

Objectives

- Prognostic biomarkers are baseline (pretreatment) measurements about patient's probable long-term outcome, either untreated or with a standard treatment.
- Predictive markers are baseline measurements that indicate whether the patient is likely (or unlikely) to benefit from a specific drug or regimen.
- Use of biomarkers in early phase development has been limited by traditional analysis methods because:
 - Cut-point separation cannot account for time varying or disease varying changes in the biomarker; 2) Complex interactions between prognostic and predictive biomarkers cannot be described; 3) The effect of suboptimal drug dosing cannot be quantified
- PK/PD methods can predict time varying effects, quantify concentration-effect relationships, and interactions and have the potential to increase the power to detect the predictive or prognostic role of biomarkers in a clinical trial setting.
- We developed a pharmacometric framework for the analysis of biomarker data to assess whether a complementary longitudinal data analysis using pharmacokinetic/pharmacodynamic (PK/PD) and biomarker modelling could add benefit in the interpretation of predictive biomarker data, as well as to evaluate therapeutic drug monitoring and adaptive phase 3 design.

Methods

The simulations in this work were performed in context of standard Phase 2B design for a biological therapy for the treatment of inflammatory bowel disease and it was based on two different dose ranges, **A**) 300 mg, 1000 mg, 2000 mg (all above ED₅₀) or placebo, and **B**) 50 mg, 300 mg, 2000 mg (all doses at ED₅₀ and above) and three different study settings: at dose range **A** or **B**, a placebo-controlled parallel study with predictive biomarker effect on drug effect (Setting 1 and 2), or prognostic biomarker effect on disease progression rate (Setting 3 and 4), or on both drug effect and disease progression (Setting 5 and 6) (Table 1). PK of this virtue drug is described using a linear 2-compartment model, whereas its PD is described as an indirect inhibition. The biomarker effect is implemented as a function on drug effect (E_{max}) (predictive biomarker) and/or disease progression rate (prognostic biomarker) as below: using a range of functions including E_{max} model with γ of 1.5, 2, 3, 5, or 50, linear model and dichotomous model (**Figure 1 and 2**). The biomarker covariate is sampled using the mean and standard deviation of C-reactive protein level from a clinical dataset following a log normal distribution.

In each setting, we assess the power to correctly identify biomarker effect using modelling versus standard statistical approaches (group comparison and 2-way ANOVA) at end of the study. Stochastic simulations and estimations were used to compute model parameter precision and accuracy as well as power for detection of biomarker effect.

Trial Design

The duration of treatment for this virtue drug is 6 months and after that there are 2 months of follow-up. At the beginning of each month for the first 6 months, dosing is conducted, while at the end of each month for 8 months, PK and PD samples are collected. In each arm, 50 subjects are enrolled and in total there are 200 subjects (4 arms). The number of trials simulated for model validation and power test is 100.

Model Equations

$$E_{drug} = \frac{E_{max} \times Conc}{EC_{50} + Conc}$$

$$E_{max} = E_{base, DRUG} \times \left(1 + \frac{BIO \times BIL^{\gamma}}{SYM^{\gamma} + BIL^{\gamma}}\right)$$

E_{drug}: drug effect, which is a function of drug concentration;

E_{max}: maximal drug effect, which is dependent on biomarker level in the scenario of predictive biomarker effect;

EC₅₀: concentration of drug at half of maximal drug effect;

E_{base, DRUG}: baseline maximal drug effect;

BIL: biomarker level;

BIO: maximal biomarker effect;

SYM: biomarker level at half of maximal biomarker effect;

γ: hill coefficient, 1.5, 2, 3, 5, 50 is used to describe biomarker effect function

