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 featuring abnormally low platelet count, are susceptible to excessive bleeding. One of the more effective treatment regimens is to increase platelet production with romiplostim. However, current romiplostim treatment strategies tend to produce undesirable responses where platelet count oscillates between dangerously low and extremely high values, as a consequence of the complex nonlinear dynamics associated with platelet production. This study aims to determine the optimum romiplostim dose profile required to maintain a stable platelet count for a specific ITP patient. Using the specific patient's platelet count data obtained in response to a series of romiplostim doses, a pharmacokinetics/pharmacodynamics 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 for weekly and bi-weekly treatment regimens. A stable platelet count is more likely to be achieved in the specific patient with weekly treatments. Bi-weekly treatments are less effective because fundamental characteristics of romiplostim make oscillations in platelet count unavoidable at this treatment frequency. Model-based decisions determined using patient-specific mathematical models are potentially useful for designing better treatment regimens for ITP patients. The strategies developed in this work provide potential solutions to the highly variable responses observed among ITP patients undergoing romiplostim treatment. The approach can also be applied to other diseases with complex system dynamics.

Keywords

Immune thrombocytopenic purpura, Biological system modeling, Model-based control, Nonlinear systems, Optimization

1. Introduction

Our objective is to develop an effective and implementable control strategy for maintaining a specific platelet count—PLT ($\times 10^9/L$), at 70—in a patient with Immune Thrombocytopenic Purpura (ITP). The normal range of PLT in healthy individuals is between 150 and 400. While ITP is generally defined as PLT

1 < 150, symptoms vary significantly with different values of PLT (Table 1). Mild cases of ITP, where 30 <
2 PLT < 150, are frequently untreated because symptoms are often unobservable [1, 2]. However, treatment
3 is usually required when PLT < 30 [3], since sustained periods of extremely low PLT (e.g., PLT < 10) can
4 lead to serious and sometimes fatal complications [4].

5 1.1. Mechanism of platelet production regulation

6 Platelet production is regulated according to the following mechanism: The hormone thrombopoietin
7 (TPO) stimulates the proliferation, maturation, and differentiation of platelet precursor cells
8 (megakaryocytes) by binding to c-Mpl, the TPO receptor on the plasma membrane of these platelet
9 precursor cells. Binding of TPO to megakaryocytes activates two pathways: the JAK/STAT5 pathway,
10 which results in cell proliferation, and the MAPK pathway, which promotes megakaryocyte differentiation
11 [5, 6], leading to the production of platelets.

12 TPO is primarily synthesized by hepatocytes at a constant rate in the liver [7] and then secreted into the
13 blood stream. Since c-Mpl is present on the plasma membrane of platelets, TPO can also bind to platelets.
14 This results in an inverse relationship between the circulating concentration of TPO and the platelet count
15 [7, 8]. When platelet count is high, more TPO will bind to platelets, thereby lowering TPO concentration
16 and consequently reducing the availability of TPO for stimulating megakaryocytes. This ultimately lowers
17 the stimulatory effect of TPO on platelet production. Therefore, as more platelets are produced, the
18 effective production rate is reduced automatically by this natural feedback regulatory mechanism whereby
19 the stimulatory TPO is sequestered from megakaryocytes by the produced platelets (Fig. 1). Conversely,
20 when platelet count is low, more TPO will be available and the increased TPO concentration will thus exert
21 an enhanced stimulatory effect on megakaryocytes, ultimately leading to increased platelet production.

22 1.2. Pathology and treatment of ITP

23 Under normal conditions, the intrinsic biological feedback regulatory mechanism described above and
24 illustrated in Fig. 1 maintains homeostatic production of platelets. In ITP patients, however, complications
25 arise because of the simultaneous incidence of increased platelet destruction and decreased platelet
26 production [9] as a result of any number of conditions including autoimmune responses, reduced TPO
27 production rate due to pathological disorders in the liver, or pathological changes in the c-Mpl receptor or

1 post-receptor signaling events in megakaryocytes [10]. While the root cause of ITP is unknown, an
2 understanding of TPO regulation of platelet production indicates that platelet production can be increased
3 to compensate for inappropriately low production by enhancing TPO levels. Therefore, a logical ITP
4 treatment option is to employ “TPO mimetics”, such as romiplostim, that act through the same mechanism
5 as TPO.

