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Platelet count control in immune thrombocytopenic purpura patient: optimum romiplostim dose profile

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Abstract: Patients with immune thrombocytopenic purpura (ITP), a disease characterized by abnormally low platelet count, are susceptible to excessive bleeding as a direct consequence. While the problem of low platelet count can be addressed fundamentally either by slowing down the rate of platelet destruction or by increasing platelet production, or both, one of the more effective means of treating ITP patients is to increase platelet production with romiplostim. However, current romiplostim treatment strategies tend to produce undesirable responses where platelet counts oscillate between dangerously low values and extremely high peaks, as a direct consequence of the complex nonlinear dynamics associated with platelet count regulation. The objective of this study is to determine the optimum dose profile of romiplostim for a specific ITP patient required to maintain a platelet count of 70×10^9/L. Using clinical data of the specific patient's platelet count obtained in response to a series of subcutaneously applied doses of romiplostim, a standard pharmacokinetics/pharmacodynamics (PKPD) model was developed, validated, and analyzed to obtain insight into the patient's physiological characteristics. The model was subsequently used to investigate the performance of three control strategies: "fixed dose" open-loop control, "variable dose" discrete PI feedback control, and "variable dose" model-based open-loop optimal control. The control strategies were implemented for weekly and bi-weekly treatment regimens. With both treatment frequencies, the fixed dose open-loop control strategy resulted in unacceptable sustained oscillating platelet count. PI feedback control and model-based optimal open-loop control led to stable platelet count profiles after approximately 50 days but only for weekly injections. In summary, a stable platelet count is more likely to be achieved consistently in the specific patient with weekly treatments. Bi-weekly treatments are less effective because, as we show, fundamental pharmaceutical characteristics of romiplostim make oscillations in platelet count unavoidable at this treatment frequency. The results show that model-based decisions determined using patient-specific mathematical models are potentially useful for designing better treatment regimens for ITP patients.

1. BACKGROUND

Our objective is to develop an effective and implementable control strategy for maintaining a specific ITP patient's platelet count, PLT ($\times10^9$/L), at 70. The normal range of PLT in healthy individuals is between 150 and 400. While ITP is generally defined as PLT < 150, symptoms vary significantly with different values of PLT. Mild cases of ITP, where 30 < PLT < 150, are frequently untreated because symptoms are often unobservable. However, treatment is required for PLT < 30 (Schipperus & Fijnheer 2011), especially since sustained periods of extremely low PLT (e.g., PLT < 10) invariably lead to serious and possibly fatal complications.

1.1 Mechanism of platelet production regulation

Platelet production is regulated according to the following mechanism: The hormone thrombopoietin (TPO) stimulates the proliferation, maturation, and differentiation of platelet precursor cells (megakaryocytes), by binding to c-Mpl, the TPO receptor on the plasma membrane of these platelet precursor cells. Binding of TPO to megakaryocytes promotes megakaryocyte proliferation and differentiation, subsequently leading to the production of platelets.

TPO is primarily synthesized at a constant rate in the liver, and then secreted into the blood stream. Since c-Mpl is also present on the plasma membrane of platelets, TPO can also

bind to platelets. The circulating concentration of TPO therefore is inversely related to platelet count (Wolber & Jelkmann 2002). When platelet count is high, more TPO will bind to platelets, thereby lowering TPO concentration and consequently reducing the availability of TPO for stimulating megakaryocytes, which ultimately then lowers the stimulatory effect of TPO on platelet production. Thus as more platelets are produced, the effective production rate is reduced automatically by this natural feedback regulatory mechanism whereby the stimulatory TPO is sequestered from megakaryocytes by the produced platelets (Fig. 1). Conversely, when platelet count is low, more TPO will be available and the increased TPO concentration will therefore exert an enhanced stimulatory effect on megakaryocytes, ultimately leading to increased platelet production.

1.2 Pathology and treatment of ITP

Under normal conditions, the intrinsic biological feedback regulatory mechanism is able to maintain homeostatic production of platelets. In ITP patients, however, complications arise because of the simultaneous incidence of increased platelet destruction and decreased platelet production (Kuter & Gernsheimer 2009). While the root cause of ITP is unknown, fundamental understanding of TPO regulation of platelet production indicates that platelet production can be increased to compensate for inappropriately low production by enhancing TPO levels. Therefore, a logical ITP treatment option is to employ "TPO mimetics" acting through the same mechanism as TPO; romiplostim is one such TPO mimetic developed for this purpose.