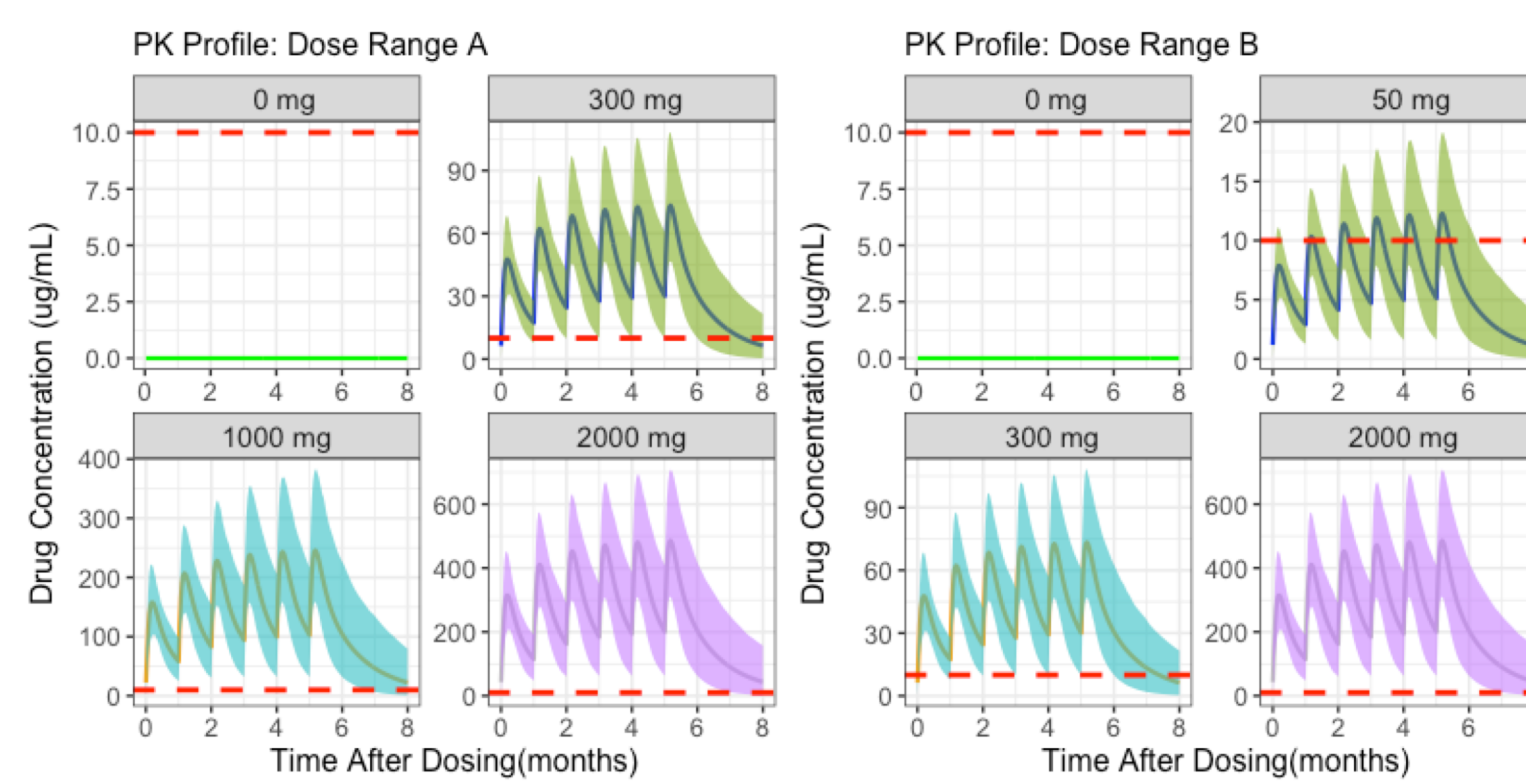


Figure 1. Simulated PK Profiles

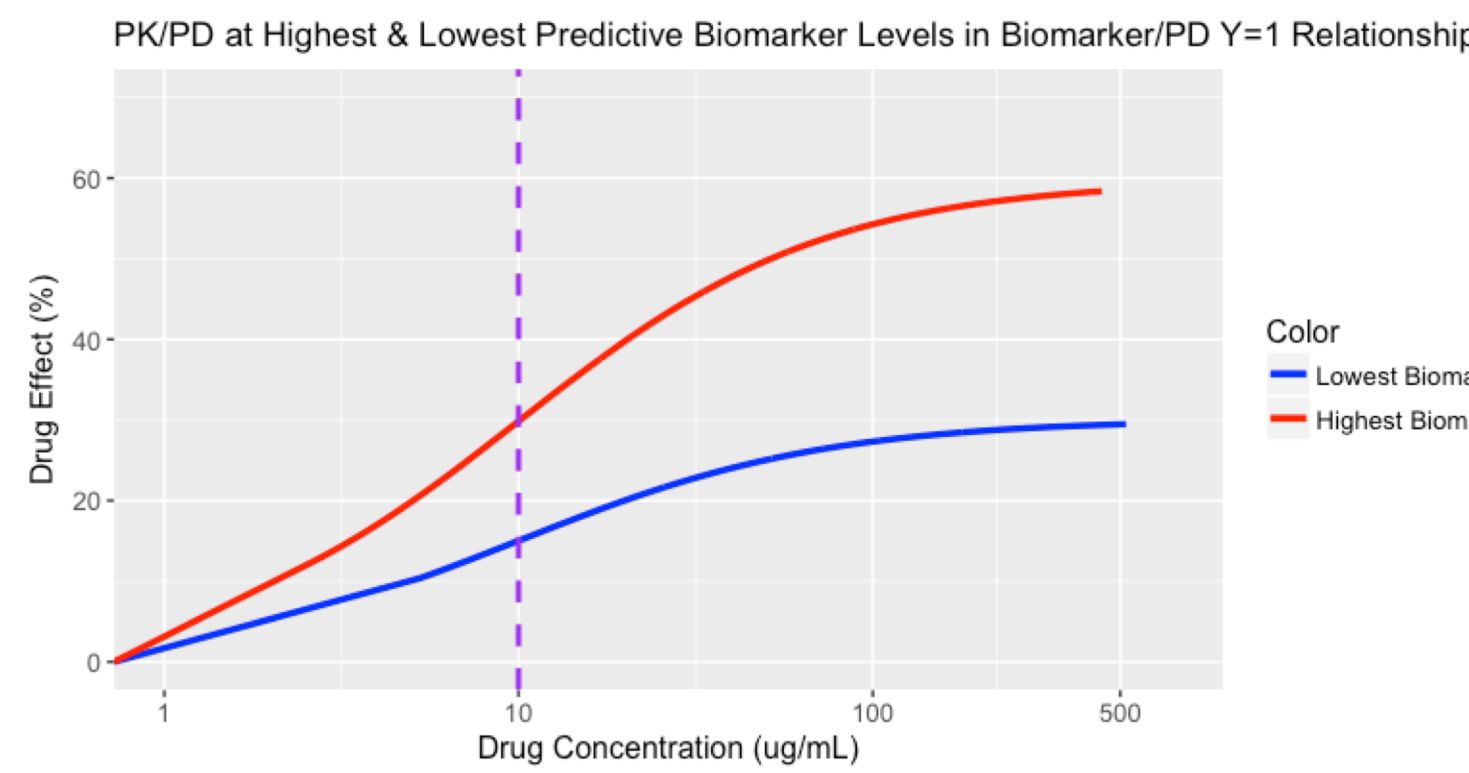


Figure 2. PK/PD Relationship in Study Settings

