

# microsamplingDesign

Finding optimal microsampling designs for non-compartmental pharmacokinetic analysis

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## Contents

<b>1</b>	<b>Introduction</b>	<b>2</b>
<b>2</b>	<b>Model details</b>	<b>2</b>
2.1	Parametrization . . . . .	2
2.2	Log-normal parameters . . . . .	3
<b>3</b>	<b>microsamplingDesign shiny application</b>	<b>4</b>
3.1	Construct a pharmacokinetic model . . . . .	4
3.2	Generate possible time points . . . . .	5
3.3	Rank time points . . . . .	5
3.4	Generate possible schemes . . . . .	7
3.5	Rank schemes . . . . .	7
<b>4</b>	<b>Finding optimal designs using code</b>	<b>9</b>
4.1	Settings . . . . .	9
4.2	Construct a pharmacokinetic model . . . . .	9
4.3	Generate time points . . . . .	10
4.4	Rank time points . . . . .	11
4.5	Generate possible schemes . . . . .	12
4.6	Rank schemes . . . . .	12
<b>5</b>	<b>Advanced options</b>	<b>14</b>
5.1	Parallelization . . . . .	14
5.2	Working with ranges . . . . .	14
<b>6</b>	<b>Memo of main functions</b>	<b>14</b>
6.1	Data generation . . . . .	14
6.2	Generate and rank time points . . . . .	14
6.3	Generate and rank schemes . . . . .	15
	<b>References</b>	<b>15</b>

## 1 Introduction

Microsampling, a novel blood sampling technique allows multiple blood samples to be taken per animal, reducing the number of animals required for pharmacokinetic-pharmacodynamic studies (Chapman et al. (2014)). Using sparse designs can in addition, avoid unnecessary sampling of these animals, provided an appropriate choice of sample times per animals is made. The `microsamplingDesign` package implements a general simulation methodology to find optimal sparse microsampling schemes aimed at non-compartmental pharmacokinetic analysis (algorithm III in Barnett et al. (2017)). This methodology consist of (1) specifying a pharmacokinetic model including variability among animals; (2) generating possible sampling times; (3) evaluating performance of each time point choice on simulated data; (4) generating possible schemes given a time point choice and additional constraints and finally (5) evaluating scheme performance on simulated data. The default settings differ from (Barnett et al. (2017)) in the default pharmacokinetic model used and the parameterization of variability among animals (see next section). A shiny web application is included, which guides users from model parametrization to optimal microsampling scheme.

## 2 Model details

A two compartmental oral dosing pharmacokinetic model (Gabrielsson and Weiner (2001)) is assumed:

$$\begin{aligned} \frac{dD_g}{dt} &= -k_a \cdot D_g \\ V_c \frac{dC}{dt} &= F \cdot k_a \cdot D_g - Cl \cdot C - Cl_d \cdot C + Cl_d \cdot C_t \\ V_t \frac{dC_t}{dt} &= Cl_d \cdot C - Cl_d \cdot C_t \end{aligned}$$

A dose of a substance ( $D_g$ ) is administered to the gut, then gradually absorbed into a central compartment leading to an increased concentration in the plasma ( $C$ ). Where it can either be excreted or exchanged with a second peripheral compartment, the peripheral tissues, where the compound has a distinct concentration ( $C_t$ ) in time, depending on the rate of exchange with the central compartment. We do not assume any excretion from the peripheral compartment.

Substance absorption and clearance are by default assumed to be capacity dependent (Michaelis-Menten kinetics):

$$\begin{aligned} k_a &= \frac{V_{a,max}}{\kappa_{a,m} + D_g} \\ Cl &= \frac{V_{e,max}}{\kappa_{e,m} + C} \end{aligned}$$

We also leave the option open for one or both of these parameters to be constant.

For details see (Gabrielsson and Weiner (2001)).

### 2.1 Parametrization

- $k_a$  is the absorption rate per unit of dose.
- $V_c$  is the volume of the central compartment (plasma)
- $V_t$  is the volume of the peripheral compartment (tissue)
- $F$  bioavailability, the fraction of the dose that reaches the systemic circulation intact (dimensionless)

- $Cl$  is the elimination rate from the central compartment (assumed the only spot where elimination occurs); in volume per time, related to the elimination rate in dose: ( $k_e = \frac{Cl}{V_c}$ )
- $Cl_d$  is the distribution parameter between central and peripheral compartment; expressed in volume per time unit. It related to rates:  $Cl_d = \frac{k_{ct}}{V_c} = \frac{k_{tc}}{V_t}$ ; with  $k_{ct}$  the rate from central to tissue (dose per time unit) , and  $k_{tc}$  the rate from tissue to central compartment.
- $V_{a,max}$  is the maximum absorption rate ( absolute rate is rate per dose x dose)
- $\kappa_{a,m}$  is the Michaelis-Menten constant for absorption
- $V_{e,max}$  is the maximum clearance rate (absolute rate is rate per concentration x concentration)
- $\kappa_{e,m}$  is the Michaelis-Menten constant for clearance.

## 2.2 Log-normal parameters

Individual animals are assumed to have the same underlying model, with different parameters simulated from an underlying log-normal distribution parametrized in terms of the mean and the coefficient of variation.

we assume a random variable  $X$  to be log-normally distributed with parameters  $\mu$  and  $\sigma$ :

$$X = \exp(\mu + \sigma Z)$$

with  $Z$  a standard normal variable.