Romiplostim has been shown to increase platelet count (to PLT $\geq$ 50) in the majority of ITP patients (Palandri et al. 2012). However, peak platelet count in response to single romiplostim treatment is highly variable from patient to patient (Bussel et al. 2006). For example, a platelet count of 130×10^9/L achieved with 1 μg/kg/week in one patient requires 3 μg/kg/week in another (Meyer, Herzig & Salama 2012), possibly due to differences among patients in the extent of decreased platelet production and increased platelet destruction.

Furthermore, the time required to reach peak platelet count after romiplostim administration, a long time delay indicative of the time required for magakaryocyte differentiation, varies significantly from patient to patient, and also with dosage, with medians ranging from 10 to 14 days (Bussel et al. 2006). The effect of one romiplostim injection on any particular patient will therefore affect the efficacy of the next, adding an additional layer of complexity to the problems created by the nonlinear dynamics and time delay. Consequently, maintaining platelet count at a stable value with romiplostim is fundamentally challenging.

The recommended manufacturer guideline is a weekly administration of romiplostim with a dose depending on the current platelet count. However, there are potential problems with this recommendation. As noted above, for many patients, the time to reach peak platelet count after romiplostim treatment is more than a week. Consequently, it is likely that

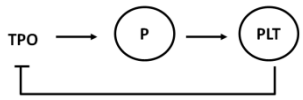

Fig. 1. Schematic of platelet production regulation. TPO: thrombopoietin; P: Precursor (megakaryocyte); PLT: platelet.

treatment will be administered while platelet count is rising, but more importantly, current platelet count measurement will not adequately reflect the full effect of the immediately preceding treatment. In this case, however, excess romiplostim will simply be sequestered by the platelets, so that its stimulatory effect on platelet production will be muted. The converse is more problematic. If a treatment is administered when platelet count is decreasing, and the dose is determined on the basis of current measurement, platelet count will almost surely continue to decrease and may decrease to an undesired low value because it takes a few days for the administered romiplostim to take effect. By the time the treatment takes effect, the actual platelet count will be nowhere near the value upon which the treatment dose was based so that the treatment is likely to have been seriously underestimated. Thus to be effective a treatment strategy must therefore take the complex dynamic characteristics of romiplostim action explicitly into consideration.

Mathematical modeling is now widely acknowledged as an efficient tool for understanding complex biological systems, and specifically for our purposes, pharmaco-kinetic/pharmaco-dynamic (PKPD) models of romiplostim have been shown to be capable of capturing the characteristics and mechanisms of romiplostim metabolism in healthy humans (Wang et al. 2010). Our strategy in this study is to obtain an appropriate mathematical model of romiplostim-mediated platelet production and regulation for the specific ITP patient in question; analyze the model to obtain insight; and use the model as the basis of model-based control investigations, framing platelet count regulation as a control problem and utilizing appropriate control theoretic principles to obtain practical solutions.

2. MATHEMATICAL MODELING

An existing PKPD model of romiplostim (Wang et al. 2010), schematically shown in Fig. 2, was implemented in Simulink/MATLAB, and modified and customized for our purposes. An extra parameter, n, was introduced into the PD model to account for any potential nonlinear effect of romiplostim on platelet production.

2.1 The PK model

The PK model consists of 4 compartments: the subcutaneous site, the serum in circulation, the peripheral part, and the drug-receptor complex. Romiplostim injection is implemented as a rectangular pulse function with width of 1/60 hour and magnitude corresponding to the dose. The sequence $u(k)$ denotes pulses of romiplostim of magnitude u implemented at discrete time point k ($k = 0, 1, 2, 3, \ldots$). The injection process is described as the product of k_{SC}, F, and $u(k)$, where k_{SC} is pre-determined to be 60 h^{-1}, and F, the

