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Analysis of clinical trials with biologics using dose–time-response models

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Biologics such as monoclonal antibodies are increasingly and successfully used for the treatment of many chronic diseases. Unlike conventional small drug molecules, which are commonly given as tablets once daily, biologics are typically injected at much longer time intervals, that is, weeks or months. Hence, both the dose and the time interval have to be optimized during the drug development process for biologics. To identify an adequate regimen for the investigated biologic, the dose–time-response relationship must be well characterized, based on clinical trial data. The proposed approach uses semi-mechanistic nonlinear regression models to describe and predict the time-changing response for complex dosing regimens. Both likelihood-based and Bayesian methods for inference and prediction are discussed. The methodology is illustrated with data from a clinical study in an auto-immune disease. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: Bayesian inference; clinical trial; KPD model; monoclonal antibody; nonlinear regression; pharmacokinetic; pharmacodynamic

1. Introduction

Therapeutic monoclonal antibodies (mAbs) are biologics that are increasingly and successfully used for the treatment of many chronic diseases, including cancer [1] and auto-immune diseases such as psoriasis or rheumatoid arthritis [2]. More than 30 mAbs have been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency [3], and hundreds of clinical trials with mAbs have been conducted [4].

Clinical development for mAbs is more complex than for traditional drugs. Conventional small drug molecules are commonly given as tablets once daily, and hence, the goal of drug development is to identify a safe and efficacious dose. MAbs are typically injected at much longer time intervals, that is, weeks or months. For example, the mAb canakinumab is administered every 8 weeks as a single dose via subcutaneous injection in patients with cryopyrin-associated periodic syndromes [5]. Hence, both the dose and the time interval have to be optimized during the drug development process. To identify an adequate regimen for the investigated mAb, clinical trials are carried out comparing different regimens with different doses and injection times. These investigated regimens can cover only a small fraction of all feasible combinations of doses and time-intervals. Hence, there is a strong need to be able to predict the response for untested regimens. Based on predictions for several considered alternative regimens, the most promising regimen can then be evaluated in a subsequent clinical trial.

For conventional drugs, dose–response models are used to characterize the drug effect for different doses and to guide the selection of an adequate dose [6–8]. For mAbs, dose–time-response models are required that can describe and predict the drug effect for complex dosing regimens. The European Medicines Agency encourages the development of models '... to investigate relationships for long-acting biologics where there is no steady state' [9]. Dose–time-response models for mAbs are mainly used for extrapolation. As noted by Box and Draper [10], mechanistic rather than empirical models are then more appropriate. Mechanistic models are based on scientific knowledge, are therefore typically more parsimonious than empirical models, and also tend to provide more reliable predictions. In medicine, the

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understanding of the pharmacology is too limited to allow for purely mechanistic models, and hence, semi-mechanistic models involving empirical elements are commonly used.

For mAbs, the mechanism of action is complex, and measurements of the concentration of the mAb are usually taken in blood, rather than in the more relevant effect compartment. To make use of the available pharmacokinetic (PK) measurements in blood, large systems of differential equations are needed that describe the dynamics of the mAb, the target and biomarkers in different compartments of the human body [11]. To be able to develop such models, a very good understanding of the mode-of-action is necessary, which is not always the case. Additionally, the estimation of the model parameters often has to be based on evidence synthesis from several clinical and pre-clinical studies, which are typically available at a late stage of drug development only. Hence we consider here simpler dose–time-response models that are based on pharmacokinetic–pharmacodynamic (PKPD) models [12], where the PK component in the unobserved effect compartment is treated as a latent variable [13]. These models were introduced in a seminal paper by Levy [14] and have a long history of successful use in pharmacological modeling [15, 16]; they are also sometimes called KPD models [17]. Such dose–time-response models are needed when PK measurements cannot be taken, as for example in ophthalmology [18], asthma and chronic obstructive pulmonary disease [19], or in some pediatric studies [20]. Dose–time-response models are also very attractive when the main focus is on prediction [21], as in our setting.

Dose–time-response models are nonlinear regression models, and both maximum-likelihood (ML) methods and Bayesian methods can be used for inference and prediction [22]. Fitting of nonlinear regression models is often challenging, both from a technical and conceptual perspective. Problems commonly encountered are convergence problems, identifiability problems, and ill-conditioning [23]. For ML methods, a potential issue is that inference is based on asymptotic theory, and may not be valid for small samples. In a Bayesian framework, prior distributions for nonlinear models have to be carefully chosen to avoid unintended informative priors [24].

For clinical trials, a good understanding of the frequentist operating characteristics of the methods used for analysis is important. To investigate these for dose–time-response models, simulations must be used. Clinical trial simulations then allow for example to evaluate the coverage properties of the approximate confidence and prediction intervals of the ML methods, and of the corresponding probability intervals for the Bayesian approach. While the analysis of a single trial by ML is fast, this is not the case for the Bayesian approach, as computer intensive Markov chain Monte Carlo (MCMC) methods are required.

