Modeling methods for analyzing tumor dynamic data from basket trials

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Objectives

- To recommend variance-model structures (inter-basket variability (IBV), inter-individual variability (IIV)) & estimation methods for analyzing basket trial tumor dynamic (TD) data, given variety of simulated "true" data scenarios
- ONGOING WORK: To compare statistical power for identifying responsive baskets (>= 30% tumor size reduction from baseline) using model-based simulation methods vs. traditional evaluation of categorical RECIST response data

Background

- In cancer therapy basket trials, patients enrolled based on specific tumor genetic abnormalities, with baskets defined by histologic type or primary site (response or progression under treatment determined by RECIST (Response Evaluation Criteria in Solid Tumors)[1])
- Past modeling of categorical RECIST data showed that models borrowing information across baskets didn't give advantage over modeling baskets separately [2]

Methods

Tumor Dynamic Model

- An empirical tumor growth dynamic model was used to simulate AND estimate tumor sum-of-longest diameters (SLD) (Y_{ibj})[3]:

$$Y_{\text{ibj}} = BLTS_{\text{ib}} * e^{-SR_{\text{ib}} * t_{\text{ibj}}} + GR_{\text{ib}} * t_{\text{ibj}} + \epsilon_{\text{ibj}}$$

where $BLTS_{ib}$ was baseline tumor size (cm) for individual i in basket b, SR_{ib} was tumor shrinkage rate (1/week), GR_{ib} was tumor growth rate (cm/week), & t_{ibj} was time (weeks) at observation j

Simulated Data & Estimation Model Scenarios

- Five hundred studies (94 patients, across 10 baskets) were simulated across time (0-32 weeks) using various "true" data scenarios & each dataset was modeled using a particular estimation scenario (Table 1)
- Simulation and estimation scenarios included varying tumor shrinkage rate distribution structures (*SR*, unimodal vs. bimodal) and inclusion/exclusion of IBV with IIV (Fig. 1)
- Compared model results using specified model comparison criteria: AIC, percent fixed effect parameter bias, coverage probability of nominal 95% confidence intervals for fixed effect parameters, and estimated IBV:IIV

Fig.1: Illustration of distribution structures for *SR* and hierarchical random effects (IBV, IIV) under different simulation scenarios

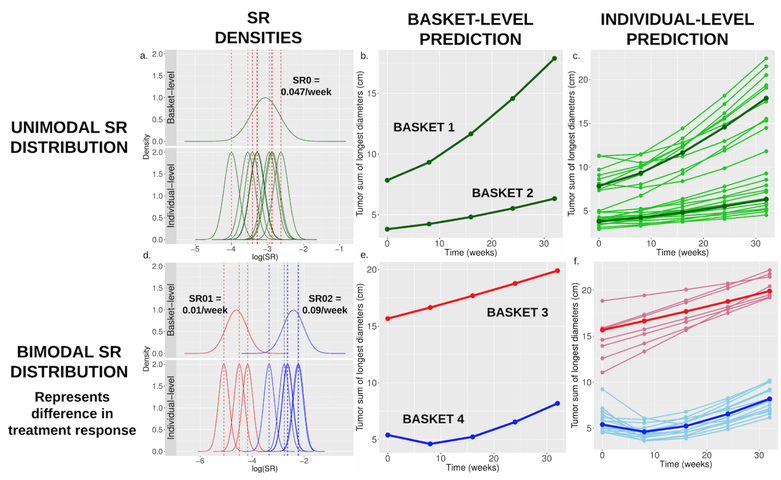


Table 1: Simulation-estimation scenarios & model recommendation results (*SR01/SR02*=means of bimodal distributions for shrinkage rate, *SR*; bimodal narrow/wide refers to distance between the two modes). Where there is a bimodal normal distribution around *SR*, baskets 1-3 were simulated from distributions centered at smaller mode (*SR01*) & remaining baskets (4-10) were simulated from distributions centered at larger mode (*SR02*). This is representative of scenarios where treatment is more effective in one histology than another.

