Comparing Closed-Loop Control of Drug Infusion using MPC and PID

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Abstract: Continuous intravenous drug delivery can require careful dosage and the maintenance of consistent blood plasma concentration levels. Here, the closed-loop control of drug concentration in simulated patients' bloodstreams was investigated. During the investigation, the closed-loop controller performance of a Proportional-Integral-Derivative (PID) and a Model Predictive Controller (MPC) were compared. From the simulation results, the MPC has shown to be a better controller because of its shorter settling time and smaller step-response overshoot, which are desirable in a clinical setting. However, the MPC has shown to be more resource-intensive on the controller system. Through the simulations conducted, it can therefore be concluded that a closed-loop controller containing an MPC control block adequately controls the drug infusion to a simulated patient.

1 INTRODUCTION

The function of human blood is to transport oxygen, nutrients, sugars and hormones to parts of the human body that need them the most, and to carry away waste materials (Felman, 2020). Blood is also used to carry drugs for medical purposes, some of which require continuous drug supply and careful monitoring of blood concentration levels. Methods for analyzing blood using electrochemical sensors, and also by non-invasive sensing, exist and are the subject of ongoing research (Shokrekhodaei and Quinones, 2020).

This paper will be focused on the design of the closed-loop control system delivering a drug into a patient intravenously based on a set-point of drug plasma concentration. Experiments will involve simulating a closed-loop control system which will be able to administer the drug to maintain drug plasma concentrations to the simulated patient. This paper will also be comparing the use of a PID controller and an MPC controller to find which controller is more suited to deliver a drug to a patient autonomously.

For similar drug infusion systems, like insulin infusion systems, it was proven that MPC closed-loop control systems are more efficient than the standard open-loop infusion of insulin, and that patients' insulin levels remained within the set-point range more often than in the open-loop case (Clarke et al., 2009) (Bruttomesso et al., 2009). The artificial pancreas has also been designed and compared with the MPC and the PID controllers, and it has been shown that the MPC outperforms the PID in this application, although both controllers provided adequate glucose control (Pinsker et al., 2016).

Unlike (Clarke et al., 2009) and (Bruttomesso et al., 2009), which both make use of glucose-insulin dynamics models, this paper uses the paediatric Paedfusor patient model used in anesthesia. Additionally, the design of the models used in (Pinsker et al., 2016) were personalized models for the MPC, but for this paper, a general patient model was designed and applied for the entire patient group to study the efficacy of the system controlling the drug infusion based off of a general model.

There have been a number of studies conducted making use of closed-loop control strategies in anesthesia (Naşcu et al., 2014) (De Keyser et al., 2015) (Padula et al., 2017) (Ntouskas and Sarimveis, 2021). To detect the level of hypnosis experienced by the patient, these papers make use of the bispectral (BIS)

index commonly used in practice (Rampil, 1998), although other measures, such as the mid-latency auditory evoked potentials (MLAEP) could also be used to form an indication of the depth of anesthesia experienced by a patient (Mantzaridis and Kenny, 1997) (Kuhnle et al., 2013).

This paper compares an MPC controller and a PID controller in controlling the delivery of anesthesia. This is done by comparing the step responses of both types of control strategies, along with analysing how both operate in the presence of sensor noise and comparing the computation time taken by both controllers. This would provide some useful information in considering the practicality of each controller in a surgical context.

This paper contains a total of five sections. Section 1 is the introduction of the paper, Section 2 contains the background material related to the paper, Section 3 expands on the methods used to run the experiments, Section 4 gives the experiment results and discusses the results, and Section 5 is the conclusion.

2 BACKGROUND

2.1 Control systems in anesthesia

For the successful implementation of a control system in anesthesia, there are a few key components that must be included. There must be a measurable control variable used to determine the effect of the drugs administered, an established set-point for the control variable, a controller and a control actuator to administer the drug, and the system must fit the appropriate pharmacokinetics and pharmacodynamics for the application (Struys et al., 2006).

The use of control systems for drug delivery in medical contexts dates as far back as the 1980s. They were initially implemented in insulin infusion systems for people with diabetes (Deckert et al., 1980) (Doyle et al., 2014) and the applications have expanded to other uses, including the control of neuromuscular systems (Solomonow, 1984) and anesthesia (Westenskow, 1987) (Dumont, 2012).

