Analysis of Clinical Trials with Biologics Using Dose-Time-Response Models

Group 2

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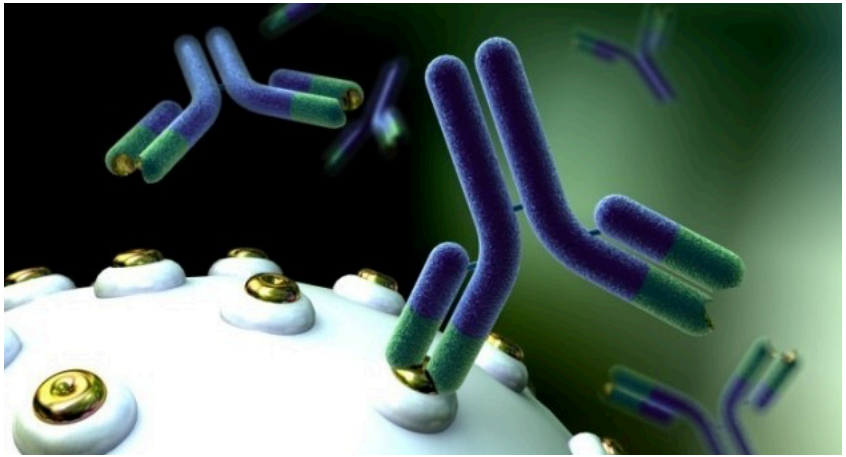
Agenda

- Background
- Methodology
- Dose-Time-Response Model
- Simulation
- Clinical Trial
- Evaluations

1 Background

Background

Monoclonal Antibodies (mAbs)



Background

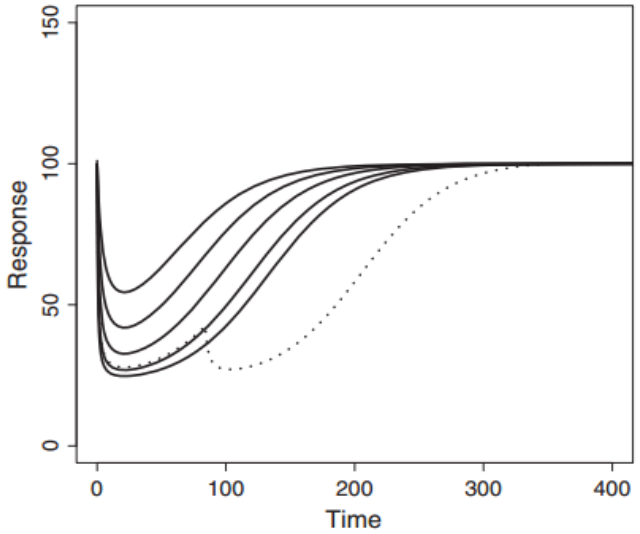
Clinical trial: Conventional Drug VS mAbs

- Conventional Drug
  - Small and fixed interval
  - Only optimize dose
  - Fast effect
- mAabs
  - Long and Flexible interval
  - Both dose and time need to be optimized
  - Slow and Long Term effect

Background

Main Idea

The proposed approach uses nonlinear regression models to describe and predict the time-changing response for complex dosing regimens.



2 Methodology

Methodology

Bayesian Inference

$$P(Model|Data) = \frac{P(Data|Model)P(Model)}{P(Data)}$$

- Observed data ⇒ prior probability and Statistical Model ⇒ Posterior probabilitys

Methodology

Bayesian VS Frequentist

Where is the ringing phone?

