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An "Incremental" Mathematical Model for Immune Thrombocytopenic Purpura (ITP)

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Abstract—We consider an "incremental" mathematical model of Immune Thrombocytopenic Purpura (ITP), an auto-immune disease, which is suitably simple to be of practical use in the clinical management of this pathology. Moreover, the model provides a possible way to solve some open problems in this specific field. © 2005 Elsevier Ltd. All rights reserved.

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1. INTRODUCTION

The integrity of blood vessels is taken in charge by platelets, which are a fraction of the blood itself. Their number usually ranges between $150 - 400 \cdot 10^3 \mu l^{-1}$. When their level is less than the lowest one, we speak about *thrombocytopenia* which, in case of a very low level, may be also cause of death, because of bleeding. *Immune (or idiopathic) thrombocytopenic purpura* (ITP) is one of the most common causes of thrombocytopenia encountered in the medical practice. Its incidence is of approximately one case per 10,000 in the general population, and it accounts for 0.16% of hospital admissions [1]. This pathology may be very complex, and its diagnosis remains one of exclusion [1–3]. Two main forms of ITP are usually encountered: the acute form, which often resolves spontaneously after six months or less in duration, and the chronic form, which is the most challenging one, from the point of view of the clinical management. Moreover,

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a rare form (*cyclical thrombocytopenia*) is also known, in which the level of platelets displays heavy oscillations [4,5]. Our concern will be the first two forms, in particular the chronic one.

The clinical management of ITP has various lines of therapy [1,3,4,6]: the first one is essentially based on high-dose steroids, intravenous immune globulin, and splenectomy (i.e., the surgical removal of the spleen). Such treatments may have many side-effects and/or be very invasive, in particular splenectomy. Concerning the latter, there is, at the moment, no way of predicting its effectiveness [6]. As a matter of fact, though different practices have been proposed in the literature [7–11], nevertheless, their conclusions are often controversial and in conflict each other (see, for example, [9,11]). In any case, most of the arguments used are of statistical nature, based on the follow-up of splenectomized patients (see, e.g., [10,12,13]).

The main problem with chronic ITP is that its pathogenesis has not been fully elucidated, and its management is primarily empirical [3,14]. In this context, mathematical modeling may be of help to understand the possible involved mechanisms (see, e.g., [15–24]). Unfortunately, very few models are suitably simple to be of practical use in the clinical management of ITP: to our knowledge, only in [19] a model is proposed to be used for transfusion management (and, by the way, its derivation is partially incorrect).

We observe that, in the clinical management, it would be useful to rank a thrombocytopenia, depending on:

(1) the production of platelets, which might be impaired,
(2) the destruction of platelets, which might be increased,
(3) the site of platelet destruction.

Concerning the first issue, often evidenced in the medical literature [25–28], it is well known that an impaired production can cause thrombocytopenia: as an example, this happens in various clinical settings, such as leukemia, myelodisplasia, as well as in some cases of ITP. The production of platelets is in the bone marrow, and we shall refer to BMP as the "bone marrow production" of platelets.

The previous aspect is complementary to the second problem, since the level of platelets is nothing but the difference between the produced ones and the destroyed ones. In order to measure platelet destruction, it is customary to look for their mean life: hereafter, MPL will denote the "mean platelet life".

Finally, in case of augmented destruction, the site where platelets are destroyed could be useful, for example, to predict the effectiveness of splenectomy.

A useful clinical test to measure the above parameters is the study of thrombokinetic by means of platelets labeled with suitable radionuclides (formerly, ^{51}Cr and, more recently, ^{111}In [20,22,26–33]). In this test, labeled platelets are reinfused in the patient, and their level in the blood is measured at prescribed time intervals. Moreover, on the third day, a scan of the body is done by using a γ-camera, allowing to measure the sites where the radioisotope is accumulated. Nevertheless, it is not completely clear how to "read" the measured data: though some standardization guidelines have been given [34,35], the underlying mechanisms have not yet been made completely clear.

In this paper, we propose an "incremental" model of the physiopathology of ITP which has the intent to provide a practical tool to be used in the interpretation of the results of the thrombokinetic via the use of radionuclides. Moreover, at least in theory, the model provides a way to predict the effectiveness of splenectomy in the management of ITP, which we hope to translate into a clinical practice, in the near future.

The paper is then organized as follows. In Section 2, we describe the basic model and its subsequent developments, which are introduced in order to take into account a number of aspects linked to the thrombokinetic. In Section 3, we then show some possible utilizations of the model, along with some practical examples of application. Finally, Section 4 contains some concluding remarks.

2. THE MATHEMATICAL MODEL

To begin with, let us start with the simplest mathematical model which describes the kinetic of platelets, to be "increased", as soon as it will become inadequate to describe the observed data. If we denote by,

- $p(t)$ the level of platelets at time t,
- γ the rate of platelet destruction,
- $g(t)$ the production of platelets at time t (i.e., $g = \text{BMP}$),

then we may, at first, state that

$$\frac{d}{dt}p = -\gamma p + g. \tag{1}$$

In particular, with the only exclusion of cyclic thrombocytopenia where the level of platelets may heavily oscillate, we may assume that g is constant and that p is at steady state. That is, the derivative of p vanishes and the equilibrium value of platelets is

$$\bar{p} = \frac{g}{\gamma}. \tag{2}$$

Moreover, it is not difficult to realize that

$$\text{MPL} = \frac{1}{\gamma}, \tag{3}$$

which implies that

$$\bar{p} = \text{BMP} \cdot \text{MPL}. \tag{4}$$

It is then evident that, since we can actually measure $\bar{p}$, we can recover either BMP or MPL, once one of them is known. In order to estimate γ, it is customary to mark with a suitable radionuclide (^{111}In, is the one currently used) a number of platelets of the patient. Then, the labeled platelets are reinfused and the level of radioactivity is measured at certain time intervals after reinfusion. If we denote by $m(t)$ a measure of the level of labeled platelets (i.e., the radioactivity of blood samples of prescribed volume), then

$$\begin{aligned} \frac{d}{dt}m &= -(\gamma + \kappa)\, m, \\ m(0) &= m_0, \end{aligned}$$

where $\kappa = 0.245d^{-1}$ is the constant of decay of ^{111}In and m_0 is the initial amount of radioactivity infused through the labeled platelets. Since the constant κ is known, we can *correct* the measures of the radioactivity of the samples, in order to take into account the nuclear decay: that is, if we measure a given sample at time t after reinfusion, we have to multiply the obtained level by $e^{\kappa t}$. In such a way, we can consider, in place of the previous equation, the following (corrected for the decay) one,

$$\begin{aligned} \frac{d}{dt}m &= -\gamma m, \\ m(0) &= m_0. \end{aligned} \tag{5}$$

REMARK 1. Hereafter, we shall assume that all measurements of radioactivity have been corrected for the nuclear decay. In such a way, we can neglect the constant κ in the equations.

