Evaluation of Compartment Models for Simulation of Infliximab Depletion

Andreas Bauer[1,*], Christoph Urach[2], Felix Breitenecker[1]

[1]Department of Analysis and Scientific Computing, Vienna University of Technology, Wiedner Hauptstraße 8-10, 1040 Vienna, Austria; *andreas.e101.bauer@tuwien.ac.at*

[2] dwh Simulation Services, Neustiftgasse 57-59, 1070 Vienna, Austria.

Simulation Notes Europe SNE 24(1), 2014, 21 - 26
DOI: 10.11128/sne.24.tn.10225
Received: Dec. 10, 2013 (Selected ERK 2013 Postconf. Publ.);
Accepted: February 15, 2014;

Abstract. Infliximab is an antibody that is approved for treatment of the inflammatory bowel diseases Crohn's disease and ulcerative colitis. It is important to predict the course of the depletion of Infliximab in the body to time the regular infusions that patients get. The base model is a two-compartment-model and three parameter identification approaches are compared: identification of each infusion period separately, identification of each patient separately and identification of all measurement points at once. The best results provides the approach to identify the parameters for each infusion period separately. Wanting to improve the quality of the results, an extended model with continuous parameter antibodies to Infliximab (ATI) is considered, but the mean error is higher than for the base model. We conclude that the presence of antibodies to Infliximab in the body carries more weight than the actual number of antibodies. Finally, a model with an additional parameter, number of previous infusions with Infliximab (PRIORIFX), is created. This model could not improve the results of the base model. This indicates that the number of previous infusions with Infliximab is not significant for the model.

Introduction

Infliximab is an antibody that is approved mainly for treatment of the inflammatory bowel diseases Crohn's disease and ulcerative colitis.

The patients receive infusions with Infliximab on a regular basis, because the concentration of Infliximab within the body must not fall below a critical level. It is important to predict the point of time, when the concentration reaches that critical level to plan the date of the next infusion more accurately. This can help to reduce the number of visits from the patients to the hospital or the doctor and to reduce the number of infusions since Infliximab is very expensive.

The goal of this paper is to model the time dependent course of the concentration of Infliximab in the body. The base model is taken from [1]. In order to improve the prediction quality of the model various approaches for parameter identification and various extensions of input parameters are considered.

1 Structure of the Models

The presented models are compartment-models. A compartment-model consists of separated compartments and flows between them. The interaction with the environment is realised through sinks and sources.

In this particular case, we consider two-compartment-models. The first compartment is the central compartment V_1 and the second compartment is the peripheral compartment V_2. The central compartment represents the well perfused, central part of the body and the peripheral compartment represents the less perfused, peripheral part of the body. There are flows from V_1 to V_2 and back. From a source there is an inflow into V_1 which represents the injection of Infliximab into the body and an outflow from V_1 into a sink which represents the clearance (Figure 1).

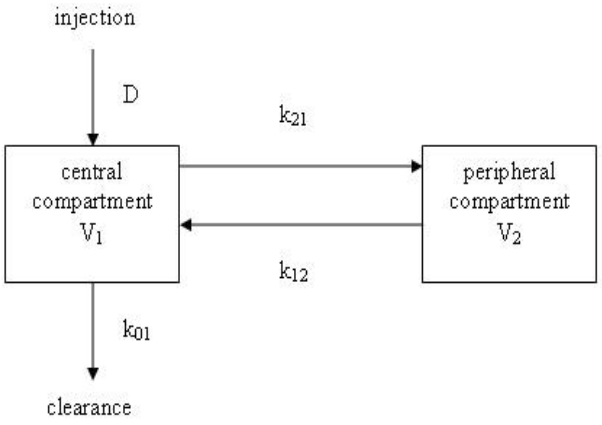

Figure 1: Illustration of the structure of the model.

1.1 Base model (M1)

The structure of the base model is taken from [1]. An overview of the five parameters of the base model and their attributes is given in Table 1.

