1. Contributions

Nowadays, biologics such as monoclonal antibodies (mAbs) are increasingly used for the treatment of many chronic diseases, including cancer and auto-immune diseases. Numerous cases have shown that there are significant improvement in the treatment outcomes by using biologics. Currently, more than 30 mAbs have been approved by the administrative government agencies. Hundreds of clinical trials with mAbs have been conducted, and more effort will be spent on the mABs studies and clinical trails in the future.

Treatment plans for mAbs are much more complicated than that for traditional medications. MAbs are injected at time long intervals, typically weeks or months, which are much longer than that of conventional medicines. Therefore, unlike the dose–response models for traditional medications, dose–time-response models are required to describe and predict the drug effect for complex mAbs treatment plan development.

To identify an adequate regimen for the investigated mAb, multiple clinical trials with different doses and injection times are conducted to compare different regimens. However, this kind of clinical trails can hardly to be complete and efficient, because the investigated regimens can cover only a small proportion of all feasible combinations of doses and time-intervals.

Hence, reliable predictions about the response for untested regimens will be of great help in the design of the following clinical trails. Based on predictions for several considered alternative regimens, the most promising regimen can then be highlighted and evaluated in subsequent clinical trials. Therefore, an accurate dose–time-response model will significantly improve the efficiency of the traditional clinical trails.

In *Analysis of clinical trials with biologics using dose–time-response models*, Lange and Schmidli (2015) constructed a dose–time-response model, using semi-mechanistic nonlinear regression models, to describe and predict the time-changing response for complex dosing regimens. This paper provided a guideline for future dose–time-response relationship modeling studies.

2. Methodology

(1) To build a simple and basic dose–time-response model based on pharmacokinetic–pharmacodynamic (PKPD) models, where the PK component in the unobserved effect compartment is treated as a latent variable

(2) To extend the basic dose-time-response model by including more factors that will potentially affect the response

(3) To estimate and predict the parameters using Maximum-likelihood (ML) and Bayesian methods

(4) To evaluate frequentist operating characteristics of the methods by using simulations

(5) To analyze clinical trails based on the predictions of the dose–time-response model

3. The Dose-Time-Response Model

The basic dose-time-response model relies on simplified mechanistic concepts. The latent kinetic component C(t) describe the drug concentration in the unobserved effect compartment. MAbs are usually administered as subcutaneous injections, as illustrated by Figure 1.

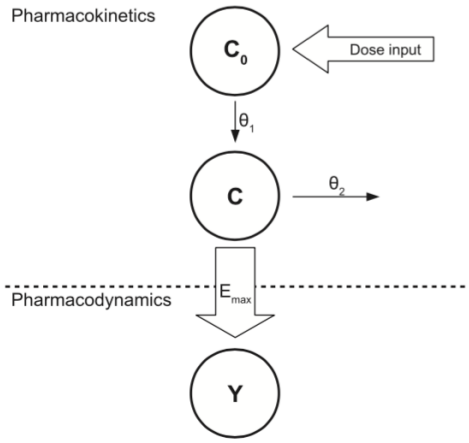

Figure 1. Schematic illustration of the pharmacokinetics of a biologic injected in a subcutaneous skin depot C0. The resulting concentration in the unobserved effect compartment C is then directly linked to the response Y via the E_{max} model.

C_0 represents the initial concentration when the drug is injected. The biologic is then transferred to the unobserved effect compartment C at an absorption rate θ_1. At the same time, the drug effect is disappear at a rate θ_2. This process can be concluded with the following differential equation

$$\frac{dC_0(t)}{dt} = -\theta_1 C_0(t)$$

$$\frac{dC(t)}{dt} = -\theta_2 C(t) + \theta_1 C_0(t).$$

Therefore, for a single dose D given at time 0, the concentration in the effect compartment over time is then

$$C(t) = \frac{D\,\theta_1}{\theta_1 - \theta_2}\left(e^{-\theta_2 t} - e^{-\theta_1 t}\right)$$

Base on direct-response E_{max}-model, we have following equation:

$$g(C(t)) = \theta_5 + \frac{\theta_4 \cdot C(t)}{\theta_3 + C(t)}.$$

Here, θ_3 is the concentration which produces a 50% maximum response. θ_4 is the maximum possible response, θ_5 is the expected response of baseline.

After simplify the equation above, the basic model is constructed. If patient i get an injection with dose Di and a continuous response y_{ij} at time t_j will be:

$$y_{ij} = \theta_5 + \frac{\theta_4 D_i \left(e^{-\theta_2 t_j} - e^{-\theta_1 t_j}\right)}{\theta_3 \left(1 - \theta_2/\theta_1\right) + D_i \left(e^{-\theta_2 t_j} - e^{-\theta_1 t_j}\right)} + \epsilon_{ij}$$

The paper also discusses six important extensions of the basic model considering different factors of placebo response, baseline covariates, multiple doses, route of administration, residual error, and indirect-response models & turnover models.