6 Romiplostim, a fusion protein analog of TPO, contains two copies of the human immunoglobulin (IgG₁)
7 Fc domain, each covalently linked at its C-terminus to a peptide chain containing two c-Mpl-binding
8 peptides [11]. It has been approved in many countries as a treatment for adult patients with chronic ITP
9 [12] and has been shown to increase platelet count (to $PLT \geq 50$) in the majority of ITP patients [13-15].

10 However, peak platelet count in response to single romiplostim treatment is highly variable from patient
11 to patient [16]. For example, a platelet count of $130 \times 10^9/L$ achieved with 1 $\mu g/kg/week$ in one patient
12 requires 3 $\mu g/kg/week$ in another [14], possibly due to differences among patients in the extent of
13 decreased platelet production and increased platelet destruction [9].

14 Furthermore, the time required to reach peak platelet count after romiplostim administration, a delay that
15 reflects the time required for megakaryocyte differentiation, varies significantly from patient to patient,
16 with medians ranging from 10 to 16 days [16, 17]. As a result of the mechanism of romiplostim action, the
17 peak response for each individual patient is generally higher at lower initial platelet counts and attenuated
18 with increasing values of platelet count—a defining characteristic of nonlinear systems. The effect of one
19 romiplostim injection on any particular patient will therefore affect the efficacy of the next, adding another
20 layer of complexity to the problems created by the nonlinear and time delay dynamics. Consequently,
21 maintaining platelet count at a stable value with romiplostim is fundamentally challenging.

22 The manufacturer recommendation is weekly administration of romiplostim, with the dose depending on
23 the current platelet count. However, as noted above, the time to reach the peak platelet count after
24 romiplostim treatment is more than a week for many patients. Thus it is likely that treatment will be
25 administered while platelet count is still rising, but more importantly, current platelet count measurement
26 will not adequately reflect the full effect of the immediately preceding treatment. In this case, however,
27 excess romiplostim will simply be sequestered by the platelets, so that its stimulatory effect on platelet
28 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 unacceptably low value because it takes a few days for administered romiplostim to take effect. By the time the treatment takes effect, the actual platelet count will not be near the value upon which the treatment dose was based so that the treatment is likely to have been seriously underestimated. To be effective, a treatment strategy must take the complex dynamic characteristics of romiplostim action into consideration.

By now, it has become well established that mathematical modeling is an efficient tool for understanding complex biological systems [18]. In the specific case in question here, pharmacokinetic/pharmacodynamic (PKPD) models of romiplostim have been used effectively to capture the characteristics and mechanisms of romiplostim metabolism in healthy humans [8] and ITP rats [12]. A relatively recent study developed a K-PD model (with the P in PK omitted to indicate the absence of data on drug concentration in the serum) for the effect of romiplostim on platelet production using data from ITP patients, approximating the pharmacokinetic part with a single compartment model [17]. The data reported in the study showed highly variable responses to romiplostim administration in ITP patients, leading the authors to divide the data into two subpopulations each characterized by significantly different parameter estimates. The K-PD model representing the population characteristics of romiplostim-induced platelet production in the patients was subsequently used to investigate two quantized dosing strategies with the objective of preventing $PLT > 400$, the conventional upper limit of platelet count in normal individuals. The simulation results showed that from 12 weeks to 42 weeks, PLT can be maintained between 20 and 400 with both dosing strategies in 75% of the subjects, while PLT was predicted to fall below 20 (high bleeding risk) in 20% of the subjects and rise above 400 (increased thrombotic risk) in the remaining 5% of the subjects over the same period.