For medical control systems, especially drug administration systems, PID controllers pose stability risks in the administration. PID controllers need to be meticulously tuned for specific scenarios and without proper tuning, they run the risk of oscillating before reaching, or during, steady state (Struys et al., 2006).

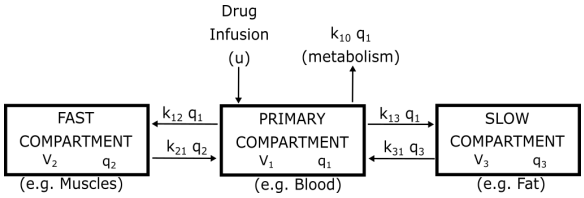

Figure 1: The three-compartment mamillary PK model.

This is because the design of PID controllers does not incorporate information about drug metabolism, which could potentially allow the administration of dangerously high drug concentrations.

2.2 Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (PK) define the movement of a drug within a patient. This involves the absorption, distribution, metabolism and elimination of the drug and this movement is highly dependent on patient-specific parameters, such as age, weight, height, and sex. Pharmacodynamics (PD) define the influence of the drug on the patient. This involves receptor binding, post-receptor effects and chemical interactions (Bibian, 2006).

For intravenous drug infusion, the pharmacokinetics of the patient are best described by the three-compartment mamillary PK model, depicted in Figure 1. This model consists of three compartments in which the drug can be distributed. The first compartment (V1) is the blood, where the drug is directly injected. The second compartment (V2) is the fast compartment, which is the muscle. Lastly, the third compartment (V3) is the slow compartment, which represents the fat (Hull, 1979).

To simulate the pharmacokinetics of a patient, a state-space model is commonly used. The state-space model is defined as:

$$\begin{bmatrix} \dot{q}_1(t) \\ \dot{q}_2(t) \\ \dot{q}_3(t) \end{bmatrix} = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \begin{bmatrix} q_1(t) \\ q_2(t) \\ q_3(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u \quad (1)$$

$$C_p = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} q_1(t) \\ q_2(t) \\ q_3(t) \end{bmatrix} + 0 \cdot u \quad (2)$$

with q_i as the mass of the drug in the $i-$th compartment,, and the k_{ij} parameters represent the transfer rate constants from compartment i to compartment

j, u is the infusion rate and C_p is the drug plasma concentration in the patient (Hull, 1979).

2.3 Control strategies

The vast number of controllers all have unique approaches to the control problem and have varied levels of complexities, but the end goal of each type of control system is to drive the behaviour of the system output. The two controllers used in this study are listed below.

2.3.1 PID

The Proportional-Integral-Derivative (PID) controller is one of the most popular control algorithms used (Kumar et al., 2011). The PID controller is made of three separate controllers and each controller serves a specific purpose in the control trajectory of the controller and each of these controllers is dependent on the system's error signal $e(t)$, which is the difference between the measured output and the system's reference signal.

The proportional feedback controller, or P-controller, linearly adjusts the controller's output to the error signal. The integral feedback controller, or I-controller, linearly adjusts the controller proportional to the integral of the error signal. This is used to decrease the steady-state error signal of the system between the output and the reference signal. The derivative feedback controller, or D-controller, decreases the overshoot of the system step response and improves the system's overall stability. The D-controller's output is proportional to the rate of change of the system error. (Gene F. Franklin, 2015).

Therefore, the controller output can be written as

$$u_{PID} = k_P\, e(t) + k_I \int_{t_0}^{t} e(\tau) d\tau + k_D\, \dot{e}(t) \qquad (3)$$

with k_P as the proportional gain, k_I as the integral gain, and k_D as the derivative gain.

2.3.2 MPC

Model Predictive Control (MPC) is an advanced control strategy that solves an open-loop optimal control problem with defined constraints and system-state dynamics on-line. A unique feature of the MPC is that it incorporates a model of the system within the control algorithm to optimize the control actions that are determined .

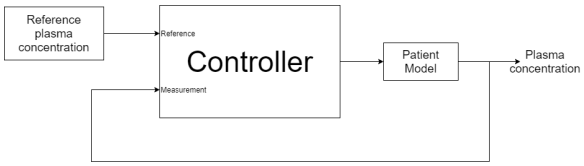

Figure 2: The closed-loop control system.