To use ML methods to derive the parameters of the model, numerical optimization procedures are necessary. As the likelihood function may have several local maxima, a good initial guess of parameter value is critical. To derive confidence and prediction intervals is based on asymptotic theory and linear approximations. Hence, the validity of intervals is questionable for small sample size. Moreover, if the true parameter is close to boundary of parameter space, the asymptotic ML theory is not applicable. For dose-time-response models, it is common that the parameters are actually on the boundary.

For Bayesian inference, incorporate the knowledge of previous clinical trial by using informative priors could be useful in estimating parameters. However, the posterior distribution calculation requires multidimensional integration. By using Markov chain Monte Carlo (MCMC) methods, we can get a distribution of sample posterior.

4. Simulations to Evaluate Operating Characteristics

In clinical trial simulations, data are generated repeatedly for a given dose–time-response model. Then the operating characteristics are evaluated by statistical methods based on the data obtained. E_{max} model is used to assess the expected value, and the results are shown in Table 1.

Table I. Summary results of the clinical trial simulations (CI=confidence interval, PI=probability interval).

		Likelihood analysis		Bayesian analysis	
Parameter	True value	Median of maximum likelihood-estimate	95% CI coverage (in %) *	Median of posterior median	95% PI coverage (in %) *
θ_1	0.07	0.067	90.7	0.087	94.8
θ_2	0.03	0.032	91.2	0.028	97.2
θ_3	10.00	9.67	97.4	13.23	92.1
θ_4	−80.00	−80.7	99.7	−82.16	92.5
θ_5	100.00	100.0	91.9	98.92	93.6
Time					
0	100.00	100.0	91.9	98.92	93.6
10	28.38	27.9	99.8	26.80	95.3
50	30.32	30.5	99.9	31.32	94.6
100	26.18	25.4	100.0	24.44	93.5
200	57.13	57.0	98.4	57.49	94.3
300	95.61	94.8	94.6	92.21	90.5

* Monte Carlo standard error: 0.7%

Both the ML and the Bayesian methods show that their point estimates are near to the true parameter values, where ML estimates are closer to the true values on average. Furthermore, the confidence and probability interval coverages are acceptable here, with the Bayesian probability interval coverages are slightly better than ML confidence interval coverages.

5. Clinical Trails

Dose–time-response models are used to analyze a clinical trail where the effects of canakinumab subcutaneous injection were examined. Active control was used in this 24-week double-blinded dose-ranging study.

The participants were randomly divided into seven groups, where five of them received single doses (either 25 mg, 50 mg, 100 mg, 200 mg, or 300 mg at day 1), one group received multiple doses (50 mg at day 1, 50 mg at week 4, 25 mg at week 8, and 25 mg at week 12), and the last group was the placebo. The logarithm of C-reactive protein (CRP) levels was used as the response in this study, where CRP is a biomarker signaling the severeness of the disease.

The data collected were used to investigate: (1) The fitness of the dose-time-response model in the clinical trail; (2) The accuracy of the dose-time-response model predictions of the untested treatment regimens response.

Ideally, the model should describe the data well for each single-dose group, and also predict the actual observed response of the treatment group with multiple injections with a reasonable level of accuracy. Here, θ_6 is added to the basic model to measure the effect of the baseline CRP levels (X_0).

Table II shows the evaluation using the Bayesian analysis for the five single-dose treatment groups.

Table II. Bayesian analysis for data from the five single-dose treatment groups.

	Posterior median	95% probability interval	
θ_1	0.177	0.077	0.293
θ_2	0.022	0.016	0.031
θ_3	8.07	3.44	15.19
θ_4	−1.41	−1.82	−1.06
θ_5	0.934	0.65	1.29
θ_6	0.431	0.38	0.53

To assess the fitness of the dose-time-response model, observed values and the fitted Bayesian model are compared in Figure 4. The dose-time-repose model describes the single-dose data well with $R^2 = 0.82$.