Since the solution of equation (5) is $m_0 e^{-\gamma t}$, we should have an exponential decay in the level of marked platelets. Nevertheless, it is known (see, for example [29]) that at least two "speeds" of decay can be observed in experimental data. As a matter of fact, in Figure 1 we have the data[1] relative to a patient (hereafter, *Patient A*), where two speeds can be recognized: an initial

[1]On the vertical axis, the unit is cpm, namely *counts per minute*, which is the number of γ-decays measured in one minute. This is the most commonly used measure of radioactivity.

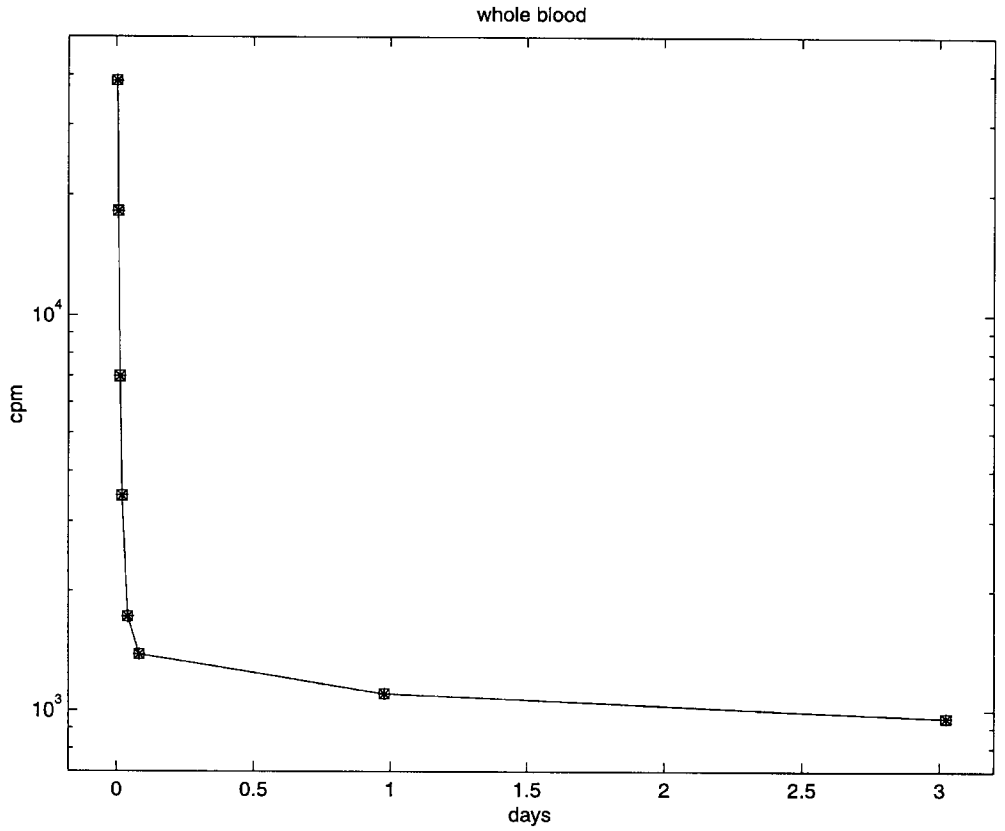

Figure 1. Patient A, $\bar{p}_1 = 193 \cdot 10^3\, p/\mu l$.

"faster" one and a subsequent "slower" one. The reason for this, is due to the presence of the so called *"exchangeable" splenic pool*: in individuals with a normal sized spleen, this pool contains approximately 1/3 of platelets, which are in dynamic equilibrium with the circulating ones [36]. The total amount of pooled platelets is larger in case of splenomegaly, i.e., when the size of the spleen is increased. However, hereafter we shall assume a "normal sized" splenic pool, since splenomegaly is not very frequent in ITP.

The above argument implies that we need a two-compartment model to adequately describe the thrombokinetic: i.e., the splenic compartment and its complementary one. Let then denote by:

- $p_1(t)$ the amount of platelets outside the spleen (Compartment 1),
- $p_2(t)$ the amount of platelets in the splenic pool (Compartment 2),
- γ_1 the rate of platelet destruction in the first compartment,
- γ_2 the rate of platelet destruction in the splenic pool,
- λ_{12} the rate of exchange between the first compartment and the splenic pool,
- λ_{21} the rate of exchange between the splenic pool and the first compartment.

One then obtains the following set of equations:

$$\begin{aligned} \frac{d}{dt}p_1 &= -(\gamma_1 + \lambda_{12})\, p_1 + \lambda_{21} p_2 + g, \\ \frac{d}{dt}p_2 &= \lambda_{12} p_1 - (\gamma_2 + \lambda_{21})\, p_2, \end{aligned} \tag{6}$$

where, as usual, g = BMP, which acts only in the first compartment. By assuming, as made above, g constant, and taking into account that the transformation matrix,

$$A = \begin{pmatrix} -(\gamma_1 + \lambda_{12}) & \lambda_{21} \\ \lambda_{12} & -(\gamma_2 + \lambda_{21}) \end{pmatrix}, \tag{7}$$

is the opposite of an M-matrix, one then obtains that a positive and asymptotically stable equilibrium $(\bar{p}_1, \bar{p}_2)^\top$ exists [37]. By considering that, because of the previous arguments, $\bar{p}_1$ is approximately twice $\bar{p}_2$, from the second equation in (6) it then follows that the following equality (approximately) holds,

$$\lambda_{12} = \frac{\gamma_2 + \lambda_{21}}{2}. \tag{8}$$

By substituting (8) into the first equation in (6), one then obtains,

$$\bar{p}_1 = \frac{g}{\gamma_1 + \gamma_2/2}. \tag{9}$$

Consequently, considering that $\bar{p}_1 \approx (2/3)\bar{p} \equiv (2/3)(\bar{p}_1 + \bar{p}_2)$, from (2) it then follows that the total number of platelets is

$$\bar{p} = \frac{g}{(2\gamma_1 + \gamma_2)/3}.$$

That is, from (1) we can interpret $(2\gamma_1 + \gamma_2)/3$ as the "cumulative" destruction rate of platelets, γ, in the whole body. From (3) we then obtain that

$$\mathrm{MPL} = \frac{3}{2\gamma_1 + \gamma_2}, \tag{10}$$

provides us with an estimate of the mean platelet life.

Let consider now the kinetic of label platelets. In particular, let:

- $m_1(t)$ be the level of labeled platelets in the first compartment,
- $m_2(t)$ be the level of labeled platelets in the splenic pool,
- m_0 be the amount of labeled platelets reinfused.

Then, in place of (6) we have,

$$\begin{aligned} \frac{d}{dt} m_1 &= -(\gamma_1 + \lambda_{12})\, m_1 + \lambda_{21} m_2, \qquad m_1(0) = m_0, \\ \frac{d}{dt} m_2 &= \lambda_{12} m_1 - (\gamma_2 + \lambda_{21})\, m_2, \qquad m_2(0) = 0. \end{aligned} \tag{11}$$

The above-modified model is now adequate to explain the behavior of the data in Figure 1, since the two observed "speeds" of decay are due to the two negative eigenvalues of the transformation matrix (7). As an example, for the data in Figure 1 we obtain,

$$\sigma_1 \approx -136.19 d^{-1}, \qquad \sigma_2 \approx -0.12 d^{-1}. \tag{12}$$

In the next section, we shall see how to recover useful clinical information from such estimates, which can be easily obtained from the experimental data.