- Frequentist Reasoning
  - Judgment from listening
- Bayesian Reasoning
  - Judgment from listening
  - Previous knowledge of phone location

Methodology

Maximum Likelihood

- Likelihood Function $\operatorname{lik}(\theta) = f_D(x_1, \ldots, x_n \mid \theta)$

Bayesian estimation

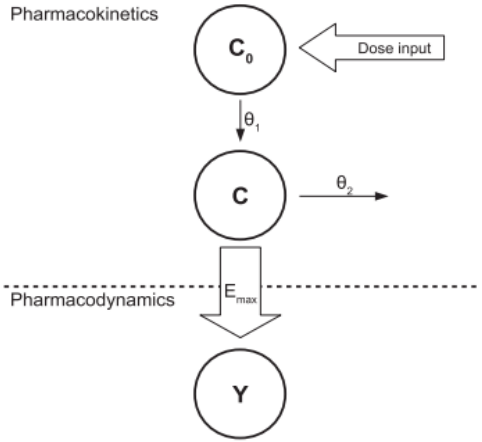
- Posterior Distribution $\theta \mapsto \frac{f(x|\theta)\, g(\theta)}{\int_\Theta f(x|\theta')\, g(\theta')\, d\theta'}$

3 Dose-Time-Response Model

Dose-Time-Response Model

Basic Model

pharmacokinetic–pharmacodynamic (PKPD) model



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

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

Dose-Time-Response Model

Direct-Response E_{max}-model

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

The Basic Model

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

4 Simulation

Simulation

To estimate the operating characteristics of the basic model

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

- A mAb is administered by subcutaneous injection
- 1000 datasets generated using a multivariate normal distribution
- E_{max} model is used to assess the expected value

Simulation

Summary of the simulation results

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%

Simulation

Simulation results

- Point estimates near to the true parameter values
- ML estimates close to the true values on average
- Acceptable confidence and probability interval coverage
- Slightly better Bayesian probability interval coverage

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5 Clinical Trial

Clinical Trial

Objectives

- To evaluate the fitness of the dose-time-response model in the clinical trial
- To evaluate the accuracy of the dose-time-response model predictions of the untested treatment regimens response

Clinical Trial

Dose-time-response models used to analyze the clinical trial

- The effects of canakinumab subcutaneous injection were examined
- 24 weeks, 400 patients
- Participants randomly divided into seven groups
  - Five groups 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)
  - The last group as the placebo
- The logarithm of C-reactive protein (CRP) levels as a proxy of the response
  - CRP is a biomarker signaling the severeness of the disease

Clinical Trial

Bayesian analysis for the five single-dose groups

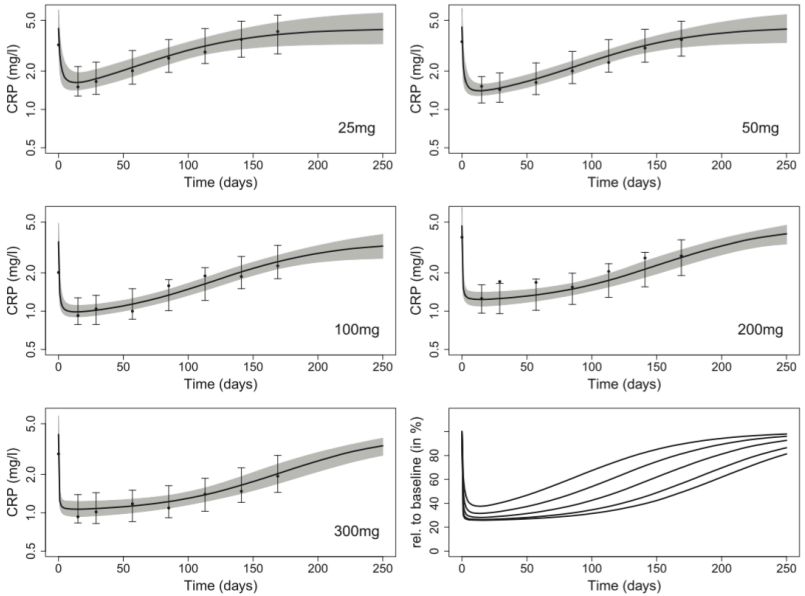
Table II. Bayesian analysis for data from the five single-dose treatment groups.

