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Optimal designs for non-compartmental analysis of pharmacokinetic parameters

Thomas Jaki Helen Barnett Tom Jacobs Helena Geys

Lancaster University

12 December 2017

Pharmacokinetic studies

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- Pharmacokinetic studies what the body does to a drug
- Frequently measures the concentration of the drug in the blood
- AUC is a measure of drug exposure
- C_{max} is the maximum concentration

PK design

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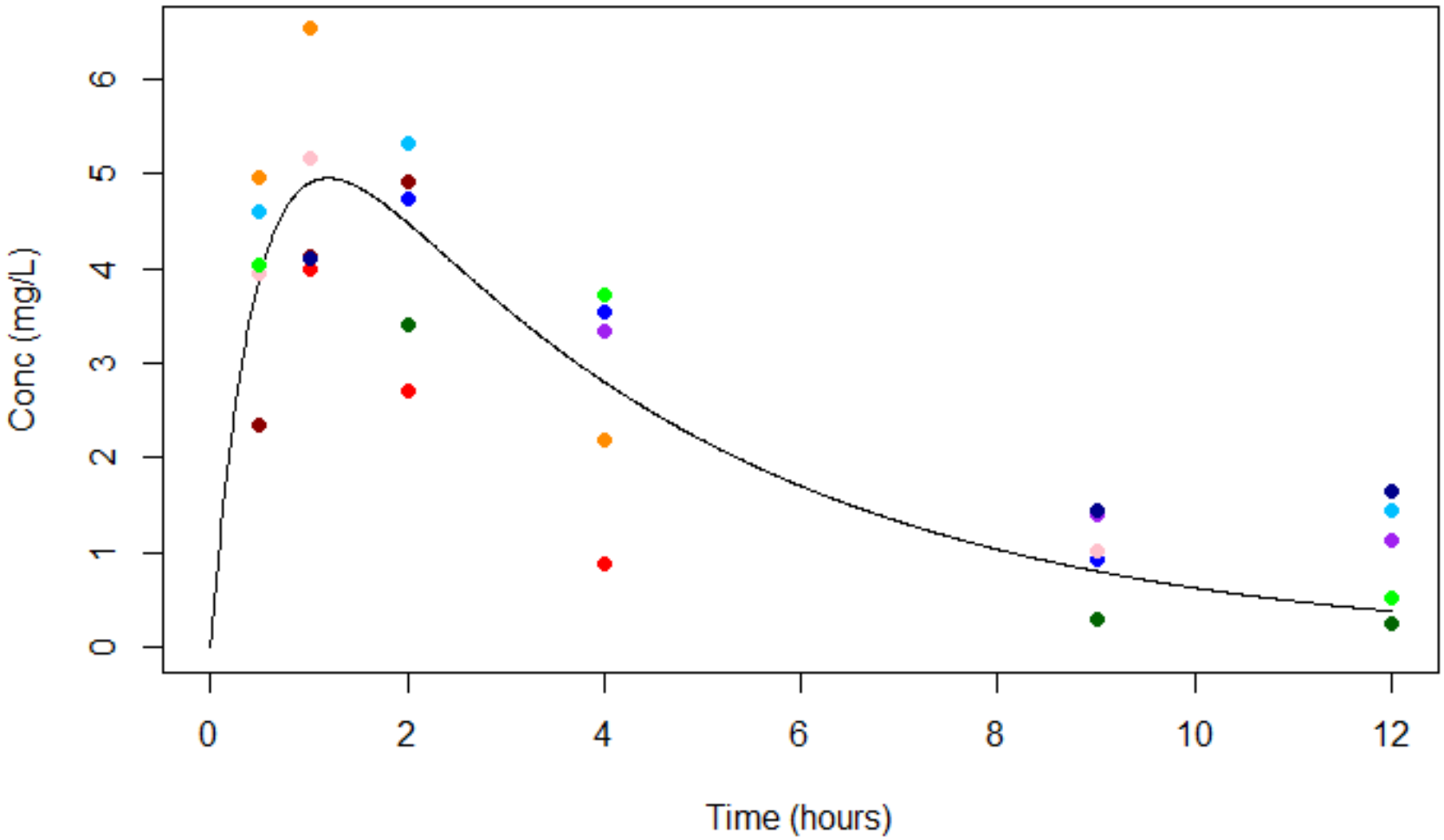

Proposed Design

Chapman et al. (2014)

TABLE 1

An example study design for toxicokinetic (TK) analysis on a one month good laboratory practice (GLP) rat study