Equation (11) can be joined with an additional one, which provides a model for the radioactivity measured in the spleen. In fact, by considering that,

- the labeled platelets destroyed in the spleen remain there for a certain amount of time (presumably, of the order of several hours or even a few days), before they are removed by macrophages,
- m_1 and m_2 are actually the levels of radioactivity of the labeled platelets in the two compartments,

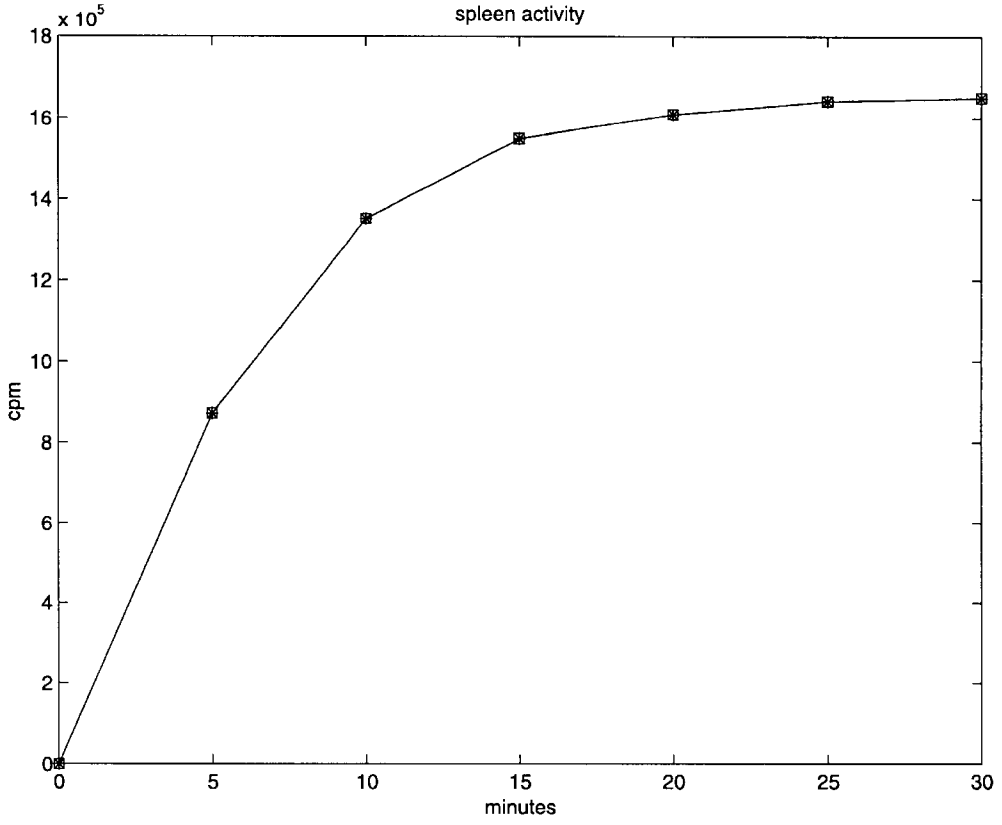

Figure 2. Patient B, spleen activity curve, five minutes frames.

then, by setting $r(t)$ the radioactivity of the spleen at time t after reinfusion, one has that, at least initially,

$$r(t) = m_2(t) + \gamma_2 \int_0^t m_2(s)\, ds.$$

That is, the radioactivity of the spleen is given by that of the labeled platelets in the splenic pool, plus that of the labeled platelets destroyed in the spleen so far. By casting the previous equation in differential form, and taking into account (11), one then obtains,

$$\frac{d}{dt} r = \lambda_{12} m_1 - \lambda_{21} m_2, \qquad r(0) = 0. \tag{13}$$

A simple analysis of the problem (11)–(13), shows that $m_1(t)$ and $m_2(t)$ both tend to 0, as $t \to \infty$: in particular with an initial "bump" for m_2. In more detail, from (8) we have a zero derivative for $m_2(t)$ when the ratio m_1/m_2 equals that of $\bar{p}_1/\bar{p}_2$, i.e., approximately 2. On the other hand, $r(t)$, at least initially, seems to reach exponentially a "plateau": a typical example can be seen in Figure 2, where five minute frames of the spleen, obtained by means of a γ-camera, are plotted. Usually, this behaviour can be observed in the first 30–40 minutes after the reinfusion of the labeled platelets. For a more detailed analysis, we refer to Section 3.

2.1. Further Development of the Model

The previous model, though more accurate than the basic one (1) is, however, not able to describe what can be observed in some cases, characterized by a very rapid destruction of platelets. This, indeed, actually happens when there is a low level of platelets, but a normal/high production

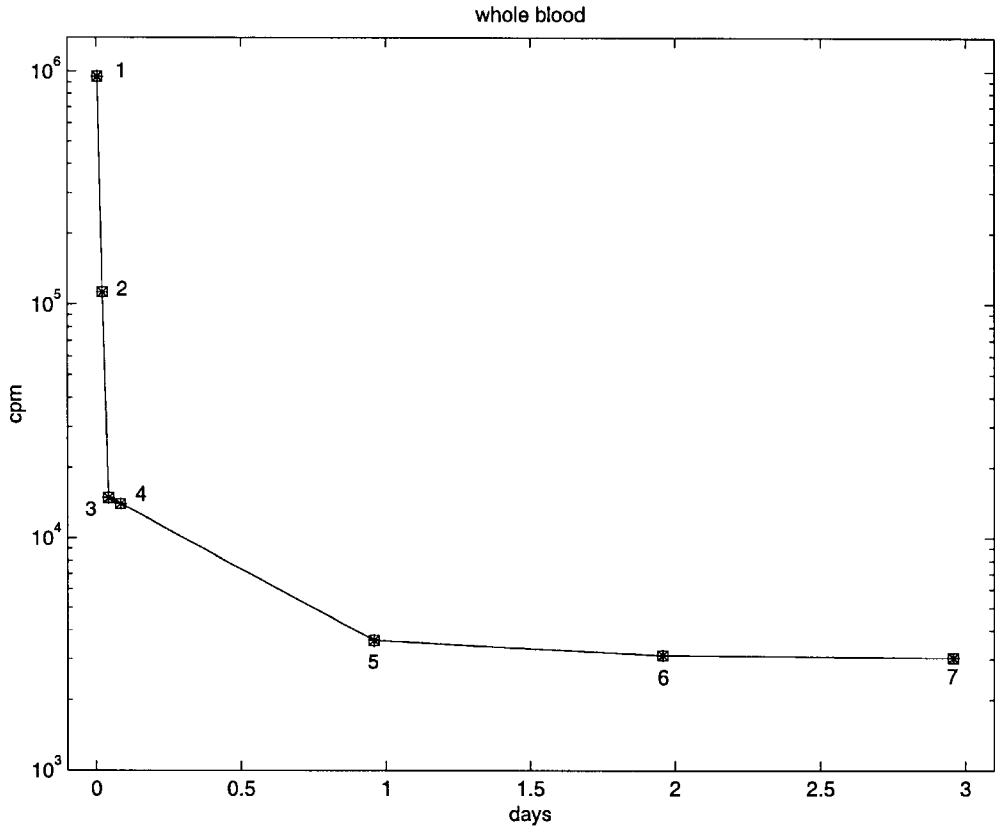

Figure 3. Patient B, $\bar{p}_1 = 10 \cdot 10^3\, p/\mu l$.

