

Using the M3 Method in Exploratory Plots and in NCA

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Objectives

- The M3 method (censored likelihood method) is routinely used in population modeling.
- The applicability of the M3 method is not limited to population modeling but can easily be extended to exploratory data analysis and NCA.
- We implemented the M3 method in an R function to explore benefits and limitations of the M3 method for data exploratory analysis and NCA.
- To characterize benefits and limitations of the M3 method, we compared the implementation with two competing approaches:
 - Removal of BLOQ values (M1)
 - Imputation of BLOQ values to LLOQ/2

Methods

Mock-up data was generated by trial simulation:

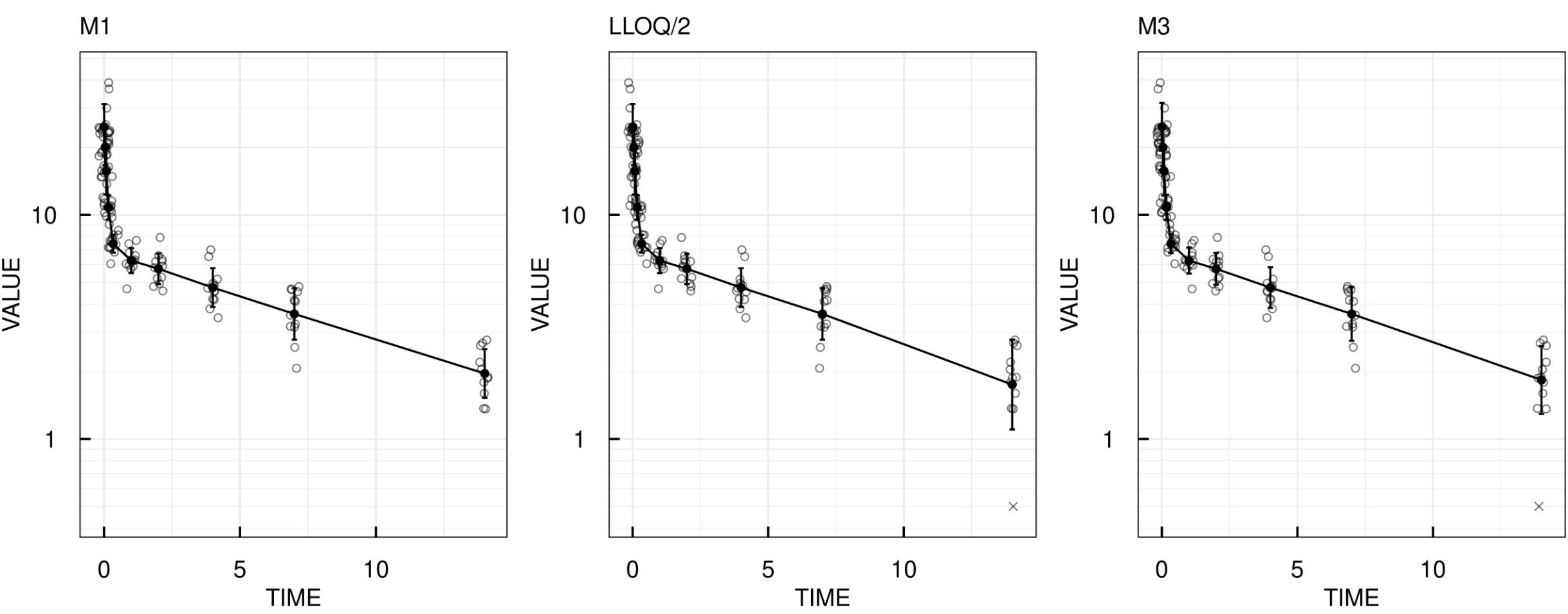
- Trial simulation (**N = 1000**) was performed
- Cohorts of **N = 12** subjects with inter-individual variability and residual variability were simulated
- Different elimination scenarios were simulated.
- For each scenario, the clearance parameter was set such that the typical prediction at the last observed time point was
 - above the LLOQ
 - at the LLOQ, or
 - below the LLOQ

