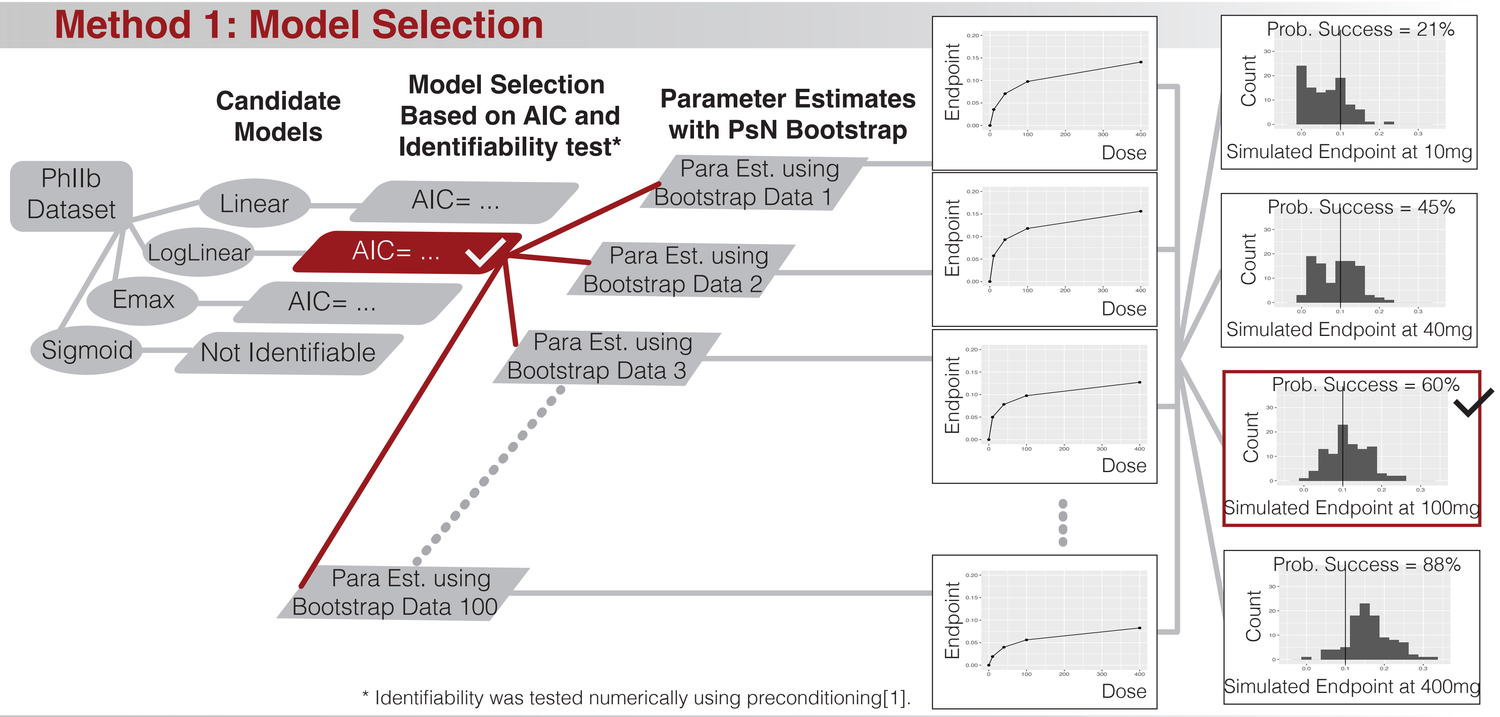
Model Averaging and Selection methods

for model structure and parameter uncertainty quantification

With nonlinear mixed effect models and various parameter estimation and uncertainty quantification techniques we are able to quantify the probability of achieving a target effect accurately. On the other hand, this modelling approach is often subject to the criticism of the strong assumptions on the model structure. Hence the analysis using model averaging and model selection methods to weaken the assumption on the model structure by considering multiple possible model candidates is desirable. In this poster we propose four possible ways to combine these uncertainties and compare their performance using simulation studies mimicking PhIIb clinical trial.