In Section 2, the most important dose–time-response models are described, and parameter estimation and prediction using both ML and Bayesian methods is presented. In Section 3, the operating characteristics of the methods are evaluated, and in Section 4, a clinical trial example illustrates predictive use of dose–time-response models. The article closes with a discussion.

2. Methods

Dose–time-response models for mAbs can in principle be based on any appropriate PKPD model [12]. The choice of a tentative model will be influenced by how the biologic is administered (intravenous bolus injection, intravenous infusion, or subcutaneous injection), the understanding of the mode-of-action, information from previous clinical and pre-clinical trials with the mAb, and past experience on other mAbs with a similar mechanism. The model building will typically start with a simple model, and will be refined if necessary. To assess whether a model is adequate, graphical methods and residual analyses are helpful. We will now first describe the most basic dose–time-response model for mAbs for the case where a single dose of the mAb is given, and then discuss various extensions.

2.1. Basic dose-time-response model

The models we use are semi-mechanistic PKPD models, which rely on simplified mechanistics concepts [17]. The time and dosing regimen dependence is mediated through the latent kinetic component $C(t)$, which describes the drug concentration in the unobserved effect compartment. Its form primarily depends on the route of administration. Monoclonal antibodies are usually administered as subcutaneous injections, and Figure 1 illustrates this scenario. A standard two-compartment model may here describe the PK. C_0 represents the subcutaneous skin depot in which the drug is injected. The biologic is then transferred to the unobserved effect compartment C by some absorption rate θ_1. At the same time, the drug is slowly eliminated by the body with some rate θ_2. This process can be described by the following set of

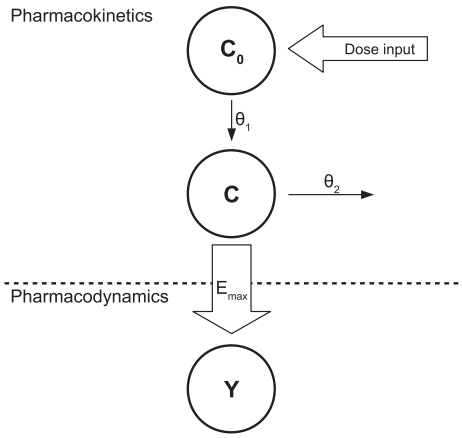

Figure 1. Schematic illustration of the pharmacokinetics of a biologic injected in a subcutaneous skin depot C_0. The resulting concentration in the unobserved effect compartment C is then directly linked to the response Y via the E_{max} model.

linear differential equations

$$\frac{dC_0(t)}{dt} = -\theta_1 C_0(t) \tag{1}$$

$$\frac{dC(t)}{dt} = -\theta_2 C(t) + \theta_1 C_0(t). \tag{2}$$

This set of differential equations can be solved analytically. For a single dose D given at time 0, the concentration in the effect compartment over time is then

$$C(t) = \frac{D\,\theta_1}{\theta_1 - \theta_2}\left(e^{-\theta_2 t} - e^{-\theta_1 t}\right). \tag{3}$$

It should be noted that the volume of distribution is set to 1, as the concentration in the effect compartment is not observed [17]. To relate the time-varying and dose-dependent latent concentration to some drug effect, we need to introduce a function $g(C)$ of the latent concentration C in the effect compartment. The most important model in this class is the direct-response E_{max}-model, for which

$$g(C(t)) = \theta_5 + \frac{\theta_4 \cdot C(t)}{\theta_3 + C(t)}. \tag{4}$$

Here, θ_5 is the expected response under placebo, that is, when $C(t) = 0$, $(\theta_5 + \theta_4)$ is the maximal possible expected response ($C(t) \to \infty$), and θ_3 is the latent concentration for which the expected response is at half of the maximal possible effect. If patient i receives a single subcutaneous injection of dose D_i and a continuous response y_{ij} is measured at time t_j for $i = 1, ..., N$ and $j = 1, ..., J$, we assume that

$$y_{ij} = \theta_5 + \frac{\theta_4 D_i\left(e^{-\theta_2 t_j} - e^{-\theta_1 t_j}\right)}{\theta_3\left(1 - \theta_2/\theta_1\right) + D_i\left(e^{-\theta_2 t_j} - e^{-\theta_1 t_j}\right)} + \epsilon_{ij} \tag{5}$$

with $\epsilon_i = (\epsilon_{i1}, ..., \epsilon_{iJ})^T \sim \mathcal{N}(0, \Sigma)$ *i.i.d.* Note that observations on the same patient may be dependent, while observations from different patients will be assumed to be independent. In the PKPD literature, the response at baseline (i.e.. at $t = 0$) is typically part of the response model (5), while in the statistical literature, only post-baseline response measurements would typically be included (with baseline response as a covariate).