Trials were analyzed by 3 BLOQ handling methods:

- Geo-mean concentration-time profiles were determined for simulated cohorts
- BLOQ values were accounted for by three methods:
 - Removal of BLOQ value (M1)
 - Imputation of BLOQ values to LLOQ/2
 - Estimation using the M3 method
- Accuracy was evaluated by the geometric mean ratio (GMR) with the uncensored sample
- Geometric mean and CV% of the GMR over 1000 trials were evaluated to characterize the performance of each BLOQ handling method

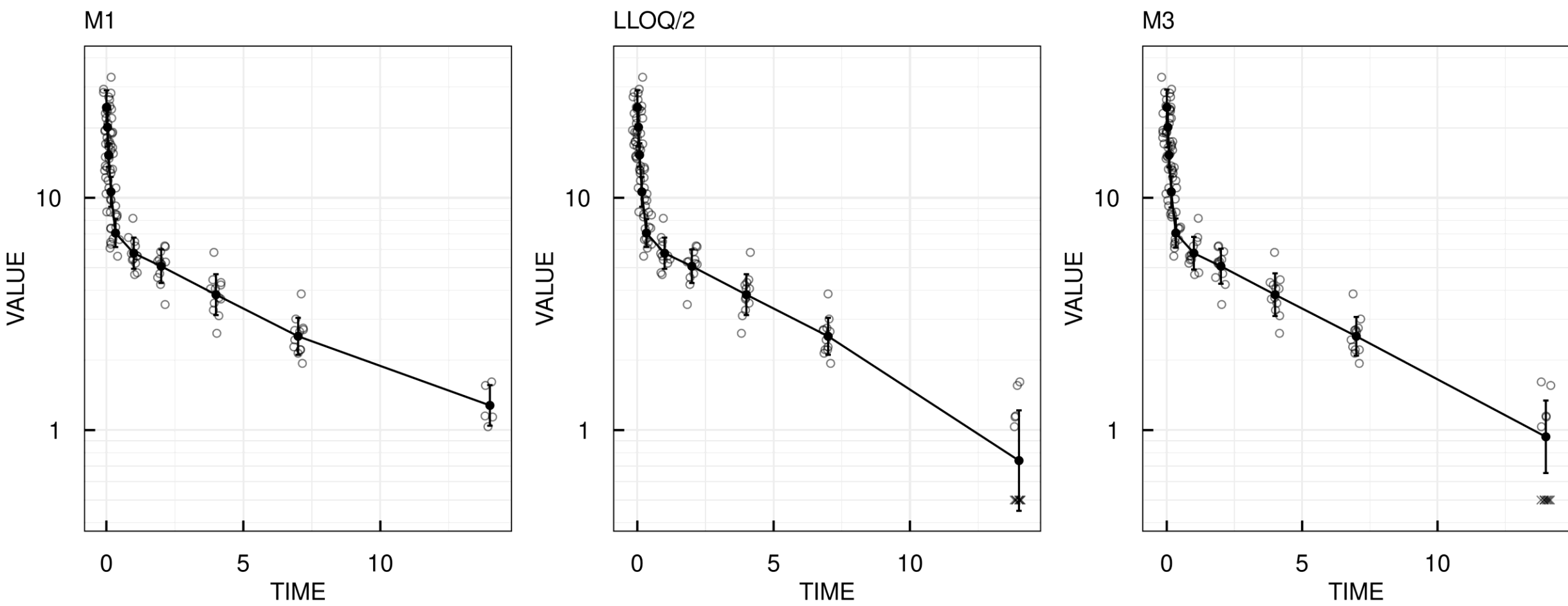
Results