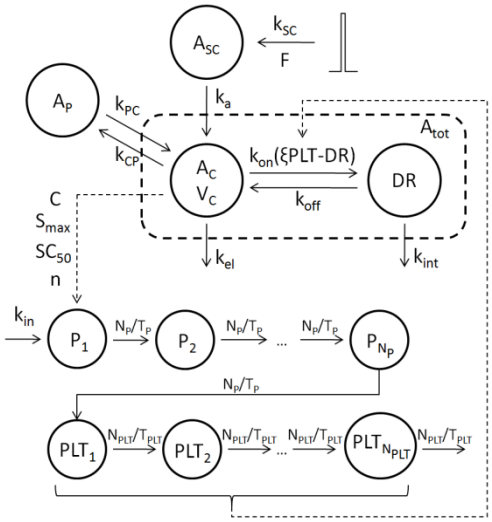

Fig. 2. Schematic diagram of the mechanisms of romiplostim-induced platelet production upon which the PKPD model is based. See main text for an explanation of the terminology. Romiplostim injection is implemented as a pulse.

absolute bioavailability of romiplostim to the specific patient, is a parameter to be estimated from data. Romiplostim absorption is represented as a first-order process with rate constant k_a. The amount of romiplostim at the subcutaneous site (A_{SC}) is then described by the following differential equation:

$$\frac{dA_{SC}}{dt} = k_{SC} \cdot F \cdot u(k) - k_a \cdot A_{SC} \tag{1}$$

After absorption, romiplostim is distributed throughout the body. The physiological processes are described by equations used in (Wang et al. 2010). A quasi-equilibrium state for the drug-receptor complex is assumed and the dissociation equilibrium constant K_D, defined as k_{off}/k_{on}, is estimated instead of the individual k_{off} and k_{on}.

2.2 The PD model

The PD model is based on the maturation-structured cytokinetic concept which accounts for the maturation process of platelet precursor cells in the bone marrow and the aging process of platelets in circulation. Ten stages are used for the precursors (number represented by N_P), as well as platelets (number represented by N_{PLT}). In addition to the intrinsic maturation rate of the precursors, k_{in}, the concentration of free romiplostim in serum, C, also exerts a stimulatory effect on the maturation of the precursors. The stimulatory effect is described by a Hill function, with S_{max} as the maximal effect, SC_{50} as the romiplostim concentration required for obtaining half the maximal effect, and n, as the customary Hill coefficient. The model assumes that all precursors and platelets mature into the next stage without being cleared from the body. The lifespans of precursors and platelets, which are indicative of how fast a cell moves from one stage to the next in the maturation or aging process, are introduced as parameters and denoted by T_P and T_{PLT}, respectively. The resulting model equations are:

$$\frac{dP_1}{dt} = k_{in} + S_{\max}\frac{C^n}{SC_{50}{}^n + C^n} - \frac{N_P}{T_P}P_1 \tag{2}$$

$$\frac{dP_i}{dt} = \frac{N_P}{T_P}\left(P_{i-1} - P_i\right), \quad i = 2,3,\ldots,N_P \tag{3}$$

$$\frac{dPLT_1}{dt} = \frac{N_P}{T_P}P_{N_P} - \frac{N_{PLT}}{T_{PLT}}PLT_1 \tag{4}$$

$$\frac{dPLT_i}{dt} = \frac{N_{PLT}}{T_{PLT}}\left(PLT_{i-1} - PLT_i\right), \quad i = 2,3,\ldots,N_{PLT} \tag{5}$$

where P_i represents the number of precursor cells in the i-th stage while PLT_i is the number of platelets in the i-th stage.

3. DATA COLLECTION, PARAMETER ESTIMATION & MODEL VALIDATION

3.1 Clinical data

Platelet count data used to determine patient-specific parameters and to validate the PKPD model were based on physician-administered romiplostim treatment records over a period of 130 days. Each round of treatment involves a complete blood count (CBC) test using a blood sample acquired via venipuncture, followed by standard analysis. The physician subsequently determines and then administers an appropriate dose of romiplostim, based on the platelet count measurement. The observed platelet count and the corresponding drug dose are then recorded.

