Infliximab: Time-Weighted Bayesian Estimation

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7 July 2016

Introduction: Time-Weighted Bayesian Estimation

Infliximab Pharmacokinetic Model

Population specifications

All patients weigh 70 kg. All patients have a baseline albumin of 4 g/dL.

There are 12 seed individuals:

1. ADA onset = 154 days, final albumin = 3 g/dL
2. ADA onset = 154 days, final albumin = 4 g/dL
3. ADA onset = 154 days, final albumin = 5 g/dL
4. ADA onset = 294 days, final albumin = 3 g/dL
5. ADA onset = 294 days, final albumin = 4 g/dL
6. ADA onset = 294 days, final albumin = 5 g/dL
7. ADA onset = 462 days, final albumin = 3 g/dL
8. ADA onset = 462 days, final albumin = 4 g/dL
9. ADA onset = 462 days, final albumin = 5 g/dL
10. ADA onset = 646 days, final albumin = 3 g/dL
11. ADA onset = 646 days, final albumin = 4 g/dL
12. ADA onset = 646 days, final albumin = 5 g/dL

Between time = 0 (baseline) and time = 546 (final), patient albumin changes in a linear sine wave fashion (amplitude = 0.1, frequency = 60 days, phase = 0)

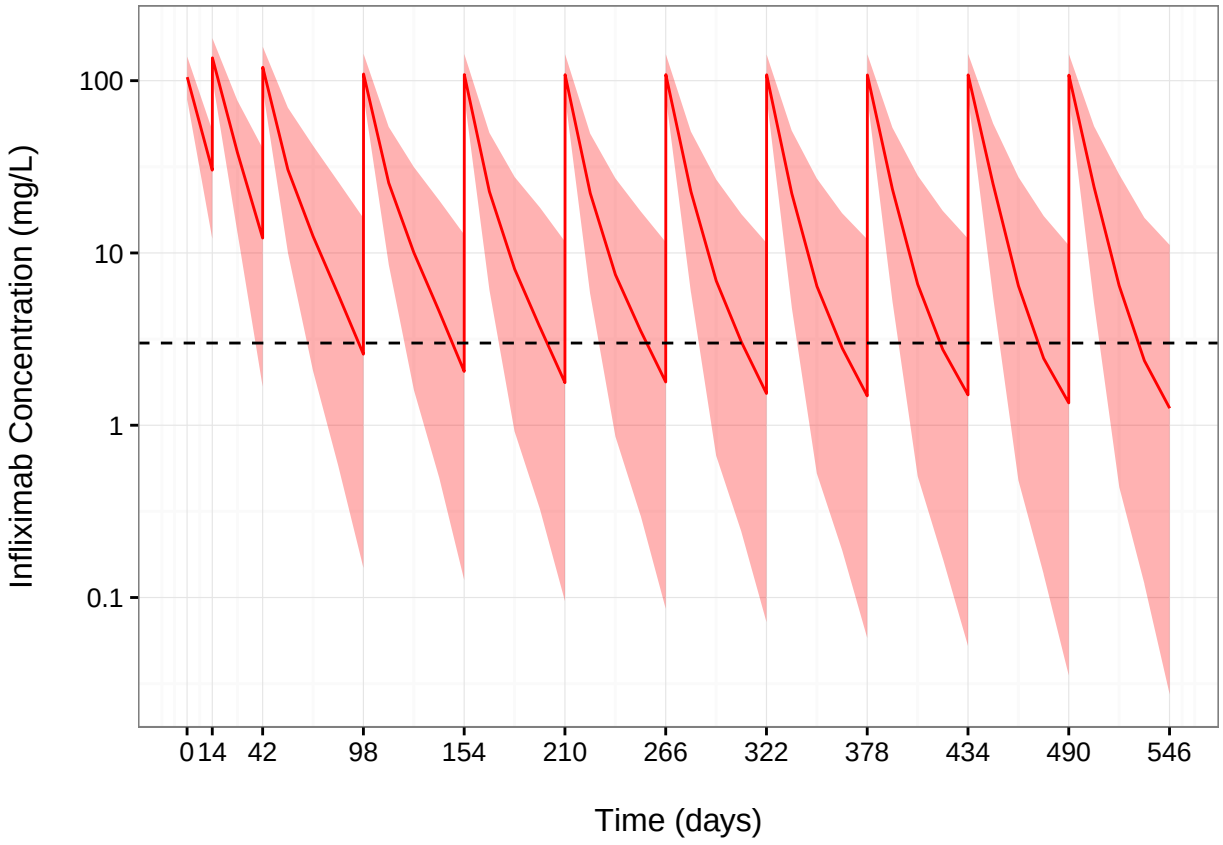
Random effect values for V1, Q and V2 change linearly between time = 0 and time = 546. CL random effect does not change as this parameter holds ADA and albumin covariate effects.