Now, we want to extract  $\mu$  and  $\sigma$  from and coefficient of variation ( $CV = sd(X)/E(X)$ ) of the original scale.

we can use the relation for the mean:

$$E(X) = \exp\left(\mu + \frac{\sigma^2}{2}\right)$$

and the relation for the coefficient of variation:

$$CV(X) = \sqrt{\exp \sigma^2 - 1}$$

Therefore:

$$\sigma = \sqrt{\ln(CV^2 + 1)}$$

and

$$\mu = \ln(E(X)) - \frac{\sigma^2}{2}$$

For the multivariate log-normal distribution, we use a the same approach per variable and can simulate a random vector:

$$\mathbf{X} = \exp(\boldsymbol{\mu} + Z\boldsymbol{\sigma}^T)$$

with  $Z \sim \mathcal{N}(\mathbf{0}, \Sigma)$  and  $\Sigma$  a specified correlation matrix. More information see (Halliwell (2015))

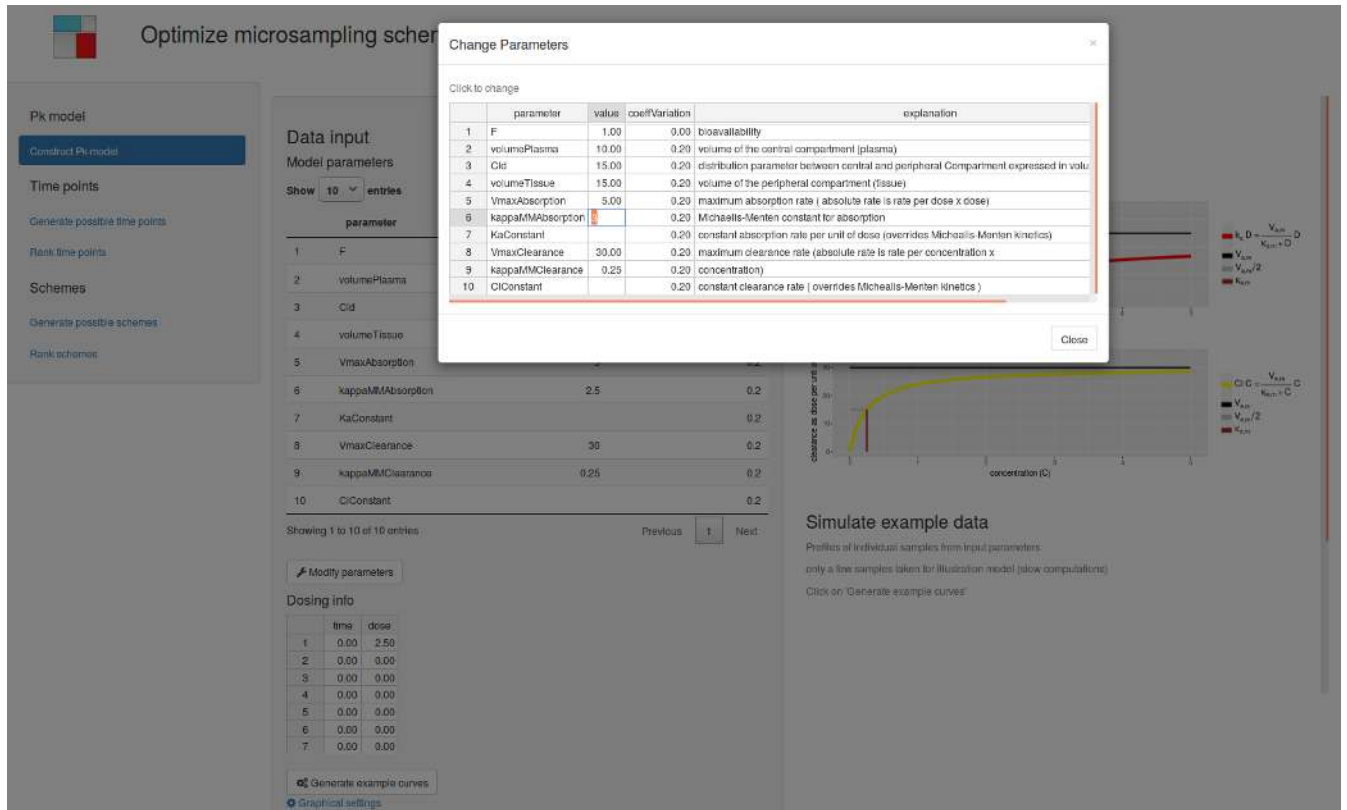


Figure 1: Construct a PK model

### 3 microsamplingDesign shiny application

Before diving into the R code of the `microsamplingDesign` package, we give a more intuitive introduction to the methodology using the included shiny application. In a local R session we can start the application:

```
library( microsamplingDesign )
runMicrosamplingDesignApp( installDependencies = TRUE )
```

The first time you want to run the application, use `installDependencies = TRUE` to automatically install the additional R-package required for this shiny application in addition to the `microsamplingDesign` package dependencies.

#### 3.1 Construct a pharmacokinetic model

Start the application by constructing a pharmacokinetic model.