3.2 Parameter estimation & model validation

Values of unknown parameters in the PKPD model were estimated by optimally matching model predictions to a subset of the patient data (up to day 86, corresponding to the first 7 romiplostim pulses and the open circles in Fig. 3) via least-squares optimization. The remaining complement of clinical data was used to validate the model. The resulting parameter estimates are summarized in Table 1.

The model was validated by using it to predict the patient's platelet count response to subsequent treatments, without further adjusting any of the model parameters, and comparing the prediction to corresponding data. The model prediction, shown in Fig. 3 along with the data, indicates a generally good fit to the data, with discrepancies at predominantly high platelet counts most likely due to the effects of platelet

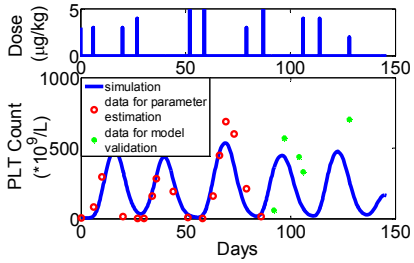

Fig. 3. Clinical treatment data and platelet count profile with the PKPD model prediction. The upper panel is the romiplostim injection profile; the lower panel is the platelet count data collected at the clinic and model prediction.

destruction mechanisms and other environmental factors that are not considered in the model. Note that it has been difficult to maintain the patient's platelet steady.

4. MODEL ANALYSIS

4.1 Parameter values

The parameter T_{PLT} representing platelet lifespan was estimated to be 4.7 days for the specific patient; for healthy subjects, it is 10.5 days (Wang et al. 2010). This indicates that the patient's platelets last only half as long as platelets in healthy subjects, consistent with commonly observed traits in ITP patients (Kuter & Gernsheimer 2009). The value for the newly introduced parameter n is close to 1, indicating that the nonlinear effect of romiplostim on platelet production in the patient is similar to that in healthy subjects. A smaller k_{int} value obtained for the patient suggests a lower than normal clearance rate of romiplostim through receptor internalization, and a higher chance of romiplostim being released back to the serum. However, the small K_D value for the patient indicates a high affinity of romiplotim to c-Mpl, leading to less dissociation of romiplostim from the drug-receptor complex. Since romiplostim acts through the same mechanism as endogenous TPO, the observed k_{int} and K_D values, combined with the increased k_{el}, suggest lower availability of TPO to megakaryocytes in the patient, leading to decreased platelet production and a lower platelet count.

4.2 Theoretical dose responses

One of the benefits of a mathematical model is that it allows one to investigate and analyze, via simulation, system responses to a variety of informative stimuli quickly and efficiently. Two sets of particularly informative examples are shown here for this specific problem.

Figure 4(a) shows the model response to a single romiplostim injection of 1 μg/kg for a variety of initial platelet count values, PLT_0, ranging from 5×10^9/L to 250×10^9/L. The response to romiplostim treatment is stronger at lower initial platelet counts and is attenuated with increasing initial values of platelet count. This result is consistent with known mechanisms of romiplostim action whereby a higher initial platelet count provides more opportunity for the excess platelets to bind and sequester the drug, thereby reducing the stimulatory effect of romiplostim. For this specific patient, when PLT_0 is higher than 150, no significant response is observed to a 1 μg/kg romiplostim injection.

Figure 4(b) shows the model response to a single injection of various doses ranging from 0.2 μg/kg to 5 μg/kg, starting from a fixed initial platelet count of 5×10^9/L. For this specific patient, the response shows three phases: an initial induction period of approximately 5 days (regardless of dosage) with no noticeable change in platelet count; a gradual increase in platelet count culminating in a peak response occurring around 14-16 days, with the peak occurring progressively later with increasing doses; a final declining phase with platelet count gradually returning to the original starting value after 25-30 days. The magnitude of the peak response is dependent on dosage nonlinearly, as an n-fold increase in the dose does not result in a corresponding n-fold increase in the magnitude of the peak response.