(BMP): this is exactly the "scenario" of ITP. In such cases, in fact, the data of blood radioactivity exhibit essentially three "speeds" of decay, as shown in Figure 3.

To explain this fact, we have supposed that the radionuclide used to label the platelets is (slowly) released in the blood, after their destruction, thus becoming available to label new platelets. This process is usually not observable in normal subjects, since the process of releasing of the marker in the blood and its subsequent recombination with new platelets can be expected to be very slow. Nevertheless, it may be actually observed in case of a very rapid destruction of the labeled platelets. In more detail, let us denote by,

- $I(t)$ the quantity of the radioactive marker (Indium) available at time t (as done before, we assume to have corrected data for the nuclear decay),
- β the rate of recombination of the marker with unlabeled platelets,
- α the rate of clearance from blood of the marker (because of some physiological reason, e.g., it is absorbed and/or filtered by some tissue, etc.).

Then, equations (6),(11) become,

$$\begin{aligned}
\frac{d}{dt}p_1 &= -(\gamma_1 + \lambda_{12})\, p_1 + \lambda_{21} p_2 - \beta p_1 (I - m_1 - m_2) + g, \\
\frac{d}{dt}p_2 &= \lambda_{12} p_1 - (\gamma_2 + \lambda_{21})\, p_2, \\
\frac{d}{dt}m_1 &= -(\gamma_1 + \lambda_{12})\, m_1 + \lambda_{21} m_2 + \beta p_1 (I - m_1 - m_2), \\
\frac{d}{dt}m_2 &= \lambda_{12} m_1 - (\gamma_2 + \lambda_{21})\, m_2, \\
\frac{d}{dt}I &= -\alpha I,
\end{aligned} \tag{14}$$

with the initial conditions $p_1(0) = \bar{p}_1$, $p_2(0) = \bar{p}_2$, $m_1(0) = I(0) = m_0$, and $m_2(0) = 0$. Equation (13), which remains unchanged, completes the above set of equations. In the previous equation, $I - m_1 - m_2$ represents the "free" marker which can recombine with unlabeled platelets (p_1) and, obviously, such recombination is proportional to their product. For simplicity, we have assumed that recombination happens only in the first compartment (i.e., outside the spleen), which is the larger one.

The dynamics of the solution of (14) is more easily understood if we assume, for simplicity, that the equilibrium level of p_1, $\bar{p}_1$, is not affected too much by the extraction of the platelets to be labeled. This is, indeed, the case, and, moreover, also the coefficient β can be expected to be very small. In such a case, the last three equations in (14) essentially decouples from the first two, thus giving

$$\begin{aligned} \frac{d}{dt}m_1 &= -(\gamma_1 + \lambda_{12})\, m_1 + \lambda_{21} m_2 + \beta \bar{p}_1 (I - m_1 - m_2), \\ \frac{d}{dt}m_2 &= \lambda_{12} m_1 - (\gamma_2 + \lambda_{21})\, m_2, \\ \frac{d}{dt}I &= -\alpha I. \end{aligned} \tag{15}$$

The latter is again a linear system, whose transformation matrix is (compare with (7))

$$\begin{pmatrix} -(\gamma_1 + \lambda_{12} + \beta\bar{p}_1) & (\lambda_{21} - \beta\bar{p}_1) & \beta\bar{p}_1 \\ \lambda_{12} & -(\gamma_2 + \lambda_{21}) & 0 \\ 0 & 0 & -\alpha \end{pmatrix}.$$

Since the term $\beta\bar{p}_1$ could be expected substantially smaller than the other coefficients, it follows that we have essentially the same two "speeds" of decay of the model (11) and, moreover, a third one, which behaves like $e^{-\alpha t}$. The latter is the slowest among the three, and concerns a (relatively) small number of platelets: as an example, for the data in Figure 3, we obtain the following estimates,

$$\sigma_1 \approx -108.47 d^{-1}, \qquad \sigma_2 \approx -1.55 d^{-1}, \qquad \sigma_3 \approx -0.02 d^{-1}. \tag{16}$$

However, we observe that the last speed of decay is related to the absorption of the radioactive marker by the tissues, more than to the destruction of the labeled platelets. The above arguments, therefore, suggest that the most useful information, from the clinical point of view, is that provided by σ_1 and σ_2, whereas σ_3 has no practical interest. It must be stressed that this interpretation of the data is valid only in case of an accelerate destruction.

3. ANALYSIS AND PRACTICAL USE OF THE MODEL

In this section, we show some possible ways to practically exploit the model (11), which turns out to be the most useful, in order to obtain relevant information from the clinical data.

In more detail, Section 3.1 is devoted to the use of the model for the interpretation of the thrombokinetic data; Section 3.2 concerns its use to establish *ex-post* the usefulness of splenectomy; finally, Section 3.3 is devoted to the use of the model to *predict* the effectiveness of splenectomy in the clinical management of ITP.

It must be emphasized that all of the above three problems are relevant in the clinical management of ITP, though they are substantially unsolved, so far.

3.1. Interpretation of Thrombokinetic Data

In the previous section, we have seen the two-compartment model (11)–(13), and its modification (15). As previously said, the latter model was used essentially to explain a third "speed" of

decay in the thrombokinetic. Nevertheless, the conclusion is that the last (and slowest) speed of decay is essentially due to recombination of "free" marker in the blood, so that we can neglect it, thus concentrating on the first two speeds only. To manage them, the model (11)–(13) is appropriate, so that our analysis will be devoted to it. We shall confine the analysis here, to the equations describing the radioactivity of the platelets, that is to equations (11) alone: the analysis of equation (13), concerning the radioactivity of the spleen, will be carried out in Section 3.3.