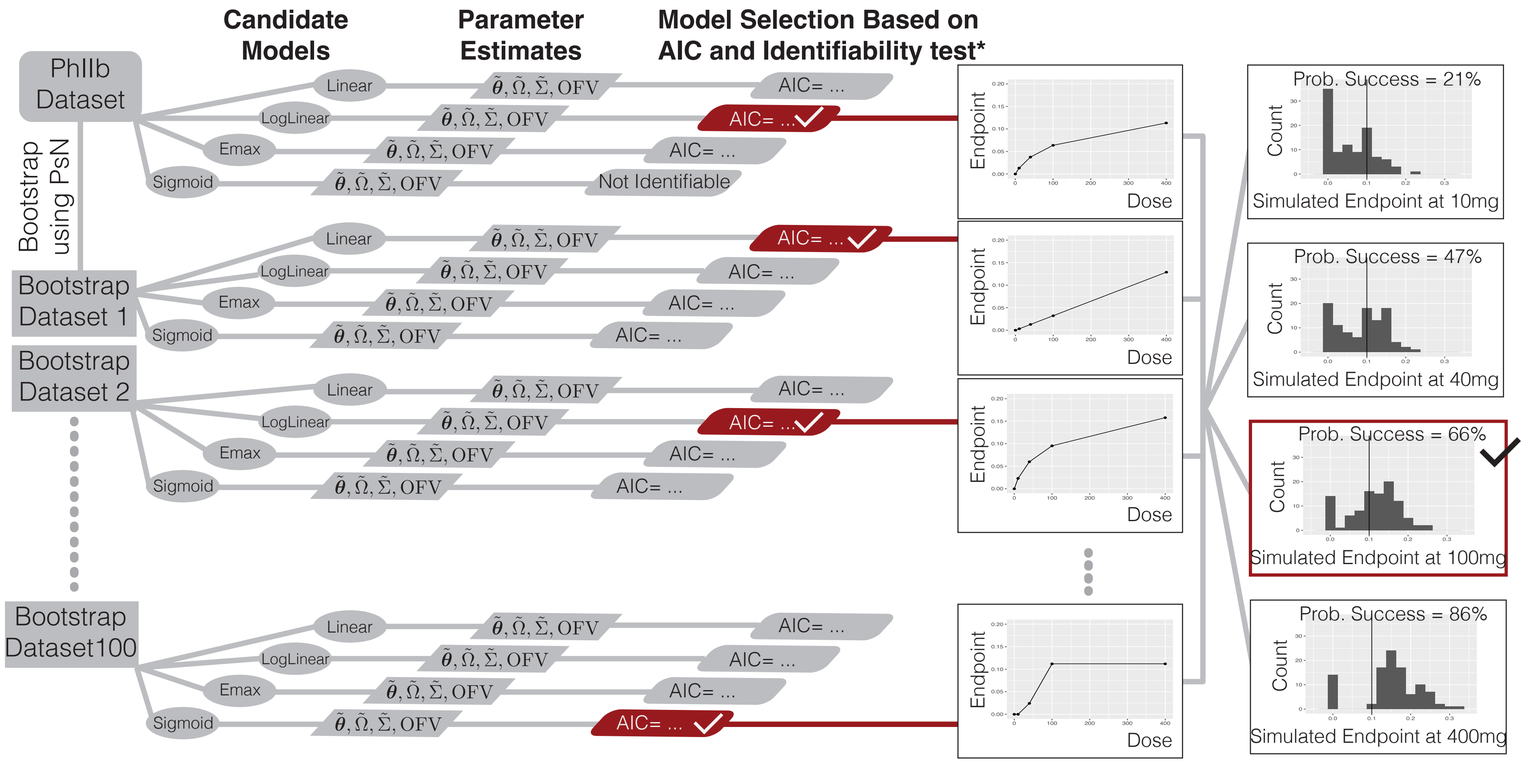
Model Averaging and Selection Methods

Method 1: Model Selection



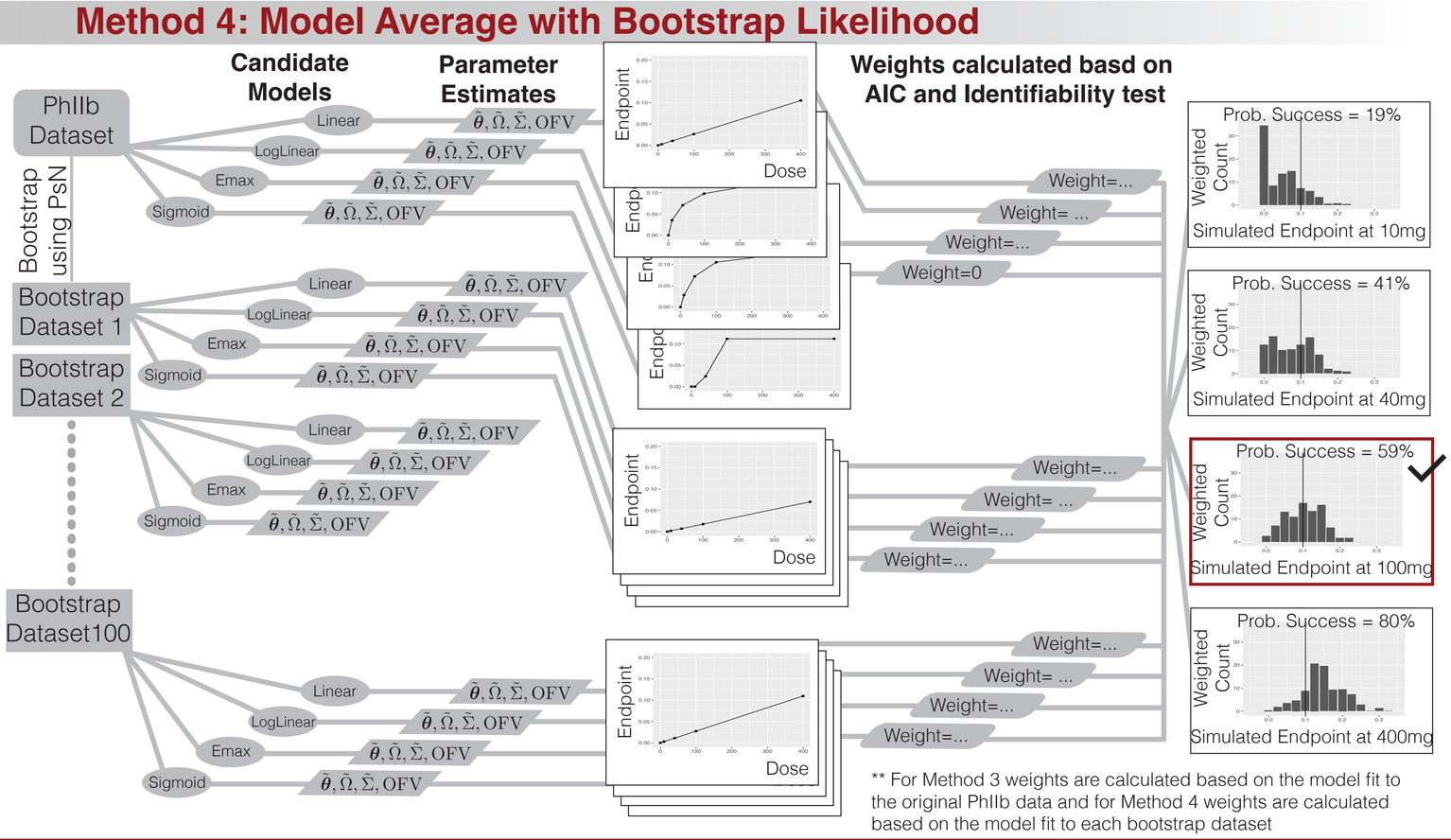
* Identifiability was tested numerically using preconditioning[1].

Method 2: Model Selection with Bootstrap Likelihood



Method 3: Model Average

Method 4: Model Average with Bootstrap Likelihood



** For Method 3 weights are calculated based on the model fit to the original PhIIb data and for Method 4 weights are calculated based on the model fit to each bootstrap dataset

Numerical Experiments

Simulation Study Setup

To demonstrate the model averaging/selection methodologies and compare the accuracy of these methods in the prediction of the minimum effective dose, we have made simulated datasets of FEV1 mimicking PhIIb clinical trial used in [2] and set up dose selection simulation studies.

Model Structure of the Simulation Model