The question we address in this work is as follows: given the practical constraint that treatments can only be administered at regular intervals, is a steady platelet count achievable in ITP patients treated with romiplostim (exemplified by the specific patient in question); and if so, what (control) strategy will produce the required dose profile to achieve this objective? Our strategy 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 into the important characteristics of the patient; 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. Specifically, this approach is used to determine the theoretical optimum romiplostim profile required to maintain platelet count, PLT ($\times 10^9/L$), at 70, with weekly or bi-weekly subcutaneous injections of various doses of romiplostim over a period of 6 months. Three control strategies were investigated: “fixed dose” open-loop control, “variable dose” proportional-integral (PI) feedback control, and “variable dose” model-based open-loop optimal control. We show that a stable platelet count profile is achievable only with weekly treatment frequency in the specific patient, due to the pharmacological characteristics of romiplostim. Our results also show that a patient-specific mathematical model and common control strategy combined can yield a better treatment regimen for patients with ITP.

2. Materials and methods

2.1. Mathematical modeling

An existing PKPD model of romiplostim [8] (Fig. 2) was modified, customized for our purposes, and implemented in Simulink/MATLAB. Although the PK data of serum romiplostim concentrations were not available in our dataset, we chose as the initial basis of our investigations, the mechanistic PKPD model developed in [8] over the semi-mechanistic K-PD model used in [17], where a single compartment is used in place of the PK model. Using a single simplified compartment to represent the PK portion of the system could potentially make it difficult to capture important physiological characteristics. For example, as noted earlier, newly produced platelets constitute an additional input (in addition to romiplostim administration) to the PK model, directly affecting the drug concentration, and thereby playing a key role in further regulating platelet production. This crucial intrinsic regulatory feedback mechanism (central to the physiological regulation of platelet production) is missing in the K-PD model. Thus the K-PD model is not appropriate for an investigation focused explicitly on designing schemes for effective control of platelet count.

The complete set of model equations is given in the supplementary material. Notations and the physiological processes they represent are listed in Table 2. Initial conditions for the resulting system of ordinary differential equations (ODEs) are presented in Supplementary Table 1. Three modifications were made to the existing model: (1) romiplostim injection was implemented in the PK model as a rectangular

pulse function with width of 1/60 hour and magnitude corresponding to the dose; (2) an extra parameter, n , was introduced into the PD model to account for any nonlinear effect of romiplostim on platelet production; (3) the maximal effect of romiplostim on platelet production (S_{max}) was decoupled from the intrinsic megakaryocyte maturation rate (k_{in}) compared to the original model. Decoupling of the intrinsic megakaryocyte maturation rate and the maximal effect of romiplostim provides a more physiologically relevant description of romiplostim-induced platelet production. With the same platelet lifespan, a higher intrinsic megakaryocyte maturation rate indicates a higher initial platelet count, which should reduce the effect of romiplostim, as noted above. A confounded representation for S_{max} and k_{in} would thus be inappropriate. In addition, as k_{in} is representative of the effect of endogenous TPO, the effect of romiplostim, which works through the same mechanism as TPO, should be additive to the entire platelet production process.

2.2. Data collection, parameter estimation, and model validation

2.2.1. Clinical data

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

2.2.2. Parameter estimation and model validation

Unknown values of 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 presented in Table 3.

To validate the model, model-generated predictions of the patient's platelet count response to subsequent treatments, without further adjustment of any of the model parameters, were compared to corresponding data. The model prediction, shown in Fig. 3 along with the collected data, indicates a generally good fit to the data, with discrepancies at predominantly high platelet counts most likely due to unmodeled effects of

platelet destruction and other environmental factors that are not considered in the model. Note that it was difficult to maintain a steady platelet count in the patient.

2.3. Model analysis

2.3.1. 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 [8]. This indicates that the patient's platelets last only half as long as the platelets in healthy subjects, consistent with commonly observed traits in ITP patients [9, 19]. 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 therefore 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 romiplostim to c-Mpl and therefore less dissociation of romiplostim from the drug-receptor complex. Since romiplostim acts via 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.

2.3.2. 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 stimuli quickly and efficiently. Two sets of particularly informative examples are shown here for this specific problem.