Name	Abbreviation	Unit	Values
Dose	DOS	mg	300-700
Sex	SEX	none	0 = male, 1 = female
Antibodies to Infliximab status	ATI	none	0 = tested negative on antibodies, 1 = tested positive on antibodies
Weight	WGT	kg	40-130
Albumin Level	ALB	g/dL	3-5

Table 1: Overview of the parameters of the base model

The size of the compartments and the flows depend on the five parameters. The size of the first compartment V_1 is depending on the weight and the sex as seen in equation (1). The size of the second compartment V_2 and the intercompartmental flow Q are constant. The clearance depends on the parameters ALB, ATI and SEX. (2) There are eleven constants (v_{ij}, CL_k) whose values are identified from the data. These constants describe the functional dependencies between the parameters and V_1 and CL:

$$V_1 = v_{11} \cdot \left(\frac{WGT}{v_{12}}\right)^{v_{13}} \cdot (v_{14})^{SEX} \quad (1)$$

$$CL = CL_1 \cdot \left(\frac{ALB}{CL_2}\right)^{CL_3} \cdot (CL_4)^{ATI} \cdot (CL_5)^{SEX} \quad (2)$$

The actual flows are calculated by dividing the quantities Q and CL from above by the size of the compartments [2]:

$$k_{01} = \frac{CL}{V_1} \quad (3)$$

$$k_{12} = \frac{Q}{V_1} \quad (4)$$

$$k_{21} = \frac{Q}{V_2} \quad (5)$$

The compartment model is described by two differential equations. The variables x_1 and x_2 describe the amount of Infliximab in compartment V_1 and V_2. x_1 decreases by the outflows k_{01} and k_{21} from V_1 and increases by k_{12} which goes into V_1 (6). In compartment V_2, there is a flow to V_1 and an inflow from V_1 [3].

A run always simulates one infusion period. The initial value for x_1 is the dose, which is injected all at once, if it is the very first infusion of Infliximab for the particular patient. Otherwise the amount of Infliximab which is left in the body at that time has to be added to the dose to get the initial value. The initial value for x_2 is zero. To get the concentration of Infliximab, the variables x_1 and x_2 have to be divided by the size of the corresponding compartment.

$$\dot{x}_1(t) = -(k_{01} + k_{21}) \cdot x_1 + k_{12} \cdot x_2 \quad (6)$$

$$\dot{x}_2(t) = k_{21} \cdot x_1 - k_{12} \cdot x_2 \quad (7)$$

1.2 Model with continuous ATI (M2)

The model M2 is similar to the base model M1. The only difference is that the parameter ATI is continuous in contrast to the model M1 where it is discrete with possible values zero and one. In the base model, the parameter ATI is simply set to one, if the value in the data is greater than zero.

The reason to incorporate the continuous ATI is that within the data there are already continuous values given for patients with antibodies and to find out the effects of different values of antibodies on the results. The unit of the continuous ATI is Unit per millilitre (U/mL). Four different techniques are used to transform the values from the data which range between 0.5 and 20 onto a certain interval:

1. Normalising the values onto the interval [0,1]
2. Linear transformation onto the interval [0.5,1]
3. Logarithmic transformation onto the interval [0,1]
4. Exponential transformation onto the interval [0,1]

1.3 Model with additional parameter (M3)

The model M3 is also similar to the base model M1. The difference is that the model M3 has an additional parameter PRIORIFX. The value of the parameter indicates, how many previous injections of Infliximab a patient has had. The size of the compartments will not change by additional injections. Thus, the formulas of the size of the compartments are still equal to those of the base model M1.

Two different approaches will be tested if a big number of injections causes an effect of habituation: the first (M3a) is that the new parameter only affects the clearance CL (10) and the second (M3b) is that it affects both the clearance CL and the intercompartmental flow Q (10, 11). In both cases, the factor PRIORIFX to the power of a constant is added to the existing formula.

$$CL = CL_1 \cdot \left(\frac{ALB}{CL_2}\right)^{CL_3} \cdot (CL_4)^{ATI} \cdot (CL_5)^{SEX} \cdot \cdot PRIORIFX^{CL_6} \quad (8)$$

$$Q = Q_1 \cdot PRIORIFX^{Q_2} \quad (9)$$

2 Parametrisation

2.1 Data

The data origins from the Vienna General Hospital and was generously placed at our disposal for this project. 662 records have been collected, but only 96 of them can be used, because only these contain all the required parameters needed for the model. The categories that have been collected besides from those that are used in the models are age, smoking habits, height of the patient and some other categories. However, our models stick with the parameters found to be significant in [4].