Let us then consider equations (11), which are linear ones. The eigenvalues of the corresponding transformation matrix (7) are given by

$$\mu_{1/2} = \frac{-b \mp \sqrt{b^2 - 4c}}{2}, \tag{17}$$

where

$$b = -\text{trace}\,(A) = \lambda_{12} + \gamma_1 + \lambda_{21} + \gamma_2,$$
$$c = \det\,(A) = (\lambda_{12} + \gamma_1)\,(\lambda_{21} + \gamma_2) - \lambda_{12}\lambda_{21}.$$

By taking into account (8), one then obtains that

$$\mu_1 + \mu_2 = -b = -\left(\frac{3}{2}\,(\lambda_{21} + \gamma_2) + \gamma_1\right),$$
$$\mu_1\mu_2 = c = (\lambda_{21} + \gamma_2)\left(\gamma_1 + \frac{\gamma_2}{2}\right).$$

From clinical observations, (see, e.g., [21,33]), it is known that the reciprocal of λ_{21}, that is, the speed of transit of platelets through the splenic pool, is of the order of ten min. Consequently, λ_{21} is of the order of $10^2\ d^{-1}$. On the other hand, it is known that the mean platelet life is, in normal subjects, of the order of ten days. Consequently, from (10) one obtains that γ_1 (as well as γ_2) is of the order of $10^{-1}\ d^{-1}$. As a result, γ_1 turns out to be negligible, with respect to λ_{21}: because of the three orders of magnitude of difference, this is still true in pathological cases, where γ_1 may be increased. From (10) one then concludes that

$$\text{MPL} \approx -\frac{\mu_1 + \mu_2}{\mu_1\mu_2}. \tag{18}$$

Moreover, from (4), and considering that $\bar{p} \equiv \bar{p}_1 + \bar{p}_2 \approx (3/2)\bar{p}_1$, where $\bar{p}_1$ is the actual level of platelets measured, we obtain that

$$\text{BMP} \equiv g \approx \frac{3}{2}\frac{\bar{p}_1}{\text{MPL}}.$$

It is evident that μ_1 and μ_2 are nothing but the (first) two "speeds" of decay which can be observed in the data of thrombokinetic. Therefore, the estimates σ_1 and σ_2 in (12),(16) are the approximations to μ_1 and μ_2 for Patient A and Patient B, respectively. As a consequence, for the data in Figures 1 and 3, corresponding to a patient with a normal level of platelets ($\bar{p}_1 = 193 \cdot 10^3\, p/\mu\text{l}$) and to a patient with a serious thrombocytopenia ($\bar{p}_1 = 10 \cdot 10^3\, p/\mu\text{l}$), respectively, the following clinical information can be obtained:

Patient A:	MPL$\approx 8.7d$,	BMP $\approx 33 \cdot 10^3 p\mu\text{l}^{-1}d^{-1}$;
Patient B:	MPL$\approx 0.7d$,	BMP $\approx 23 \cdot 10^3 p\mu\text{l}^{-1}d^{-1}$.

For both patients, BMP is in the normal range, whereas MPL is in the normal range (8–12d) for Patient A, but it is significantly reduced in Patient B. For the latter patient, there is a clear diagnosis of ITP, since there is no evidence of more important systemic diseases.

Let us continue the analysis of equations (11): this will allow us to recover information about the labeled platelets in the splenic pool, i.e. m_2, by only having measurements on m_1, which are relatively easy obtainable (blood samples).

The solution of (11) can be seen to be given by:

$$\frac{m_1(t)}{m_0} = \frac{\mu_2 + \lambda_{12} + \gamma_1}{\mu_2 - \mu_1} e^{\mu_1 t} - \frac{\mu_1 + \lambda_{12} + \gamma_1}{\mu_2 - \mu_1} e^{\mu_2 t}, \tag{19}$$

$$\frac{m_2(t)}{m_0} = \frac{(\mu_1 + \lambda_{12} + \gamma_1)(\mu_2 + \lambda_{12} + \gamma_1)}{\lambda_{21}(\mu_2 - \mu_1)} \left(e^{\mu_1 t} - e^{\mu_2 t}\right), \tag{20}$$

where μ_1 and μ_2 are given by (17). From the latter equation, one obtains that, since c is "small" with respect to b^2, then

$$0 > \mu_2 \gg \mu_1,$$

which is indeed confirmed by the experimental data (see, e.g., (12),(16)). The initial transient for m_1, at speed μ_1, ends as soon as (see (11))

$$(\lambda_{12} + \gamma_1) m_1 \approx \lambda_{21} m_2. \tag{21}$$

After which, the slower decay at speed μ_2 begins. Let us now consider the behaviour of $m_2(t)$, which is 0 at $t = 0$. Obviously, we have an initial (fast) increment, up to the time where

$$\lambda_{12} m_1 = (\lambda_{21} + \gamma_2) m_2. \tag{22}$$

From (20) it is not difficult to verify that this happens exactly at the time

$$t \equiv t^* = \frac{\log(-\mu_1) - \log(-\mu_2)}{\mu_2 - \mu_1}. \tag{23}$$

At $t = t^*$, the ratio m_2/m_1 equals that of $\bar{p}_1/\bar{p}_2$, that is approximately 2 (see (8)). We observe that, since both γ_1 and γ_2 are small with respect to both λ_{12} and λ_{21}, from (21),(22) it follows then that t^* essentially coincides also with the width of the transient of m_1 (actually, slightly larger). Coming back to m_2, for $t > t^*$, $m_2(t)$ begins to decay: as soon as $e^{\mu_1 t}$ becomes negligible with respect to $e^{\mu_2 t}$, then (see (19),(20)),

$$\frac{m_2}{m_1} \approx \frac{\mu_2 + \lambda_{12} + \gamma_1}{\lambda_{21}} \approx \frac{\lambda_{12}}{\lambda_{21}} \gtrapprox \frac{1}{2}.$$

As an example, in Figure 4 there is the plot of m_1 and m_2 for an "almost physiological" set of parameters (having normalized $m_0 = 1$), which well illustrates the above features. In such a case, the value of $t^* \approx 55$ min (in the clinical routine, we have found it essentially ranging between $20 - 120$ min, with a median of 77 min: see Figure 5, where the histogram concerning 21 cases is plotted). We end this section underlying the usefulness of the information on m_2 that we can recover, through the model (11), from the measurements on m_1: indeed, direct measurements of m_2 are very invasive (splenic biopsy) and potentially dangerous.

3.2. Result of Splenectomy: Retrospective Analysis

As we said in the introduction, splenectomy is one of the treatments which is used in the clinical management of ITP. In the next section, we shall deal with the possibility of predicting its effectiveness, but now we only mention a possible way of using the proposed mathematical model, in order to assess *ex-post* its effectiveness. Indeed, also this problem is not actually well understood, and in the medical literature it is only possible to find statistics about the *long term*