The MPC uses the system model to make predictions of the future behaviour of the system and its dynamics over a defined period, called the "prediction horizon." From these predictions, the MPC will implement the first few predictions made in the defined, shorter period called the "control horizon." Once the control manoeuvre is implemented, the MPC will predict the possible control actions for the next prediction horizon (Findeisen and Allgöwer, 2002) (Raković and Levine, 2018).

3 METHODS

The designed closed-loop control system will be simulated as depicted in Figure 2. The closed-loop control system is made up of the following elements.

3.1 The control loop

The system's reference defines the value the system aims to achieve. The reference signal will be the plasma concentration within the patient. In the simulation, this will be specified by a selected concentration.

The plant to be used for the system is the patient. To understand the influence of the drug on the patient, a thorough understanding of pharmacokinetics (PK) is needed. For the closed-loop control system, the patient will be simulated as a three-compartmental state-space Paedfusor PK model of the patient (Absalom et al., 2003). The same model used for the plant will be used as the internal model of the MPC. The measured output from the simulated patient model will be the drug concentration in the patient's plasma. This output will be fed back into the controller to close the loop.

The controllers used, the MPC and PID controllers, will be implemented separately to compare the performance given by each controller.

3.1.1 MPC

To determine a step response with no overshoot and with the shortest settling time possible, the MPC con-

troller was designed with the parameters listed in Table 1.

The sampling time was selected assuming that the plasma concentration measurements will be taken every 10 s, and then the drug will be delivered. The prediction horizon sample number was chosen as a value that would allow for an adequate amount of future predictions, without calculating too many future predictions, saving computational resources. The control horizon is chosen as 10% of the prediction horizon. The weights were determined by designing the MPC controller with the MATLAB MPC Designer by adjusting the robustness of the controller to have no overshoot and a short settling time (The MathWorks, a).

Table 1: MPC controller parameters.

Parameter	Value
Sample time (T_s)	10 s
Prediction horizon	20
Control horizon	2
Weights	
MV	0
MV Rate	0.146
OV	0.412

MV: Manipulated Variable
OV: Output Variable

3.1.2 PID

The parameters of the PID controller were determined by using MATLAB's PID Tuner to automatically determine the parameters based on the desired response (Xue et al., 2007). The parameters are listed in Table 2. Unfortunately, a system response with no overshoot was unattainable, therefore a system response with as small an overshoot as possible was considered.

Table 2: PID controller parameters.

PID parameter	Value
P (proportional term)	2.789
I (integral term)	0.06746
D (derivative term)	-5.0887

3.2 Added measurement noise

To analyse how the systems will respond in the presence of noise, measurement noise was added according to Table 3. The signal-to-noise ratio (SNR) is the ratio of the power of a desired signal relative to the power of the noise within the signal (Kieser et al., 2005), in decibels (dB). The SNR is defined as:

$$SNR_{dB} = 10log_{10}\frac{P_{Signal}}{P_{Noise}}\ dB \tag{4}$$

with P_{Signal} as the power of the desired signal, respectively.

Table 3: Magnitude of Measurement Noise Added for each Simulation.

Simulation	SNR [dB]
1	40
2	30
3	20
4	15
5	10
6	5
7	0
8	-3

3.3 Patient Group

To analyse the influence that inter-patient variability would have on the system, the designed system was tested on a simulated patient group. The 14 simulated patients used in this paper was randomly generated using the patient characteristic data from (Kuhnle et al., 2013), which is also listed in Table 4.

Table 4: Simulated Patient Group (Kuhnle et al., 2013).

Patient characteristic data	Mean (SD) (range)
Number of patients (n)	14
Age (yr)	8.6 (4.3) (4.0 - 16.5)
Weight (kg)	29.2 (14.6) (15.0 - 60.0)
Height (cm)	125.9 (26.2) (67.0 - 160.0)

3.4 Measuring plasma concentration

To measure the anesthetic plasma concentration in a patient directly is undesirable because it would be an invasive procedure, where the patient's blood would need to be drawn and the anesthetic would need to be measured in real time. Therefore, measures of hypnosis have been found that can correlate the level of anesthesia a patient experiences to the amount of plasma in a patient's plasma. These measures include electroencephalogram (EEG) modelling (Rampil, 1998), power spectrum analysis (Pichlmayr et al., 2012), bispectral (BIS) index (Ontario et al., 2004) and evoked potentials (Walsh et al., 2005).