Low clearance scenario: less than 5% BLOQ samples at t_{last}



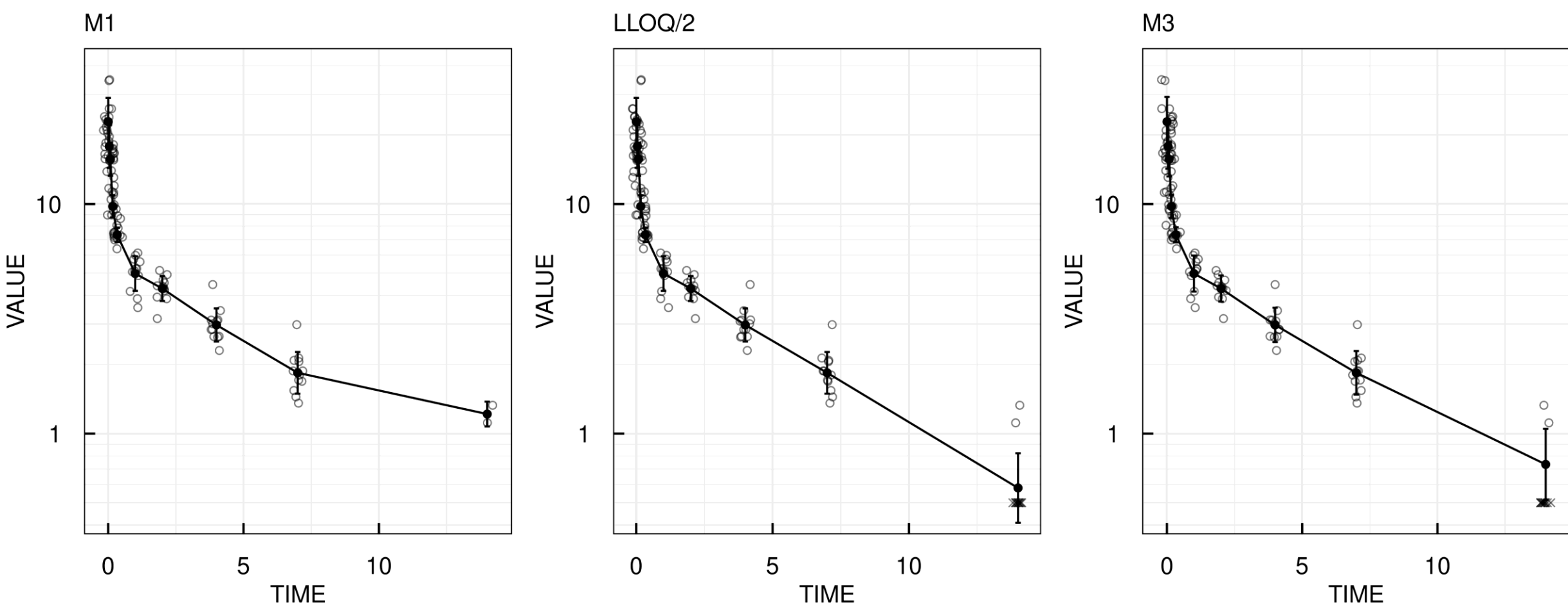
- At low %BLOQ, only few data points were removed or imputed by the M1 and LLOQ/2 methods
- Without censored data, the M3 method returned exactly the geo mean
- **All three methods performed equally**

Medium clearance scenario: around 50% BLOQ samples at t_{last}



- Removal of 50% BLOQ samples led to overestimated C_{last}
- Imputation by LLOQ/2 led to underestimation of C_{last}
- **The M3 method accurately inferred C_{last}**

