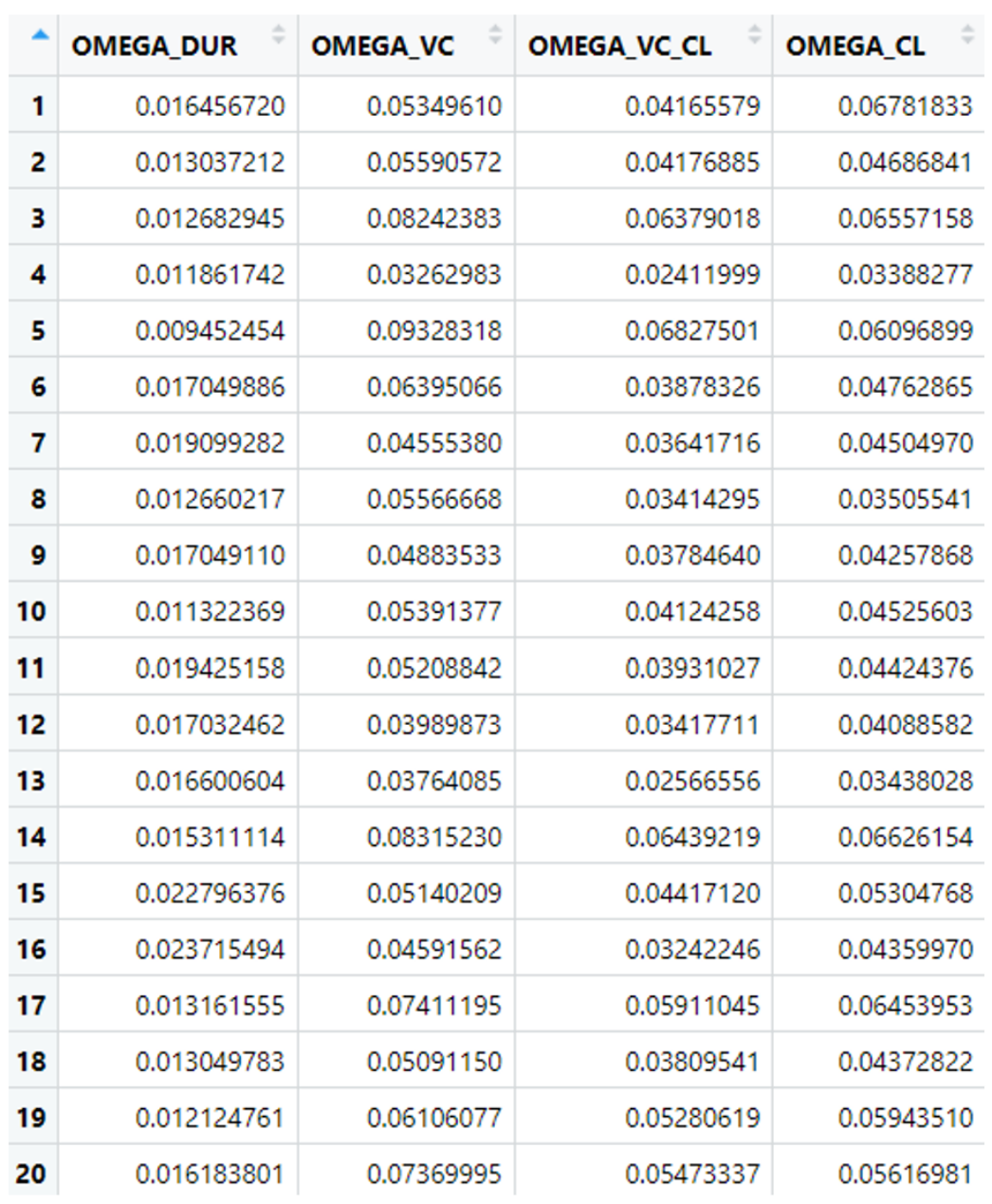
	THETA_METAB_CL	THETA_DUR	THETA_VC	THETA_VP	THETA_Q	THETA_CL	THETA_PROP_RUV
1	0.3420152	0.4001608	4.459646	5.290195	1.416429	1.666606	-1.927298
2	0.1738883	0.4266739	4.396864	5.245673	1.407995	1.665644	-1.934434
3	0.3284971	0.4010363	4.428710	5.255376	1.447283	1.624419	-1.914324
4	0.2891740	0.4514804	4.402907	5.247178	1.432668	1.590744	-1.916089
5	0.2967472	0.4200698	4.378103	5.255568	1.418177	1.600710	-1.939001
6	0.3122362	0.4520053	4.350599	5.238994	1.400307	1.670535	-1.890955
7	0.3840589	0.4115158	4.409696	5.256278	1.416708	1.618341	-1.939972
8	0.2907336	0.4128586	4.433943	5.272458	1.389822	1.556367	-1.935423
9	0.2839398	0.4182716	4.436617	5.261957	1.435893	1.621179	-1.945256
10	0.3208899	0.4292120	4.372998	5.243614	1.434859	1.602401	-1.934796
11	0.4598269	0.4054681	4.441339	5.289672	1.427058	1.539004	-1.906078
12	0.2482513	0.4080169	4.423582	5.293913	1.431013	1.695347	-1.925422
13	0.3397210	0.4299612	4.375113	5.254563	1.441393	1.614294	-1.928899
14	0.2523017	0.4166141	4.423721	5.323518	1.451921	1.689868	-1.951732
15	0.3466076	0.4432192	4.402994	5.278468	1.422469	1.621358	-1.907966
16	0.2357138	0.4058574	4.471438	5.235459	1.390837	1.645606	-1.899980
17	0.3365663	0.4202063	4.461243	5.286846	1.405416	1.578730	-1.931658
18	0.3494635	0.4165212	4.376891	5.275995	1.424602	1.649093	-1.926959
19	0.2548389	0.4277279	4.414186	5.276266	1.432472	1.636093	-1.911126
20	0.3586375	0.4311308	4.334309	5.267897	1.398277	1.607141	-1.957351