Animal number	Sampling timepoint					
	#1	#2	#3	#4	#5	#6
1	x			x	x	
2	x			x		x
3		x		x	x	
4		x	x			x
5	x		x	x		
6	x		x		x	
7	x		x			x
8		x			x	x
9		x	x		x	
10		x		x		x
	$n = 5$	$n = 5$	$n = 5$	$n = 5$	$n = 5$	$n = 5$

All the main study animals are sampled. There are a total of ten animals per sex per group (80 rats). TK profiles are made up from composite samples as follows: six timepoints (#1 to #6), three samples per animal (see x in rows), five samples per timepoint (see x in columns). This gives a total of 30 TK samples per sex per group. Previously 18 samples per sex per group were taken sampling satellite animals (an additional 18 rats).

Objective

To provide an optimal sparse sampling scheme

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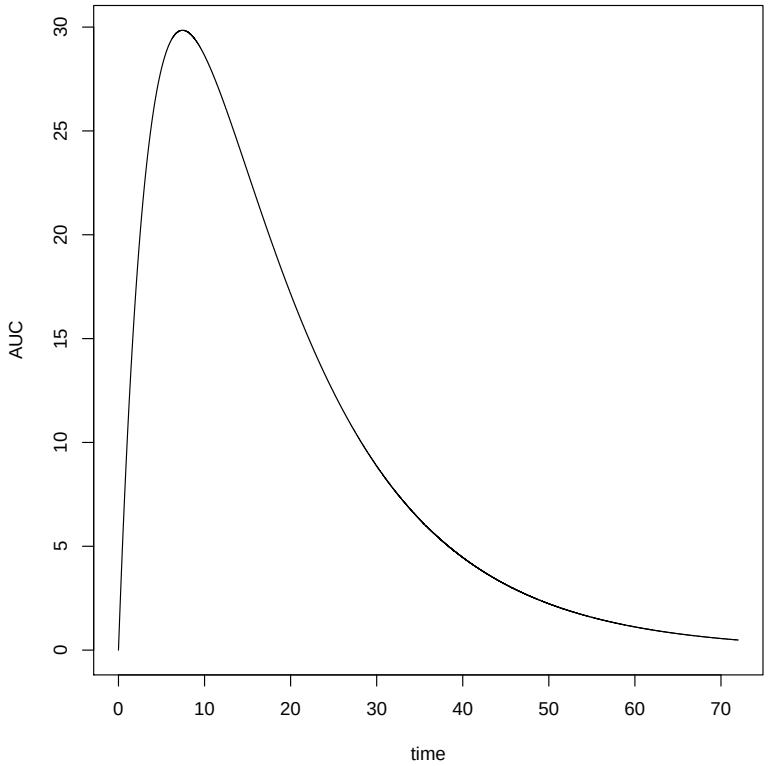
Requirements:

- Non-compartmental - We must use non-compartmental methods as much as possible
- Robust - We must consider the performance of the scheme across a range of scenarios