2.2. *Model extensions*

The basic dose–time-response model discussed in the previous section may often have to be modified, and we now discuss some of the most important types of extensions. For the model-building, residual plots and other diagnostic tools are essential [22, 23].

2.2.1. Placebo response. In the basic model (5), we assume that the expected response dose not change with time in a placebo group. In many cases, this is not a realistic assumption because of placebo-effects, regression to the mean, or disease progression. To model a time-changing response in a placebo group, one may replace θ_5 in (5) by $\sum_{r=5}^{R} \theta_r \gamma_r(t)$, where the θ_i are unknown real-valued parameters and the $\gamma_i(t)$ are arbitrary real valued known functions. This functional form allows great flexibility: in simple cases, the placebo response may be a linear trend or a quadratic function. When a more complex placebo response is expected, B-splines might be a more appropriate choice. More sophisticated models to describe disease progression and how this is changed by the drug may be needed in some cases [18, 25].

2.2.2. Baseline covariates. Some of the PK or PD parameters may be patient-specific. If baseline covariates such as the baseline response or body weight can explain some of these differences, parameters may be modeled as functions of baseline covariates. For example, if in the basic model (5), the intercept θ_5 appears to be patient-specific, then the term $\sum_{p=6}^{R} \theta_p X_{i(p-5)}$ may be added to the basic model, where $X = (X_{i1}, ..., X_{iP})$ are values for patient i for relevant covariates. Baseline covariates may not explain all differences among patients in model parameters, and then random-effects models can be considered [26].

2.2.3. Multiple doses. A key use of dose–time-response models is the prediction of the response for dosing schedules not yet investigated. For example, if the time-changing response after a single dose of the mAb given at time $t = 0$ is described by model (5), one may want to know how the response profile would look like if a second dose is given at time $t = 84$. The basic model can be naturally extended to handle multiple dosing. Assuming linear kinetics, the latent concentration profile for multiple doses is obtained by superposition of the concentration profiles for single doses [12]. Many mAbs show linear kinetics over the dose range of interest [27]. If a patient receives K subcutaneous injections with dose D_k injected at time τ_k, $k = 1, ..., K$, then the latent drug concentration in the effect compartment is given by

$$C(t) = \sum_{k=1}^{q} \frac{D_k \theta_1}{\theta_1 - \theta_2} \left\{ \exp\left[-\theta_2 \left(t - \sum_{j=0}^{k-1} \delta_j\right)\right] - \exp\left[-\theta_1 \left(t - \sum_{j=0}^{k-1} \delta_j\right)\right] \right\}, \tag{6}$$

where $\delta_0 = \tau_1$, $\delta_j = \tau_{j+1} - \tau_j$ for $j = 1, ..., K-1$, and $q \in \{1, ..., K-1\}$ is such that $\tau_q < t \leqslant \tau_{q+1}$ and $q = K$ if $t > \tau_K$. Including this in model (4), a dose–time-response model for multiple doses is obtained. Figure 2 shows typical dose–time-response profiles using such a model. This illustrates that the dose–time-response models presented earlier can describe complex response profiles for various dosing regimens.

2.2.4. Route of administration. We mentioned earlier that the form of the latent concentration in the effect compartment $C(t)$ depends on the route of administration. So far, we focused on subcutaneous injection. Other common scenarios for biologics are the administration as an intravenous bolus or an

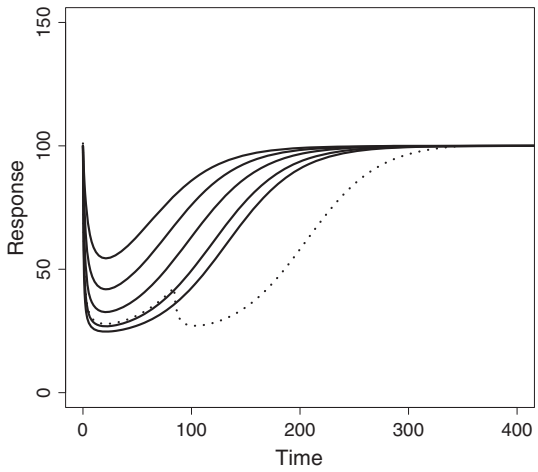

Figure 2. Dose–time-response profiles for five different single doses given at time 0 (solid lines) and for repeated dosing at time 0 and 84 (dotted line).

intravenous infusion with duration δ. In these cases, the latent concentration is

$$C(t) = D\ \exp(-\theta t) \qquad \text{for an intravenous bolus and} \tag{7}$$

$$C(t) = \frac{D}{\delta\theta}\left(1 - e^{-\theta\delta}\right) e^{-\theta I_{\{t-\delta>0\}}(t-\delta)} \qquad \text{for an intravenous infusion.} \tag{8}$$

