



nlmixr² supports **FOCEI generalized likelihood** with accurate distributions and **user defined likelihoods**

nlmixr² FOCEI generalized likelihood **gives similar estimates** to the normal FOCEI

FOCE generalized log-likelihood using nlmixr²

Objectives:

Create a generalized log-likelihood that allows specification of common probability distributions or user-defined likelihood distributions in nlmixr²'s first-order conditional estimation method with interaction (FOCEI)^[1].

Methods:

For FOCEI, the likelihoods of the individual parameters were adjusted to use the numerically approximated individual Hessian instead of using the standard normal approximation as applied in NONMEM^[2]/nlmixr². Since this uses numerical approximation, the step size is optimized to give the most accurate Hessian. First the gradients of the likelihood are calculated using a Stan-based automatic differentiation^[3] and forward-sensitivities of the ODE system^[4]. The Hessian is then calculated by numerical differentiation. The numerical differentiation step size for the Hessian is tuned with the harmonic mean of every observations' gradient^[5]. This step size then gives a more accurate Hessian approximation.

To make sure that the methodology is correct we validated using the generalized likelihood method to make sure the results were similar in the normal case. While we expected longer run times because of a higher computation burden, if the methodology is reasonable with the normal likelihood, we expect it to be reasonable with other likelihoods. Hence, we validated the generalized likelihood method using the same models to compare nlmixr² to NONMEM and Monolix and comparing the results.

Results:

The nlmixr² generalized likelihood methods had similar parameter estimates as the normal likelihood methods. The generalized likelihood generally took longer and resulted in similar objective functions when comparing the two methods. Additionally, the covariance calculation for the generalized likelihood method was more likely to have an unsuccessful covariance step and more likely to give small values for standard errors. Overall, the values were still comparable for the standard errors.

With these results we can have confidence that the method will give reasonable results for non-normal likelihoods.

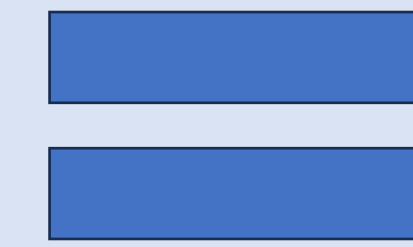
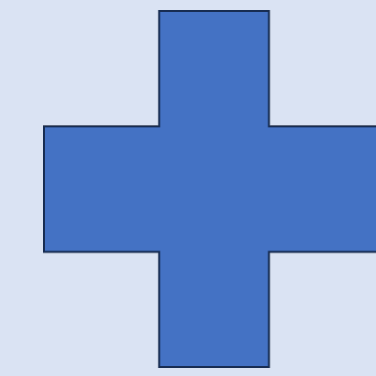
Conclusions:

The generalized likelihood, as implemented in nlmixr², uses new methods that provide reasonable estimates for the tested models, and is ready to be used with other likelihood-based problems.

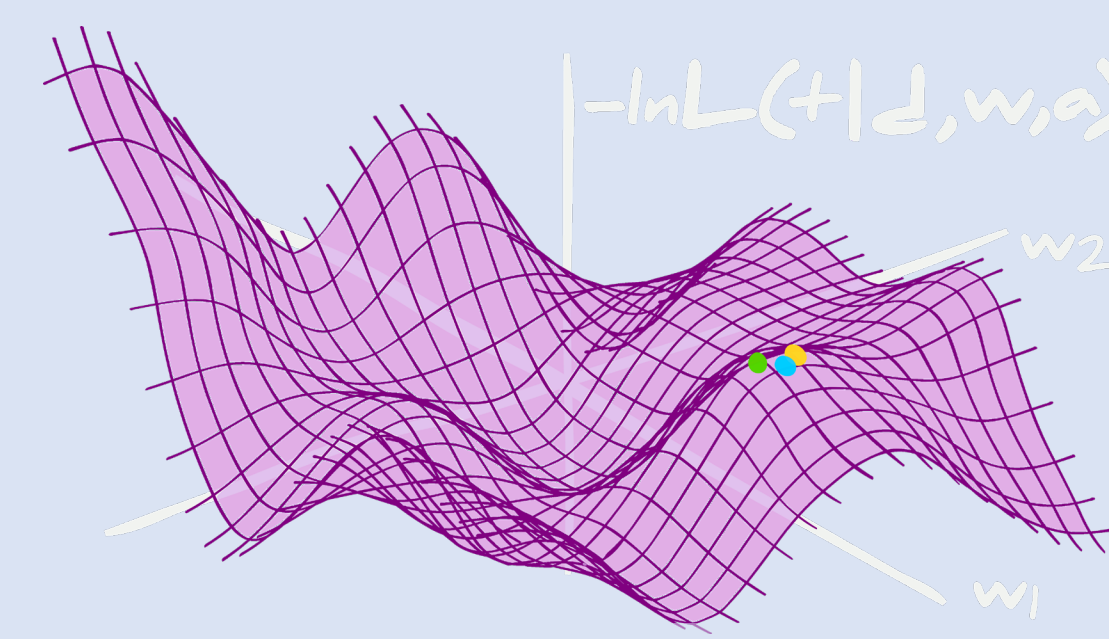
Citations:

- [1] <https://cran.r-project.org/package=nlmixr2>
- [2] Beal SL et al. 1989-2011. NONMEM Users Guides. Icon Development Solutions, Ellicott City, Maryland, USA.
- [3] <https://arxiv.org/abs/1509.07164>
- [4] <https://doi.org/10.1007/s10928-015-9409-1>
- [5] <https://arxiv.org/pdf/2110.06380.pdf>

nlmixr² needs to model Non-Normal distributions



Stan gives exact likelihoods for common distributions with gradients^[3] using Automatic Diff. (AD); Hessians Generated Numerically from gradients



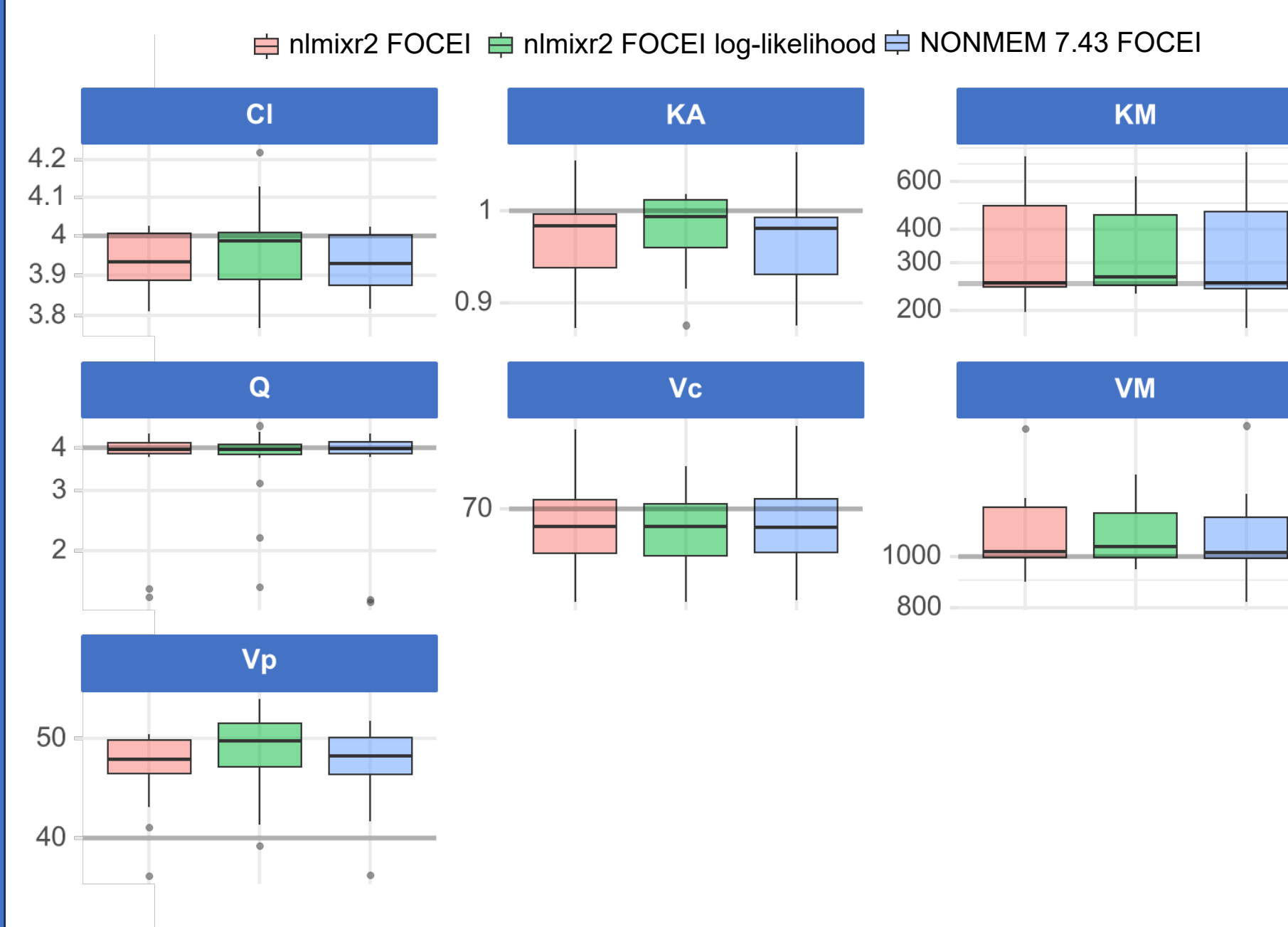
Generalized Likelihood

<https://www.aquila-consortium.org/method/machine%20learning/nn.html>

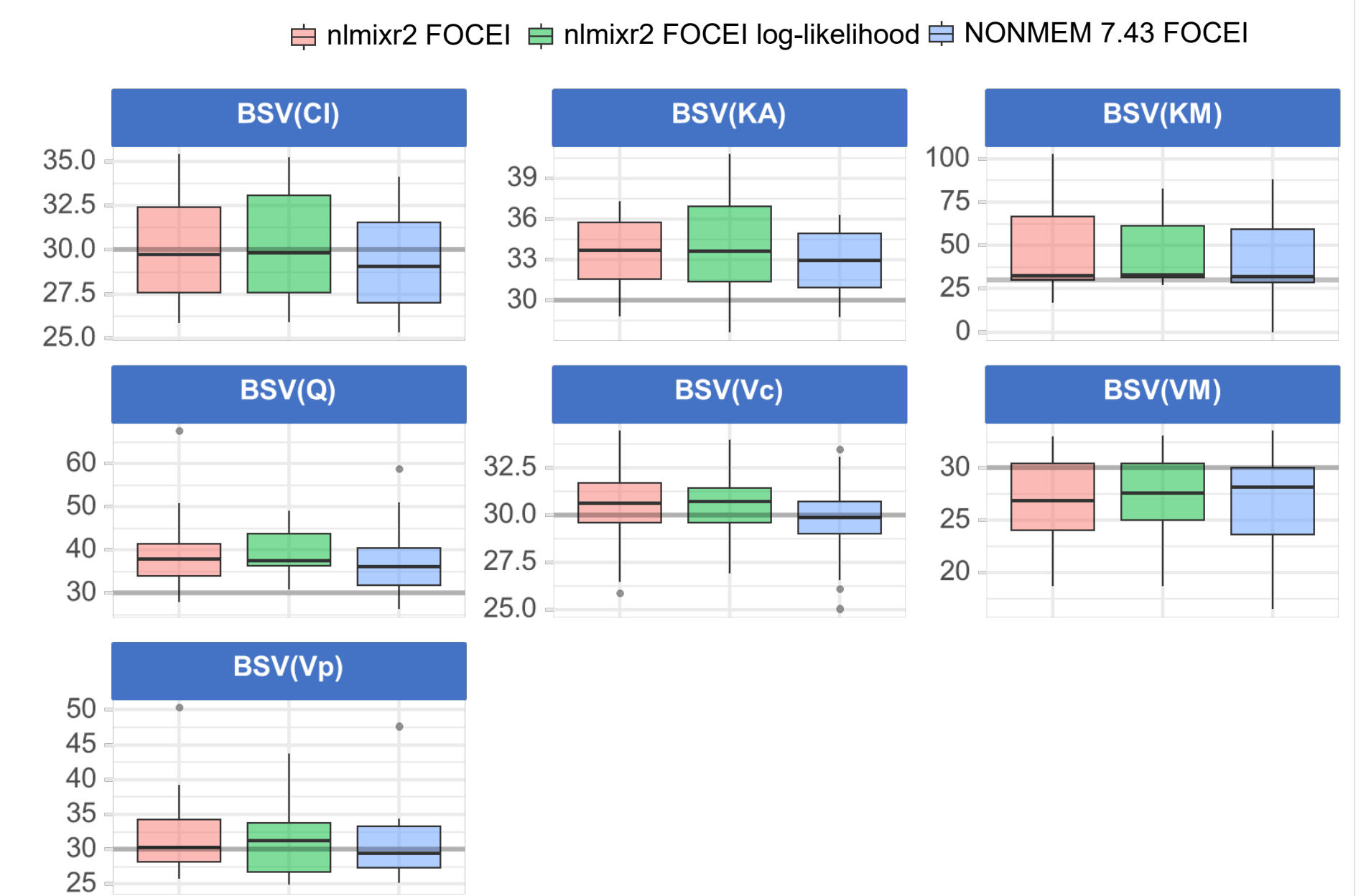


nlmixr² Log Likelihood Method resulting in Comparable Parameter Estimates & Standard Errors compared to NONMEM