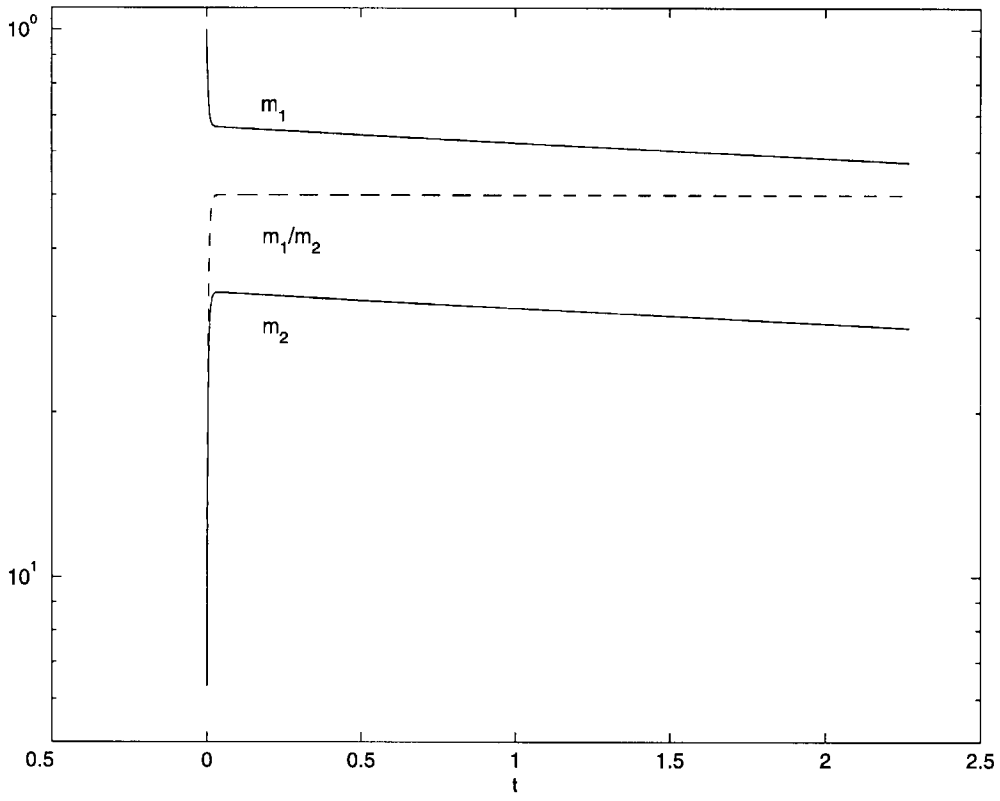

Figure 4. Simulation of problem (8)–(11), for about two days, with $m_0 = 1$, $\gamma_1 = 0.05\,d^{-1}$, $\gamma_2 = 0.1\,d^{-1}$, $\lambda_{21} = 140\,d^{-1}$.

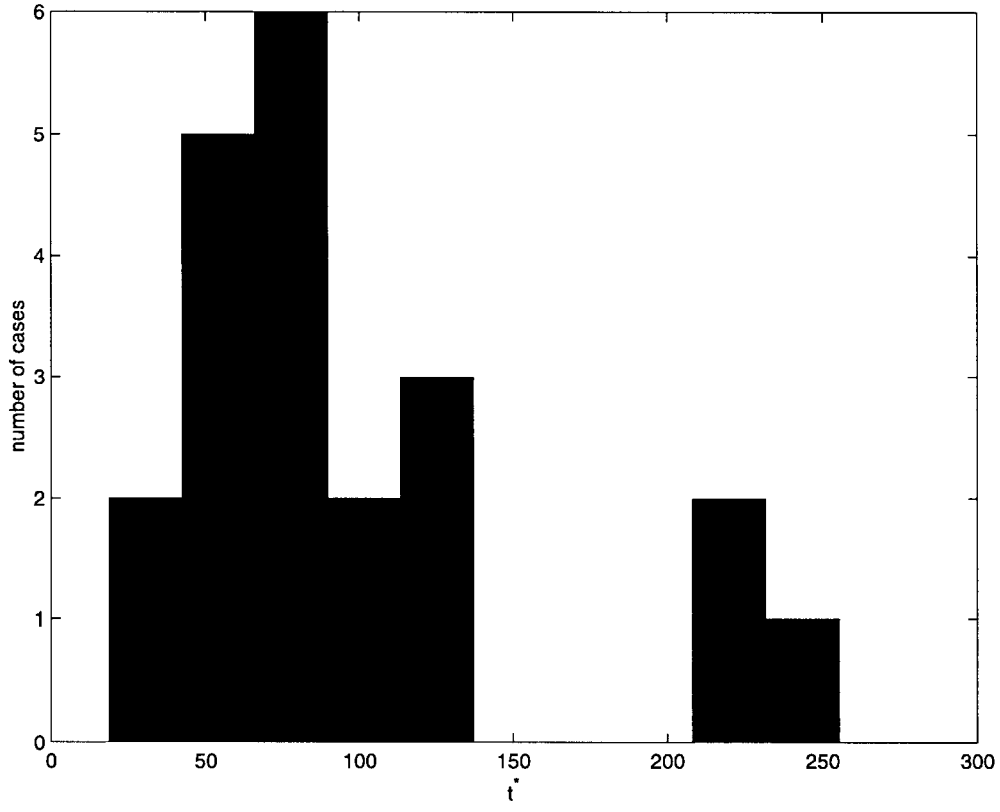

Figure 5. Estimates of the transient width t^* in (23) for 21 patients.

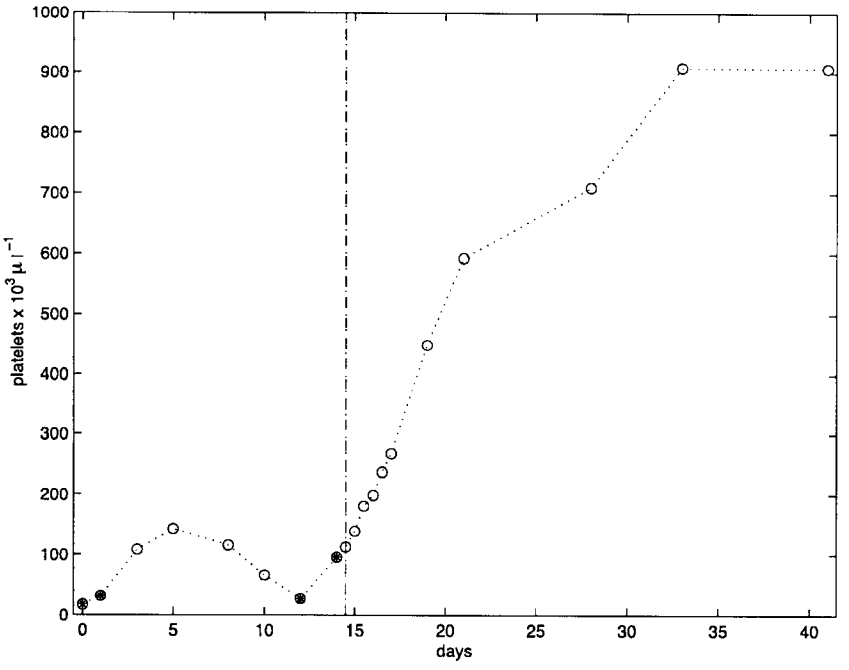

Figure 6. Platelets counts pre and post-splenectomy (vertical line). The filled circles correspond to therapy with intravenous immune globulin.

follow-up of splenectomized patients [10,12,13]. The analysis of this section will be made on a single set of data, but it is clear how it can be generalized.