High clearance scenario: more than 90% BLOQ samples at t_{last}

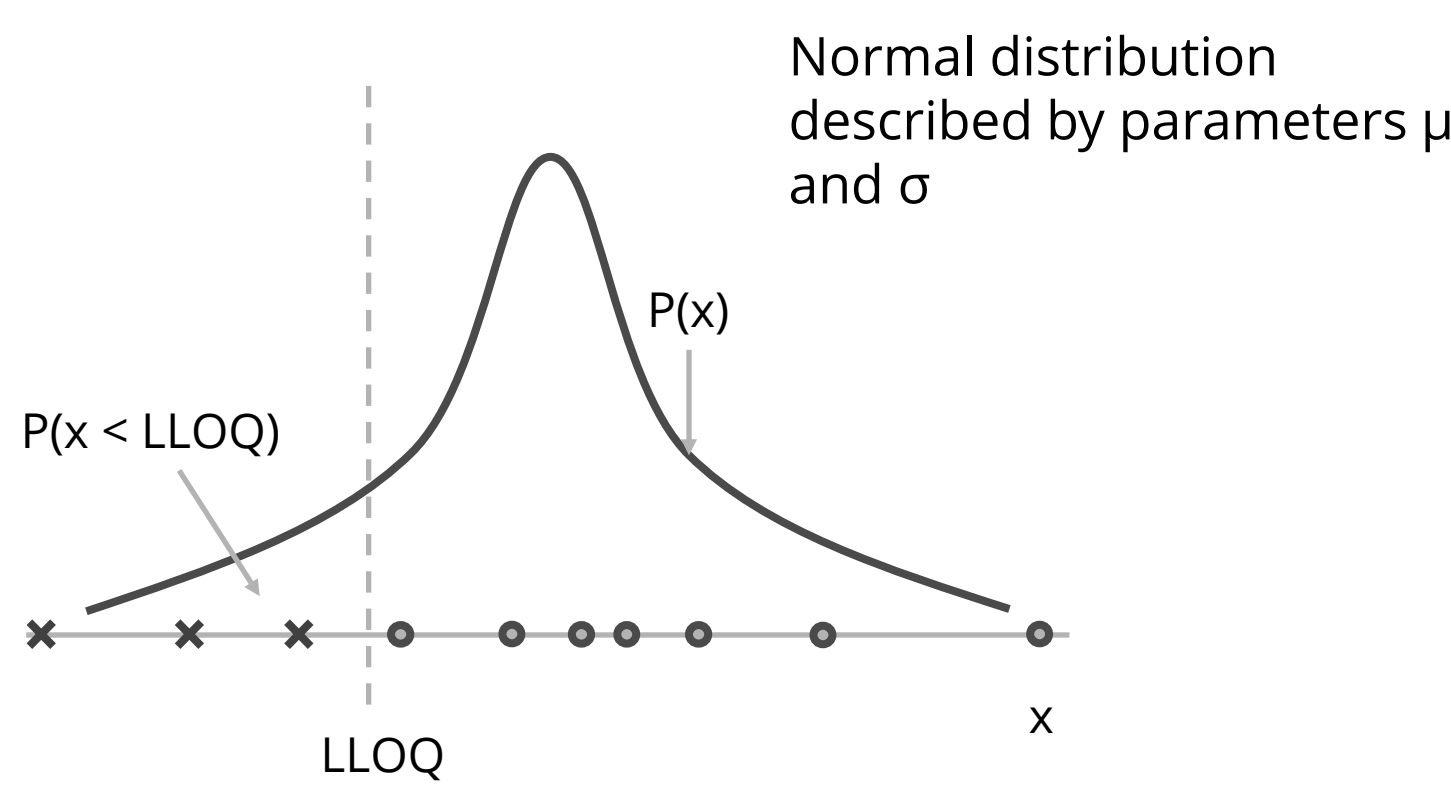


- **The M1 method falsely suggested a third compartment**
- The LLOQ/2 method dealt well with the specific situation
- The M3 method struggled due to the low number of informative data points