Fig. 4 shows the model response to a single romiplostim injection of 1 $\mu\text{g/kg}$ for a variety of initial platelet count values, PLT_0 , ranging from $5 \times 10^9/\text{L}$ to $250 \times 10^9/\text{L}$. The response to romiplostim treatment is stronger at lower initial platelet counts and is attenuated with increasing initial platelet count values. This result is consistent with known mechanisms of romiplostim action, with a higher initial platelet count providing 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 $\mu\text{g/kg}$ romiplostim injection.

Fig. 5 shows the model response to a single injection of various doses ranging from 0.2 $\mu\text{g/kg}$ to 5 $\mu\text{g/kg}$, starting from a fixed initial platelet count of $5 \times 10^9/\text{L}$. 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 at 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.

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

3. Development of treatment protocols using an engineering control systems approach

Once it was confirmed that the PKPD model provides a reasonable representation of romiplostim-induced platelet production for the patient in question, the model was used to investigate platelet count control strategies. The primary objective was to determine the sequence of romiplostim injections required to maintain a target platelet count, y^* ($\times 10^9/\text{L}$), of 70. The injections are represented as $u(k)$, rectangular pulses of magnitude u implemented at discrete time point k ($k = 0, 1, 2, \dots$), every Δt time units. Three distinct control techniques—open-loop control, discrete closed-loop PI control, and optimal open-loop control—were used to determine the injection sequence $u(k)$, and the respective performances were evaluated via simulation for two sampling periods: weekly ($\Delta t = 7$ days) or bi-weekly ($\Delta t = 14$ days). Note that while $u(k)$ is allowed to take any value on the real line in this study, in practice romiplostim can be administered only in quantized doses.

3.1. Control system design

3.1.1. 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 typical injection doses $u(k)$ of 2, 1, and 0.5 $\mu\text{g/kg}$ at typical weekly and bi-weekly treatment frequencies in order to determine which of these doses implemented at which of these frequencies, if any, comes close to meeting the stated control objective.

3.1.2. Discrete 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 follows:

$$u(k) = K_p \cdot \varepsilon(k) + K_I \cdot \sum_{i=1}^k \varepsilon(i), \quad k = 0, 1, 2, \dots \quad (1)$$

where K_p and K_I are controller parameters.

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

We observed that the platelet count response profile is very sensitive to u_0 , the initial injection dose implemented at $k = 0$. This is because of the physiological mechanism of romiplostim-induced platelet production (described in Section 1.1). As shown in Figure 5, the effect of this mechanism is such that the peak response to romiplostim injections, and when that peak occurs, depend nonlinearly on dosage. This is particularly so when the initial platelet count is low, as is the case for all our simulations. Under such conditions, a very high initial dose will result in a very strong response whose peak is delayed until ~ 20 days after the injection. Conversely, a very low initial dose produces a weaker peak response with a shorter delay. Furthermore, as shown in Figure 4, the stimulatory effect of romiplostim on platelet production is highly sensitive to initial platelet count, with the strongest response occurring at very low platelet counts and virtually no response when platelet count is high. Thus, at low initial platelet count, both the “effective process gain” and the response time delay, parameters that are known to affect the performance of PI controllers significantly, are very sensitive to initial injection dose. Consequently, this initial condition is

1 treated as an extra parameter and determined independently. Because romiplostim is implemented as
 2 pulses, the PI controller output is implemented without the usual zero-order hold.

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

7 3.1.3. Model-based open-loop optimal control

8 Under this strategy, the dynamic model is used to determine a romiplostim dose sequence $u(k)$ ($k=1, 2,$
 9 $\dots, N_f$) that minimizes the sum-of-squared errors, represented mathematically as follows:

$$10 \min_{u(k)} \Phi(u(k)) = \sum_{i=1}^{N_f} (\varepsilon(i))^2 \quad (2)$$

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

16 4. Results

17 4.1. Open-loop control

18 The performance of the open-loop control strategy shown in Fig. 6 indicates that this simple and
 19 straightforward strategy is unable to maintain a stable platelet count at the desired target value. The obvious
 20 oscillatory responses, not unexpected in light of the foregoing model analysis, are the result of a “nonlinear
 21 convolution” of the theoretical “basis function” of Fig. 4. As expected, the peak platelet count values are
 22 lower for lower doses, and the “effective period” of the observed oscillations is longer for the bi-weekly
 23 treatment regimen.