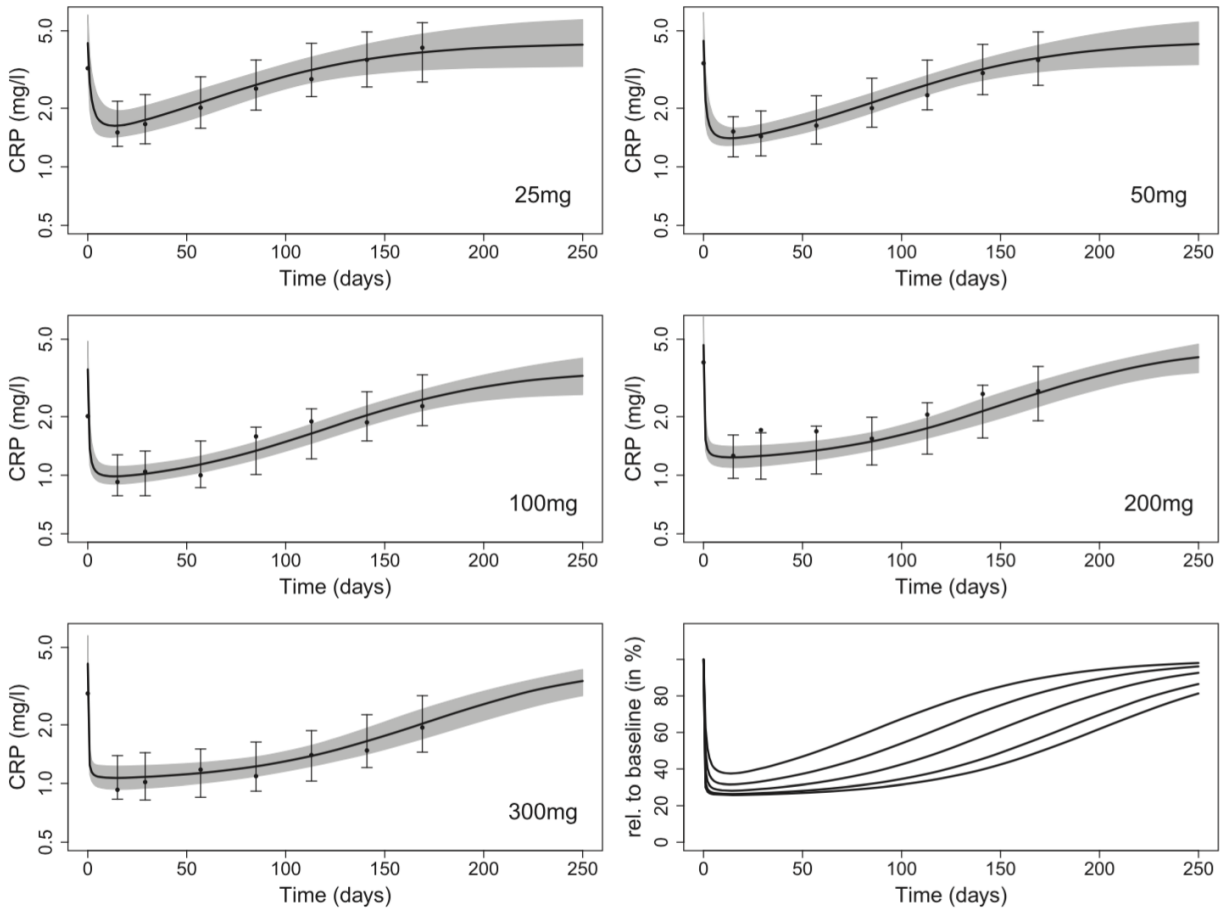

Figure 4. Bayesian analysis for the five single dose groups in the clinical trial. The dots represent the means of the CRP levels, the solid curves the median of the posterior CRP levels, the grey area the 95% posterior probability interval, and the vertical lines the 95% prediction probability interval. The last plot displays all posterior median curves relative to their baseline value.

Figure 5 is a comparison of the data from the multiple dose group of the trial and the prediction from the dose–time-response model derived from the Bayesian analysis of the single-dose data. All of the

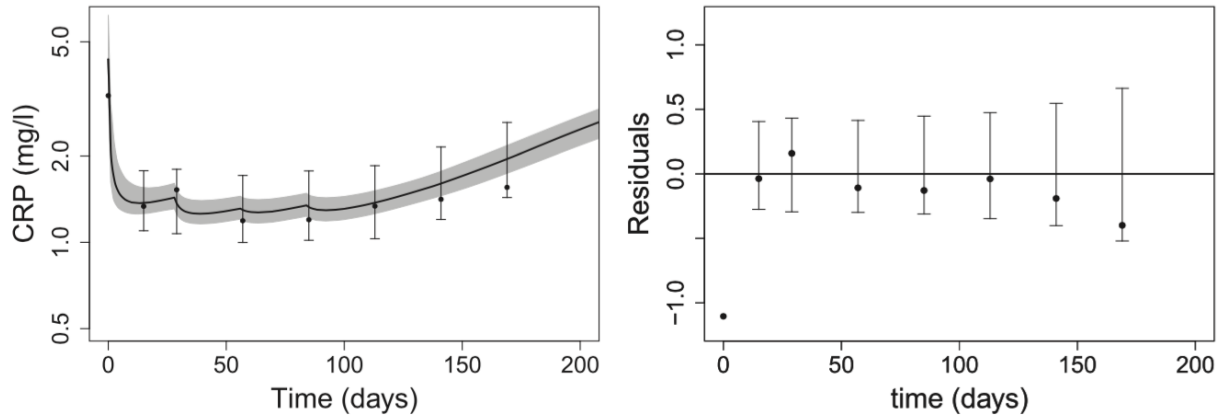

Figure 5. Bayesian prediction of the repeated dosing regimen based on the dose–time-response model derived from single-dose regimens

data points are within the 95% prediction intervals, which implies a good accuracy of the dose-time-response model predictions of the response over time for the multiple dose treatment.