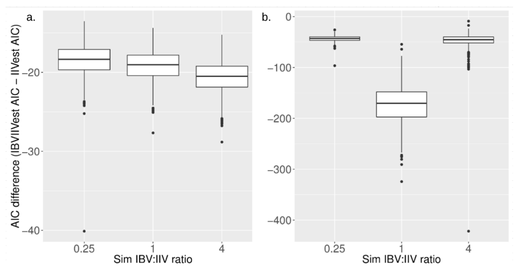
Sim. scenario name	Sim. data: *SR* distribution structure	Sim. data: variabilities included	Sim. data: IBV:IIV	Est. model name	Est. model: *SR* distribution structure	Est. model: estimation methods
uniIBVIIV	unimodal normal	IBV + IIV	1, 0.25, 4	IBVIIVest	unimodal	FOCE or SAEM
				IIVest		
nbIBVIIV	bimodal normal (narrow) (*SR01* = 0.047/week; *SR02* =0.07/week)	IBV + IIV	1, 0.25, 4	IBVIIVest	unimodal	FOCE or SAEM
				bMIXest	bimodal--$MIX model for *SR*, common variances	FOCE
wbIBVIIV	bimodal normal (wide) (*SR01* =0.01/week; *SR02* = 0.09/week)	IBV + IIV	1, 0.25, 4	IBVIIVest	unimodal	FOCE or SAEM
				bMIXest	bimodal--$MIX model for *SR*, common variances	FOCE

Results: Estimation Model Comparisons

Simulated Scenario: uniIBVIIV

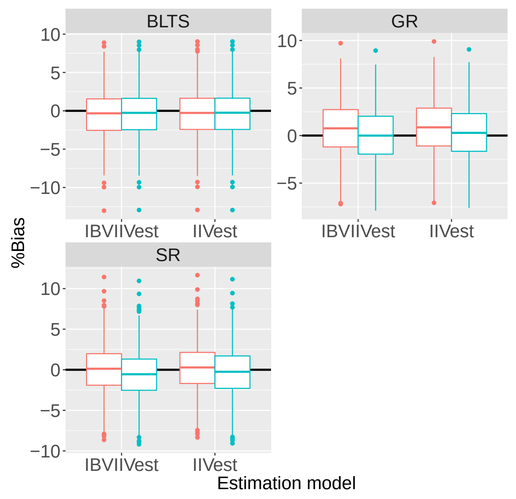
AIC Comparison

Fig. 2 Comparing AIC across est. models & methods (a) FOCE, b) SAEM)



Bias in Fixed Effect Parameters

Fig. 3 Percent bias in fixed effect parameters across estimation models and methods (red=foce; blue=saem) for IBV:IIV = 1



- Parameter biases for $BLTS$, GR, and SR were small and centered symmetrically around zero across all models, methods, and IBV:IIV ratios

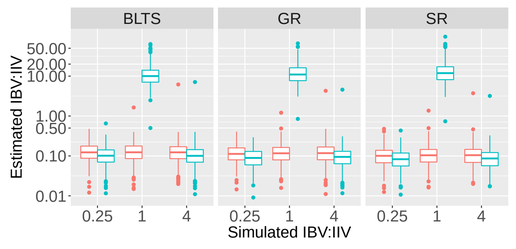
Coverage Probability of Nominal 95% Confidence Intervals for Fixed Effect Parameters

Table 2 Median percent coverage of fixed effect nominal parameter values across est. models, methods and sim. IBV:IIV

Est model	Est method	IBV:IIV	BLTS %coverage	GR %coverage	SR %coverage
IBVIIVest	foce	0.25	92.8	93.6	95.4
IBVIIVest	saem	0.25	74.8	68.6	67.8
IIVest	foce	0.25	93.6	93.4	94.6
IIVest	saem	0.25	95.4	97.4	97.2
IBVIIVest	foce	1	93.8	94.2	94.4
IBVIIVest	saem	1	72.8	70.4	67.8
IIVest	foce	1	94.2	94.2	95.0
IIVest	saem	1	94.6	97.0	96.6
IBVIIVest	foce	4	93.2	94.4	93.8
IBVIIVest	saem	4	73.8	70.2	69.2
IIVest	foce	4	93.6	95.2	94.0
IIVest	saem	4	95.4	96.2	96.2

Estimated IBV:IIV

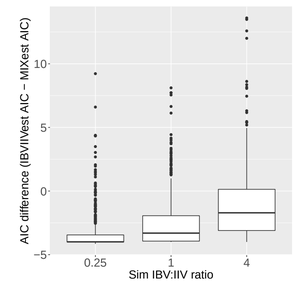
Fig. 4 Est. IBV:IIV across parameters, est. methods (red=foce; blue=saem), & sim. IBV:IIV for the IBVIIVest model