To begin with, let us consider the data plotted in Figure 6, which are the platelet levels of the first author, who underwent splenectomy about two years ago, because of ITP: the surgical operation took place in correspondence of the vertical dashed line, so that we have the data of the previous two weeks and about one month after splenectomy. Before splenectomy, the baseline level of platelets was approximately $5 \cdot 10^3\, p/\mu l$: temporary increases of this level were due to therapy with intravenous immune globulin (see filled circles in the figure). After splenectomy, the level of platelets steadily increased up to about $910 \cdot 10^3\, p/\mu l$, which was maintained for at least two weeks. From this fact, by using (9) we can infer that, before splenectomy,

$$\gamma_1 + \frac{\gamma_2}{2} \approx \frac{g}{5 \cdot 10^3\, p/\mu l},$$

whereas, after splenectomy, which is equivalent to set $\gamma_2 = 0$,

$$\gamma_1 \approx \frac{g}{910 \cdot 10^3\, p/\mu l}.$$

The transient phase, probably due to the cicatrization of wounds. Consequently, one easily obtains that

$$\gamma_2 \approx 362\, \gamma_1,$$

which means that the destruction rate of platelets in the spleen was 362 times faster than the destruction rate outside it! Therefore, splenectomy has been (fortunately[2]) appropriate, in this case.

Moreover, additional information can be also obtained. In fact, assuming a normal MPL after splenectomy (say, $10d$), one obtains that, before splenectomy (see (10)),

$$\mathrm{MPL} = \frac{3}{2} \frac{\gamma_1}{\gamma_1 + (\gamma_2/2)} 10\, d \approx 2\, h.$$

[2]Comment of the first author.

A final scenario of the situation before splenectomy is given by the additional information that, after the "plateau" in Figure 6, the level of platelets reached, after about one month, $260 \cdot 10^3\, p/\mu l$: indeed, a physiological negative feedback control exists on platelet production, essentially based on specific chemical mediators (cytokines) of which the predominant one is, for platelet production, the thrombopoietin [23]. Subsequent levels of platelets, after about two years, raised from this level and came back again to it. Therefore, we can assume that the new level of production is due to a modified BMP, that is, the term g in equation (6). As a consequence, we have that the ratio between BMP before and after the splenectomy is approximately given by

$$\frac{910}{260} = 3.5.$$

That is, when platelet destruction was high, the bone marrow increased approximately 3.5 times its production of platelets. This result agrees with what can be found in the medical literature (see, e.g., [26]).

3.3. Result of Splenectomy: Perspective Analysis

This aspect is the most interesting and challenging one, since, as previously said in the introduction, the prediction of the outcome of splenectomy in the management of ITP is an open problem (see, e.g., [6]). As a matter of fact, splenectomy may be ineffective: in such a case, it is evident that it would have been preferable not to perform it.

From the mathematical point of view, assuming stationary conditions (as we have always done so far), if we were able to have an estimate for γ_1, from (9) we could then in principle predict the new level of platelets after the splenectomy, say p^*, as

$$p^* = \frac{g}{\gamma_1}, \tag{24}$$

that is, by formally removing the destruction term due to the spleen. Since we have already seen in Section 3.1 how to obtain an estimate for $\gamma_1 + (\gamma_2/2)$, we only need a way to have an estimate for either γ_1 or γ_2. If we consider the model (11)–(13), we obtain, by summing the first and the last equation,

$$\frac{d}{dt} m_1 + \frac{d}{dt} r = -\gamma_1 m_1.$$

From this equation, it follows then that, by having a suitable set of measurements for the radioactivity in the blood, m_1, and that in the spleen, r, then an estimate for γ_1 should be obtainable somehow. Unfortunately, the measures of m_1 and r are obtained by using different equipments. As a matter of fact:

(1) the radioactivity in the blood is obtained by measuring a fixed volume of blood in a γ-counter,

(2) the radioactivity of the spleen is measured from the image obtained through a γ-camera.

Therefore, the first measurement is a relative one, whereas the second measurement is an absolute one. Moreover, also the efficiencies of the two equipments greatly differ. Consequently, it is very difficult to directly use these measurements in order to recover the required information.

In order to derive an alternative (and practical) "device" for predicting the effectiveness of splenectomy, it is then convenient to better analyze equation (13) alone. After some calculus, one obtains that:

$$\frac{r(t)}{m_0} = \left(1 + \frac{\gamma_1}{\mu_1}\right) \frac{\mu_2 + \lambda_{12} + \gamma_1}{\mu_1 - \mu_2} e^{\mu_1 t} + \left(1 + \frac{\gamma_1}{\mu_2}\right) \frac{\mu_1 + \lambda_{12} + \gamma_1}{\mu_2 - \mu_1} e^{\mu_2 t} + \frac{\gamma_2/2}{\gamma_1 + (\gamma_2/2)}. \tag{25}$$

From the arguments in Section 3.1 (see (10),(18)), we obtain that,

$$-\frac{3}{2} \frac{\mu_1 \mu_2}{\mu_1 + \mu_2} \approx \gamma_1 + \frac{\gamma_2}{2}. \tag{26}$$

Consequently, we could estimate $\gamma_2/2$, and then (24), by having an experimental estimate of the left-hand side in (25) for t suitably large.

Nevertheless, this could be not reliable, due to the fact that equation (13) could be no more a valid model for t very large, due to a possible removal of the radionuclide accumulated in the spleen, after the destruction of the labeled platelets. A possible way to overcome this problem is to observe that, at $t = t^*$, it is likely that most of the labeled platelets are still "alive". Consequently,

$$\frac{r(t^*)}{m_0} \approx \frac{m_2(t^*)}{m_0} \approx \frac{1}{3}.$$

Nevertheless, if $\gamma_2 \gg \gamma_1$, then we can expect the limit of (25), as $t \to \infty$, to be close to 1, whereas, if $\gamma_2 \ll \gamma_1$, it can be expected to be much closer to 0. Consequently, having measured the "initial plateau" for $r(t)$ around $t = t^*$ (see Figure 2), it could be possible to measure $r(t)$ after some time (say hours or one to two days) and compare the two measurements: in case they differ substantially, this would mean that γ_2 and γ_1 have a different magnitude.

In more detail, for t suitably large, the ratio

$$\alpha \equiv \frac{r(t)}{r(t^*)} \approx \frac{(\gamma_2/2)/(\gamma_1 + \gamma_2/2)}{1/3}.$$

Consequently,

$$\frac{\alpha}{3}\left(\gamma_1 + \frac{\gamma_2}{2}\right) \approx \frac{\gamma_2}{2}.$$

Since we have the estimate (26), we can then obtain an estimate (actually, an underestimate) of the *weight* of $\gamma_2/2$ in the cumulative destruction rate $\gamma_1 + (\gamma_2/2)$. Consequently, when the latter rate is high and $\alpha/3$ is close to 1, this would give a clear indication for splenectomy. Evidently, if $\alpha/3$ is much smaller than 1, this would mean that the destruction in the first compartment dominates, and, in this case, splenectomy would be useless.