In some cases, the biologic may pass through several compartments before reaching the effect compartment. If the kinetics of the system can be described by linear differential equations, the concentration profile in the effect compartment is then a sum of exponential terms $\exp(-\theta_k t)$. For example, when an mAb is administered as an intravenous bolus, a kinetic model with two exponential terms as used for subcutaneous injections could be appropriate. When adding more compartments, some care has to be taken to avoid identifiability problems of the parameters. For example, in the E_{max}-model with subcutaneous injection (5), the same dose–time-response profiles are obtained for the parameter sets $(\theta_1, \theta_2, \theta_3, \theta_4, \theta_5)$ and $(\theta_2, \theta_1, \theta_3\frac{\theta_1}{\theta_2}, \theta_4, \theta_5)$. To avoid this flip-flop problem, constraints on the parameter space can be imposed, for example, one may require that $\theta_1 > \theta_2$.

2.2.5. Residual error. In the basic model (5), the residual errors are assumed to be correlated with unstructured error covariance matrix. If the number of timepoints where the response is measured is large or few subjects are included in the study, a more parsimonious error covariance model would be preferable, if found to be appropriate. More complex residual error models where the residual variance is a function of the expected response may also be necessary in some cases [28].

2.2.6. Indirect-response models and turnover models. In the basic model, the latent concentration in the effect compartment is directly related to the response. Indirect-response or turnover models are alternative models that may be more appropriate in some cases, depending on the mode-of-action of the mAb. In these models, the production or elimination of a substance by the body is either stimulated or inhibited by the mAb. The PK component of such models can again be treated as a latent variable [29].

2.3. Statistical inference and prediction

For nonlinear regression models, ML methods are commonly used for inference. As it is hardly possible to maximize the likelihood analytically, one has to rely on numerical optimization procedures, such as the quasi-Newton algorithm. The likelihood function may have several local maxima, and hence, the performance of these iterative procedures often crucially depends on a good initial guess of the parameter values, which may be difficult [22]. In practice, different starting values may have to be tried out, and the optimization procedure may have to be changed in case of convergence problems. Specifically, these issues occur if some of the parameters are weakly identified by the data, or if the likelihood has its maximum close to the boundary of the parameter space.

Approximate confidence intervals for the individual parameters are typically derived based on asymptotic theory. The construction of confidence intervals for the parameters relies on the fact that, under appropriate regularity conditions, the ML estimator is asymptotically normally distributed with covariance matrix equal to the inverse of the Fisher information matrix. Confidence intervals for the expected response and for the prediction intervals can be constructed similarly [23]. The derivation of confidence and prediction intervals relies on asymptotics and linear approximations, and hence, the validity of these intervals is questionable for small sample sizes. Moreover, as one of the mentioned regularity conditions, the asymptotic ML theory is not applicable if the true parameter is at the boundary of the parameter space. For dose–time-response models, parameter constraints have often to be imposed for identifiability reasons, and it is then not uncommon that ML estimates are actually on the boundary.

In Bayesian inference, the Bayes' theorem is used to derive the posterior distribution of the parameters from the prior distribution and the likelihood. In the context of dose–time-response models, weakly informative priors may be used if the data are expected to overwhelm any vague information available. However, the choice of an appropriate weakly informative prior for nonlinear models requires some care to avoid unintended informative priors [24]. If scientific expertise or experience from previous trials is available, one may incorporate this knowledge by using informative priors [30]. This is especially useful for parameters that are not well identified by the data from the clinical trial.

For dose–time-response models, direct calculation of the posterior distribution is usually not possible, as this requires multidimensional integration. However, a sample from the posterior can be generated

without the need to evaluate this integral, using MCMC methods [31], as implemented in WinBUGS [32] or JAGS [33]. For these nonlinear regression models, MCMC is typically computer intensive, as the Markov chain often exhibits strong autocorrelation and hence requires many iterations.

3. Operating characteristics

3.1. Motivation

In clinical trial simulations, data are generated repeatedly for a given dose–time-response model and then analyzed to assess the frequentist performance of a statistical method. As noted earlier, confidence and prediction intervals based on ML theory hold asymptotically only, and their coverage properties for sample sizes used in a clinical trial are certainly of interest. Frequentist properties for Bayesian approaches are relevant as well, especially if priors are used that are intended to be non-informative. The clinical trial simulations also allow to investigate technical aspects, for example the convergence properties of algorithms used for ML estimation.

Performing a likelihood analysis for one simulated dataset is typically not numerically expensive for the dose–time-response models considered here. Hence, running these for a thousand simulated datasets is still possible in a manageable amount of time. This is different for the time-consuming Bayesian analysis requiring MCMC algorithms. Consequently, doing so for many simulated datasets will not be possible in a reasonable amount of time on a single computer. However, with access to computing clusters, this becomes a feasible task.