	Predictive Biomarker Effect	Prognostic Biomarker Effect	Predictive & Prognostic Biomarker Effect
Dose Range A (300 mg, 1000 mg, 2000 mg and placebo)	Setting 1	Setting 3	Setting 5
Dose Range B (50 mg, 300 mg, 2000 mg and placebo)	Setting 2	Setting 4	Setting 6

Table 1. 6 Study Settings: 2 Dose Ranges & 3 Biomarker Effects

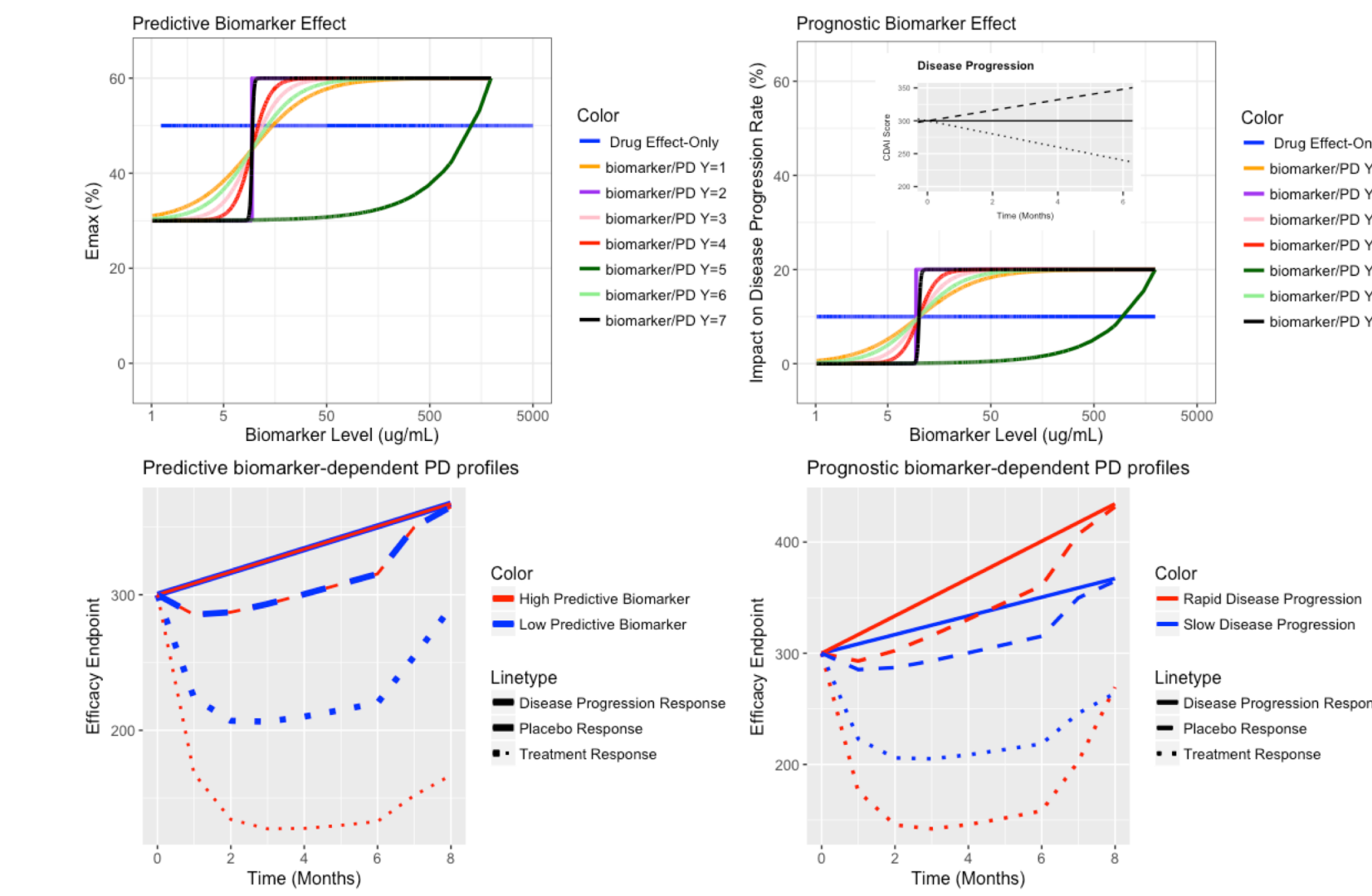
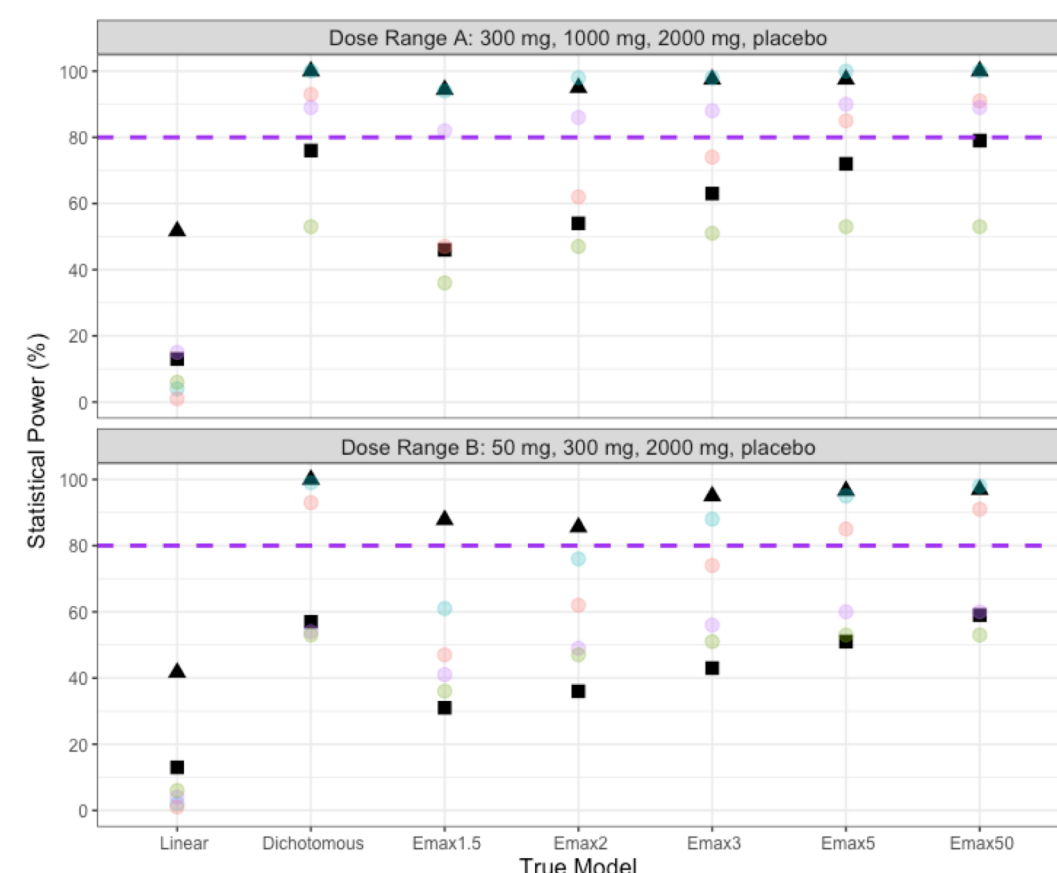