Theoretical AUC

The theoretical AUC from 0 to the last observed time point for treatment k is

$$AUC_k = \int_0^{t_{last}} \mu_{tk} dt.$$

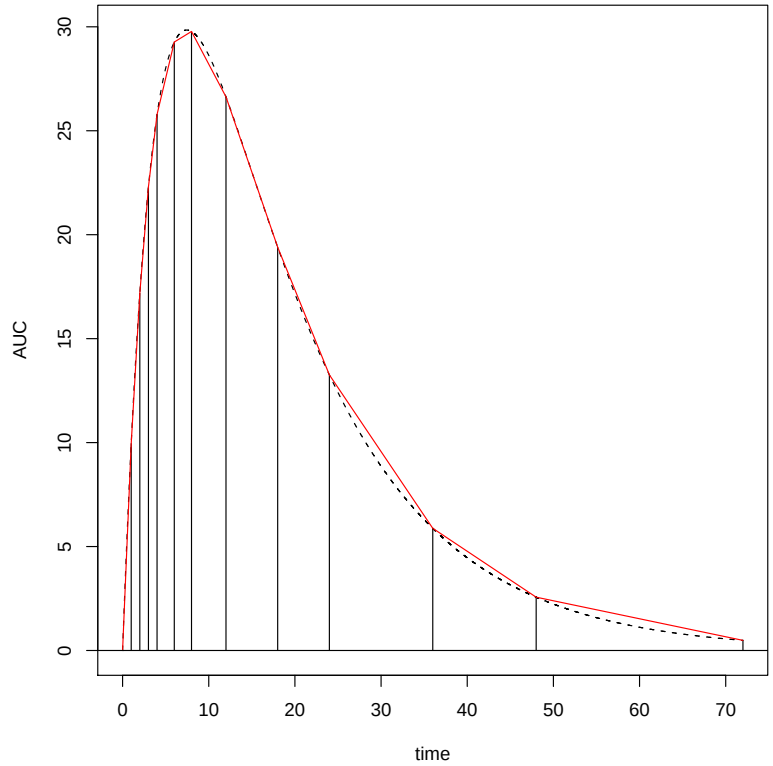


Using the linear trapezoidal rule

$$AUC_k = \sum_{j=1}^{J} w_j \mu_{t_j k}$$

The weights, w_j, equal

$$\begin{aligned} w_1 &= \frac{1}{2}(t_2 - t_1) \\ w_j &= \frac{1}{2}(t_{j+1} - t_{j-1}) \\ w_J &= \frac{1}{2}(t_J - t_{J-1}) \end{aligned}$$



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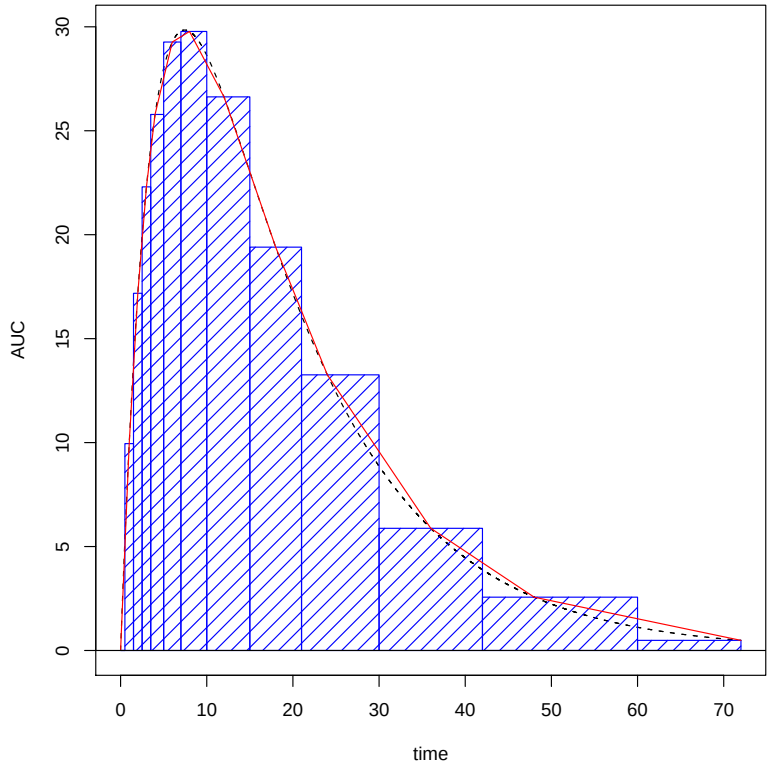

Example:

Bazzoli et al. (2010)

Our assumed model is a one-compartmental first order kinetics with oral administration:

$$Y_{jn} = \frac{k_{an} F D}{V_n (k_{an} - k_{en})} (e^{-k_{en} t_j} - e^{-k_{an} t_j}) + \epsilon_{jn},$$

(for $j = 1, \ldots, 6$ time points and $n = 1, \ldots, 10$ subjects.)

- The values of F and D are fixed
- The other three parameters, V, k_a and k_e have exponential random effects
- The ϵ_{jn} are Normally distributed with constant coefficient of variation

Two-stage procedure

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- Two stages:
    1. Choose the most appropriate time points
    2. Given chosen time points, choose the sparse sampling scheme
- The choices of time points ensure that we capture the most important parts of the PK profile

Procedure: Choosing Timepoints

1. Define a set of possible timepoints
2. Generate a large number of complete data sets from an underlying model
3. Rank the timepoints based on distance from true model
4. Repeat for 2-3 for different models
5. Apply a Minimax criterion to the ranks to find the robust optimal timepoint choice