3.2. Simulation setup and results

To illustrate the evaluation of operating characteristics, we consider a clinical trial where a mAb is administered by subcutaneous injection. A model describing this situation was already discussed in Section 2.1, and an example of such a dose–time-response model for different dose regimens is shown in Figure 2. We assume that 30 patients are randomized to five treatment groups, each patient receiving a single dose of $0.25, 0.5, 1, 2$, or 3 units of the mAb. We did not include a placebo group to match to the case study in the following section. We further assume that the response of interest is normally distributed and measured at time 0,7,14,21,28,56,84,112,140, and 168 for each patient. For the clinical trial simulation, 1000 datasets are generated using a multivariate normal distribution. For the expected value, we used the E_{max} model (5), with true parameters shown in Table I. The true values of the error covariance matrix were set to $(\Sigma)_{ij} = 70^2 \cdot 0.8^{|t_i - t_j|/7}$. Each of these datasets is then analyzed by likelihood and Bayesian methods, respectively, and both point estimates and confidence (probability) intervals are calculated for each of the model parameters. Furthermore, point estimates and confidence (probability) intervals are derived for the expected response of a patient who received two doses of 2 units on day 0

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%

and 84 (Figure 2). For the ML analysis, we used the R-function *optim* to perform the optimization, and we used the true values of the parameters as starting values. Of course, this might not be very realistic and needs to be considered when assessing the quality of the results. For the Bayesian analysis, the following weakly informative priors were used: We assumed θ_1 to be uniformly distributed between 0.005 and 5, and in order to assure $\theta_2 < \theta_1$, we used a uniform prior on $(0.005, \theta_1)$ for θ_2. We also assumed uniform priors for the other parameters, namely on the interval $(0.001, 100)$ for θ_3, on $(-200, 200)$ for θ_4, on $(0, 200)$ for θ_5, and finally an inverse-Wishart prior for the covariance Σ, via $\Sigma^{-1} \sim Wishart(R, \rho)$. We set ρ to 10 and R to $10 \cdot \Sigma$ to obtain a weakly informative prior distribution [32]. The corresponding WinBUGS or JAGS code is provided in the appendix.

Table I shows the simulation results. Both the ML and the Bayesian methods provided point estimates near to the true parameter values, with ML estimates tending to be closer. Furthermore, the coverage of the confidence and probability intervals seems acceptable in this example. The coverage of the Bayesian probability intervals was somewhat better than the coverage of ML-confidence intervals in the sense of being typically closer to 95%.

4. Clinical trial example

4.1. Background

We will now discuss the use of dose–time-response models for the analysis of a clinical trial where the effects of canakinumab were examined. Canakinumab is a human mAb designed to bind and neutralize the activity of human IL-1β, a pro-inflammatory cytokine. The study at hand focuses on its treatment against acute gouty arthritis, a painful inflammatory disease that is especially common among people above 70 years old [34]. This double-blinded dose-ranging study lasted 24 weeks and used an active control. The participating patients were subsequently randomized to seven treatment groups, that is, they received either a single dose of canakinumab (either 25 mg, 50 mg, 100 mg, 200 mg, or 300 mg at day 1), or multiple doses of canakinumab (first 50 mg at day 1, then 50 mg at week 4, then 25 mg at week 8, and finally 25 mg at week 12) or daily oral doses of an active comparator. Each group consisted of approximately 50 patients, except for the active-control group that consisted of approximately 100 patients. An important endpoint is the C-reactive protein (CRP) level, a biomarker for the severeness of inflammation. It was measured every 4 weeks (and additionally on day 15) in each of the seven treatment arms. We used the logarithmized CRP values as the response in the following analysis.

The data from this clinical trial will be used to investigate whether the dose–time-response models discussed in Section 2 are able to fit such data, and also whether they can predict the response for untested treatment regimens. Hence, we will only consider the data from the five single-dose arms to fit a dose-time-response model, and then use the model to predict the multiple dose treatment regimen with four injections. Ideally, the model should describe the data well for each of the single-dose arms, and also predict well the actual observed measurements from the treatment arm with multiple injections.

4.2. Dose–time-response model

Canakinumab was administrated by subcutaneous injection. Hence as a dose–time-response model, one may first consider the E_{max} model defined by (5) in Section 2.1, where the parameters of the latent PK effect compartment (θ_1, θ_2), the E_{max} parameter θ_4, and the EC_{50}-parameter θ_3 are the same for each patient. Because of the flip-flop identifiability problem for this model discussed in Section 2.2, the constraint $\theta_1 > \theta_2$ is imposed. Graphical exploration suggested that the baseline CRP levels (X_0) are important. As described in Section 2.2, we accounted for this by adding an additive linear predictor $\theta_6 \cdot X_0$ in the model, and included only post-baseline CRP levels as responses in our dose–time-response model.