Figure 3. Biomarker/PD Relationship and Representative Simulated PD Profiles

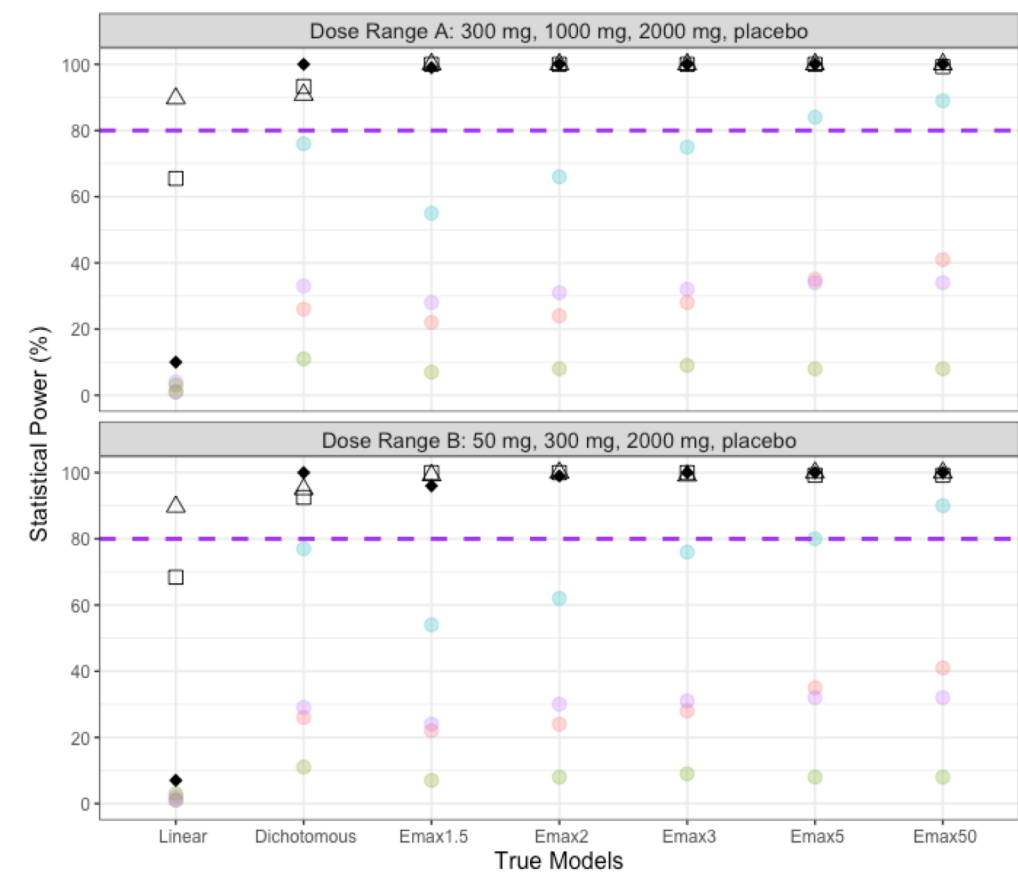
Results

All studied scenarios with biomarker effect on model parameters using PK/PD modeling method had a power more than 80% for the biomarker effect detection except the linear biomarker effect model. In addition, PK/PD modeling approach could differentiate prognostic biomarker from predictive biomarker in all models, and differentiate dual biomarker effect from single biomarker effect except in linear model. In comparison, 2-way ANOVA was not able to detect any biomarker effect in the settings of predictive biomarker and dual biomarker effect for both dose ranges with a power of more than 80%, while in the scenario of prognostic biomarker effect, most of the models could detect such a prognostic biomarker effect using 2-way ANOVA except linear model. For t-test, it can be used for biomarker defection in certain scenarios, depending on the biomarker cutoff value, dose levels grouped and study settings (**Figure 3a-c**).

a) Predictive Biomarker Effect (Setting 1 & 2)



b) Prognostic Biomarker Effect (Setting 3 & 4)



c) Predictive & Prognostic Biomarker Effect (Setting 5 & 6)

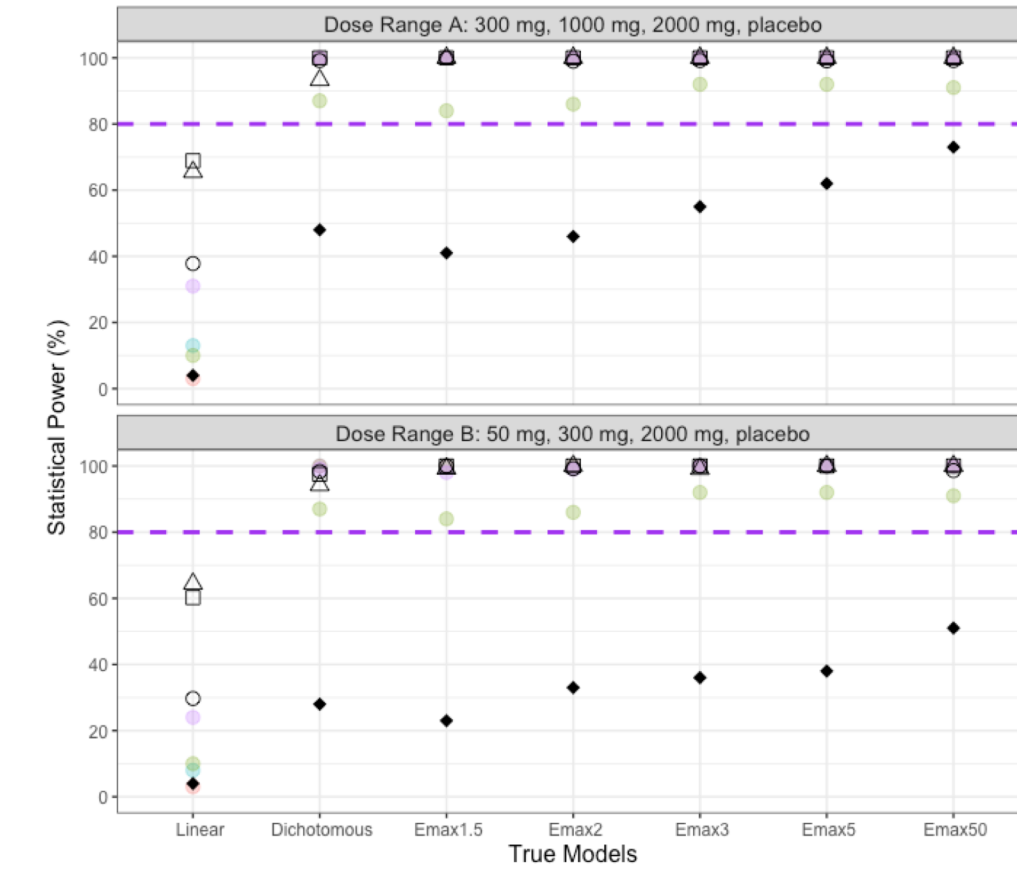
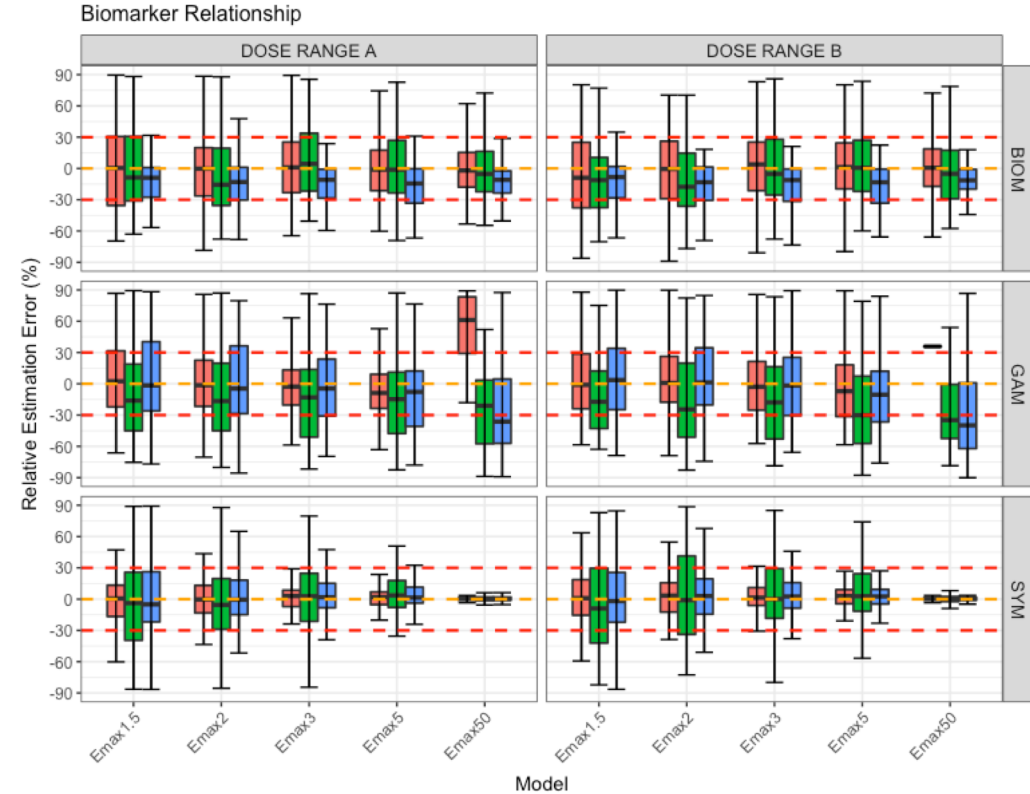