Example parameters are shown on start up. To modify these parameters click on **Modify parameters** and a spreadsheet is displayed allowing modifying parameter values and their coefficient of variation (see Figure 1).

Next include dosing information by filling out one or several lines, click on **Generate example curves** to check simulated time-concentration curves (see Figure 2).

One can adapt the scale of the graphs by clicking on **Graphical settings**.

Note that the pharmacokinetic model in the application does not contain any measurement error.

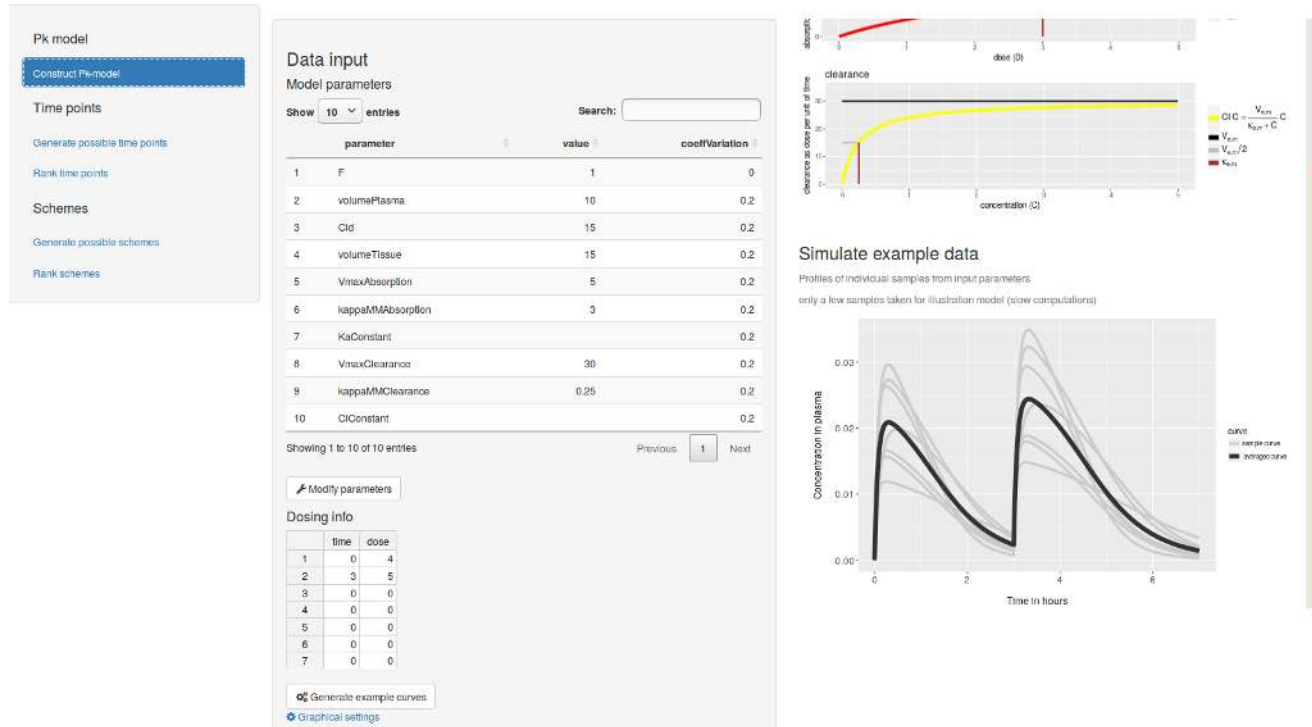


Figure 2: Check model by generating example curves

### 3.2 Generate possible time points

Time point options are generated from a time constraints table specifying the number of time points per time zone and minimum sampling interval in each row. Note that the endTime is not included in the zone itself but is the startTime of the next zone.

Finally click on the button **Generate time points**, to receive all possible combinations in table form (see Figure 3).

### 3.3 Rank time points

Time points options are ranked by measuring the difference between approximating the average time-concentration curve based on a limited number of time points on sample data and the actual average curve at the maximal number of time points you want to consider. This is a measure of bias caused by choosing a certain time point option rather than sampling at the maximum number of time points.

In the application ranking time points takes 2 steps:

#### 3.3.1 Generate sample data

Specify the approximate number of animals you would like to use in you scheme and the number of simulated datasets to generate. Then press **Generate data to rank time points**. A selection of simulated data will be displayed (see Figure 4).

#### 3.3.2 Rank time points

After checking the generatated data, click on **Rank time points** to estimate the bias of each time point option. Calculations might take a few minutes, depending on the the number of simulation samples and