$$\mathrm{FEV1} = \left(\mathrm{FEV1\_Baseline} + \begin{cases} 0 & \text{if visit} = 1,2 \\ \mathrm{FEV1\_Placebo} + \mathrm{Drug\_Effect} & \text{if visit} = 3,4,5,6 \end{cases}\right) \times (1+\epsilon_1) + \epsilon_2$$

$$\mathrm{FEV1\_Placebo} = 0.17 + \eta_1$$

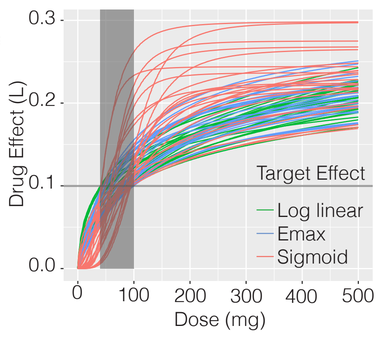
$$\mathrm{FEV1\_Baseline} = 2.5\exp(\eta_2) \times \text{Covariate model}(\text{FEV1 \% of normal}, \text{Age}, \text{Sex})$$

$$\text{Inter-individual variability:} \quad \eta_1 \sim \mathcal{N}(0, 0.3^2) \qquad \eta_2 \sim \mathcal{N}(0, 0.1^2)$$

$$\text{Residual variability:} \quad \epsilon_1 \sim \mathcal{N}(0, 0.1^2) \qquad \epsilon_2 \sim \mathcal{N}(0, 0.1^2)$$

Drug Effect Simulation

For each simulation study, we have simulated 75 datasets using the above nonlinear mixed effect model. 33% of the datasets were simulated using a Log linear, 33% Emax, and 33% Sigmoid drug effect. The dose effect relationships of Simulation Study 2 is depicted in right. Parameters of each simulated drug effect is randomly generated with the constraints given in the table below.