Setting	Method	Geomean	Geo CV%	%NA	%BLOQ
5*LLOQ	LLOQ/2	1	0	0	0
	M1	1	0	0	0
	M3	1	0.000889	0	0
2*LLOQ	LLOQ/2	0.989	2.31	0	1.96
	M1	1.02	3.48	0	1.96
	M3	1	0.659	0	1.96
1.5*LLOQ	LLOQ/2	0.935	5.12	0	14
	M1	1.1	7.33	0	14
	M3	1	2.36	0	14
LLOQ	LLOQ/2	0.851	7.8	0	49.4
	M1	1.39	13.2	0	49.4
	M3	1.02	11.6	0	49.4
LLOQ/1.5	LLOQ/2	0.923	11	0	81.9
	M1	1.91	16.9	8.7	81.9
	M3	1.12	29.3	8.7	81.9
LLOQ/2	LLOQ/2	1.12	13.6	0	93
	M1	2.37	18.1	41.9	93
	M3	1.36	35.6	41.9	93
LLOQ/4	LLOQ/2	2.09	19.5	0	99.4
	M1	4.19	22.2	92.9	99.4
	M3	2.63	37.1	92.9	99.4

- Evaluation over 1000 trials confirmed that the M3 method performed accurately (geomean of the GMR ≈ 1) for %BLOQ up to 80%.
- The M1 method drastically overestimated concentrations at higher %BLOQ potentially leading to misinterpretation of the data.
- The LLOQ/2 method underestimated or overestimated concentrations depending on the %BLOQ.

The M3 Method Mathematically



- Single obs. likelihood of the i th datapoint:
 - $< \text{LLOQ}$ obs: $L_i(\mu, \sigma) = P(x_i < \text{LLOQ} | \mu, \sigma)$
 - $\geq \text{LLOQ}$ obs: $L_i(\mu, \sigma) = P(x_i | \mu, \sigma)$
- Log-likelihood of the full sample sums up all the single observation log likelihoods:
 - $LL(\mu, \sigma) = \sum_i \log L_i(\mu, \sigma)$

The M3 Method in R

```
#' Estimate mu and sigma of the normal distribution from a left-censored sample
#
# @param x Sample
# @param LLOQ LLOQ Value
# @return List with mean ('mean') and standard deviation ('sd').

norm_M3 <- function(x, LLOQ = -Inf) {

  # Indicator for BLOQ values and number of samples
  is_BLOQ <- x <= LLOQ
  N <- length(x)

  # Set all BLOQ values to LLOQ
  x[is_BLOQ] <- LLOQ[is_BLOQ]

  # Definition of the objective function to be optimized
  obj <- function(pars) {
    # pars = (mu, sigma)
    mu <- pars[1]
    sigma <- pars[2]
    # Log-Likelihood for above LLOQ samples
    probs_ALOQ <- dnorm(x[!is_BLOQ], mean = mu, sd = sigma, log = TRUE)
    # Log-Likelihood of the BLOQ samples
    probs_BLOQ <- pnorm(x[is_BLOQ], mean = mu, sd = sigma, log = TRUE)
    # Return -2 LL
    -2*sum(c(probs_BLOQ, probs_ALOQ))
  }

  # Estimate mu and sigma
  fit <- optim(par = c(mean(x), sd(x)), fn = obj, method = "Nelder-Mead")
  mymean <- fit$par[1]
  mysd <- N/(N-1) * fit$par[2]

  # Return result
  list(mean = mymean, sd = mysd)
}
```

Conclusions

- The M3 method was simple to implement and applicable for data exploratory analysis and NCA
- The M3 method allowed for better characterization of C_{last} and the terminal slope, potentially influencing model development decisions
- The M1 method should be avoided because it bears the risk of data misinterpretation
- The M3 method became unreliable when the number of informative data points dropped below 90%

References:

- [1] Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. Journal of pharmacokinetics and pharmacodynamics. 2008 Aug;35:401-21.
- [2] Beal SL. Ways to fit a PK model with some data below the quantification limit. Journal of pharmacokinetics and pharmacodynamics. 2001 Oct;28:481-504.
- [3] Monolix 2023R1, Lixoft SAS, a Simulations Plus company

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