Figure 6 is a comparison of the fitted dose–time-response model with the standard fitted E_{max} (dose-response) model in estimating the difference to baseline. It is obtained by using Bayesian approach to fit the model for three time points at day 15, 85, and 169. Although the fits of data are similar for both models, the confidence band of the dose-time-response model is narrower than that of dose-response

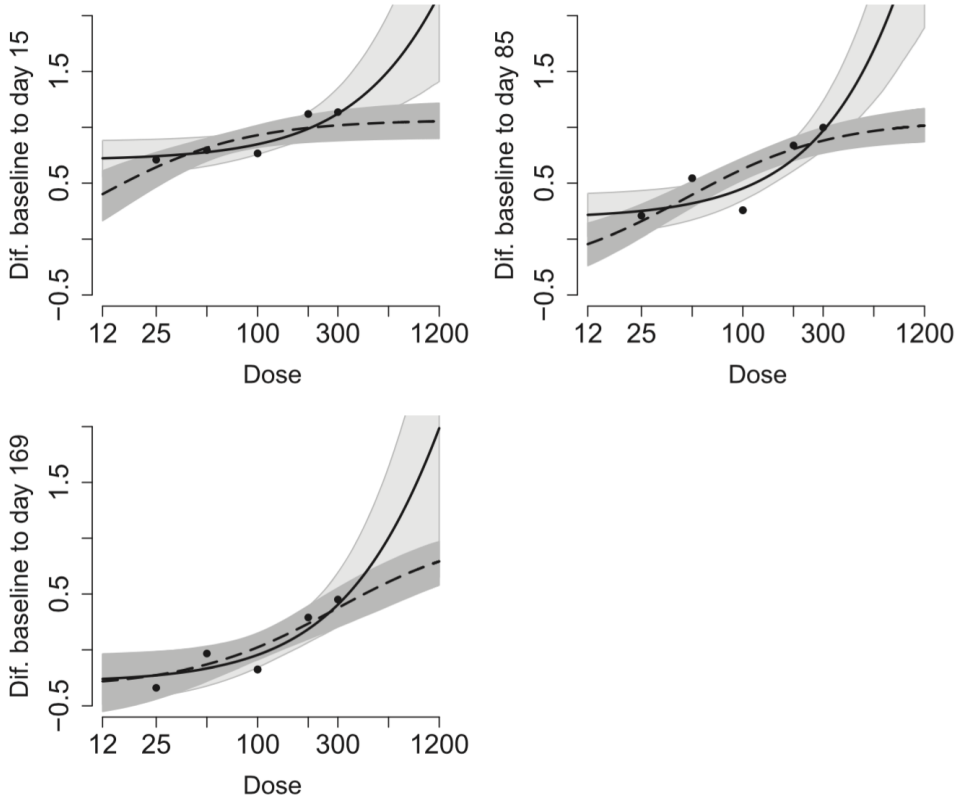

Figure 6. Comparison of the dose–time-response model with the standard E_{max} model. The dots represent the means of the measurements, the solid line the fitted E_{max} model, and the dashed line the fitted dose-time-response model. The light grey area and the dark grey area mark the respective 95%-confidence bands of the expected response.

model, especially for the higher doses. This suggests that the predictions for higher doses in the dose-time-response model are more accurate on average.

6. Limitations

The followings are four major limitations of the paper:

- ML methods make inferences based on asymptotic theory, but it may not be valid for small samples in the experiments.
- In a Bayesian framework, unintended informative prior problems may occur because of inappropriate prior distributions for nonlinear models.

- A sample from the posterior is generated using MCMC methods, rather than direct calculations. Therefore, the estimation results are subject to the accuracy problem.
- In the clinical trail, only five single-dose arms and one multiple-dose arm are carried out for assessment, which may not be complete enough to achieve the accuracy of the model evaluation.

7. Issues and Challenges

There are three critical issues and challenges in terms of theories and technology:

- Form both technical and conceptual perspectives, It is often challenging to ensure the fitness of nonlinear regression models.
- Convergence problems, identifiability problems, and ill-conditioning problems are commonly encountered during the experiments.
- Bayesian analysis requiring MCMC algorithms is computer-intensive and time-consuming. Doing so for many simulated datasets need a significant amount of computing powers and time.