Dosing and Sampling Specifications

1. Simulations run from time = 0 to time = 546 days (approximately 18 months)
2. There are 4 sampling intervals:
    - Sampling interval 1; 0 to 98 days
    - Sampling interval 2; 98 to 210 days
    - Sampling interval 3; 210 to 378 days
    - Sampling interval 4; 378 to 546 days
3. Trough concentrations are sampled at the end of each sampling interval, i.e., time = 98, 210, 378 and 546 days since first dose
4. There are 2 or 3 2-hour infliximab infusions administered in each sampling interval
    - Sampling interval 1; 0, 14 and 42 days
    - Sampling interval 2; 98 and 154 days
    - Sampling interval 3; 210, 266 and 322 days
    - Sampling interval 4; 378, 434 and 490 days

Label Scenario

Every patient receives a 5 mg/kg dose of infliximab at every infusion time (i.e., 350 mg infused over 2 hours)



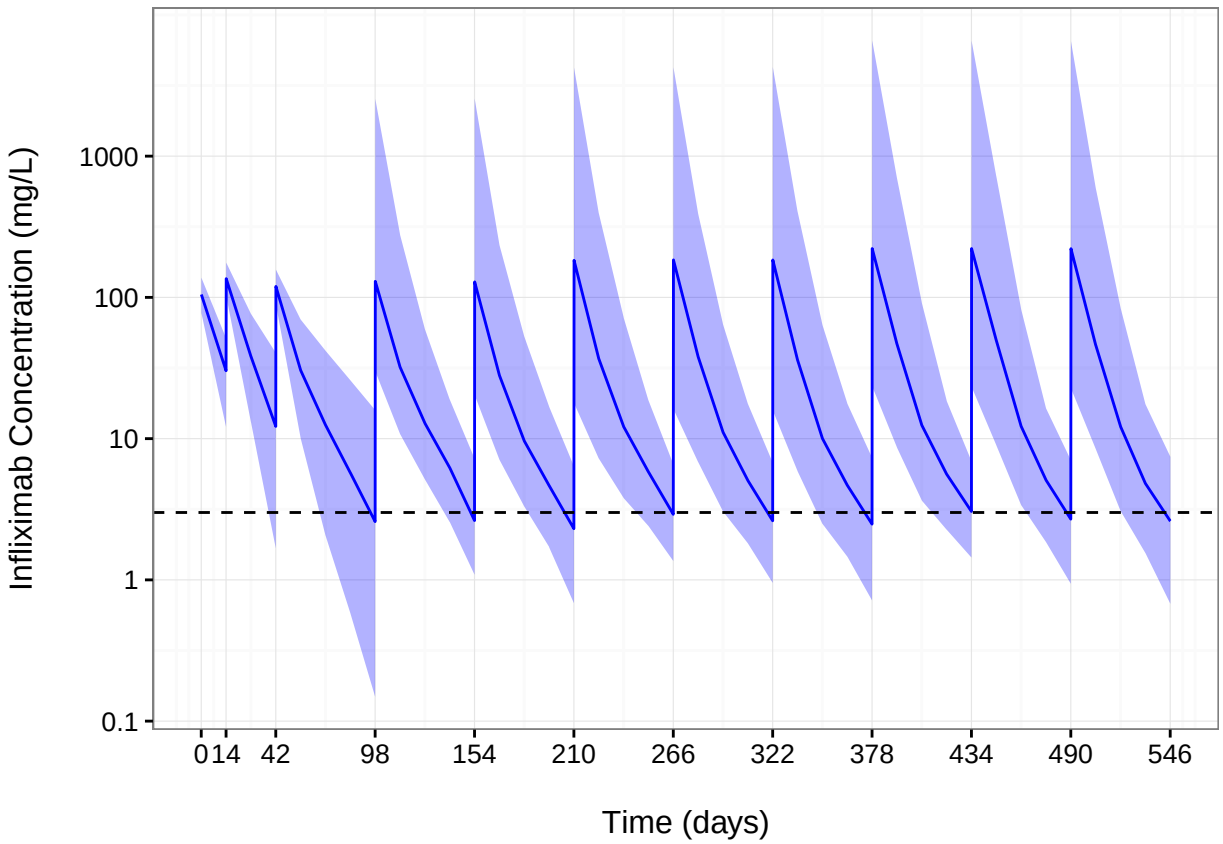
For each individual, the time spent under the target trough concentration (3 mg/L) for the entire 546 day period was calculated.

```
##   time   median   stat.95lo stat.95hi
## 4  546 109.2116 0.002026993  334.1519
```