24 4.2. Discrete PI controller without zero-order hold

25 The “optimally tuned” PI controller parameters determined for weekly and bi-weekly injections are
 26 shown in Table 4. The system performance for weekly injections under this control strategy is shown in

Fig. 7, with the top panel showing the romiplostim doses used to achieve the platelet count trajectory shown in the bottom panel. Note that after about 7 treatments, or 49 days, the platelet count stabilized and remained essentially constant at the desired target value. Thereafter, a steady dose of approximately 1 $\mu\text{g}/\text{kg}$ is needed to sustain the platelet count at $70 \times 10^9/\text{L}$.

The performance under a bi-weekly treatment regimen based on the same control strategy, shown in Fig. 8, is not as good as the result shown in Fig. 7 for the weekly treatment regimen. Collectively, the oscillatory response and the discrete measurements used by the controller, indicated by the circles superimposed on the continuous response, give an illusion of reasonable performance. At the discrete time points where the measurements are taken and the control action is implemented, the measured values are indeed somewhat close to the desired target value; however, these infrequently sampled measured values fail to represent the true nature of the full response.

4.3. Model-based open-loop optimal control

The results under model-based open-loop optimal control, shown in Fig. 9, are similar to the corresponding results under optimally tuned PI control shown in Figs. 7 and 8. Fig. 9 shows the results for (a) weekly treatments and (b) bi-weekly treatments, with the top panel in each case showing the corresponding romiplostim doses. As in Fig. 7, after about 49 days, the platelet count achieved its target in a stable manner, with a steady weekly dose of approximately 1 $\mu\text{g}/\text{kg}$ sufficient to maintain the platelet count at target.

As in Fig. 8, the bi-weekly treatment resulted in a response that, after 75 days, oscillated around the desired target value of 70, with sustained oscillations. The sustained oscillation is a natural consequence of intrinsic romiplostim action as predicted in Fig. 5 for the ITP patient in question. Observe the natural intrinsically periodic response to a single injection (see also [20] where it is noted that platelet count returns to the baseline level 2 weeks after discontinuing romiplostim treatment).

5. Discussion

While the dosages in the dose profile of romiplostim in this study can take on any positive values, current treatment strategy allows only quantized doses. One possible solution is to build a device to deliver romiplostim in smaller quantities, similar to the insulin pumps used in patients with type I diabetes

mellitus. To build a device specifically for ITP patients, two design issues, similar to those associated with the design of the insulin pump, will surface regarding the algorithms incorporated in the device: validation of the model used to determine the control action and specification of desirable characteristics of the platelet count profile [21]. In the case of ITP, the desirable characteristics of the platelet count profile can be simply set at a constant value, as was done in this study. Our results also have shown that employing a validated mathematical model in conjunction with PI feedback control can maintain platelet count in the patient at a stable value given appropriate platelet count measurement frequency. Hence, the major obstacle in building a romiplostim-delivery device will be determining how to take platelet count measurement at an appropriate frequency. According to our results, a weekly clinic visit should be adequate for obtaining platelet count measurement once a romiplostim-delivery device is available.

6. Conclusions

In this study, a PKPD model was developed for an ITP patient to capture romiplostim-induced platelet production and provide the basis for developing effective treatment strategies for the specific patient. Three different control strategies were investigated. The results show that a stable platelet count can be achieved with weekly injection profiles determined by either “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 completely ineffective. Bi-weekly treatments led to sustained oscillations as a result of the 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 $70 \times 10^9/L$.

Although response to romiplostim treatment is highly variable from one ITP patient to another, this study has demonstrated that the use of patient-specific mathematical models for making model-based decision could be a promising approach to achieving stable platelet count control. We believe that this personalized treatment approach will benefit individual patients by providing them with the appropriate dose of romiplostim at the right time.