Choosing Time Points

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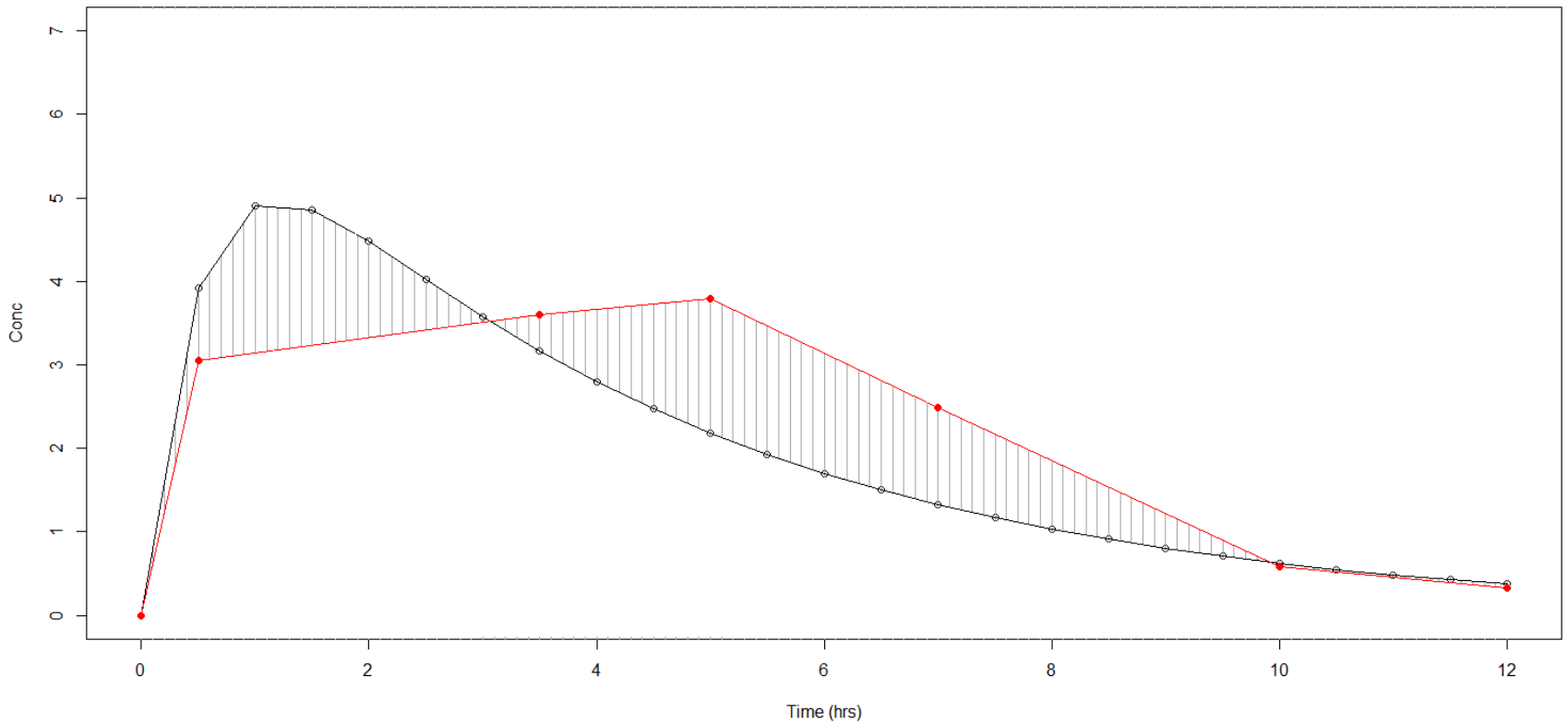

Figure: Measuring the difference between the population curve and the simulated data at chosen time points.

Choosing Timepoints

- Distance $d_{g,i}$ at grid point g for simulated dataset i
- For a given choice of time points $\{t_j\}$

$$\Psi(\{t_j\}) = \frac{1}{M} \sum_{i=1}^{M} \sum_{g=1}^{G} |d_{g,i}|$$

- The best time point choice minimizes Ψ

Choosing Timepoints

- In order to ensure that we have enough sampling points around the predicted t_{max}, we split the sampling grid into zones, and place restrictions on these zones.
- For example:
  - **Zone 1** : Choose 1 from {0.5}
  - **Zone 2** : Choose 3 from {1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0}
  - **Zone 3** : Choose 1 from {4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5}
  - **Zone 4** : Choose 1 from {12.0}