4.3. Inference

An initial analysis of the clinical trial data with both likelihood and Bayesian methods revealed that the parameter θ_1 is not identifiable from the data. In our model, θ_1 describes how quickly the drug is absorbed by the effect compartment, or because the concentration is directly linked to the effect how quickly the monitored biomarker reaches its minimum. As the patients are not examined until 15 days after the injection, the data give us only limited information about the absorption parameter. This can be seen in Figure 3, as the profile likelihood for θ_1 is essentially constant for values greater than 0.5 day^{-1}. From previous studies, the absorption rate from the subcutaneous skin depot to the blood was estimated

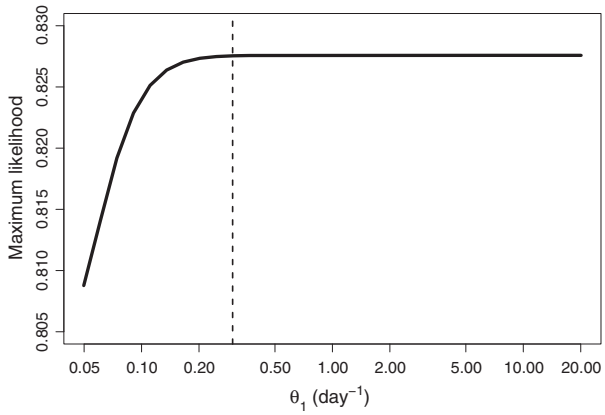

Figure 3. Profile likelihood plot against the parameter θ_1. An upper bound based on previous studies is 0.3 day^{-1} (vertical dotted line).

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

as $k_a = 0.3$ day^{-1} [35]. As the absorption into the effect compartment must be slower than into the blood, this provides an upper bound $\theta_1 < 0.3$ day^{-1}. Although this information can be incorporated in the ML analysis, the ML estimator is then on the boundary of the parameter space, and standard inference results may not be appropriate. In the Bayesian framework, such information is included by setting the prior for θ_1 to zero for values larger than 0.3 day^{-1}. For the other parameters, vague priors are used, namely normal distributions with expected value 0 and standard deviation 100 for θ_4, for θ_5, and θ_6, and a uniform prior on the interval $(0.01, 100)$ for θ_3. To assure $\theta_1 > \theta_2$, we chose an uniform prior on $(0.005, \theta_1)$ for θ_2. For the covariance Σ, we used an inverse-Wishart prior via $\Sigma^{-1} \sim Wishart(R, \rho)$. We set ρ to 7 and R to $7 \cdot \Sigma_0$, where $(\Sigma_0)_{ij} = 0.9^{|t_i - t_j|/14}$, to obtain a weakly informative prior distribution [32]. We focus in the following on the Bayesian analysis, as the likelihood analysis does not provide additional insights.

Table II shows the main results of the Bayesian analysis. To assess how well the dose–time-response model fits the data, observed values and the fitted Bayesian model are compared in Figure 4. As can be seen, the dose–time-response model is able to describe the single-dose data very well ($R^2 = 0.82$). Further graphical residual analyses did not show any patterns that would suggest inadequacy of the model.

For mAbs, the dose–time-response models are mainly intended to be used for prediction of the response-profile for untested treatment regimens. Hence, we will now use the model fitted on single-dose data to predict a treatment regimen with four injections at different times (50 mg at day 1 and week 4, 25 mg at weeks 8 and 12). Such a treatment arm was also included in the clinical trial, and hence allows to validate the dose–time-response model. Figure 5 shows the data from the multiple dose arm of the trial and also the prediction from the dose–time-response model derived from the Bayesian analysis of the single-dose data. All of the data points are within the 95% prediction intervals. Hence, the model appears to predict the change of the response over time for the multiple dose treatment quite well.

4.4. Comparison to dose–response model

For conventional drugs, dose–response models at a fixed timepoint are often used. Although such models could also be used for mAbs, dose–time-response models are more useful. Some advantages are obvious and have already been discussed earlier, such as the handling of complex dosing regimens and the possibility of making predictions over time. In this section, we compare dose–response and dose–time-