Acknowledgment

This work is supported by the National Science Foundation under Grant CBET 0925202. The authors would like to thank Dr. Ulhas P. Naik at Thomas Jefferson University for useful discussions.

References

- [1] L. Kahanov, L. Eberman, S. Grammer, Diagnosis and Treatment of Idiopathic Thrombocytopenic Purpura, *International Journal of Athletic Therapy & Training*, 17 (2012) 25-28.
- [2] R. Stasi, M.L. Evangelista, E. Stipa, F. Buccisano, A. Venditti, S. Amadori, Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management, *Thromb Haemost*, 99 (2008) 4-13.
- [3] M. Schipperus, R. Fijnheer, New therapeutic options for immune thrombocytopenia, *Neth J Med*, 69 (2011) 480-485.
- [4] R. Stasi, Immune thrombocytopenic purpura: the treatment paradigm, *European Journal of Haematology*, 82 (2009) 13-19.
- [5] S. Jeanpierre, F.E. Nicolini, B. Kaniewski, C. Dumontet, R. Rimokh, A. Puisieux, V. Maguer-Satta, BMP4 regulation of human megakaryocytic differentiation is involved in thrombopoietin signaling, *Blood*, 112 (2008) 3154-3163.
- [6] I. Matsumura, Y. Kanakura, Molecular control of megakaryopoiesis and thrombopoiesis, *International Journal of Hematology*, 75 (2002) 473-483.
- [7] E.M. Wolber, W. Jelkmann, Thrombopoietin: the novel hepatic hormone, *News Physiol Sci*, 17 (2002) 6-10.
- [8] Y.M.C. Wang, W. Krzyzanski, S. Doshi, J.J. Xiao, J.J. Perez-Ruixo, A.T. Chow, Pharmacodynamics-Mediated Drug Disposition (PDMDD) and Precursor Pool Lifespan Model for Single Dose of Romiplostim in Healthy Subjects, *Aaps Journal*, 12 (2010) 729-740.
- [9] D.J. Kuter, T.B. Gernsheimer, Thrombopoietin and platelet production in chronic immune thrombocytopenia, *Hematol Oncol Clin North Am*, 23 (2009) 1193-1211.
- [10] D.J. Kuter, The physiology of platelet production, *Stem Cells*, 14 Suppl 1 (1996) 88-101.
- [11] B. Wang, J.L. Nichol, J.T. Sullivan, Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand, *Clinical Pharmacology & Therapeutics*, 76 (2004) 628-638.
- [12] Y.M.C. Wang, B. Sloey, T. Wong, P. Khandelwal, R. Melara, Y.N. Sun, Investigation of the Pharmacokinetics of Romiplostim in Rodents with a Focus on the Clearance Mechanism, *Pharmaceutical Research*, 28 (2011) 1931-1938.
- [13] S. Panzer, New therapeutic options for adult chronic immune thrombocytopenic purpura: a brief review, *Vox Sanguinis*, 94 (2008) 1-5.
- [14] O. Meyer, E. Herzig, A. Salama, Platelet Kinetics in Idiopathic Thrombocytopenic Purpura Patients Treated with Thrombopoietin Receptor Agonists, *Transfusion Medicine and Hemotherapy*, 39 (2012) 5-8.
- [15] F. Palandri, N. Polverelli, F. Lifrieri, L. Catani, M.B. Giannini, M. Baccarani, N. Vianelli, Romiplostim as early treatment of immune thrombocytopenia with severe immunodeficiency, *Hematology reports*, 4 (2012).
- [16] J.B. Bussel, D.J. Kuter, J.N. George, R. McMillan, L.M. Aledort, G.T. Conklin, A.E. Lichtin, R.M. Lyons, J. Nieva, J.S. Wasser, I. Wiznitzer, R. Kelly, C.F. Chen, J.L. Nichol, AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP, *New England Journal of Medicine*, 355 (2006) 1672-1681.
- [17] J.J. Perez-Ruixo, B. Green, S. Doshi, Y.M. Wang, D.R. Mould, Romiplostim Dose Response in Patients With Immune Thrombocytopenia, *Journal of Clinical Pharmacology*, 52 (2012) 1540-1551.
- [18] F.J. Doyle, J. Stelling, Systems interface biology, *Journal of the Royal Society Interface*, 3 (2006) 603-616.
- [19] L.A. Harker, L.K. Roskos, U.M. Marzec, R.A. Carter, J.K. Cherry, B. Sundell, E.N. Cheung, D. Terry, W. Sheridan, Effects of megakaryocyte growth and development factor on platelet production, platelet life span, and platelet function in healthy human volunteers, *Blood*, 95 (2000) 2514-2522.
- [20] S. Thota, G. Kistangari, H. Daw, T. Spiro, Immune thrombocytopenia in adults: An update, *Cleveland Clinic journal of medicine*, 79 (2012).
- [21] G.M. Steil, A.E. Panteleon, K. Rebrin, Closed-loop insulin delivery - the path to physiological glucose control, *Advanced Drug Delivery Reviews*, 56 (2004) 125-144.