Choosing Time Points

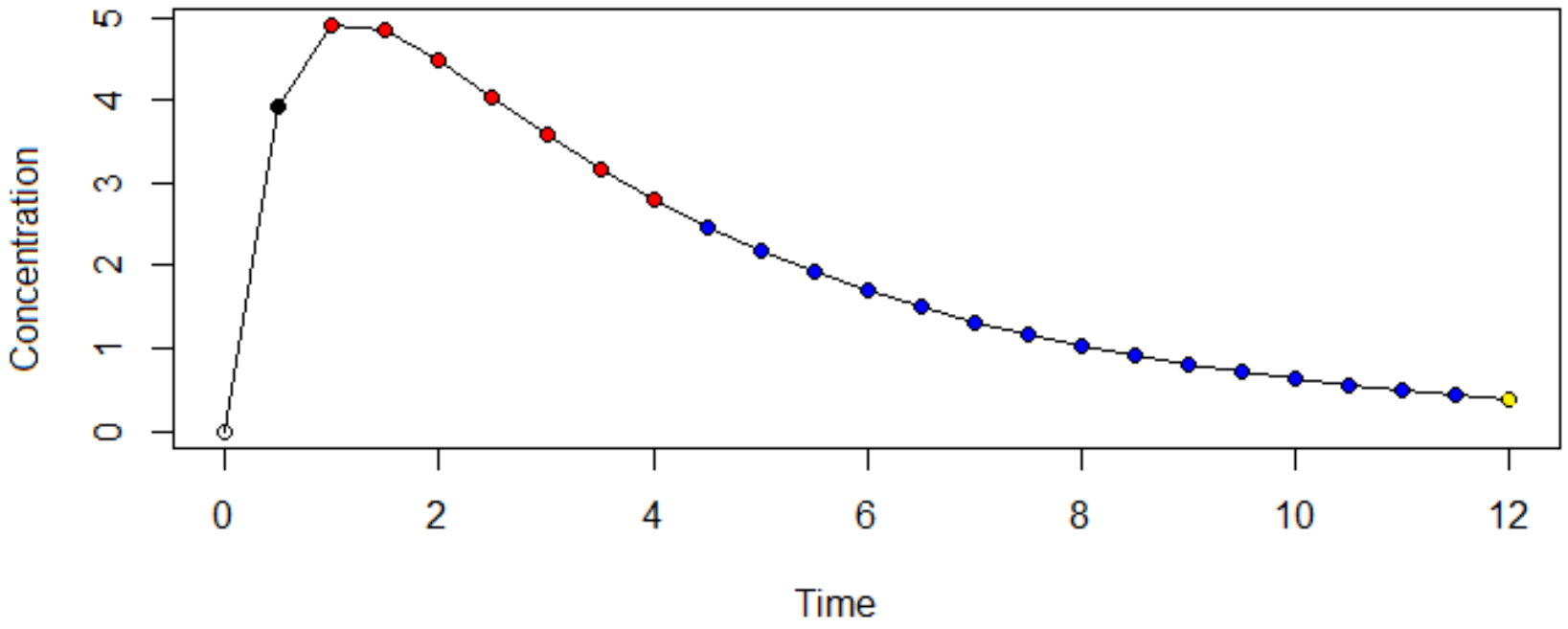

Figure: Zones

Minimax Criteria

- Given P different scenarios
- Let R be defined as $R(\{t_j\}_v, p) = R_{p,v}$, the rank of $\{t_j\}_v$ for the pth scenario
- Then our robust choice of optimal design is the solution to:

$$\arg\min_{\{t_j\}_v} \max_{p} R(\{t_j\}_v, p).$$

Choosing Timepoints

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Table: Time Point Choices

	Top 5 Time Choices				
	225	**260**	**235**	**224**	**234**
8 Scenarios					
1 (LLL)	21	24	13	16	18
2 (LLH)	13	12	22	20	27
3 (LHL)	39	35	22	28	21
4 (HLL)	32	36	45	42	52
5 (LHH)	40*	30	29	36	41
6 (HHL)	26	31	40	38	42
7 (HLH)	34	40*	50*	51*	55*
8 (HHH)	27	33	40	41	44
Max	40	40	50	51	55
Total	232	241	261	272	300