Table 1. Parameter values for healthy individuals (Wang et al. 2010) and the ITP patient

Parameter	healthy subjects value (unit)	ITP patient value (unit)
PK model		
k_a	0.0254 (h^{-1})	0.0124 (h^{-1})
k_{CP}	0.0806 (h^{-1})	0.143 (h^{-1})
V_C	0.0683 (L/kg)	0.0778 (L/kg)
k_{PC}	0.0148 (h^{-1})	0.0098 (h^{-1})
k_{el}	0.0382 (h^{-1})	0.0910 (h^{-1})
k_{int}	0.173 (h^{-1})	0.0248 (h^{-1})
K_D	0.131 (ng/mL)	0.0028 (ng/mL)
ξ	0.0215 (fg/platelet)	0.0190 (fg/platelet)
F	0.499 (-)	0.271 (-)
PD model		
SC_{50}	0.0520 (ng/mL)	0.0560 (ng/mL)
S_{max}	11.07 (h^{-1})	5.999 (h^{-1})
N_p	10 (-)	10 (-)
N_{PLT}	10 (-)	10 (-)
T_P	142 (h)	219 (h)
T_{PLT}	253 (h)	113 (h)
n	1 (-)	0.9948 (-)

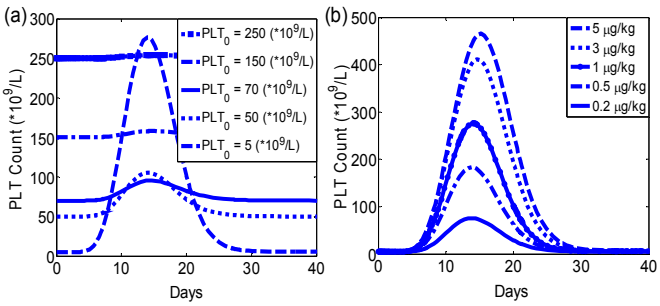

Fig. 4. Model response to (a) single romiplostim injection of 1 μg/kg for various initial platelet counts; (b) a single romiplostim injection of various doses, with an initial platelet count of 5×10^9/L.

Finally, observe that the response to a single injection is intrinsically periodic, with a period T of approximately 28 days. Consequently, the treatment frequency should be carefully designed taking this important characteristic response time into consideration. For example, a treatment regimen restricted to once every 28 days will result in what will appear to be perfect sustained oscillations in time (with possibly varying amplitude). Similarly, since measurements can only be taken at specific discrete points in time, the sampling period Δt must also be selected carefully in order to avoid missing critical information about the true state of the patient's platelet count.

5. ENGINEERING CONTROL SYSTEMS APPROACH TO THE DEVELOPMENT OF TREATMENT PROTOCOLS

Having confirmed that the PKPD model provides a reasonable representation of the characteristics of romiplostim-induced platelet production for the patient in question, the model was used to investigate platelet count control strategies. The primary objective is to determine a sequence of romiplostim injections required to maintain a target platelet count, y^* ($\times10^9$/L), of 70. The injections are represented as $u(k)$, rectangular pulses of magnitude u

implemented at discrete time point k (k = 0, 1, 2, …), every Δt time units. Three distinct control techniques are used to determine the injection sequence $u(k)$ and the respective performances evaluated via simulation for two sampling periods: weekly (Δt = 7 days) or bi-weekly (Δt = 14 days). The three control strategies are: (i) open-loop control; (ii) optimally-tuned proportional-integral (PI) control; and (iii) optimal open-loop control. Note that while $u(k)$ is allowed to take any value on the real line in this study, in practice romiplostim can only be administered in quantized doses.

5.1 Control system design

5.1.1 Open-loop control

The strategy here is to implement a constant value of $u(k)$ regardless of actual platelet count measurements (hence "open loop"). The primary rationale for such a strategy is its simplicity. The model was used to investigate patient outcome in response to injection doses $u(k)$ of 2, 1, and 0.5 μg/kg for weekly and bi-weekly treatments in order to determine which of these typical doses implemented at which of these typical frequencies comes closest to meeting the stated control objective if at all.

5.1.2 Optimally-tuned PI controller without zero-order hold

With this classical feedback control strategy, $u(k)$ is determined at each discrete time point k on the basis of $\varepsilon(k)$, the error between the platelet count measurement and the desired value. The control action $u(k)$ is computed as:

$$u(k) = K_P \cdot \varepsilon(k) + K_I \cdot \sum_{i=1}^{k} \varepsilon(i), \quad k = 0,\ 1,\ 2,\ \ldots \qquad (13)$$

where K_P and K_I are controller parameters.