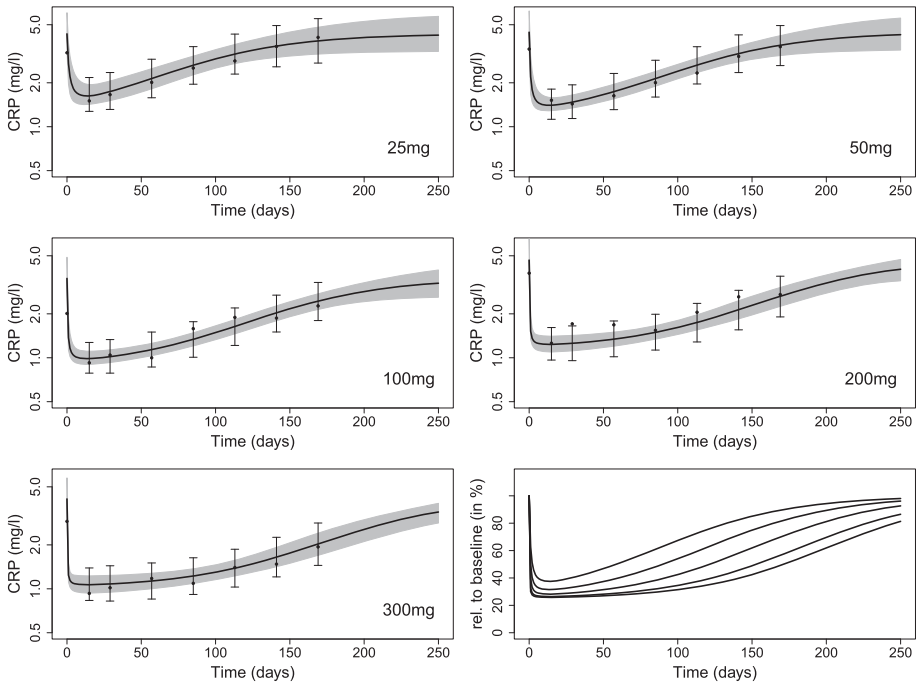

Figure 4. Bayesian analysis for the five single dose arms in the clinical trial. The dots represent the means of the C-reactive protein-levels, the solid curves the median of the posterior, the grey area the 95% posterior probability interval, and the vertical lines the 95% prediction probability interval.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

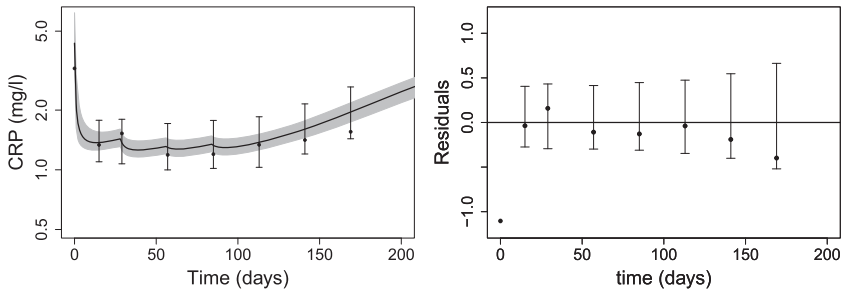

Figure 5. Bayesian prediction of the repeated dosing regimen based on the dose–time-response model derived from single-dose regimens.

response models for the clinical trial example with canakinumab in patients with acute gouty arthritis. For the dose–response model, the standard Emax model seems to be appropriate. As before, we account for the different intercepts among the patients by including baseline CRP as a covariate. Hence, for a fixed timepoint t, the normally distributed response (CRP) for a patient who received dose D and had a baseline response of X_0 is assumed to have an expected value of

$$\alpha_1 + \alpha_4 \cdot X_0 + \frac{\alpha_2 \cdot D}{\alpha_3 + D} \tag{9}$$

and a residual error variance of σ^2. We used a Bayesian approach to fit this model for three timepoints t: one in the beginning (day 15), one in middle (day 85), and one at the end of the trial (day 169), resulting in three fitted models. We used weakly informative priors for all of the parameters, that is, a uniform distribution on the interval $(0, 5)$ for α_1, on $(-100, 100)$ for α_2, on $(0.001, 10000)$ for α_3, and on $(-10, 10)$ for α_4. At each of the three timepoints, we then used the fitted *Emax* model and the fitted dose–time-response model (Table II) to estimate the difference to baseline. The results are visualized in Figure 6.

Apart from a vertical shift, the results look similar at each of the three timepoints. The confidence bands of the dose–time-response model are narrower than those of the dose–response model, especially when