Choosing Timepoints

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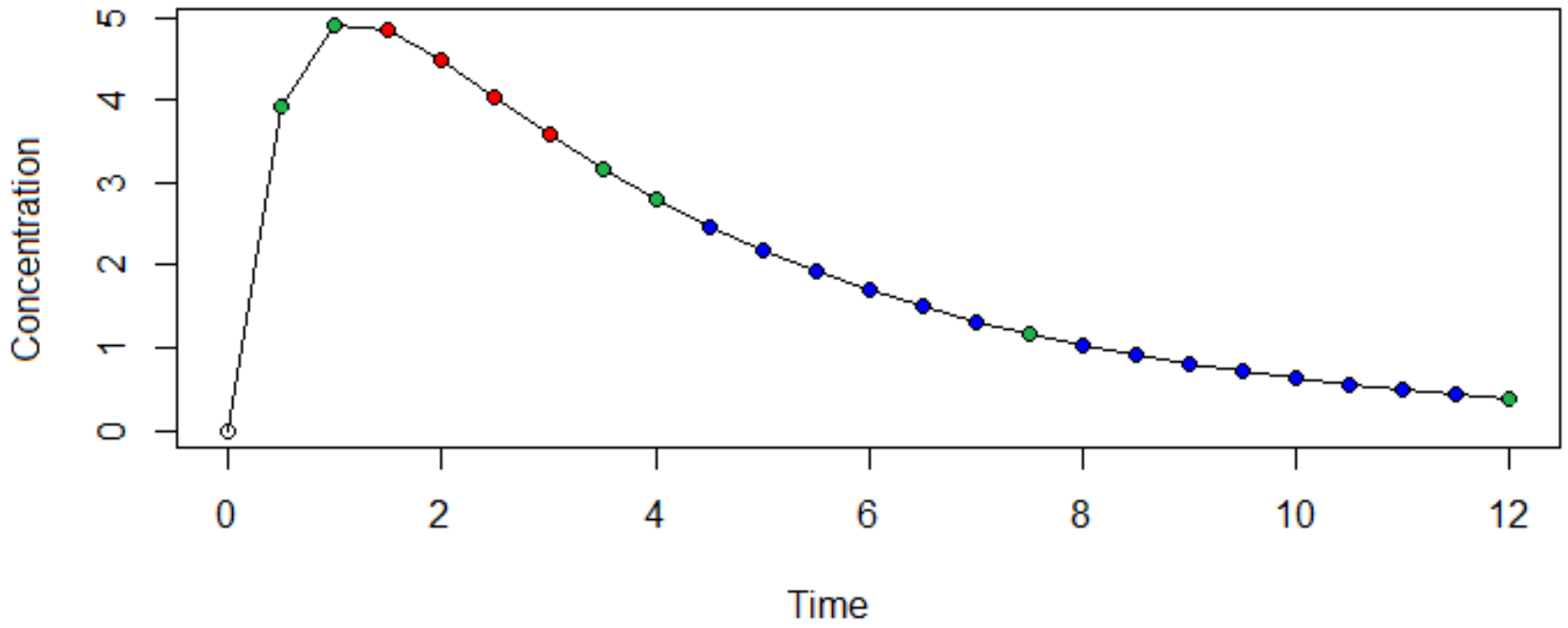

Figure: Zones

Procedure: Choosing Sampling Scheme

1. Define a set of feasible sparse schemes
2. Generate a large number of complete data sets from an underlying model
3. Rank the schemes based on chosen optimality criteria
4. Repeat 2-3 for different models
5. Apply the Minimax criteria to the ranks to find the robust optimal scheme

Feasible Schemes

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Animal number	Sampling timepoint					
	#1	#2	#3	#4	#5	#6
1	✗		✗			✗
2	✗			✗		✗
3		✗	✗			✗
4		✗	✗		✗	
5		✗			✗	✗
6		✗		✗	✗	
7		✗		✗		✗
8	✗		✗	✗		
9	✗			✗	✗	
10	✗		✗		✗	
	n=5	n=5	n=5	n=5	n=5	n=5

- 10 subjects and 6 time points.
- Each subject is sampled at 3 time points

Feasible Schemes

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Animal number	Sampling timepoint					
	#1	#2	#3	#4	#5	#6
1	✗		✗			✗
2	✗			✗		✗
3		✗	✗			✗
4		✗	✗		✗	
5		✗			✗	✗
6		✗		✗	✗	
7		✗		✗		✗
8	✗		✗	✗		
9	✗			✗	✗	
10	✗		✗		✗	
	n=5	n=5	n=5	n=5	n=5	n=5

- At each time point, 5 out of 10 subjects are sampled
- Schemes cannot be repeated

Optimility criteria

$$\Psi = \mathrm{Var}(\text{PK } \widehat{\text{parameter}})$$

Optimility criteria

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$$\Psi = \mathrm{Var}(\text{PK } \widehat{\text{parameter}})$$

or a robust version

$$\Psi = w_1 * \mathrm{Var}(\widehat{\text{AUC}}) + (1 - w_1) * \mathrm{Var}(\widehat{\text{C}_{\text{max}}}),$$

Does the criterion matter?