## Optimize microsampling schemes for non-compartmental analysis

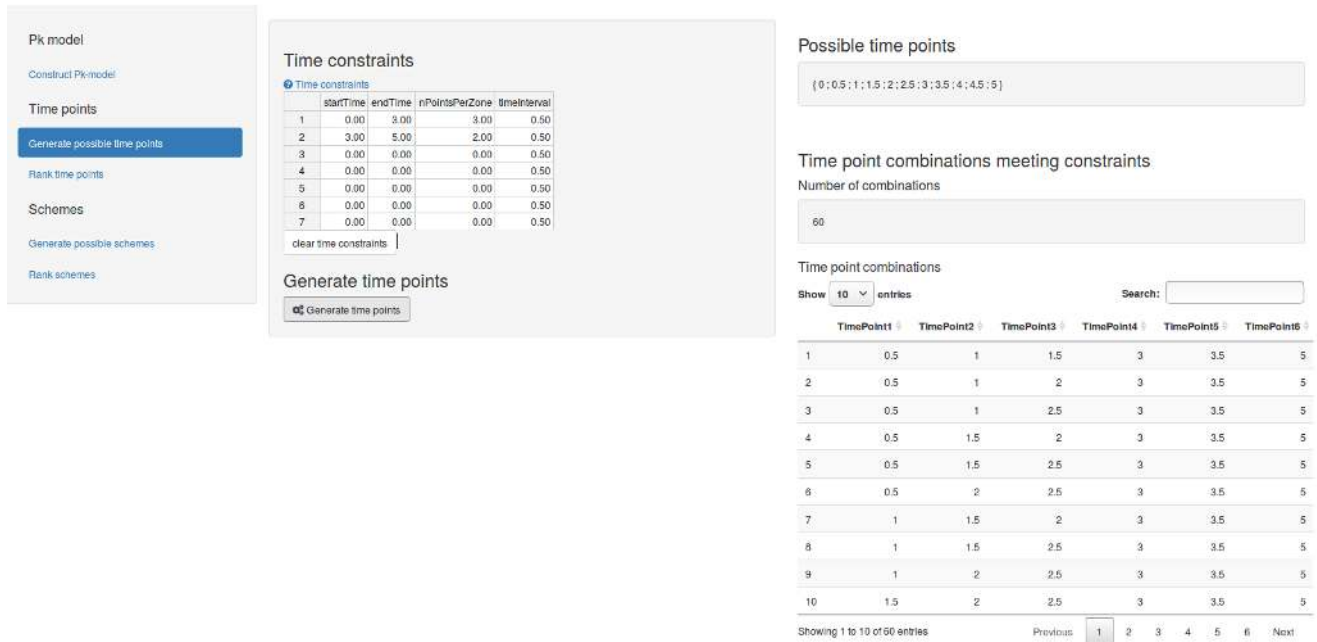


Figure 3: Generate time points



## Optimize microsampling schemes for non-compartmental analysis

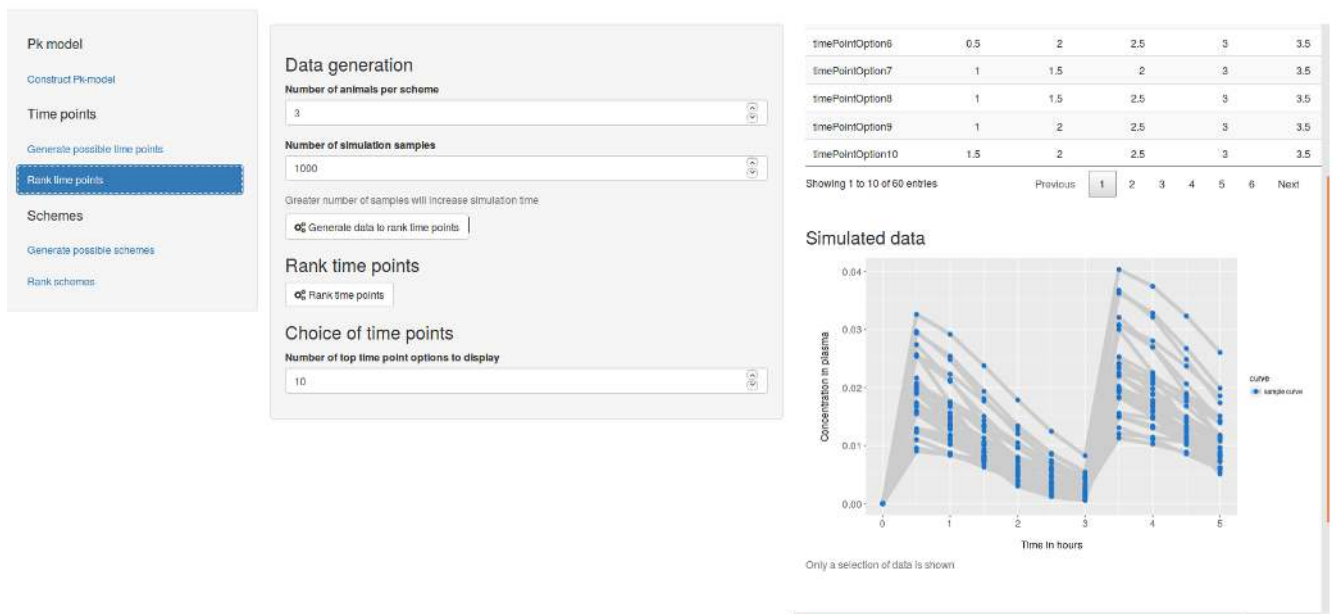


Figure 4: Generate data to rank time points



## Optimize microsampling schemes for non-compartmental analysis

**Data generation**

Number of animals per scheme: 3

Number of simulation samples: 1000

Greater number of samples will increase simulation time

Generate data to rank time points

**Rank time points**

Rank time points

**Choice of time points**

Number of top time point options to display: 10

**Time point ranking**

Show 10 entries Search:

	name	criteria	rank	TimePoint1	TimePoint2	TimePoint3	Ti
1	timePointOption6	0.001848	1	0.5	2	2.5	
2	timePointOption3	0.001852	2	0.5	1.5	2.5	
3	timePointOption4	0.001856	3	0.5	1.5	2	
4	timePointOption2	0.001864	4	0.5	1	2	
5	timePointOption3	0.001894	5	0.5	1	2.5	
6	timePointOption1	0.001909	6	0.5	1	1.5	
7	timePointOption56	0.002575	7	0.5	2	2.5	
8	timePointOption55	0.002579	8	0.5	1.5	2.5	
9	timePointOption53	0.002621	9	0.5	1	2.5	
10	timePointOption16	0.002641	10	0.5	2	2.5	