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

Fig. 2. Schematic representation of the pharmacokinetic/pharmacodynamic (PKPD) model illustrating mechanisms of romiplostim-induced platelet production. Subcutaneous injection of romiplostim is described by rate constant k_{SC} and bioavailability F , with the dose implemented as a rectangular pulse. Romiplostim at the subcutaneous site, whose amount is represented by A_{SC} , is absorbed into the blood stream, represented by rate constant k_a . Free romiplostim is distributed between the serum and the peripheral part with rate constants k_{PC} and k_{CP} . The specific serum volume is denoted as V_c . The amount of romiplostim in the serum and the peripheral part are denoted as A_c and A_p , respectively. Romiplostim can also bind to platelets in the blood stream and form a drug-receptor complex. Formation of such complex, whose amount is represented by DR , is described with rate constant k_{on} . A proportionality constant ξ representing the average number of receptor on each platelet is defined to determine the total amount of receptor on platelets. Dissociation of romiplostim from the drug-receptor complex is described by rate constant k_{off} . Two mechanisms are responsible for romiplostim clearance: receptor internalization, represented by rate constant k_{int} , and metabolic clearance of romiplostim, represented by k_{di} . The total amount of romiplostim in circulation, A_{tot} , is the summation of A_c and DR . Free romiplostim, with concentration denoted as C , exerts a stimulatory effect on megakaryocyte maturation through a process described by a Hill function, with S_{max} as the maximal effect, SC_{50} as the concentration required to reach half the maximal effect, and n as the Hill coefficient. $P_1, P_2, \dots, P_{N_P}$ are the number of megakaryocytes in different stages, where N_P is the number of stages of megakaryocyte. Similarly, $PLT_1, PLT_2, \dots, P_{N_{PLT}}$ are the number of platelets in different stages, where N_{PLT} is the number of stages of platelet. Megakaryocytes and platelets move into the next stage at a rate inversely proportional to their respective lifespans, T_P and T_{PLT} . The intrinsic megakaryocyte maturation rate, denoted as k_{in} , maintains the homeostasis of platelet production when romiplostim is absent.

Fig. 3. Clinical treatment data and platelet count profile with the PKPD model. Upper panel: romiplostim injection profile. Lower panel: platelet count data collected at the clinic and corresponding model prediction. Data in red circles are used to obtain patient-specific parameters for the PKPD model.

Fig. 4. Model response to single romiplostim injection of $1 \mu\text{g/kg}$ for various initial platelet counts. Higher initial platelet count leads to attenuated platelet count response, a result that is consistent with the fundamental mechanism of platelet count regulation.

Fig. 5. Model response to a single romiplostim injection of various doses. Each dose response consists of 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.