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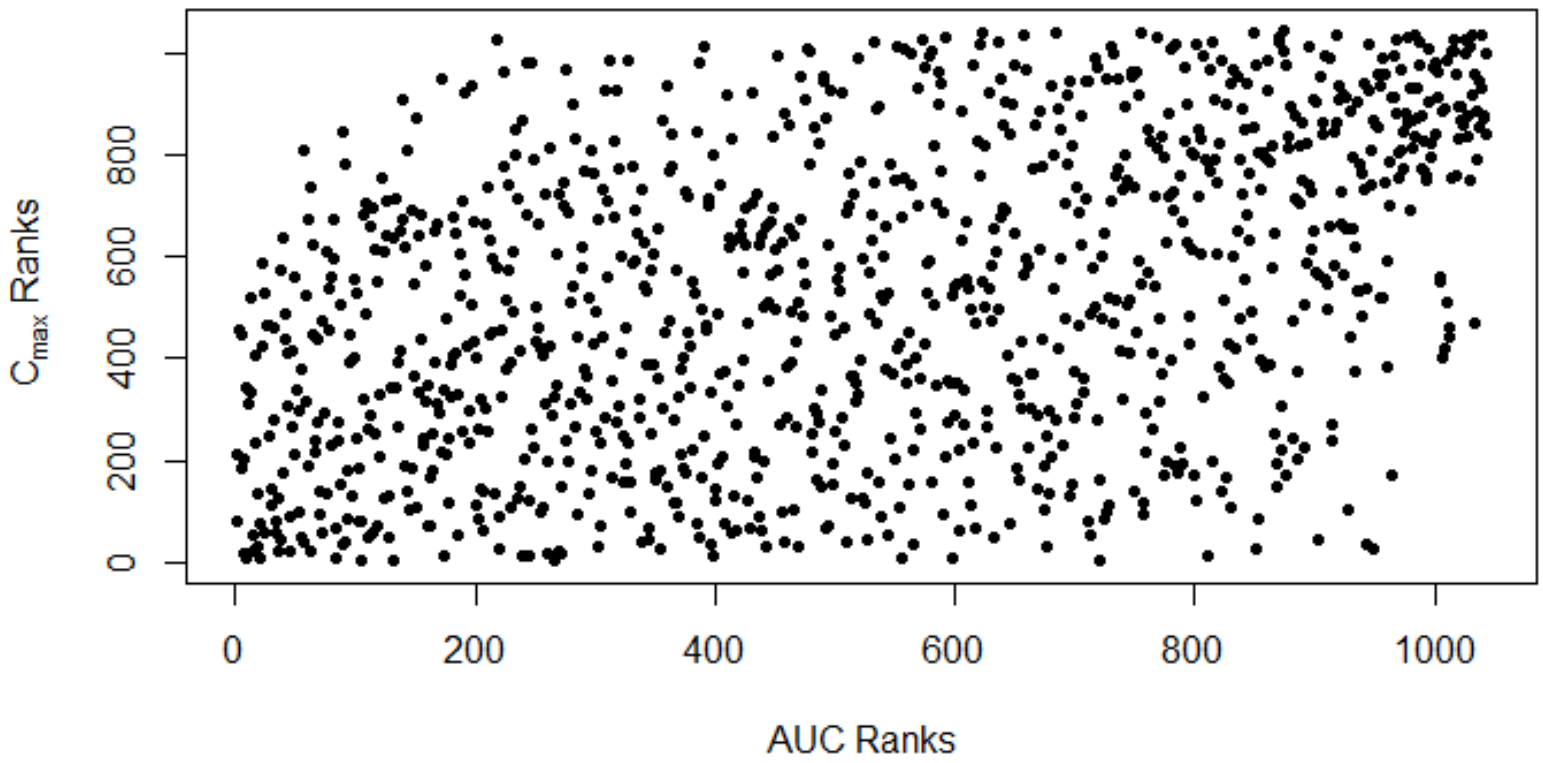

Figure: The relationship between ranks given to schemes using the variances of $\widehat{AUC}$ and $\widehat{C_{max}}$