Showing 1 to 10 of 10 entries Previous 1 Next

**Chosen sampling points**

TimePoint1	TimePoint2	TimePoint3	TimePoint4	TimePoint5	TimePoint6
0.50	1.50	2.50	3.00	3.50	5.00

Figure 5: Rank time points and select one

time point options. When calculations are finished, time point options are tabulated from small to large deviation from the best accuracy. You can select a time point option by clicking on a row in the time point ranking table (see Figure 5).

### 3.4 Generate possible schemes

Given the time points, we will construct schemes specifying which subjects are sampled at which time points.

To generate these schemes, fill out the scheme's dimensions and the maximum number of repetitions of individual schemes. You can already assess the possible number of schemes by clicking on **Check number of schemes before constraints** which is much faster than generating the schemes first. Reconsider scheme dimensions when the number of schemes is too large. The possible number of schemes can also be cut down by imposing *scheme constraints*. Finally click on **Generate schemes** to receive all schemes meeting constraints. This might take a few minutes (see Figure 6).

### 3.5 Rank schemes

Schemes are ranked by their precision of estimating the area under the curve (AUC) and maximum concentration (Cmax) on simulated data.

Again we work in 2 steps:

#### 3.5.1 Generate sample data

Generate data by specifying the number of simulation samples and click **Generate data to rank schemes** (see Figure 7).

#### 3.5.2 Rank schemes

After data generation, specify the objective function by attaching a relative importance to different non-compartmental statistics and click on **Rank schemes** (see Figure 8). This might take some time.



## Optimize microsampling schemes for non-compartmental analysis

**Pk model**

Construct Pk-model

**Time points**

Generate possible time points

Rank time points

**Schemes**

Generate possible schemes

Rank schemes

### Scheme dimensions

Number of subjects: 4

Number of observations per subject

min: 4

max: 5

Repetition of individual schemes

Warning: repeating individual schemes will greatly increase the possible number of schemes

Maximum number of repetitions individual schemes: 1

### Scheme constraints

check	value
1 minObsPerTimePoint	2.00
2 maxConsecSamples	3.00
3 Choose a constraint	1.00
4 Choose a constraint	1.00
5 Choose a constraint	1.00

Reset scheme constraints

**Generate schemes**

Check number of schemes before constraints

Too large a number will slow down compilation, reconsider scheme dimensions

Generate schemes

### Time points

{ 0.5; 1.5; 2.5; 3; 3.5; 5 }

### Number of schemes before applying constraints

1,001

If too large a number ( 100,000 ), reconsider 'scheme dimensions'

### Number of schemes meeting constraints

547

### Schemes meeting constraints

Show 10 entries

	scheme	subject	timePoint1	timePoint2	timePoint3	timePoint4	timePoint5	timePoint5
1	schema1	subject1	true	true	true	true	false	true
2	schema1	subject2	true	true	false	true	true	true
3	schema1	subject3	true	false	false	true	true	true
4	schema1	subject4	true	true	true	true	false	true
5	schema2	subject1	true	true	false	true	true	true
6	schema2	subject2	true	false	true	false	true	true
7	schema2	subject3	true	true	true	true	true	false
8	schema2	subject4	true	true	false	false	true	true
9	schema3	subject1	true	false	false	false	true	true
10	schema3	subject2	true	false	true	true	true	false

Showing 1 to 10 of 2,188 entries

Figure 6: Generate schemes



## Optimize microsampling schemes for non-compartmental analysis

**Pk model**

Construct Pk-model

**Time points**

Generate possible time points

Rank time points

**Schemes**

Generate possible schemes

Rank schemes

### Data generation

Number of simulation samples: 1000

Take a small number for testing, and a large number e.g. 1000 for the final run

Generate data to rank schemes

### Rank Schemes

Objective function

Relative importance area under the curve (AUC): 50

Relative importance maximum concentration (Cmax): 50

Rank schemes

### Choice of Scheme

Number of top schemes to display: 10

4	schema1	subject4	true	true	true	true	false
5	schema2	subject1	true	true	false	true	true
6	schema2	subject2	true	false	true	false	true
7	schema2	subject3	true	true	true	true	true
8	schema2	subject4	true	true	false	false	true
9	schema3	subject1	true	false	false	false	true
10	schema3	subject2	true	false	true	true	true

Showing 1 to 10 of 2,188 entries

### Simulated data

Concentration in plasma

Time in hours

curve

samplecurve

Only a selection of data is shown

Figure 7: Generate data to rank schemes





## Optimize microsampling schemes for non-compartmental analysis

Only a selection of data is shown.