Output: e.g., THETAs sampled from the variance-covariance matrix

This iterative process is called once to sample the parameters from the variance-covariance matrix (THETAs and, on user's request, OMEGAs and SIGMAs) and is called a second time to sample the OMEGAs and SIGMAs from the scaled inverse Chi-squared or Wishart distributions (see diagram below). Before sampling the OMEGAs/SIGMAs, the structural blocks of the OMEGA/SIGMA matrix are automatically detected. Different degrees of freedom corresponding to these blocks may be entered by the user.

Inputs:
i. OMEGA or SIGMA matrix
ii. Degrees of freedom (odf or sdf)


Detect OMEGA / SIGMA blocks
For every block
Next block
Is block(2 or more)?
No
Yes
Sample from scaled inverse Wishart dist.
Sample from scaled inv. χ² dist.



	OMEGA_DUR	OMEGA_VC	OMEGA_VC_CL	OMEGA_CL
1	0.016456720	0.05349610	0.04165579	0.06781833
2	0.013037212	0.05590572	0.04176885	0.04686841
3	0.012682945	0.08242383	0.06379018	0.06557158
4	0.011861742	0.03262983	0.02411999	0.03388277
5	0.009452454	0.09328318	0.06827501	0.06096899
6	0.017049886	0.06395066	0.03878326	0.04762865
7	0.019099282	0.04555380	0.03641716	0.04504970
8	0.012660217	0.05566668	0.03414295	0.03505541
9	0.017049110	0.04883533	0.03784640	0.04257868
10	0.011322369	0.05391377	0.04124258	0.04525603
11	0.019425158	0.05208842	0.03931027	0.04424376
12	0.017032462	0.03989873	0.03417711	0.04088582
13	0.016600604	0.03764085	0.02566556	0.03438028
14	0.015311114	0.08315230	0.06439219	0.06626154
15	0.022796376	0.05140209	0.04417120	0.05304768
16	0.023715494	0.04591562	0.03242246	0.04359970
17	0.013161555	0.07411195	0.05911045	0.06453953
18	0.013049783	0.05091150	0.03809541	0.04372822
19	0.012124761	0.06106077	0.05280619	0.05943510
20	0.016183801	0.07369995	0.05473337	0.05616981

Output: e.g., OMEGAs sampled from the scaled inverse χ^2 and Wishart distributions.

INPUTS / OUTPUTS

Inputs:

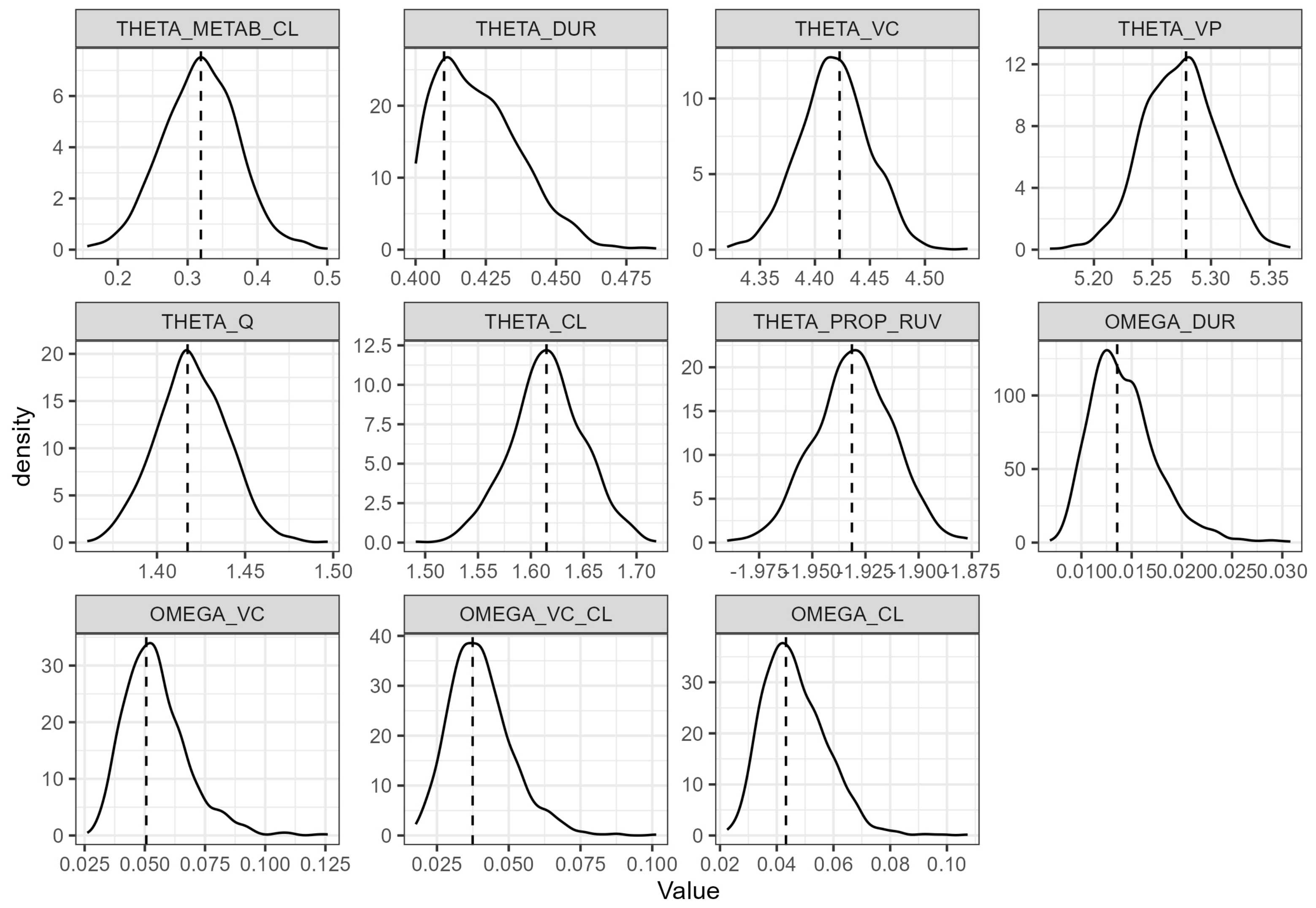
- Campsis model: it includes all model parameters and the variance-covariance matrix. All parameters include min and max values.
- Settings for random sampling:
  - ➢ By default, parameters are randomly sampled from the variance-covariance matrix
  - ➢ **Wishart** argument: OMEGAs/SIGMAs are sampled from the scaled inverse Chi-squared or Wishart distribution. In that case, degrees of freedom are required.
  - ➢ **odf** argument: degrees of freedom for the OMEGAs, single value (same for all) or a vector (one specific value per OMEGA block)
  - ➢ **sdf** argument: degrees of freedom for the SIGMAs, single value (same for all) or a vector (one specific value per SIGMA block)
  - ➢ **Check min/max** values: TRUE/FALSE
  - ➢ **Check positive definiteness** of OMEGA/SIGMA matrix: TRUE/FALSE
- Import from data frame: alternatively, model parameters can be provided in the form of an external data frame from a different source (e.g., from a bootstrap or SIR run).

Outputs:

The output of the procedure is an object containing the original Campsis model and the set of sampled parameters, in the form of a data frame, ready for simulations with uncertainty.

EXAMPLES

```r
library(campsis)

# Re-use an existing model from the library
model <- model_suite$testing$other$`2cpt_zo_allo_metab_effect_on_cl` %>%
  add(Omega(name="VC_CL", index=2, index2=3, value=0.8, type="cor")) %>%
  setMinMax(Theta("DUR"), min=0.40, max=Inf) # To illustrate min/max limits

# A) Sample OMEGAs/SIGMAs from the variance-covariance matrix
repModelA <- model %>%
  replicate(1000, settings=AutoReplicationSettings(wishart=FALSE, checkPosDef=TRUE, checkMinMax=TRUE))

# B) Sample OMEGAs/SIGMAs from the scaled inverse Wishart distribution
repModelB <- model %>%
  replicate(1000, settings=AutoReplicationSettings(wishart=TRUE, odf=40, sdf=1000, checkMinMax=TRUE))

# C) Sample parameters from an external source (e.g. CIR)
data <- read.csv("data.csv")
repModelC <- model %>%
  replicate(1000, settings=ManualReplicationSettings(data=data))

# Export the first replicate from repModelA to a Campsis model (as an example)
modelA <- repModelA %>%
  export(dest=CampsisModel(), index=1)

# Easy integration with Campsis to run trial simulations with replicates
settings <- Settings(Hardware(cpu=8, replicate_parallel=TRUE))
results <- progressr::with_progress(
  simulate(model=repModelA, dataset=dataset, seed=1, dest="mrgsolve", settings=settings)
)
# Show the sampled parameters using density plots (see plot below)
print(repModelB)
```



REFERENCES

[1] https://cran.r-project.org/web/packages/campsis/index.html
[2] https://github.com/Calvagone/campsis or www.campsis.org
[3] https://cran.r-project.org/web/packages/campsismod/index.html
[4] https://github.com/Calvagone/campsismod