	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

θ_6 is added to the basic model to measure the effect of the baseline CRP levels (X_0)

Clinical Trial

Comparison of observed values and the fitted Bayesian model

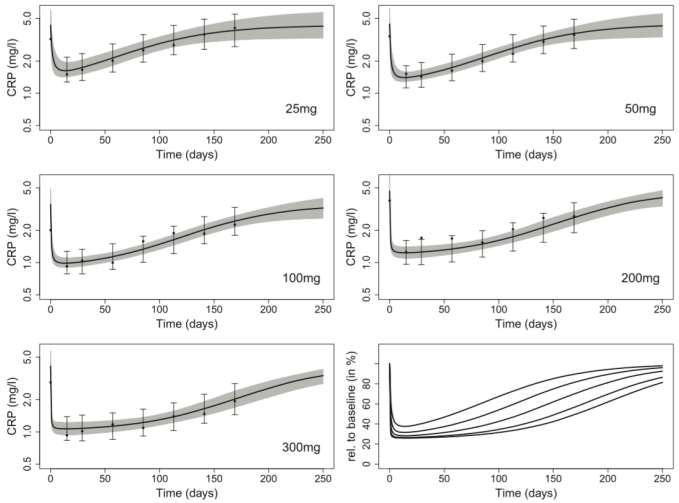


- Dots: CRP mean
- Solid curve: CRP median
- Grey area: 95% posterior probability interval
- Vertical lines: 95% prediction probability interval
- Last plot: all posterior median curves relative to their baseline value

Clinical Trial

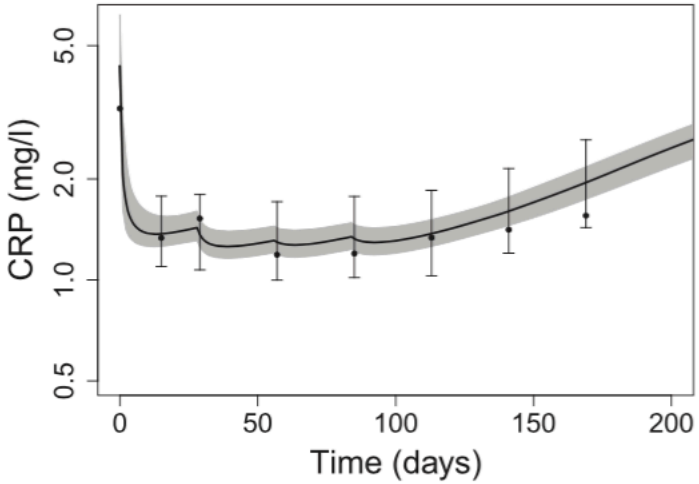
Accuracy evaluation

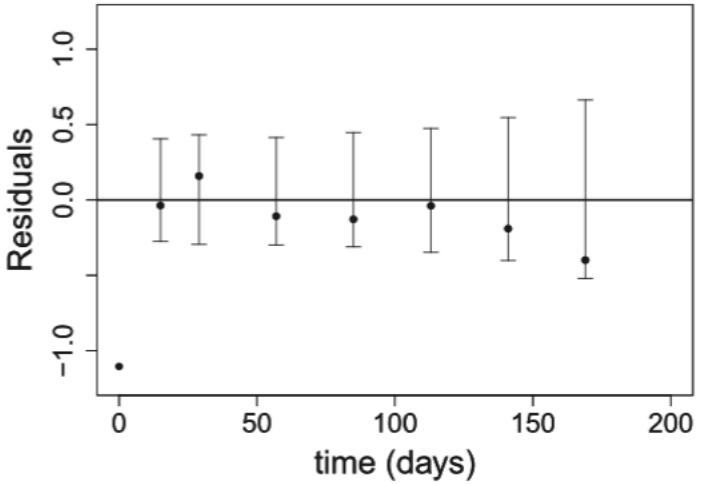
- With $R^2 = 0.82$, the dose-time-response model describes the single-dose data well