**Scheme ranking**

Show 10 entries Search:

	name	var_auc	var_cMax	criterion	rank
1	scheme33	0.000096	0.000017	0.611456023930336	1
2	scheme89	0.000096	0.000017	0.612626511928707	2
3	scheme267	0.000096	0.000017	0.613056145960246	3
4	scheme90	0.000099	0.000017	0.614233625211224	4
5	scheme87	0.000099	0.000017	0.614482496676645	5

Showing 1 to 5 of 5 entries Previous 1 Next

**Chosen scheme**

Show 10 entries Search:

	timePoint1	timePoint2	timePoint3	timePoint4	timePoint5	timePoint6
subject1	true	true	true	false	true	false
subject2	true	true	false	true	true	false
subject3	true	false	true	false	true	true
subject4	true	false	false	true	true	true

Showing 1 to 4 of 4 entries Previous 1 Next

Figure 8: Rank schemes

Finally select a scheme by clicking on the **Scheme ranking** table.

When a final scheme is chosen, first click on **Generate report** and next on **Download report** to receive a word document summarizing the main results.

## 4 Finding optimal designs using code

### 4.1 Settings

```
settings <- list()
settings$nSamples <- 100 # increase for real life example
set.seed(124)
```

### 4.2 Construct a pharmacokinetic model

```
library( microsamplingDesign )
pkModel <- getExamplePkModel()
```

some useful functions:

```
modelParameters <- getParameters( pkModel )
knitr::kable( modelParameters[ , c(1:2) ] )
```

parameter	value
F	1.00
volumePlasma	10.00
Cld	15.00
volumeTissue	15.00
VmaxAbsorption	5.00
kappaMMAbsorption	2.50
KaConstant	NA
VmaxClearance	30.00
kappaMMCclearance	0.25
ClConstant	NA

To generate your own pharmacokinetic model see:

```
?construct2CompModel
```

### 4.3 Generate time points

Possible time points are generated from a full set of time points:

```
fullTimePointsEx <- seq( 0 , 16 , 0.5 )
print( fullTimePointsEx )
#> [1] 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5
#> [15] 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5 11.0 11.5 12.0 12.5 13.0 13.5
#> [29] 14.0 14.5 15.0 15.5 16.0
```

With the choice of options constraints by *timeZones*:

```
#timeZonesEx <- getExampleTimeZones()
timeZonesEx <- data.frame( startTime = c( 0 , 2 , 3 ) ,
  endTime = c( 2 , 3 , 16 ) ,
  nPointsPerZone = c( 2 , 1 , 2 ) )
knitr::kable( timeZonesEx )
```

startTime	endTime	nPointsPerZone
0	2	2
2	3	1
3	16	2

*timeZones* concept is defined such that : time zero is never included, last timePoint is always included.

Correct names should be used!

Now we can generate all time point options from a vector of possible time points under constraints defined in *timeZones*:

```
setOfTimePoints <- getAllTimeOptions( timeZones = timeZonesEx ,
  fullTimePoints = fullTimePointsEx )
# ?SetOfTimePoints # class definition
#str( setOfTimePoints ) # to see all slots in the example
slotNames( setOfTimePoints )
#> [1] ".Data" "fullTimePoints" "nFullTimePoints"
#> [4] "nTimePointsSelect" "nTimePointOptions" "ranking"
knitr::kable( head( getData( setOfTimePoints ) ) )
```

	TimePoint1	TimePoint2	TimePoint3	TimePoint4	TimePoint5	TimePoint6
timePointOption1	0.5	1.0	2.0	3	3.5	16
timePointOption2	0.5	1.5	2.0	3	3.5	16
timePointOption3	1.0	1.5	2.0	3	3.5	16
timePointOption4	0.5	1.0	2.5	3	3.5	16
timePointOption5	0.5	1.5	2.5	3	3.5	16
timePointOption6	1.0	1.5	2.5	3	3.5	16

```
knitr::kable( tail( getData( setOfTimePoints ) ) )
```

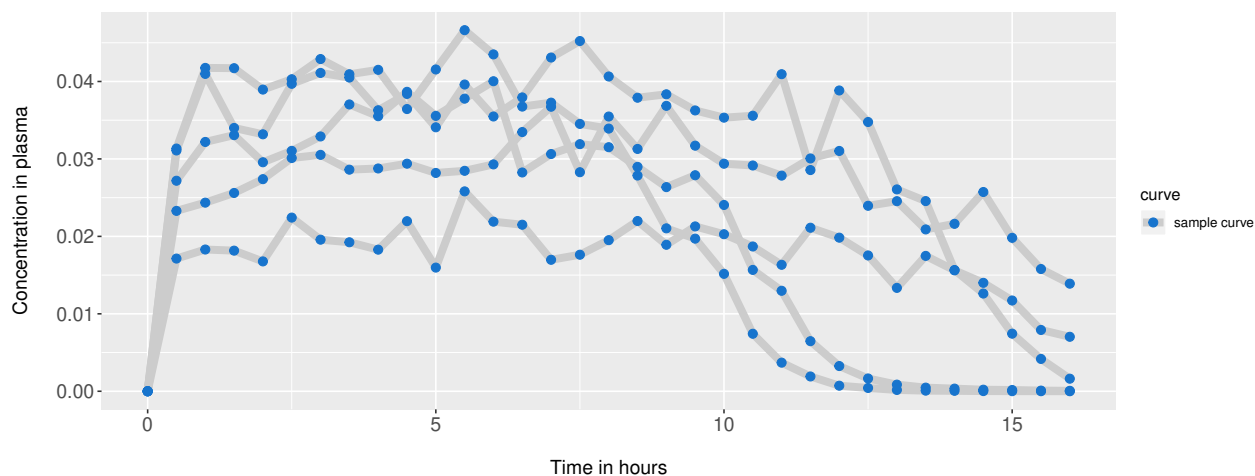
	TimePoint1	TimePoint2	TimePoint3	TimePoint4	TimePoint5	TimePoint6
timePointOption1945	0.5	1.0	2.0	15	15.5	16
timePointOption1946	0.5	1.5	2.0	15	15.5	16
timePointOption1947	1.0	1.5	2.0	15	15.5	16
timePointOption1948	0.5	1.0	2.5	15	15.5	16
timePointOption1949	0.5	1.5	2.5	15	15.5	16
timePointOption1950	1.0	1.5	2.5	15	15.5	16