While negative $u(k)$ values are mathematically possible from this expression, they are physiologically meaningless: the implemented control action is therefore constrained to a minimum value of $u(k) = 0$.

For a wide variety of physiological reasons, the platelet count response profile is very sensitive to u_0, the initial injection dose implemented at $k = 0$. Consequently, this initial condition is treated as an extra parameter and determined independently. Because romiplostim is implemented as pulses, the PI controller output is implemented without the usual zero-order hold.

Rather than tune the PI controller using standard tuning rules, the controller parameters were determined via optimization. Specifically, optimal values were determined for u_0, K_P and K_I using the optimization routine *fminsearch* by minimizing the resulting sum-of-squared errors between the set-point and the platelet count, over a prescribed time horizon of 24 weeks.

5.1.3 Model-based open-loop optimal control

Under this strategy, the dynamic model is used to determine a romiplostim dose sequence $u(k)$ (k =1, 2,…N_f) that minimizes the sum-of-squared errors, represented mathematically as:

$$\min_{u(k)} \Phi(u(k)) = \sum_{i=1}^{N_f} \left(\varepsilon(i)\right)^2 \qquad (14)$$

where, as with the PI feedback control strategy, $\varepsilon(i)$ is the error between the platelet count measurement and the desired value. The number of time points N_f is chosen arbitrarily as 500 in this study, and the time points at which the errors are calculated are evenly distributed over the simulation time of 24 weeks. The dose sequence $u(k)$ is computed directly using an optimization algorithm *fminsearch* for weekly and bi-weekly treatment frequencies.

5.2 Results and discussion

5.2.1 Open-loop control

The performance of the open-loop control strategy shown in Fig. 5 indicates that this simple and straight forward strategy is unable to maintain a stable platelet count at the desired target value. The obvious oscillatory responses, not unexpected in light of the foregoing model analysis, are the result of a "nonlinear convolution" of the theoretical "basis function" of Fig. 4(b). As expected, the peak platelet count values are lower for lower doses, and the "effective period" of the observed oscillations is longer for the bi-weekly treatment regimen.

5.2.2 Optimally-tuned PI controller without zero-order hold

The simulation results of system performance for weekly injections under this control strategy are shown in Fig. 6(a), with the top panel showing the romiplostim doses used to achieve the platelet count trajectory shown in the bottom