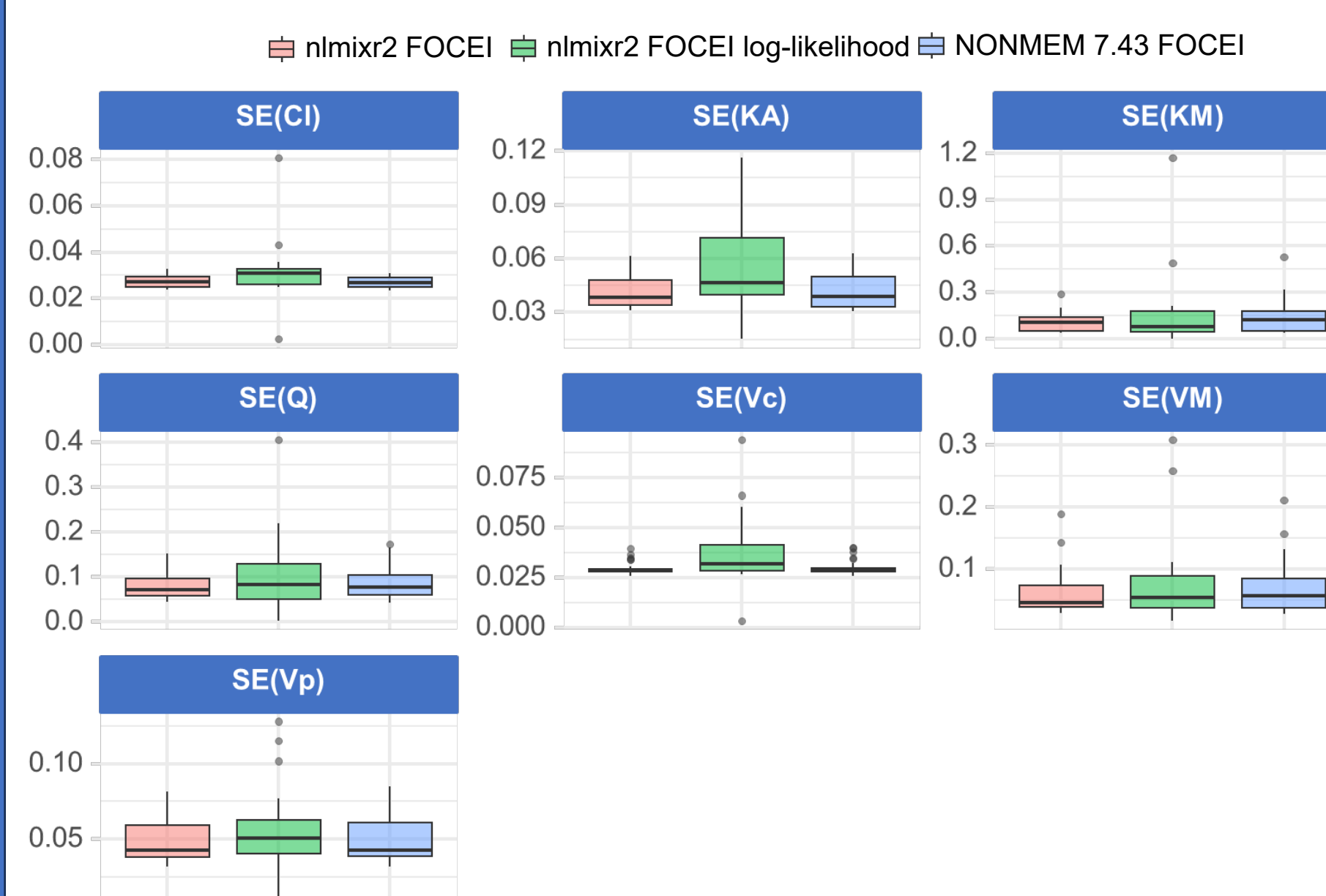
Similar Population Estimates



Similar Between Subject Variabilities



Similar Standard Errors



Validation dataset used:

- Rich sampled profiles for 10, 30, 60 and 120 mg dosing
 - 30 subjects each as single dose (over 72h),
 - multiple dose (4 daily doses),
 - single and multiple dose combined,
 - steady state dosing,
- Models: 1-and 2-compartment
 - with and without 1st order absorption,
 - with either linear or Michaelis-Menten (MM) clearance
- All between subject variabilities were set at 30% CV,
- Residual error at 20% CV
- Overlapping PK parameters were the same for all models.

Applying this is easy!
Bring your laptop and follow the QR Code



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