The work conducted in (Kuhnle et al., 2013) found a strong correlation between plasma concentration and mid-latency auditory evoked potentials (MLAEP) (Plourde, 2006) which suggests that it may be possible to estimate blood plasma concentration from MLAEP, in the case of the anesthesia application.

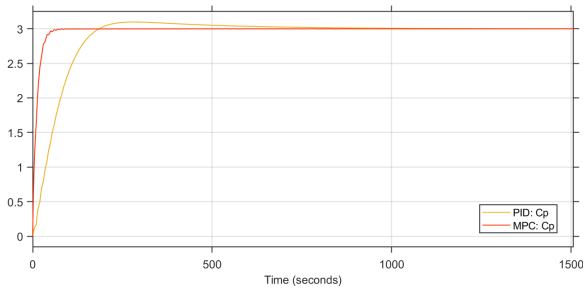

Figure 3: Comparison of the plasma concentrations from the MPC and PID control loops (in μg.ml^{-1}).

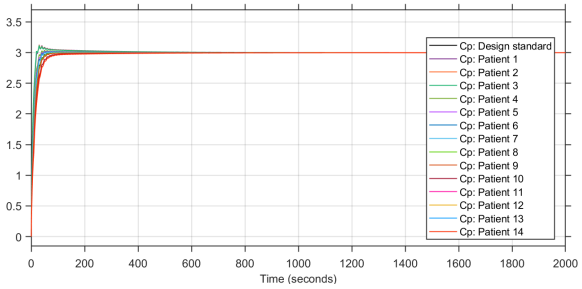

Figure 4: Step responses of the patient groups' plasma concentration with the MPC controller (in μg.ml^{-1}).

4 SIMULATION RESULTS

The following section expands on the results achieved from the simulations. The simulations were run using MATLAB and Simulink.

4.1 Step response

The objective of the control system is to reach the reference plasma concentration as quickly as possible without overshooting the reference value because in a practical system, overshooting the reference value could lead to complications as a result of drug overdose. This will simulate a drug being delivered intravenously to a patient to reach a desired plasma concentration. The reference plasma concentration is set to 3 μg.ml^{-1}.

To compare the performance of the MPC controller to the PID controller, the step responses of both controllers are plotted together. The step response of the plasma concentration from the patient group's average patient is depicted in Figure 3. The step response of the MPC is better than that of the PID. The 2% settling time of the MPC controller is at 47.9 s and that of the PID is at 146.2 s. Additionally, the step response of the MPC has no overshoot, while that of the PID has a slight overshoot, reaching a maximum of 3.04 μg.ml^{-1}.

4.2 Inter-patient variability

To determine how the systems would operate with a wide variety of patients, it was tested on the patient group described in Table 4. The results labelled "Cp: Design standard" are the results of the average patient, who was used to design the system and whose results are depicted in Figure 3.

4.2.1 MPC

The results of the step response of the MPC closed-loop controller for the patient group is shown in Figure 4. The results vary according to the age of the patient. Patients that are younger than the average patient tend to have shorter settling times and overshoot the reference plasma concentration. Patients that are older than the average patient do not overshoot the reference value, but their 2% settling time is longer than that of the average patient.

The reason for younger patients overshooting the reference plasma concentration is likely because they have more rigorous pharmacokinetics because of their smaller compartmental models and the same rate transfer constants as those of older patients.

To analyse the influence of the internal patient model on the control system, an MPC controller was implemented with the average patient as the internal patient model, with an age of 8.6 years, weight of 29.2 kg and height of 125.9 cm. This MPC controller design was used to control the anesthetic infusion for the same patient population, and the performance of this control system is depicted in Figure 5.

From Figure 5, the plasma concentration of the patients that are younger than the internal patient model oscillate before reaching steady state. This would be undesirable in practice as it would result in irregular, and potentially dangerous, infusion to the patient. It is therefore better to incorporate an internal patient model which corresponds to the patient undergoing anethesia to allow for safer sedation for the patient population.