note 0 never chosen , time 16 always included

## 4.4 Rank time points

To rank the timePoint options inside a *SetOfTimePoints* object , we first need to simulate *PkData*.

```
model <- getExamplePkModel()
fullTimePoints <- getTimePoints( setOfTimePoints )
pkDataForTimePoints <- getPkData( pkModel = model , timePoints = fullTimePoints ,
  nSubjectsPerScheme = 5 , nSamples = settings$nSamples )
plotObject( pkDataForTimePoints , nCurves = 5 )
```



This is just small number of samples, in reality one would use a larger number such as 1000.

We can then use the rank function to find the optimal time points:

```
rankedTimePoints <- rankObject( setOfTimePoints , pkData = pkDataForTimePoints ,
  nGrid = 150 , nSamplesAvCurve = settings$nSamples )
rankingTimePoints <- getRanking( rankedTimePoints )
knitr::kable( head( rankingTimePoints ) )
```

name	criterion	rank
timePointOption1306	0.0055133	1
timePointOption1216	0.0055254	2
timePointOption1300	0.0055293	3
timePointOption1307	0.0055303	4
timePointOption1217	0.0055424	5
timePointOption1301	0.0055463	6

```
#knitr::kable( tail( rankingTimePoints ) )
indTimeChoice <- getTopNRanking( rankingTimePoints , 1 )
bestTimeChoice <- setOfTimePoints[ indTimeChoice , ]
bestTimeChoice
#> TimePoint1 TimePoint2 TimePoint3 TimePoint4 TimePoint5 TimePoint6
#> 0.5 1.0 2.5 8.0 14.5 16.0
```

## 4.5 Generate possible schemes

```
timePointsChoice <- bestTimeChoice
```

To generate schemes we can define additional constraints:

```
constraintsExample <- getConstraintsExample()[c( 2 , 4 ) , ]
knitr::kable( constraintsExample )
```

	check	level	value
2	maxConsecSamples	subject	3
4	minObsPerTimePoint	scheme	2

Constraints are defined on 2 levels: *subject* or *scheme*.

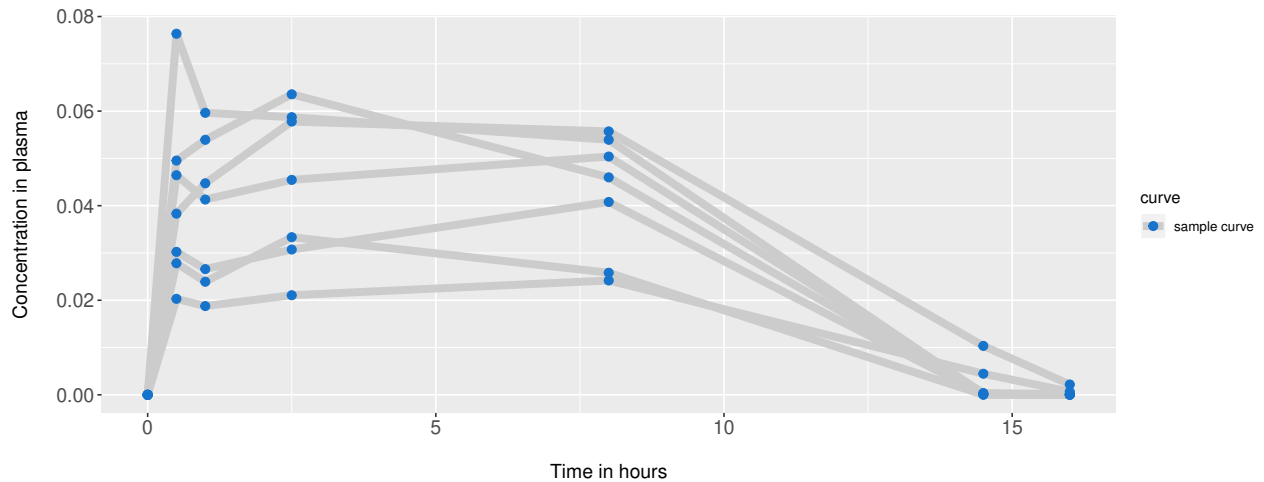
```
setOfSchemes <- getSetOfSchemes( minNSubjects = 4 , maxNSubjects = 5 ,
  minObsPerSubject = 4 , maxObsPerSubject = 5 ,
  timePoints = timePointsChoice , constraints = constraintsExample ,
  maxRepetitionIndSchemes = 1 , maxNumberOfSchemesBeforeChecks = 10^8 )
slotNames( setOfSchemes )
#> [1] ".Data" "timePoints" "nSchemes"
#> [4] "nSubjects" "designConstraints" "ranking"
```

The number of combinations can get very large especially with `maxRepetitionIndSchemes > 1`.