Simulated Scenario: nbIBVIIV

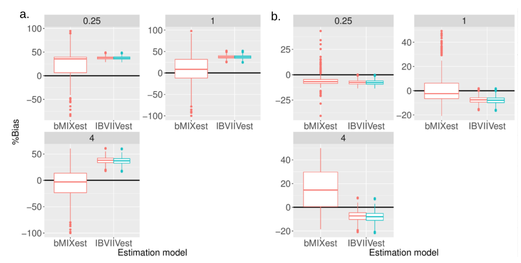
AIC Comparison

Fig. 5 Comparing AIC across est. models & IBV:IIV ratios



Bias in Fixed Effect Parameters

Fig. 6 Percent bias in estimating the small (a, *SR01* = 0.047/week) and large (b, *SR02* = 0.07/week) modes of the bimodal distribution for shrinkage rate across sim. IBV:IIV (panels)



- Parameter estimates for *SR01*/*SR02* were positively/negatively biased for the IBVIIVest models (FOCE, SAEM)
- The bMIXest model's biases were more symmetrically distributed around zero

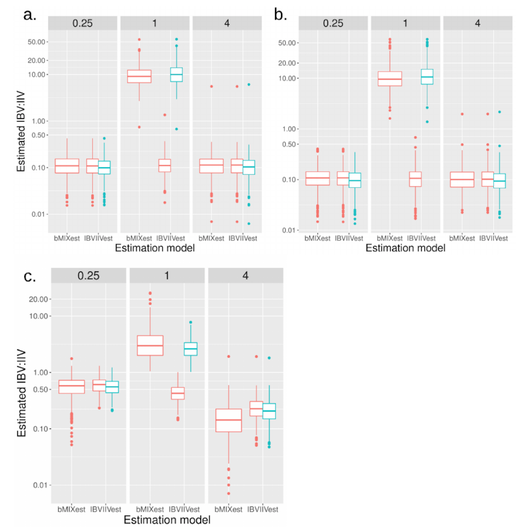
Coverage Probability of Nominal 95% Confidence Intervals for Fixed Effect Parameters

Table 3 Median percent coverage of fixed effect nominal parameter values across est. models, methods, and sim. IBV:IIV

Est model	Est method	IBV:IIV	BLTS %coverage	GR %coverage	SR1 %coverage	SR2 %coverage	SR % wt. coverage
IBVIIVest	foce	0.25	93.8	93.8	NA	NA	93.0
IBVIIVest	saem	0.25	71.0	72.0	NA	NA	99.8
bMIXest	foce	0.25	35.2	36.0	24.8	29.4	NA
IBVIIVest	foce	1	92.6	93.2	NA	NA	94.2
IBVIIVest	saem	1	70.2	70.0	NA	NA	96.0
bMIXest	foce	1	64.6	66.0	49.6	51.2	NA
IBVIIVest	foce	4	93.2	94.8	NA	NA	96.0
IBVIIVest	saem	4	71.0	70.4	NA	NA	89.6
bMIXest	foce	4	85.8	86.2	51.8	67.8	NA

Estimated IBV:IIV

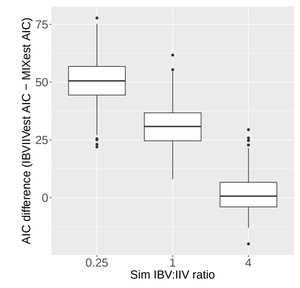
Fig. 7 Est. IBV:IIV across parameters (a=*BLTS*, b=*GR*, c=*SR*), est. methods (red=foce; blue=saem), sim. IBV:IIV (panels) & est. models



Simulated Scenario: wbIBVIIV

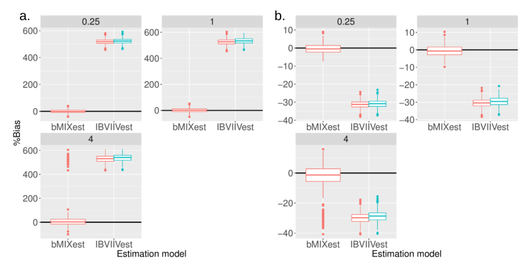
AIC Comparison

Fig. 8 Comparing AIC across est. models & IBV:IIV ratios



Bias in Fixed Effect Parameters

Fig. 9 Percent bias in estimating the small (a, *SR01* = 0.01/week) and large (b, *SR02* = 0.09/week) modes of the bimodal distribution for shrinkage rate across sim. IBV:IIV (panels)