Clinical Trial

Bayesian prediction for the multiple dose treatment

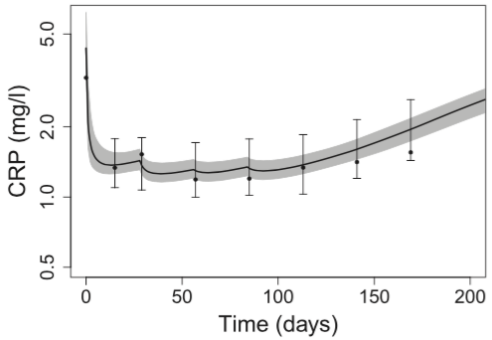


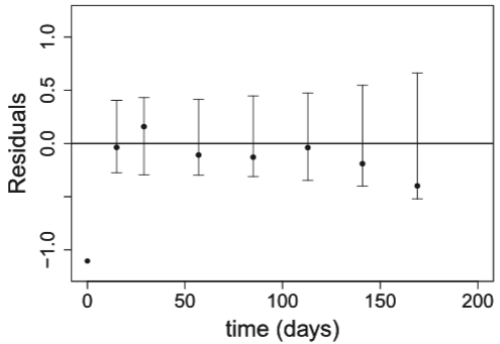


Clinical Trial

Results of the Bayesian prediction

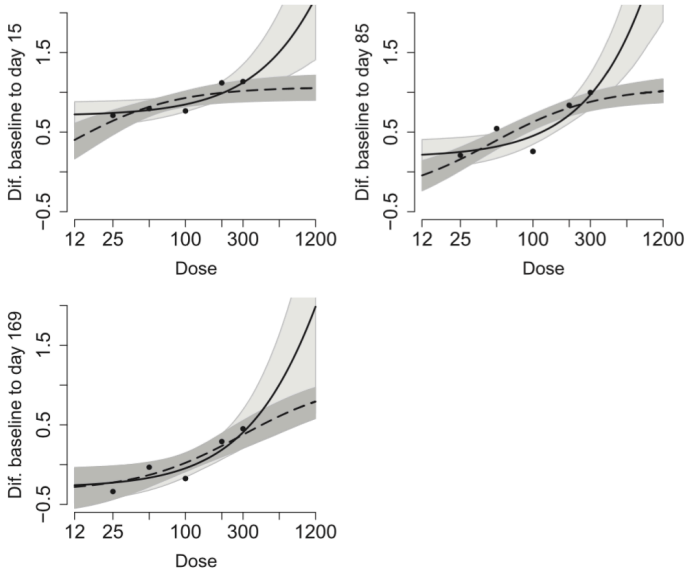
- All data points within the 95% prediction intervals
- Good accuracy of the dose-time-response model predictions of the response over time for the multiple dose treatment





Clinical Trial

Dose-time-response model VS Standard E_{max} model

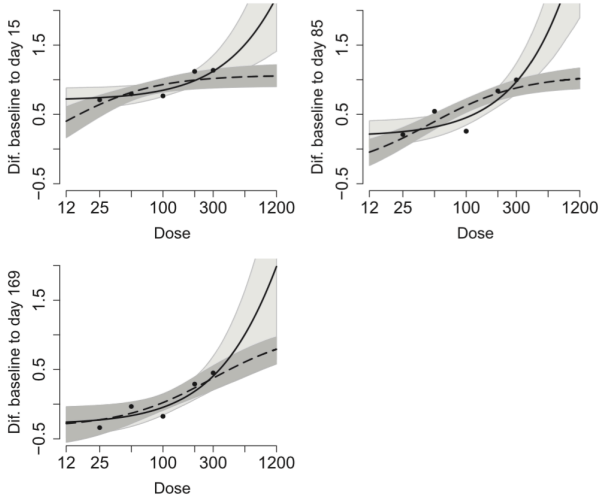


- Dots: CRP mean
- Solid line: fitted E_{max} model
- Dashed line: fitted dose–time-response model
- Light/Dark grey area: respective 95% confidence bands of the expected response

Clinical Trial

Results of Comparison

- Similar fits of data for both models
- More accurate predictions for higher doses in the dose-time-response



6 Evaluations

Evaluations

Limitations

- ML methods may not be valid for small samples in the experiments
- Bayesian framework may cause unintended informative prior problems
- Sample generated using Markov chain Monte Carlo (MCMC) methods are subject to the validity problem

Evaluations

Issues & Challenges

- Challenging to ensure the fitness of nonlinear regression models
- Bayesian analysis requires MCMC algorithms, which is computer-intensive and time-consuming

Thanks!