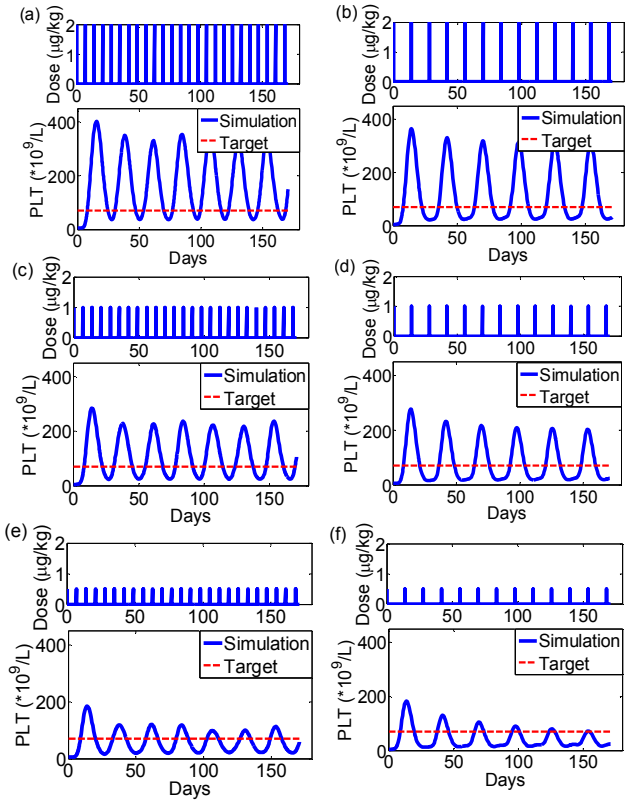

Fig. 5. Performance under the open-loop control strategy

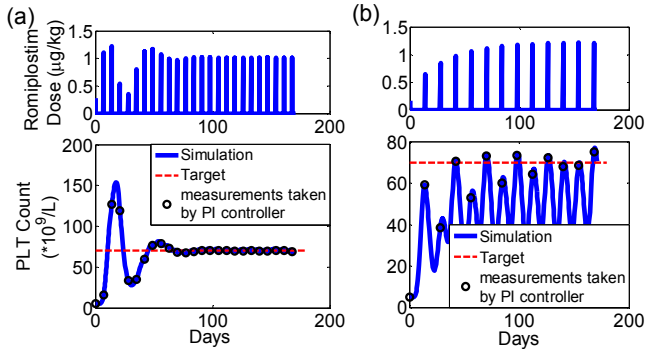

Fig. 6. Results from optimally-tuned discrete PI control for (a) weekly and (b) bi-weekly treatments.

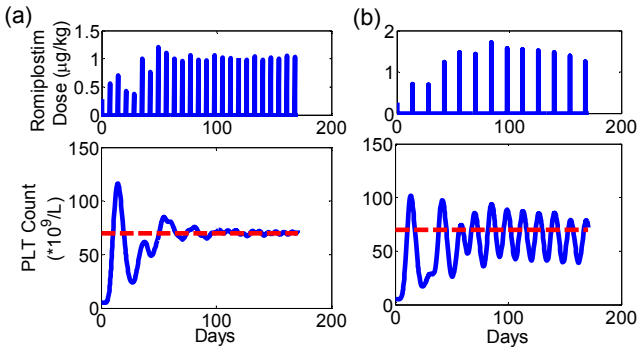

Fig. 7. Results from optimal open-loop control for (a) weekly and (b) bi-weekly treatments.

panel. Observe that after about 7 treatments, or 49 days, the platelet count has stabilized and remained essentially constant at the desired target value. Thereafter, a steady dose of approximately 1 μg/kg is needed to sustain the platelet count at 70. The performance under a bi-weekly treatment regimen based on the same control strategy, shown in Fig. 6(b), is not as good as the result in Fig. 6(a) for the weekly treatment regimen. Note in particular the oscillatory response, and how the discrete measurements used by the controller, indicated by the circles superimposed on the continuous response, collectively give an illusion of reasonable performance. At the discrete time points where the measurements are taken and control action implemented, the measured values indeed are somewhat close to the desired target value; however, these infrequently sampled measured values fail to represent the true nature of the full response.

5.2.3 Model-based open-loop optimal control

The results under model-based open-loop optimal control, shown in Fig. 7, are similar to the corresponding results under optimally-tuned PI control shown in Fig 6. Figure 7 shows (a) the results for weekly treatments; (b) for bi-weekly treatments, with the top panel in each case showing the corresponding romiplostim doses. As in Fig. 6(a), after about 49 days, the platelet count has achieved its target in a stable manner with a steady weekly dose of approximately 1 μg/kg sufficient to maintain the platelet count at target.

As in Fig. 7(b), the bi-weekly treatment resulted in a response which, after 75 days, oscillates around the desired targetvalue of 70, with sustained oscillations. The sustained oscillation is a natural consequence of intrinsic romiplostim action as predicted in Fig. 4(b) for the ITP patient in question, indicating that bi-weekly treatments will not achieve a stable platelet count.

6. SUMMARY & CONCLUSIONS

In this study, a PKPD model was developed for an ITP patient in order to capture romiplostim-induced platelet count dynamics appropriately for subsequent use as the basis for the development of effective treatment strategies.

Three different control strategies were investigated. The results show that a stable platelet count can be achieved with weekly injection profiles determined by either the "optimally-tuned" PI feedback control or by optimal open-loop control. The simple and straightforward open-loop control strategy involving the implementation of a constant dose was entirely ineffective. Bi-weekly treatments led to sustained oscillations as a result of intrinsic pharmacological characteristics of romiplostim. Weekly treatments on the other hand produced better results with platelet count maintained more readily at the target value of 70×10^9/L.

Since ITP patient's response to romiplostim treatment is highly variable from patient to patient, this study has demonstrated that the use of patient-specific mathematical models for making model-based decision appears to be a promising approach to achieving stable platelet count.

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