The diagnoses of the patients were also recorded. 81 patients were diagnosed with Morbus Crohn (MC) and the other 15 with Colitis Ulcerosa (CU). Since it is unsure, if a single model can be used for patients with both diagnoses and the size of the sample of CU patients is too small, only MC patients are considered.

2.2 Identification of the constants

The constants in the equations (1) and (4) respectively in (10) and (11) have to be identified to make the models fit the given data. For this problem, the method of least squares is used which minimises the squares of the residuals.

The residuals are the differences of the amount of the concentration from the data and the value of the function x_1 of the model at given time. The implementation is done in MATLAB with the pre-implemented function lsqnonlin. The algorithm which is used is the Levenberg-Marquardt-algorithm, an extended Newton-algorithm. Three different approaches to identify the constants are carried out.

The patient history is the complete course of concentration of Infliximab. It can be divided into several infusion periods. Within every infusion period the concentration is measured with a few samples. In Figure 2, a simulated patient history with discrete measurement points is shown.

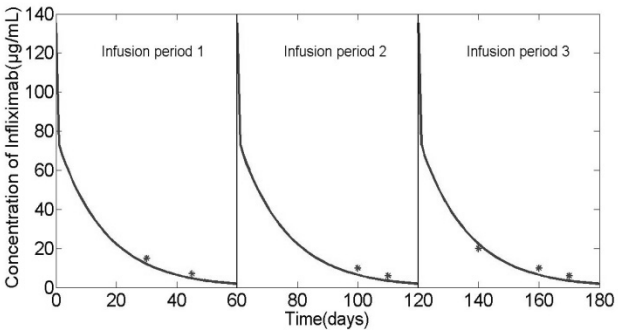

Figure 2: Simulated history of a patient split in its infusion periods and measurement points.

Identification of infusion periods (P1).

The first approach is to identify the constants for every single period between two infusions separately. That means, all data points between the date of an infusion and the following infusion are taken and the constants are identified that the function x_1, which describes the amount of Infliximab in compartment V_1, fits these data points best. This is done for all periods. This approach produces many different sets of identified constants. The mean values for each constant are calculated and used in the general model.

In most of the cases, there is only one data point in an infusion period, so the constants are identified to fit that single point. At most there are three points, thus in almost every case a near perfect fit can be achieved, because in M1 and M2, there are 11 and, in M3, up to 14 constants to identify. In this scenario, problems with overfitting can occur, because the number of parameters is much greater than the number of data points.

Identification of records of patients (P2).
In this approach, the constants are identified separately for each patient. That means, all data points of a patient are taken and the constants are identified. Again, the mean values of all the sets of constants are calculated and used in the general model.

This approach is chosen, because maybe the aggregation of several infusion periods of a patient can provide additional information about the elimination process which cannot be drawn from single infusion periods.

Identification of all records at once (P3).
In the third approach, all given data points are taken without attribution to a specific infusion period or patient and the constants are identified in one run.

3 Results

For the results, only patients are considered that have multiple data points within an infusion period. Thereafter, the data consists of 41 records and is split in a training set of 18 records and a validation set of 23 records. The training set contains data from 8 different patients with 12 different infusion periods. The mean errors in this chapter are always relating to the validation set.

The simulation results show that the concentration of Infliximab falls exponentially, almost linear, in the beginning. Then the graph almost has a kink and after that the concentration decreases exponentially, but much slower, towards zero (Figure 3). When the concentration comes close to zero after about 60 days the next infusion would be administered.