Any questions ?

Maximum Likelihood

- Maximum likelihood is the procedure of finding the value of one or more parameters for a given statistic which makes the known likelihood distribution a maximum.
- http://mathworld.wolfram.com/MaximumLikelihood.html
- http://statweb.stanford.edu/~susan/courses/s200/lectures/lect11.pdf

MLE

- Maximum-likelihood estimation (MLE) is a method of estimating the parameters of a statistical model given data.
- In general, for a fixed set of data and underlying statistical model, the method of maximum likelihood selects the set of values of the model parameters that maximizes the likelihood function.

Bayesian Analysis

- Bayesian analysis is a statistical procedure which endeavors to estimate parameters of an underlying distribution based on the observed distribution
- prior distribution -> observed distribution -> posterior distribution
- Bayesian analysis is somewhat controversial because the validity of the result depends on how valid the prior distribution is, and this cannot be assessed statistically.
- http://mathworld.wolfram.com/BayesianAnalysis.html

Bayesian Inference

- A method of statistical inference in which Bayes' theorem is used to update the probability for a hypothesis as more evidence or information becomes available.
- Bayesian updating is particularly important in the dynamic analysis of a sequence of data.

$$\mathrm{P}(Model|Data) = \frac{\mathrm{P(Data|Model)P(Model)}}{P(Data)}$$

Monte Carlo Method

- Any method which solves a problem by generating suitable random numbers and observing that fraction of the numbers obeying some property or properties.
- The method is useful for obtaining numerical solutions to problems which are too complicated to solve analytically.
- Monte Carlo methods are mainly used in three distinct problem classes: optimization, numerical integration, and generating draws from a probability distribution.
- http://mathworld.wolfram.com/MonteCarloMethod.html

Monte Carlo Integration

- In mathematics, Monte Carlo integration is a technique for numerical integration using random numbers.
- Many algorithms usually evaluate the integrand at a regular grid, Monte Carlo randomly choose points at which the integrand is evaluated. This method is particularly useful for higher-dimensional integrals.
- $\int f\,dV \approx V\langle f\rangle \pm V\sqrt{\frac{\langle f^2\rangle - \langle f\rangle^2}{N}}$, where $\langle f\rangle \equiv \frac{1}{N}\sum_{i=1}^{N} f(x_i)$ $\langle f^2\rangle \equiv \frac{1}{N}\sum_{i=1}^{N} f^2(x_i)$
- http://mathworld.wolfram.com/MonteCarloMethod.html

MCMC Method

- Markov chain Monte Carlo (MCMC) methods are a class of algorithms for sampling from a probability distribution based on constructing a Markov chain that has the desired distribution as its equilibrium distribution.
- The state of the chain after a number of steps is then used as a sample of the desired distribution.
- Markov chain is collection of random variables $\{X_t\}$ (t = 0, 1, ...) having the property that, given the present, the future is conditionally independent of the past. i.e.

$$P(X_t = j \mid X_0 = i_0, X_1 = i_1, \ldots, X_{t-1} = i_{t-1}) = P(X_t = j \mid X_{t-1} = i_{t-1}).$$

Multivariate Normal Distribution

- A generalization of the one-dimensional (univariate) normal distribution to higher dimensions
- A random vector is said to be k-variate normally distributed if every linear combination of its k components has a univariate normal distribution
- The probability density function of the d-dimensional multivariate normal distribution is given by

$$y = f(x, \mu, \Sigma) = \frac{1}{\sqrt{|\Sigma|(2\pi)^d}} e^{-\frac{1}{2}(x-\mu)' \Sigma^{-1}(x-\mu)}$$

- http://www.mathworks.com/help/stats/multivariate-normal-distribution.html