Fig. 6. Performance under open-loop control. (a) $2 \mu\text{g/kg}$ every 7 days; (b) $2 \mu\text{g/kg}$ every 14 days; (c) $1 \mu\text{g/kg}$ every 7 days; (d) $1 \mu\text{g/kg}$ every 14 days; (e) $0.5 \mu\text{g/kg}$ every 7 days; (f) $0.5 \mu\text{g/kg}$ every 14 days. The results show that the open-loop strategy is ineffective in maintaining a stable platelet count.

Fig. 7. Platelet count control: weekly treatments with optimally-tuned discrete PI controller. Stable platelet count is achieved with this control strategy within 50 days, with steady-state romiplostim doses of approximately $1 \mu\text{g/kg}$.

Fig. 8. Platelet count control: bi-weekly treatments with optimally-tuned discrete PI controller. Platelet count continues to oscillate even after a long period of time has elapsed. Although measurements taken from 70 days onward show values close to the target value, the complete platelet count profile remains mostly, below the target—an indication of the inadequacy of this measurement and treatment frequency.

Fig. 9. Platelet count control: weekly and bi-weekly treatments under optimal open-loop control. (a) With weekly injections, platelet count is stable after approximately 50 days. (b) With bi-weekly injections, beyond 80 days, the platelet count profile shows sustained oscillations with a period of approximately two weeks. This coincides almost perfectly with the natural period of the response to a single injection, with the implication that treatment regimen of single injections administered bi-weekly will always result in sustained oscillations.

Table 1
Physiological implications of platelet count

Platelet count, PLT ($\times 10^9/L$)	Description	Symptoms	Treatment suggestion
150 < PLT < 400	normal	None	none
30 < PLT < 150	mild ITP	might be asymptomatic or symptoms including: excessive bruising, spontaneous nose bleeds, spontaneous bleeding from gums, and prolonged bleeding from cuts	no treatment required
PLT < 30	high risk of bleeding	subarachnoid bleeding, gastrointestinal bleeding, and intracranial hemorrhage	treatment usually required; evaluations should be made for the decision of treatment
PLT < 10	severe ITP		treatment required

Table 2
List of parameters in the PKPD model

Parameter	Unit	Description
PK model		
k_a	h^{-1}	first-order rate constant for the absorption of romiplostim from subcutaneous site to plasma
k_{CP}	h^{-1}	first-order rate constant for romiplostim entering the peripheral part from serum
V_C	L/kg	specific serum volume
k_{PC}	h^{-1}	first-order rate constant for romiplostim entering serum from the peripheral part
k_{el}	h^{-1}	first-order rate constant for romiplostim being eliminated from serum
k_{int}	h^{-1}	first-order rate constant for romiplostim being internalized by platelets
K_D	ng/mL	dissociation equilibrium constant for drug-receptor complex; defined as k_{off}/k_{on}
ζ	fg/platelet	maximum amount of drug-receptor complex per platelet
F	-	bioavailability of romiplostim to patient
PD model		
SC_{50}	ng/mL	drug concentration needed to reach half-maximum response
S_{max}	h^{-1}	maximum platelet production rate achievable with romiplostim
N_p	-	number of stages of precursor cells (megakaryocytes)
N_{PLT}	-	number of stages of platelet
T_P	h	lifespan of precursor cells (megakaryocytes)
T_{PLT}	h	lifespan of platelets
n	-	Hill coefficient for possible nonlinear effect on platelet production by romiplostim

Table 3
Parameter values for healthy individuals and the ITP patient

Parameter	healthy subjects	ITP patient
	value (unit)	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)	6.00 (h ⁻¹)
N_p	10 (-)	10 (-)
N_{PLT}	10 (-)	10 (-)
T_P	142 (h)	219 (h)
T_{PLT}	253 (h)	113 (h)
n	1 (-)	0.99 (-)

Table 4
Parameter values for optimally tuned discrete PI controller

Treatment	K_p	K_I	Initial Dose ($\mu\text{g/kg}$)
Weekly	5.19×10^{-3}	7.59×10^{-5}	0.27
Bi-weekly	4.74×10^{-3}	2.72×10^{-5}	0.16

Fig. 1

Fig. 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9