Minimax Criteria

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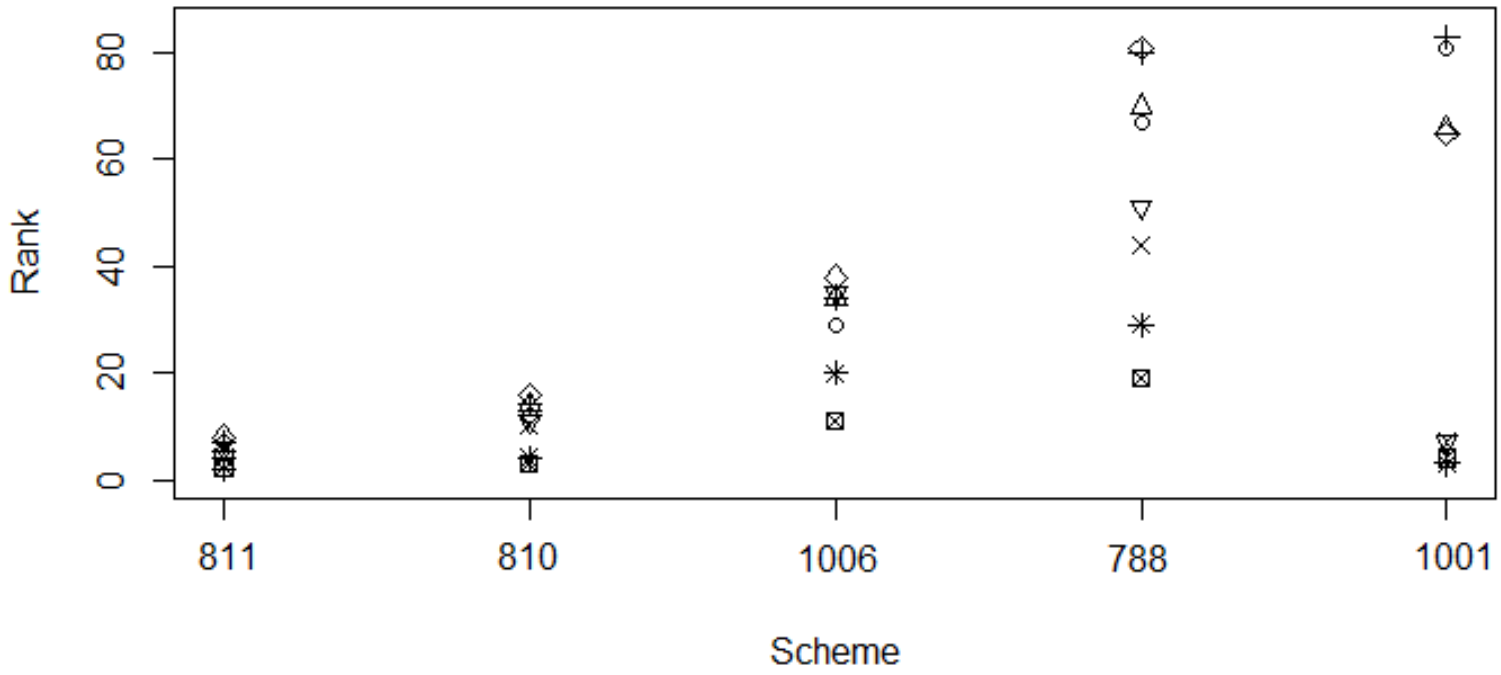

Figure: Using timepoints (0.5, 1.0, 3.5, 4.0, 7.5, 12.0). Top 5 overall schemes according to minimax criteria applied to equally weighted scaled sum. Ranks for each of the eight scenarios are plotted.

Chosen Scheme

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Table: Optimal Sparse Sampling Scheme. ✗indicates that the individual subject scheme is shared by the scheme from Chapman et al. (2014) and ○ indicates that it is not.

Animal number	Sampling timepoint					
	#1	#2	#3	#4	#5	#6
1		○	○	○		
2	○	○			○	
3	○				○	○
4		✗	✗			✗
5			○	○		○
6		✗			✗	✗
7		✗		✗		✗
8	✗		✗	✗		
9	✗			✗	✗	
10	✗		✗		✗	
	n=5	n=5	n=5	n=5	n=5	n=5

Why bother?

- Variability in estimates reduced by up to 15%
  (and about 3-5% against the Chapman et al (2014) design)
- Optimizing time points yields a further reduction of about 2.5%
- Optimal designs for NCA are frequently very different from optimal designs for NLME models

Discussion

- Developed algorithms to find optimal designs for PK analysis using non-compartmental methods
- Both algorithms can be shown to converge to true optimal design
- Can be computationally expensive
- R package `Pkdesign` to be published soon

References

Bazzoli C, Retout S, and Mentré F. (2010). Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. *Computer Methods and Programs in Biomedicine*, 98(1):55-65.

Chapman K, Chivers S, Gliddon D, Mitchell D, Robinson S, Sangster T, Sparrow S, Spooner N, and Wilson A. (2014). Overcoming the barriers to the uptake of nonclinical microsampling in regulatory safety studies. *Drug discovery today*, 19(5):528-532.