4.2.2 PID

The step responses of the patient group simulated with the PID closed-loop control system are depicted in Figure 6.

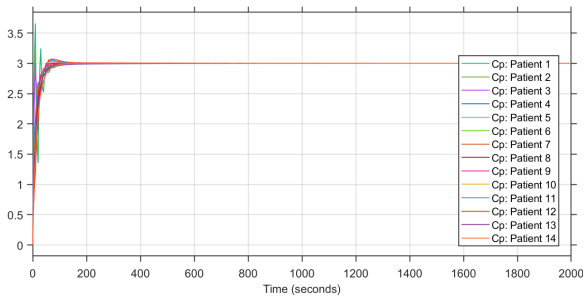

Figure 5: Step responses of the patient groups' plasma concentration for the MPC controller with constant internal model (in μg.ml^{-1}).

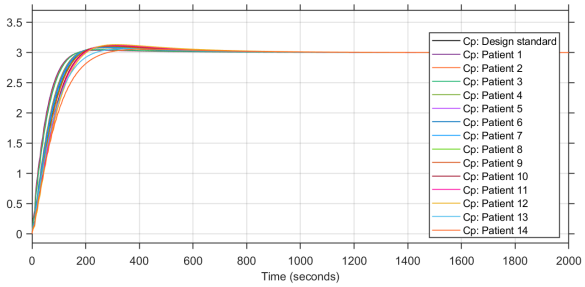

Figure 6: Step responses of the patient groups' plasma concentration with the PID controller (in μg.ml^{-1}).

From the results, it is clear to see that there is also inter-patient variability at play with the PID controller. Patients that are younger than the average patient have quicker settling times when compared to the average patient. This could be for the same reason that younger patients overshoot in the MPC simulations.

4.3 Execution time

To compare how resource intensive each system is, the two controller's execution times were measured for the simulation of the patient group over a 2000 s window. Simulink is a model-based design software package and it is not optimized for real time operation. However, the simulation times are still useful as a basis for comparison (The MathWorks, b).

The execution times for each patient and the average execution time are shown in Table 5. For the MPC control loop, the average execution time was 6.777 s and the PID control system executed for an average time of 5.691 s. The execution times also indicate that the PID controller remains more consistent in terms of computation time when controlling infusion for the different patients with varying PK models, indicated by a smaller standard deviation. This indicates that the PID system would be less resource intensive in a practical setting as it does not need as much processing power to execute the control loop as the MPC controller would need.

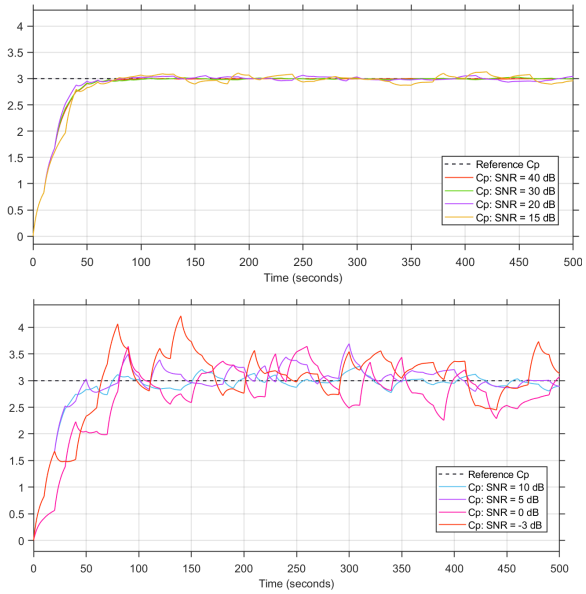

Figure 7: Simulated patient's plasma concentrations with measurement noise in the MPC control loop (Upper plot: SNR 40 dB to 15 dB. Lower plot: SNR 10 dB to -3 dB.)

Table 5: Execution Times for all 14 Patients According to the MPC or PID Controller used.

	MPC [s]	**PID [s]**
Average	6.78	5.69
Standard deviaton	2.25	0.73

4.4 Measurement noise

For the measurement noise simulations, the MPC control system's performance is depicted in Figure 7 and the PID controller's performance is depicted in Figure 8 and the root mean squared error (RMSE) of the various noise levels for both controllers are listed in Table 6.