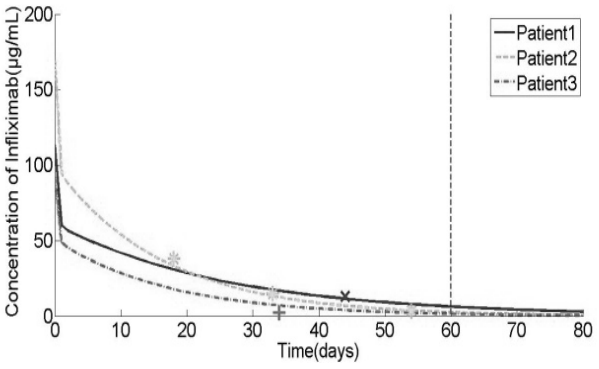

Figure 3: Simulation results of the base model with optimised parameters for three different patients and corresponding data points.

3.1 Comparison of the different parameter identification approaches

The evaluation of the mean errors of the parameter identification approaches shows that the identification per infusion period (P1) has the lowest mean error (Table 2).

Infusion periods (P1)	Patients (P2)	All Records at once (P3)
7,16	7,52	8,18

Table 2: Mean errors of the three parameter identification approaches.

These results indicate that no additional information can be extracted from putting the several infusion periods of a patient in the identification process together. A possible explanation is that single data points which lie quite aside from the others disturb the outcome of the identification process. Since there are only 8 patients, but 12 infusion periods, and the parameters are finally averaged over the number of patients respectively infusion periods, this data point has more impact on the results of the identification per patient.

From now on, we use the parameters from identification process (P2), which provided the best results, for all models.

3.2 Model with continuous ATI (M2)

The results of the model with continuous ATI with the four different transformations in comparison with the base model show that all the models with continuous ATI have higher mean errors (Table 3). That indicates that using the ATI as a continuous parameter does not improve the model.

binary	linear on [0,1]	linear on [0.5,1]	logarithmic	exponential
7,16	7,86	7,69	7,82	7,92

Table 3: Mean errors of the models with continuous ATI in comparison with the model with binary ATI.

The linear transformation onto the interval [0.5, 1] has the least mean error of the considered transformations. This leads to the conclusion that even small numbers of antibodies to Infliximab have a noticeable impact on the depletion of Infliximab in the body, because said transformation puts the small values to at least one half whereas the others put them close to zero.

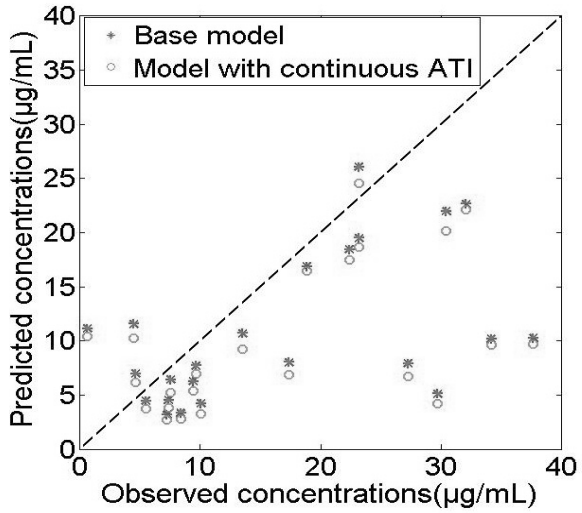

Figure 4: Comparison of the errors of the base model and model M2 with linear transformation onto [0.5, 1]

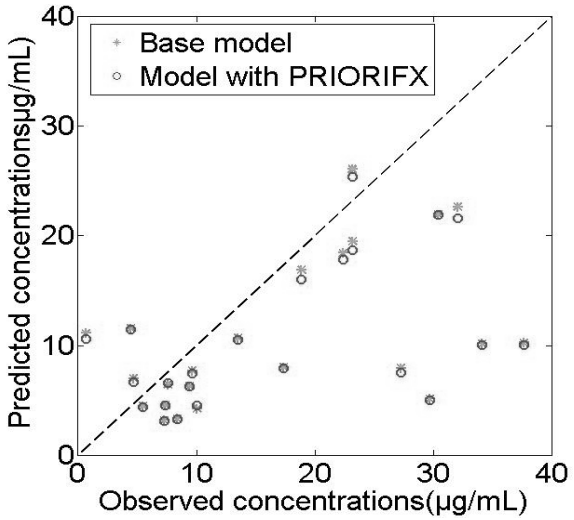

Figure 5: Comparison of the errors of the base model and model M3b

The concentration values of the model with continuous ATI are generally lower than those of the base model (Figure 4). Since the base model is already too low in most cases, this causes the bigger mean error of the given model.