Clinical Scenario

Scenario where every patient receives a 5 mg/kg dose of infliximab for every infusion time in the first sampling interval (i.e., at 0, 14 and 42 days). Then:

- Trough concentration at time = 98 days is sampled (DV)
- Dose for the next sampling interval is determined as:
  - If a sample < trough target OR sample >= trough upper (5 mg/L) then the new dose will be equal to (trough target/sample)*previous dose
  - If a sample is within the pre-specified range, then the patient continues with the previous dose
- Cycle is repeated at sampling times = 210 and 378 days



We can see a significant improvement in the proportion of people who are achieving constant concentrations above the target trough (median line is predominantly above the line in the clinical scenario compared to the label scenario).

Calculate time spent under the target trough:

```
##   time   median   stat.95lo stat.95hi
## 4  546 48.32051 0.002612252  161.4866
```

The median time spent under the target trough at time = 546 days in the clinical scenario is half compared to the label scenario.

Bayesian Estimation and Dose Optimisation Scenarios

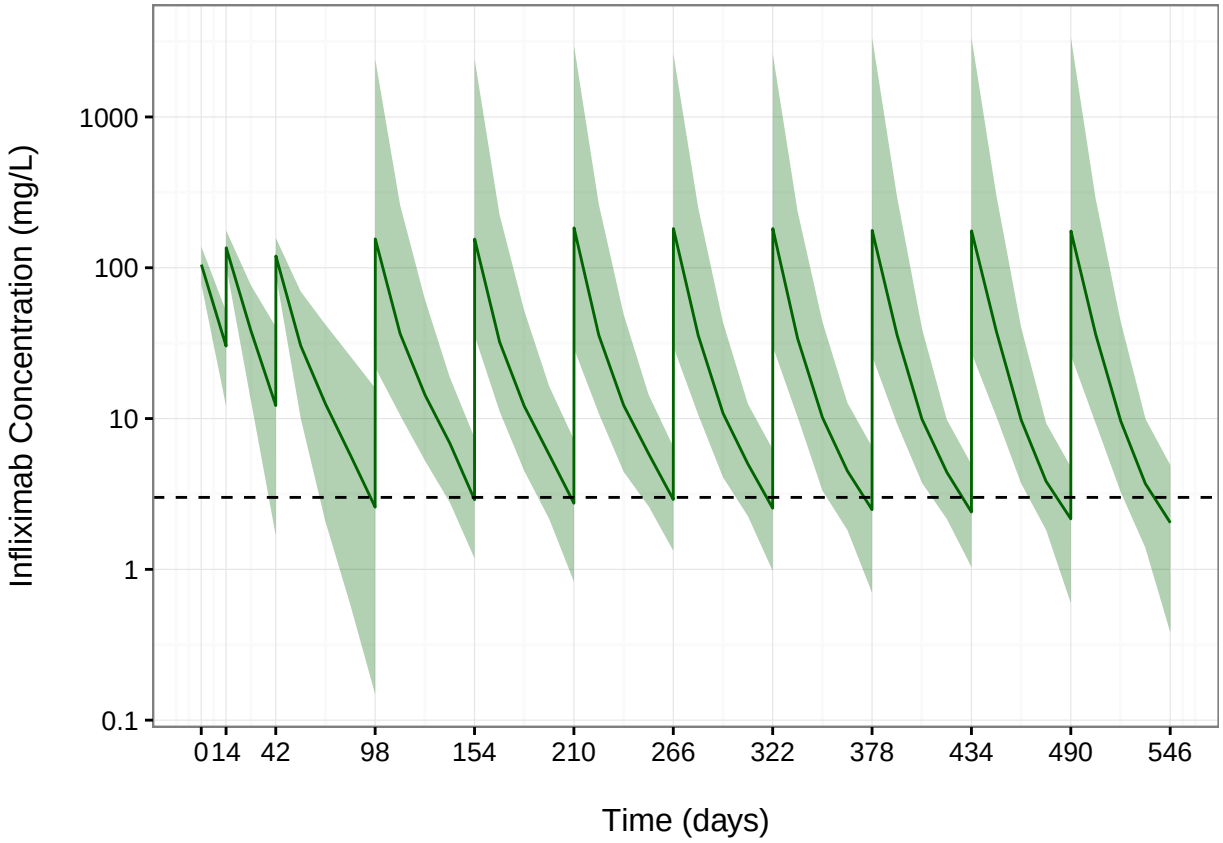
Scenario where every patient receives a 5 mg/kg dose of infliximab for every infusion time in the first sampling interval (i.e., at 0, 14 and 42 days). Then:

- Trough concentration at time = 98 days is sampled (DV)
- Individual values for pharmacokinetic parameters are obtained from empirical Bayes estimates using known administered doses, the sample, and covariate information at time = 0 and the sampling time
- Doses for the next sampling interval are determined by maximum likelihood estimation (minimise the error between trough concentration given optimised doses and the target trough concentration)
  - Optimised doses for the next sampling interval are allowed to be different
  - Initial estimates for doses are obtained by using the method described earlier in “Clinical Scenario”
  - If an initial estimate for a dose was greater than 1,000,000 mg - then doses were not optimised for the patient and they were just administered 1,000,000 mg

- Cycle is repeated at sampling times = 210 and 378 days
  - Bayes estimates obtained from subsequent sampling intervals are based on all previous samples, not just the most recent one
- When simulating the next interval given the individual parameters estimated from the previous interval, covariate values from the last sample are carried forward
  - We can predict the concentrations, however we cannot predict changes in their covariate profile

No Time-Weighting, All Covariate Information is available

All observations are weighted equally when maximising the posterior likelihood. Covariate information at the time of sampling as available.

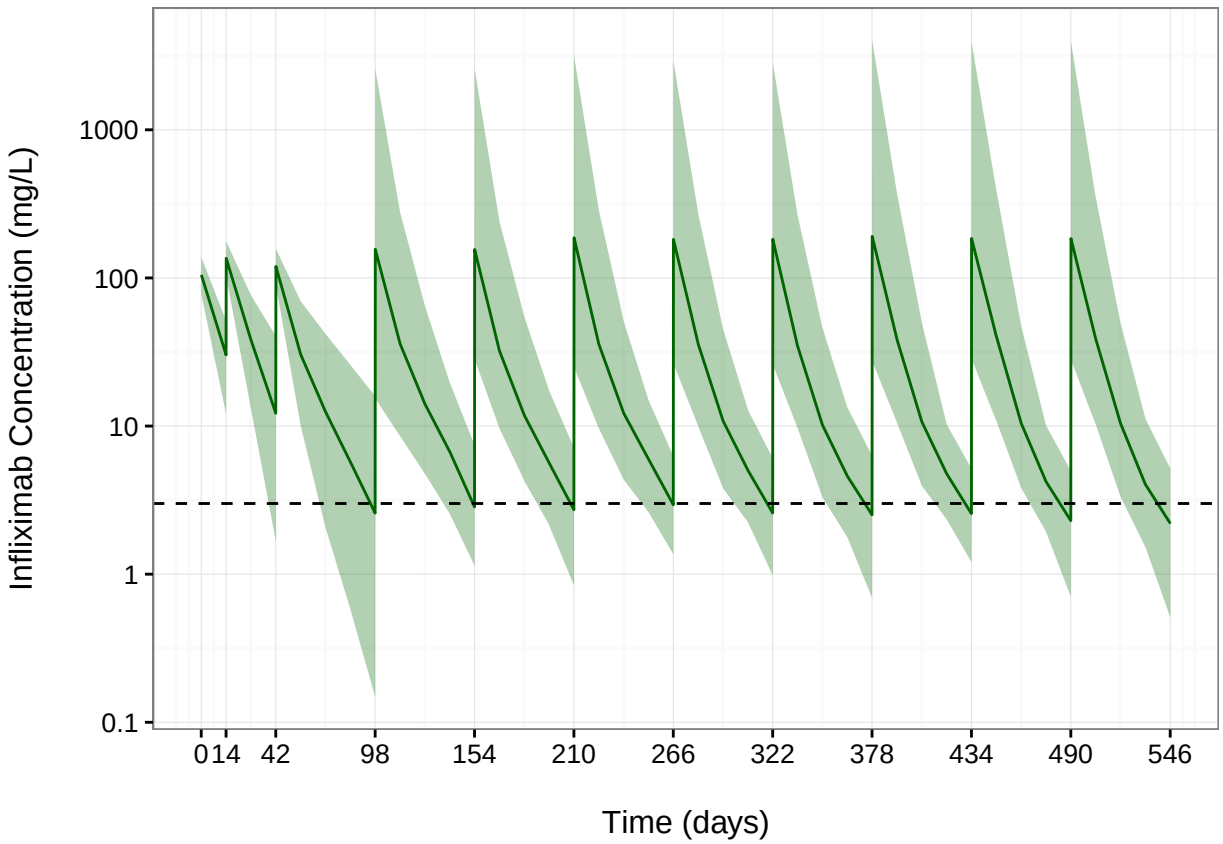


Calculate time spent under the target trough:

```
##   time   median   stat.95lo stat.95hi
## 4  546 49.33545 0.002264106  173.4192
```

Peck 1.005 Time-Weighting, All Covariate Information is available

All observations are time-weighted using the Peck method with Q = 1.005 when maximising the posterior likelihood. Covariate information at the time of sampling as available.

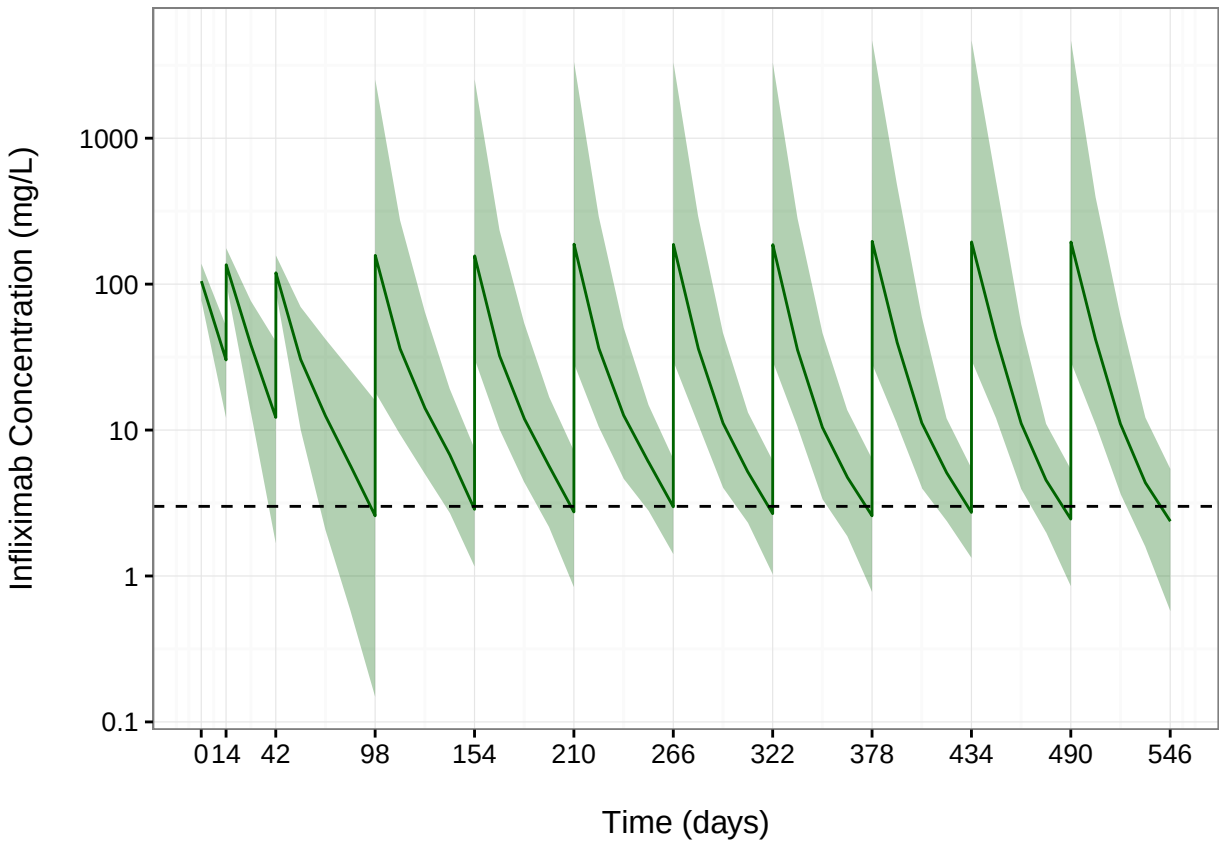


Calculate time spent under the target trough:

```
##   time   median   stat.95lo stat.95hi
## 4  546 46.83784 0.002297573  156.7774
```

Peck 1.01 Time-Weighting, All Covariate Information is available

All observations are time-weighted using the Peck method with Q = 1.01 when maximising the posterior likelihood. Covariate information at the time of sampling as available.