- Parameter estimates for *SR01*/*SR02* were positively/negatively biased for the IBVIIVest models (FOCE, SAEM); degree of bias much larger than for nbIBVIIV simulated scenario
- The bMIXest model's biases were more symmetrically distributed around zero

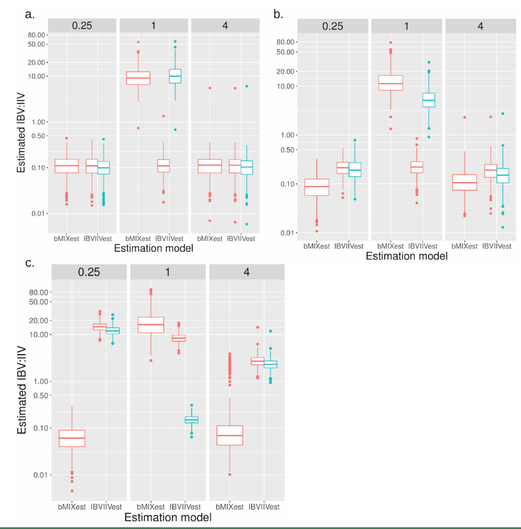
Coverage Probability of Nominal 95% Confidence Intervals for Fixed Effects Parameters

Table 4 Median percent coverage of fixed effect nominal parameter values across est. models, methods and sim. IBV:IIV

Est model	Est method	IBV:IIV	BLTS %coverage	GR %coverage	SR1 %coverage	SR2 %coverage	SR % wt. coverage
IBVIIVest	foce	0.25	94.0	84.4	NA	NA	0.0
IBVIIVest	saem	0.25	71.2	76.2	NA	NA	100.0
bMIXest	foce	0.25	93.8	94.4	92.4	87.0	NA
IBVIIVest	foce	1	92.6	84.8	NA	NA	100.0
IBVIIVest	saem	1	72.0	74.4	NA	NA	100.0
bMIXest	foce	1	92.6	94.6	93.2	88.6	NA
IBVIIVest	foce	4	93.2	88.6	NA	NA	13.6
IBVIIVest	saem	4	72.8	74.6	NA	NA	100.0
bMIXest	foce	4	85.4	88.0	81.0	82.2	NA

Estimated IBV:IIV

Fig. 10 Est. IBV:IIV across parameters (a=*BLTS*, b=*GR*, c=*SR*) est. methods (red=foce; blue=saem), sim. IBV:IIV (panels) & est. models



Conclusion

- Based on comparison criteria, model estimation recommendations for the uniIBIIV, nbIBVIIV, and wbIBVIIV simulation scenarios were the IIVest (FOCE), IBV+IIVest (FOCE), and bMIXest (FOCE) models, respectively
- Models that provided good fits for estimation of TD data have limitations under simulation conditions: 1) could not accurately distinguish IBV from IIV (favored IIV) 2) $MIX model in NONMEM7.3 sorted subjects on individual rather than basket level
- Limitations negatively impact models' ability to accurately simulate TD in new tumor types (baskets) and correctly identify responsive baskets
- Modeling tools that allow $MIX models to sort subjects on basket-level would be advantageous during simulation (STAN) – ONGOING WORK

References

[1] E A Eisenhauer, P Therasse, J Bogaerts, L H Schwartz, D Sargent, R Ford, J Dancey, S Arbuck, S Gwyther, M Mooney, L Rubinstein, L Shankar, L Dodd, R Kaplan, D Lacombe, and J Verweij. New response evaluation criteria in solid tumours: revised recist guideline (version 1.1). *Eur J Cancer*, 45(2):228–47, Jan 2009.

[2] Boris Freidlin and Edward L Korn. Borrowing information across subgroups in phase ii trials: is it useful? *Clin Cancer Res*, 19(6):1326–34, Mar 2013.

[3] Y Wang, C Sung, C Dartois, R Ramchandani, B P Booth, E Rock, and J Gobburu. Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. *Clin Pharmacol Ther*, 86(2):167–74, Aug 2009.