## 4.6 Rank schemes

To rank schemes, we need matching Pkdata (number of animals and timePoints):

```
timePointsEx <- getTimePoints( setOfSchemes )
pkData <- getPkData( pkModel, timePoints = timePointsEx ,
  nSubjectsPerScheme = 5 , nSamples = settings$nSamples )
plotObject( pkData , nCurves = 7 , addZeroIsZero = TRUE )
```



To rank schemes, we have to define an objective function, based on the a scheme based statistic ( AUC , ... ) a weight representing its relative importance.

```
exampleObjective <- data.frame(
  criterion = c( "auc" , "cMax" , "tMax" ) ,
  weight = c( 9 , 1 , 1 ) )
knitr::kable( exampleObjective )
```

criterion	weight
auc	9
cMax	1
tMax	1

But be carefull cMax and tMax might be very variable when multiple doses are administered.

```
setOfSchemesRanked <- rankObject( setOfSchemes , pkData = pkData ,
  objective = exampleObjective , varianceMeasure = "var" , scaleWith = "max" )
#> start Ranking Schemes on cluster with 1 cores
schemeRanking <- getRanking( setOfSchemesRanked )
knitr::kable( head( schemeRanking ) )
```

name	var_auc	var_cMax	var_tMax	criterion	rank
scheme2174	0.0038693	8.35e-05	5.923712	0.3944018	1
scheme1117	0.0038757	7.02e-05	7.022727	0.3984378	2
scheme1083	0.0039049	7.02e-05	7.022727	0.4006205	3
scheme1520	0.0040224	7.02e-05	7.022727	0.4093937	4
scheme1554	0.0040353	7.02e-05	7.022727	0.4103594	5
scheme1759	0.0041947	7.51e-05	6.038283	0.4151664	6

```
knitr::kable( tail( schemeRanking ) )
```

	name	var_auc	var_cMax	var_tMax	criterion	rank
2272	scheme92	0.0109541	0.0001181	6.096364	0.9445893	2272
2273	scheme295	0.0105663	0.0001506	7.516439	0.9478580	2273
2274	scheme367	0.0104885	0.0001597	7.754015	0.9494683	2274
2275	scheme218	0.0107443	0.0001266	8.381313	0.9563801	2275
2276	scheme219	0.0109218	0.0001298	7.503510	0.9626993	2276
2277	scheme365	0.0108802	0.0001506	7.516439	0.9713021	2277

```
indTopSchemes <- getTopNRanking( schemeRanking , nSelect = 1 )
indBottomSchemes <- getTopNRanking( schemeRanking , nSelect = 1 , top = FALSE )
```

```
bestScheme      <- setOfSchemesRanked[ , , indTopSchemes ]
knitr::kable( bestScheme )
```

	timePoint1	timePoint2	timePoint3	timePoint4	timePoint5	timePoint6
subject1	TRUE	FALSE	TRUE	TRUE	TRUE	FALSE
subject2	TRUE	FALSE	TRUE	TRUE	FALSE	TRUE
subject3	TRUE	FALSE	FALSE	TRUE	TRUE	TRUE
subject4	FALSE	TRUE	FALSE	TRUE	TRUE	TRUE
subject5	TRUE	TRUE	TRUE	FALSE	TRUE	TRUE

```
worstScheme     <- setOfSchemesRanked[ , , indBottomSchemes ]
knitr::kable( worstScheme )
```

	timePoint1	timePoint2	timePoint3	timePoint4	timePoint5	timePoint6
subject1	TRUE	TRUE	FALSE	TRUE	FALSE	TRUE
subject2	TRUE	TRUE	FALSE	FALSE	TRUE	TRUE
subject3	TRUE	FALSE	TRUE	FALSE	TRUE	TRUE
subject4	FALSE	TRUE	TRUE	TRUE	FALSE	TRUE
subject5	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE

## 5 Advanced options

### 5.1 Parallelization

Parallelization by forking is supported on linux machines and can be used to seed up simulating pkData, generating or ranking timepoints or schemes. You need to specify the number of cores inside these functions (*nCores*):

```
setOfSchemesRanked <- rankObject(setOfSchemes , pkData = pkData ,
objective = exampleObjective ,      varianceMeasure = "var" , scaleWith = "max" ,
nCores = 2 )
```

### 5.2 Working with ranges

Using ranges of parameters is also supported, see

```
?rankObjectWithRange
```

for details.

## 6 Memo of main functions

### 6.1 Data generation

- *getExamplePkModel*: Get an example of a PkModel
- *construct2CompModel* Construct your own 2 compartmental model
- *getPkData* to generate data from your a PkModel
- *plotObject* visualize model or data

### 6.2 Generate and rank time points

- *getAllTimeOptions*
- *getPkData*
- *rankObject*

### 6.3 Generate and rank schemes

- *getSetOfSchemes*
- *getPkData*
- *rankObject*

## References

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