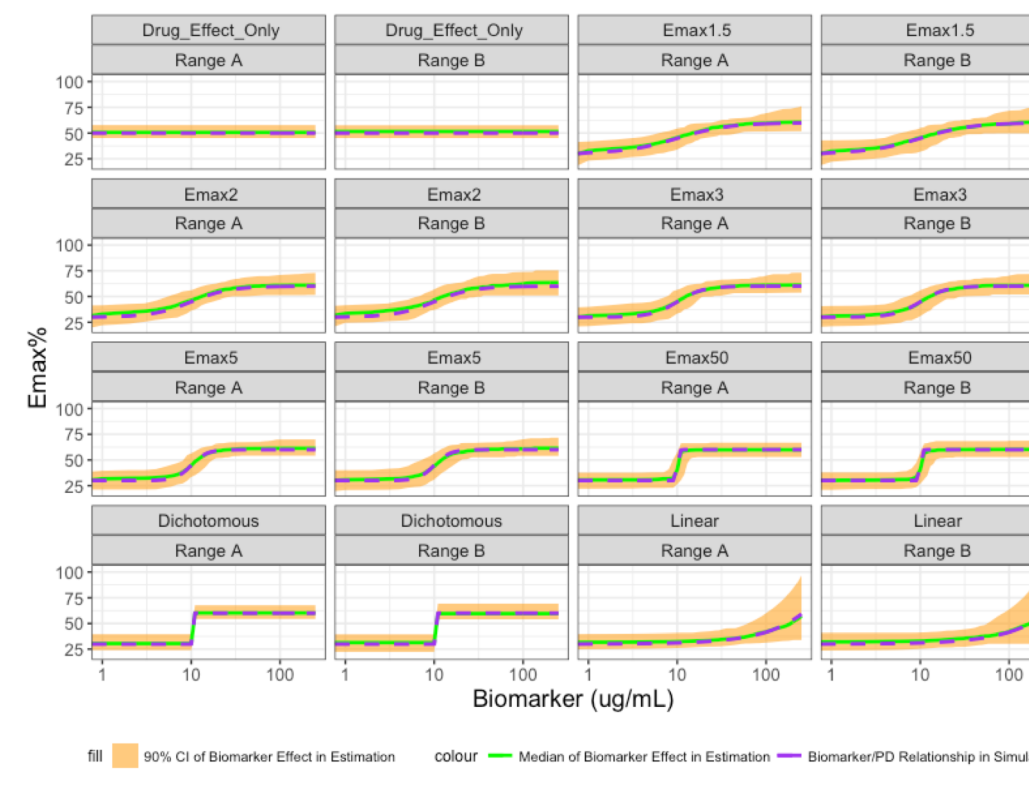
Figure 4. Power Comparison of Different Approaches in Three Biomarker Effect Settings with Two Different Dose Ranges

Model parameters could be estimated with reasonable precision and bias with small sample sizes, except the precision of biomarker relationship parameters (BIOM, GAM, SYM) (Figure 4a). Overall, the relationship between biomarker level and biomarker effect is well estimated in all the settings (Figure 4b-e). A larger sample size could be considered to eliminate it.