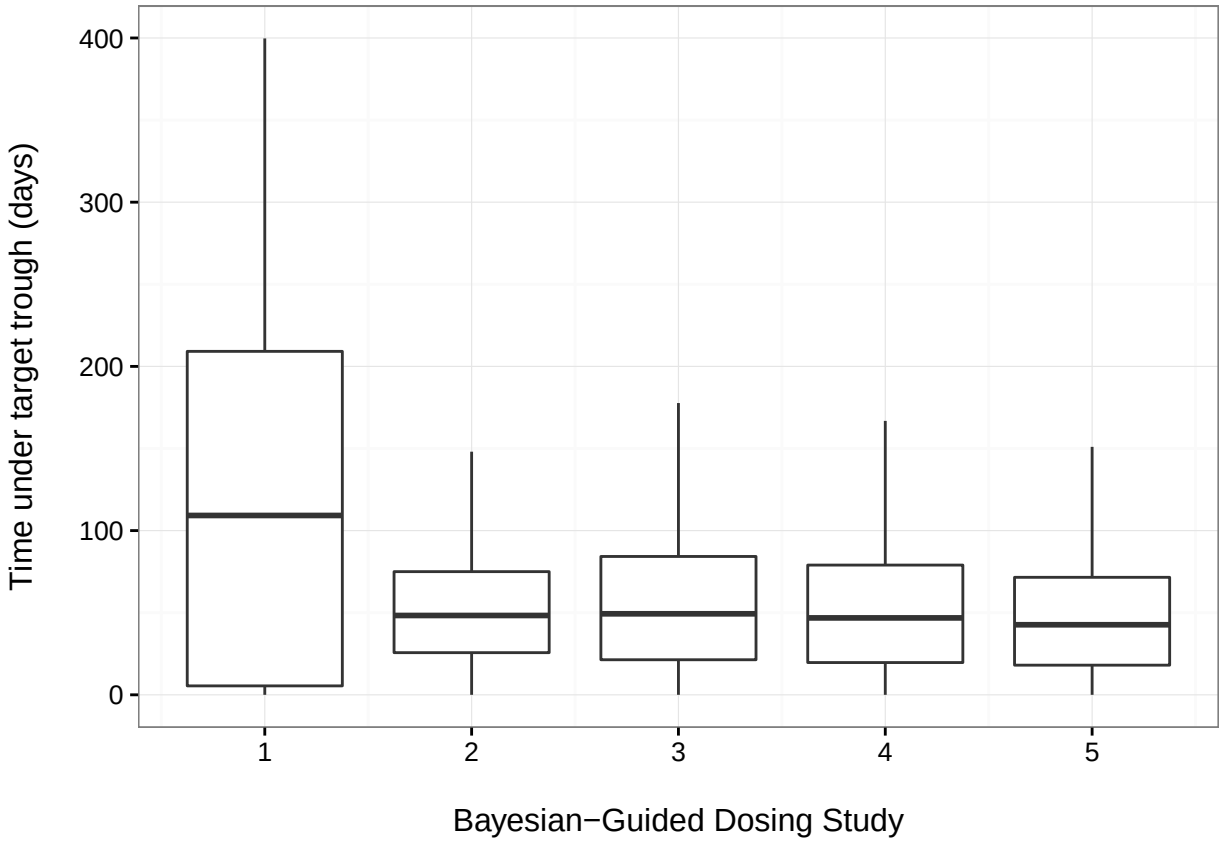


Calculate time spent under the target trough:

```
##   time   median   stat.95lo stat.95hi
## 4  546 42.66231 0.002290826  148.5095
```

No Time-Weighting versus Time-Weight (Peck, Q = 1.005 and 1.01), All Covariate Information Available

Time under target trough concentration



Proportion of individuals below target trough concentration

```
##   BTT    n
## 1 895 1200
```