According to Table 6, the MPC controller has better noise suppression than the PID controller. In a real-system, noise is an inevitable factor to consider, so this justifies that the MPC controller is a better controller to use.

4.5 Changing reference

To fully demonstrate the set-point following of closed-loop control, the system is tested under the condition of changing the reference concentration during the simulation.

The results of the changing reference are depicted in Figure 9. The results obtained from these simu-

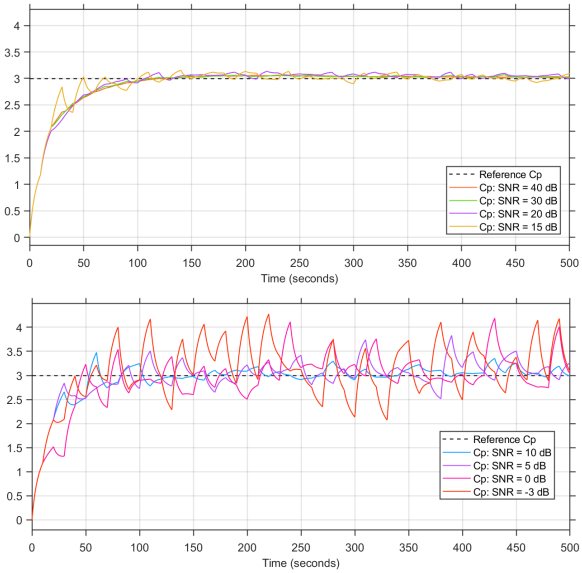

Figure 8: Simulated patient's plasma concentrations with measurement noise in the PID control loop (Upper plot: SNR 40 dB to 15 dB. Lower plot: SNR 10 dB to -3 dB.)

Table 6: RMSE of the MPC and PID controllers at different SNR

SNR	MPC	PID
40	0.775	0.721
30	0.711	0.697
20	0.594	0.580
15	0.587	0.579
10	0.585	0.547
5	0.575	0.582
0	0.574	0.568
-3	0.555	0.588

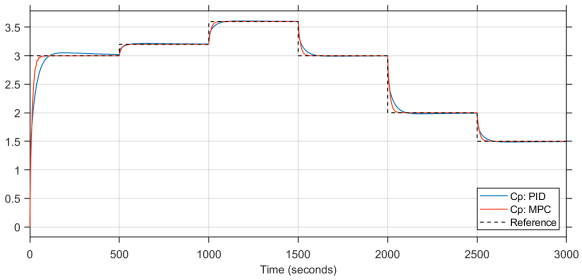

Figure 9: Changing the reference plasma concentrations in the MPC and the PID controller.

lations are similar to those in the step response simulations, with the PID controller's step response depicting longer settling time and slight overshoots. For larger reference changes, the settling time of the PID controller is longer than that of the MPC controller and the overshoot is greater than that of the MPC controller. For smaller reference changes, the MPC and PID step responses are similar.

5 CONCLUSIONS

From the data gathered from both the MPC and PID controllers, it can be concluded that the MPC controller is the more suited controller to use in the control of drug plasma concentration. Even though the MPC requires more processing power to operate than the PID, it is more appropriate for this setting because of its faster settling time, no overshoot, and shows better operation in noise. Additionally, based on the results from the changing reference tests, the MPC controller's response follows the set point changes more consistently than that of the PID controller.

For a less costly implementation, the PID control system could be investigated further as the maximum overshoot it produces may be within an acceptable range and it is a less resource intensive control system, as shown by of the more consistent computation time achieved when running the simulations for a number of patients. However, PID controllers need to be meticulously tuned for applications such as this because they run the risk of oscillating before or during steady state if they are not properly tuned.

As mentioned in (Ntouskas and Sarimveis, 2021) and (Gonzalez-Cava et al., 2021), for optimal control, irrespective of the control strategy used, the inter-patient variability must be considered further as the patients that lie at the edges of the PK models do not follow the references given as precisely as the average patients. This could be done by adapting the patient models to make more considerations for patients that lie at the edges of these PK models. Although the plasma concentrations of these patient models do not deviate too wildly from the reference points provided, it would be desirable to have them follow the reference point as closely as possible for safer and more predictable plasma concentration levels.

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