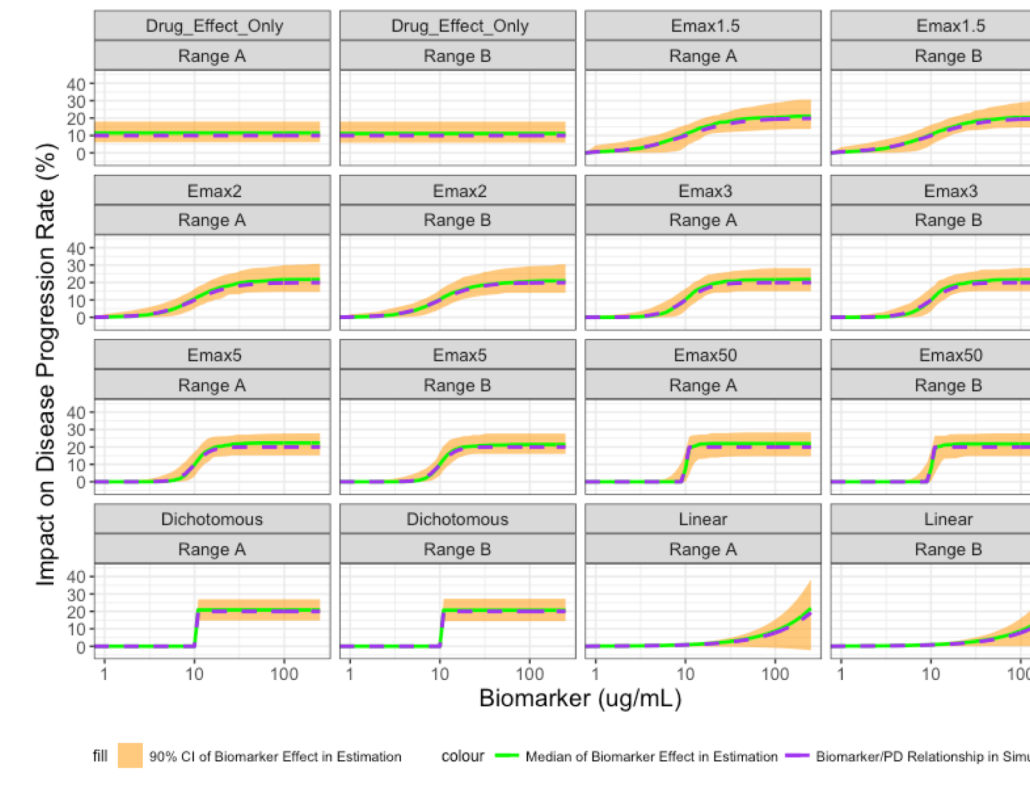
a) Precision & Accuracy of Biomarker Effect Parameters in Emax Function



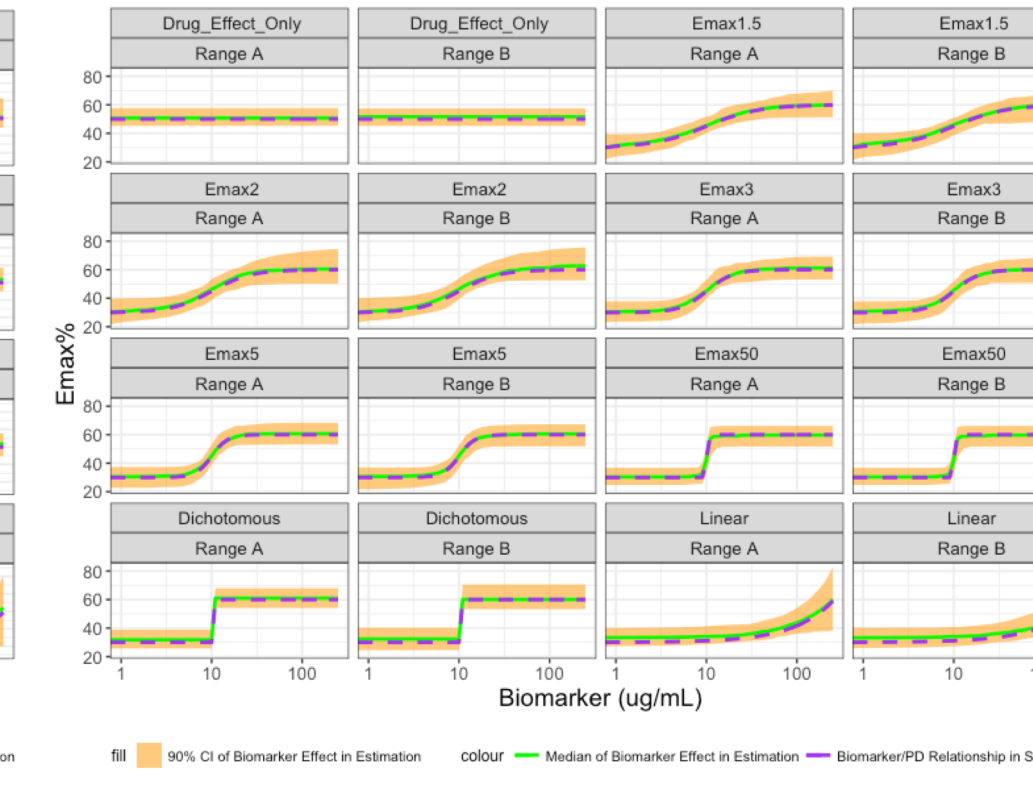
b) Relationship between Biomarker Lever and Predictive Biomarker Effect in Setting 1 & 2