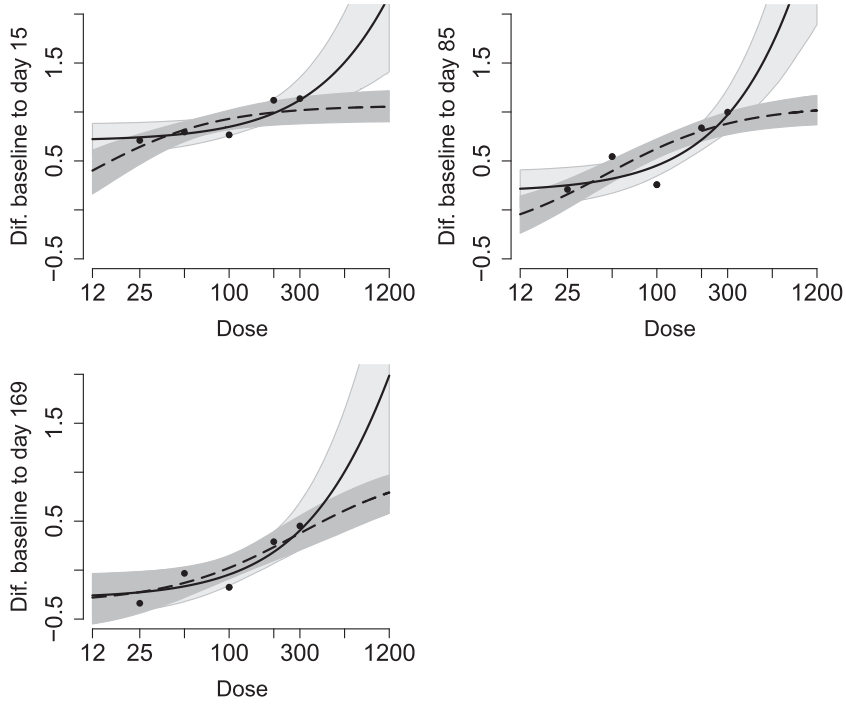

Figure 6. Comparison of the dose–time-response model with the standard *Emax* model. The dots represent the means of the measurements, the solid line the fitted *Emax* model, and the dashed line the fitted dose–time-response model. The light grey area and the dark grey area mark the respective 95%-confidence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

extrapolating beyond the range of observed doses. Although the fit of the observed data is similar for both dose–response and dose–time-response models, the extrapolations for higher than observed doses are very different for the two models. The predictions of the dose–response model for higher doses do not seem trustworthy when considering the entirety of the data.

5. Discussion

For biologics such as mAbs, finding an appropriate treatment regimen is difficult, as both the dose and timing between doses needs to be specified. This search space is much larger than for conventional drugs, where usually just an adequate dose has to be identified. We proposed here the use of dose–time-response models, which are semi-mechanistic models relying on simplified pharmacological concepts, and can be expected to provide more reliable predictions than empirical models. Extrapolations are always more challenging than interpolations, and hence, the possibility of grossly wrong predictions has to be acknowledged. Nevertheless, the successful application of dose–time-response models for many conventional drugs and for some mAbs [18] suggests that the models can be used with some confidence. This was also illustrated in the clinical trial example in patients with gout, where the response-time profile for a multiple dosing regimen could be well predicted from single-dose data. In this example, the effect of the mAb on the response was fast, that is, took less than 1 month. However, dose–time-response models have been used for conventional small drug molecules where the drug effects happen on much longer timescales, that is, months or years [21].

For conventional drugs, both dose–response models and more elaborate PKPD models are often used in parallel. Dose–response model are considerably simpler to fit, require a less detailed understanding of the precise mechanism of action, can be based on dose and response data only, and are easier to communicate. On the other hand, PKPD models can provide more scientific insight, and are particularly useful at a late stage of drug development, where information from many studies can be integrated. The situation is very similar for mAbs, where dose–time-response models and PK/PD models are complementary approaches. Although PK measurements of the mAb in blood may provide useful information, sophisticated models described by large sets of differential equations are then required to make use of

this information. Additionally, as noted by Lowe [11], the posology of mAbs and other biologics is less related to PK compared with the posology of conventional drugs.

Both ML and Bayesian methods can be used for inference and prediction with dose–time-response models. For a sufficiently large number of patients, and well-chosen visit times, both approaches typically lead to similar conclusions. Bayesian methods allow to include prior information, which is particularly useful if some of the model parameters are only partially identifiable from the clinical trial data. The semi-mechanistic nature of the model is often important there, as some of the parameters then have a scientific meaning [31]. This facilitates use of prior information derived from previous clinical trial with the experimental mAb, or from publication on other mAbs with the same mechanism of action.

We considered here the use of dose–time-response models in the analysis of clinical trials with biologics. Another important application of such models is in the design of clinical trials with mAbs, as currently used designs may not be optimal. Locally optimal designs for dose–time-response models were studied by Fang and Hedayat [36] and Dette *et al.* [37], which both address the optimal timing of visits. The optimal design of clinical trials with biologics with respect to the choice of doses is described by Lange and Schmidli [38].

Appendix

WinBUGS or JAGS code for the dose–time-response model defined by (3) and (5) in Section 2.1.

```
model{
# statistical model for single-dose-treatment, m=number of observation time-
# points, time=vector of observation timepoints, n.patients=number of patients
# observed at each timepoint, D=dose
for (j in 1:n.patients){
   y[j,1:10] ~ dmnorm(mu[],Sigma.inv[,])
}
for(i in 1:m){
   c[i] <- D*theta1/(theta1-theta2)*( exp(-theta2*time[i]) - exp(-theta1*time[i]) )
   mu[i] <- theta5 + theta4*c[i]/(theta3 + c[i])
}

# priors
Sigma.inv[1:10,1:10]  ~ dwish(R[,],10)
Sigma <- inverse(Sigma.inv[,])
theta5 ~ dunif(0,200)
theta4 ~ dunif(-200,200)
theta3 ~ dunif(0.001,100)
# constraint theta1 > theta2 > 0
theta2 ~ dunif(0.005,theta1)
theta1 ~ dunif(0.005,5)
}
```

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