3.3 Model with additional parameter (M3)

The models with the additional parameter PRIORIFX have higher mean errors (Table 4). Hence, the parameter PRIORIFX has no significant impact on the depletion of Infliximab in the body.

Base model	M3a	M3b
7,16	7,36	7,27

Table 4: Mean errors of the models with PRIORIFX in comparison with the base model.

The model M3b, whose clearance and intercompartmental flow depend on the parameter PRIORIFX, shows a slightly less mean error than the model M3a with PRIORIFX-depending clearance and constant flow Q.

In half of the cases, the model with PRIORIFX provides nearly the same results as the base model. In the other cases, the predicted values of the given model are lower than those of the base model (Figure 5).

4 Conclusion

In this paper, different models for the depletion of Infliximab in the body have been presented. The models were all two-compartment-models.

Firstly, three parameter identification approaches have been compared: identifying each infusion period separately, identifying each patient separately and identifying all data points at once. The identification of each infusion period separately has provided the best results. Hence, no additional information could be drawn from putting the several infusion periods of a patient together. Since the data set is not only small, including 8 different patients and 12 infusion periods, but also prone to measurement errors the results concerning prediction quality could be distorted, because if a data point lies quite aside from the others then it influences the optimised parameters of one of 8 patients, but only one of 12 infusion periods.

When the parameters are finally averaged, it has more impact on the patient-wise identification. To eliminate the possibility of this issue, the availability of a bigger data sample would be necessary.

In the base model, the parameter ATI was only binary. Since the data provides continuous values for that parameter, a model with continuous ATI was set up. Although different transformations of data have been tried out, the incorporation of the continuous ATI has not improved the results. This indicates that the presence of antibodies to Infliximab in the body carries more weight than the actual number of antibodies.

The number of previous infusions of Infliximab of a patient has been collected in the data. In order to examine a possible habituation effect, the parameter PRIORIFX was added to the set of parameters. However, the incorporation of the parameter PRIORIFX has not improved the results. So, the parameter PRIORIFX has no significance for the model. This leads to the conclusion that the presumption of a habituation effect is not supported.

Acknowledgement

This contribution is a post-conference publication from ERK 2013 Conference (22nd International Electrotechnical and Computer Science Conference, September 16 - 18, 2013, Portorož, Slovenia), with sessions organized by SLOSIM, the Slovenian simulation society (EUROSIM member). The contribution is a modified publication from the paper published in the Proceedings of ERK 2013, [5].

References

[1] Estelberger W, Popper N. C15 – Clearance Identification – Definition. *SNE*; 2002.12 (35-36): 65-66.

[2] Macheras P, Iliadis A. *Modeling in Biopharmaceutics, Pharmacokinetics and Pharmacodynamics: Homogeneous and Heterogeneous Approaches*. First Edition. New York: Springer; 2006.

[3] Richter O. *Mathematische Modelle für die klinische Forschung: enzymatische und pharmakokinetische Prozesse*. First Edition. Berlin: Springer; 1982.

[4] Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, Davis HM, Zhou H. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol*. 2009; 65 (12): 1211–1228. doi: 10.1007/s00228-009-0718-4.

[5] Bauer A, Urach C, Breitenecker F. Evaluation of Compartment Models for Simulation of Infliximab Depletion. In: Zajc B, Trost A, editors. ERK 2013. *Proceedings of the twenty-second International Electrotechnical and Computer Sience Conference*; 2013 Sept; Portorož. Ljubljana: Slovenia Section IEEE; P.141-144.