c) Relationship between Biomarker Lever and Prognostic Biomarker Effect in Setting 3 & 4



d) Relationship between Biomarker Lever and Predictive Biomarker Effect in Setting 5 & 6



e) Relationship between Biomarker Lever and Prognostic Biomarker Effect in Setting 5 & 6

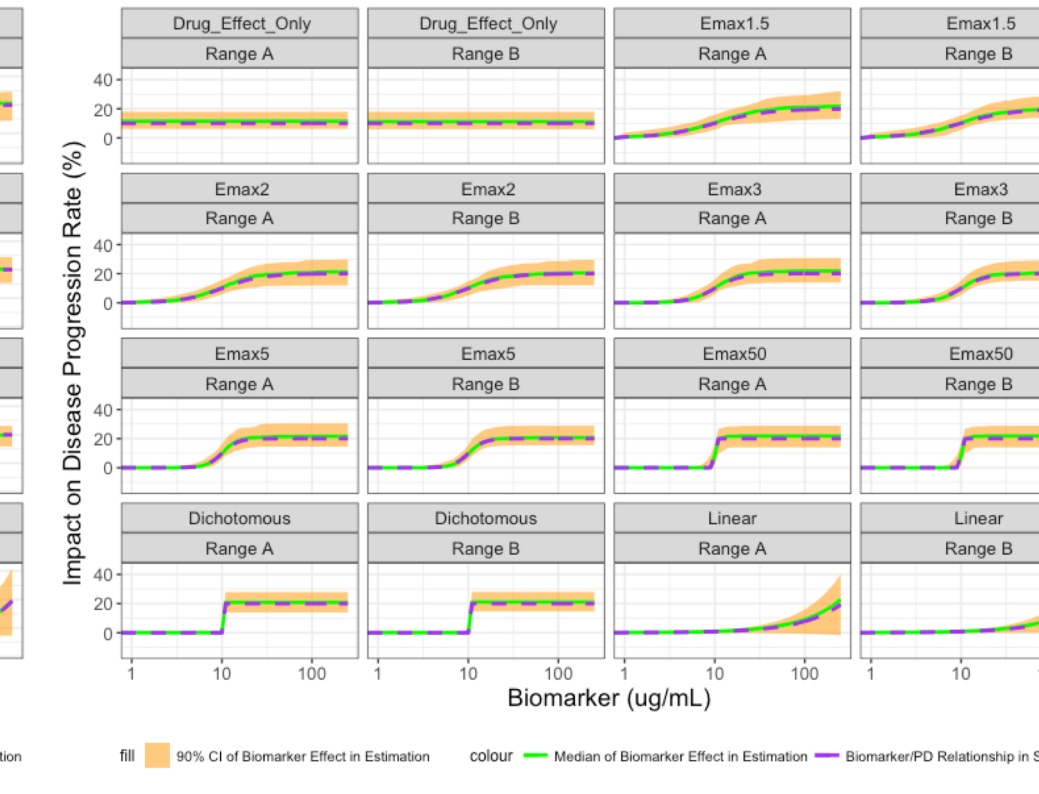


Figure 5. Precision and Accuracy of Parameter Estimation within Two Dose Ranges and Three Biomarker Effect Scenarios ($Relative\ Estimation\ Error(\%) = (P_{est} - P_{true}) / P_{true} \times 100\%$)

Conclusions

A framework has been developed for analyzing continuous predictive and prognostic biomarker. Model-based framework has demonstrated a higher power in differentiating prognostic biomarker from predictive biomarker effect. In addition, it also outperformed commonly used statistical method, including t-test and 2-way ANOVA. This platform has improved the ability to characterize both exposure-response relationship and the predictive value of the biomarker by simultaneous modeling of PK/PD data from all dose cohorts while including a predictive/prognostic biomarker covariate.

References

- [1] Buyse et al; Biomarkers and Surrogate End Points-the Challenge of Statistical Validation. Nature Reviews Clinical Oncology 7, 309-317 (2010)