	Theoretical Dose that achieves the target effect	Correct Decision
Simulation Study 1	10-40mg	40mg
Simulation Study 2	40-100mg	100mg
Simulation Study 3	100-400mg	400mg
Simulation Study 4	No drug effect	Stop

Dose Selection using Study Protocol[2]

Choose the minimum dose among 10mg, 40mg, 100mg, 400mg that satisfies below criteria:
(if none satisfies both criteria, "Stop" decision is made)
Criterion 1: p-value of pairwise ANOVA of active arm and placebo arm is less than 0.05.
Criterion 2: arm-average of the placebo-baseline adjusted effect to be greater than 0.1L.

Dose Selection using Model Based Approach

Step1: Likelihood ratio test between a model without drug effect and with drug effect.
If the model fails to pass the likelihood ratio test, stop decision is made.
Step2: Choose the minimum dose with more than 50% of probability of achieving the target effect.
If the probability of achieving the target effect is less than 50% at dose=400mg stop decision is made.

Dose Selection using Model-Average/Selection Based Approach

Include no drug effect model as one of the candidate models.
Choose the minimum dose with more than 50% of probability of achieving the target effect.
If the probability of achieving the target effect is less than 50% at dose=400mg stop decision is made.

Simulation Study Results

Simulation Study 1 (correct dose choice = 40mg)

	10mg	40mg (correct)	100mg	400mg	Stop
Study Protocol	1	16	19	18	21
Correct Model	12	41	14	7	1
Method 1	16	39	11	8	1
Method 2	15	40	11	8	1
Method 3	14	34	15	10	2
Method 4	15	33	17	8	2

Simulation Study 2 (correct dose choice = 100mg)

	10mg	40mg	100mg (correct)	400mg	Stop
Study Protocol	0	4	18	25	28
Correct Model	2	14	33	20	6
Method 1	3	15	18	35	4
Method 2	3	14	21	35	2
Method 3	2	16	16	35	6
Method 4	2	16	20	33	4

Simulation Study 3 (correct dose choice = 400mg)

	10mg	40mg	100mg	400mg (correct)	Stop
Study Protocol	0	4	9	25	37
Correct Model	1	7	12	28	27
Method 1	2	7	6	45	15
Method 2	1	7	7	50	10
Method 3	1	5	7	45	17
Method 4	1	6	8	48	12

Simulation Study 4 (no drug effect, correct choice = Stop)

	10mg	40mg	100mg	400mg	Stop (correct)
Study Protocol	0	0	0	1	74
Method 1	2	0	0	0	73
Method 2	1	0	0	0	74
Method 3	1	0	0	0	74
Method 4	1	0	0	0	74

Simulation Study 1 (correct dose choice = 40mg) with decision made with >80% confidence

	10mg	40mg (correct)	100mg	400mg	Stop
Study Protocol	1	16	19	18	21
Correct Model	4	24	22	16	9
Method 1	5	24	24	16	6
Method 2	3	24	16	26	6
Method 3	3	25	12	23	12
Method 4	3	23	14	23	12

Simulation Study 4 (no drug effect, correct choice = Stop) without Identifiability Test

	10mg	40mg	100mg	400mg	Stop (correct)
Study Protocol	0	0	0	1	74
Method 1	1	1	0	0	73
Method 2	1	1	0	2	71
Method 3	1	0	0	0	74
Method 4	1	1	0	2	71

[1] Yasunori Aoki, Rikard Nordgren, and Andrew C. Hooker. "Preconditioning of Nonlinear Mixed Effects Models for Stabilisation of Variance-Covariance Matrix Computations." The AAPS journal (2016): 1-14.
[2] Yasunori Aoki, Bengt Hamrén, Daniel Röshammar, and Andrew C. Hooker, "Averaged Model Based Decision Making for Dose Selection Studies", PAGE 23 (2014) Abstr 3121 [www.page-meeting.org/?abstract=3121]

Conclusion

We have proposed four ways to incooperate model structure and parameter estimation uncertainty into the model based Phase IIb dose selection. Based on our numerical experiments, we have observed that model selection using bootstrap likelihood (Method 2) has performed consistently better than other methods when predicting the minimum effective dose. These methods can be used as a way to pre-specify the possible model structures before obtaining the data so as to increase the objectivity of the model based analysis using nonlinear mixed effect models. The proposed methods are made available in an open-source GUI based software at www.bluetree.me (also available as an r-script).

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