4. CONCLUSIONS

In this paper, we have proposed a new mathematical model for the kinetic of platelets. Such a model is able to provide a way to obtain useful clinical parameters (e.g., MPL and BMP) from the blood data of thrombokinetic via labeled platelets, also providing clear guidelines for their "reading".

The proposed mathematical model is also able to provide a practical tool for a retrospective analysis to assess the usefulness of splenectomy, in the management of ITP.

Last, but not least, it suggests a possible, practical way to *predict* the outcome of splenectomy in the management of ITP, which is an open problem in the medical literature (and for ITP patients). We hope to carry out a corresponding medical experimentation in the next future.

REFERENCES

1. J. Bussel and D. Cines, Immune thrombocytopenic purpura, neonatal alloimmune thrombocytopenia, and posttransfusion purpura, In *Hematology: Basic Principles and Practice, Third Edition*, Chapter 126, (Edited by R. Hoffman *et al.*), Churchill Livingstone, New York, (2000).
2. J.N. George, S.D. Berkowitz and G.E. Raskob, Platelets: Acute thrombocytopenia, In *Hematology 1998*, pp. 371–383, American Society of Hematology, Education Program Book, Miami Beach, FL, (1998).
3. R. Yang and Z.C. Han, Pathogenesis and management of chronic idiopathic thrombocytopenic purpura: An update, *Int. J. of Hematology* **71**, 18–24, (2000).
4. K. Dan, K. Inokuchi, E. An and T. Nomura, Cell-mediated cyclic thrombocytopenia treated with azathioprine, *British J. of Haematology* **77**, 365–370, (1991).
5. F. Kimura *et al.*, Cyclic change of cytokines in a patient with cyclic thrombocytopenia, *British J. of Haematology* **94**, 171–174, (1996).
6. D.B. Cines and V.S. Blanchette, Immune thrombocytopenic purpura, *New Engl. J. Med.* **346** (13), 995–1008, (2002).

7. F. Fabris *et al.*, Age as the major predictive factor of long-term response to splenectomy in immune thrombocytopenic purpura, *British J. of Haematology* **112**, 637–640, (2001).
8. M. Kuwana *et al.*, HLA class II alleles in Japanese patients with immune thrombocytopenic purpura. Associations with anti-platelet glycoprotein autoantibodies and responses to splenectomy, *Tissue Antigens* **56**, 337–343, (2000).
9. C. Law, M. Carcaccio, P. Tam, N. Heddle and J.G. Kelton, High-dose intravenous immune globulin and the response to splenectomy in patients with idiopathic thrombocitopenic purpura, *New Engl. J. Med.* **336** (21), 1494–1498, (1997).
10. Y. Najean, J.D. Rain and C. Billotey, The site of destruction of autologous 111In-labelled platelets and the efficiency of splenectomy in children and adults with idiopathic thrombocytopenic purpura: A study of 578 patients with 268 splenectomies, *British J. of Haematology* **97**, 547–550, (1997).
11. M. Ruivard *et al.*, The response to high-dose intravenous immunoglobulin or steroids is not predictive of outcome after splenectomy in adults with autoimmune thrombocytopenic purpura, *British J. of Haematology* **105**, 1130–1132, (1999).
12. M. Gibson, J.K. Sehon, S. White, G.B. Zibari and L.W. Johnson, Splenectomy for idiopathic thrombocytopenic purpura: A five-year retrospective review, *Am. Surg.* **66** (10), 952–954, (2000).
13. N. Vianelli *et al.*, Long-term follow-up of idiopathic thrombocytopenic purpura in 310 patients, *Haematologica* **86**, 504–509, (2001).
14. T. Gernsheimer, J. Stratton, P.J. Ballem and S.J. Slichter, Mechanisms of response to treatment in autoimmune thrombocytopenic purpura, *New Engl. J. Med.* **320** (15), 974–980, (1989).
15. J. Eller, I. Györi, M. Zöllei and F. Krizsa, Modelling thrombopoiesis regulation-I, model description, and simulation results, *Computers Math. Applic.* **14** (9–12), 841–848, (1987).
16. I. Györi and J. Eller, Modelling thrombopoiesis regulation-II, mathematical investigation of the model, *Computers Math. Applic.* **14** (9–12), 849–859, (1987).
17. L.A. Harker *et al.*, Effects of megakaryocyte growth and development factor on platelet production, platelet life span, and platelet function in healthy human volunteers, *Blood* **95**, 2514–2522, (2000).
18. J. Hersh, Mathematical analysis of the relative contributions of decreased production and increased peripheral destruction in idiopathic thrombocytopenic purpura and implications in splenectomy, *J. Theor. Biol.* **203**, 153–162, (2000).
19. J.K. Hersh, E.G. Hom and M.E. Brecher, Mathematical modeling of platelet survival with implications for optimal transfusion practice in the chronically platelet transfusion-dependent patient, *Transfusion* **38**, 637–644, (1998).
20. A.M. Peters, I. Klonizakis, J.P. Lavender and S.M. Lewis, Use of ^{111}Indium-labelled platelets to measure spleen function, *British J. of Haematology* **46**, 587–593, (1980).
21. A.M. Peters and J.P. Lavender, Factors controlling the intrasplenic transit of platelets, *European J. of Clinical Investigation* **12**, 191–195, (1982).
22. A.M. Peters, S.H. Saverymuttu, B. Wonke, M. Lewis and J.P. Lavender, The interpretation of platelet kinetic studies for the identification of sites of abnormal platelet destruction, *British J. of Haematology* **57**, 637–649, (1984).
23. M. Santillán, J.M. Mahaffy, J. Bélair and M.C. Mackey, Regulation of platelet production: The normal response to perturbation and cyclical platelet disease, *J. Theor. Biol.* **206**, 585–603, (2000).
24. H.E. Wichmann and M.D. Gerhardts, Platelet survival curves in man considering the splenic pool, *J. Theor. Biol.* **88**, 83–101, (1981).
25. R.V.B. Emmons *et al.*, Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction, *Blood* **87**, 4068–4071, (1996).
26. L.A. Harker and C.A.Finch, Thrombokinetics in man, *The J. of Clinical Investigation* **48**, 963–974, (1969).
27. Y. Najean, J.D. Rain and V. Dufour, Platelet production in idiopathic thrombocytopenic purpura, *Nouv. Rev. Fr. Hematol.* **35**, 431–436, (1993).
28. A. Tomer, S.R. Hanson and L.A. Harker, Autologous platelet kinetics in patients with severe thrombocytopenia: Discrimination between disorders of production and destruction, *J. Lab. Clin. Med.* **118** (6), 546–554, (1991).
29. I. Branehög, J. Kutti and A. Weinfeld, Platelet survival and platelet production in idiophatic thrombocytopenic purpura, *British J. of Haematology* **27**, 127–143, (1974).
30. A. du P. Heyns *et al.*, Platelet turnover and kinetics in immune thrombocytopenic purpura: Results with autologous ^{111}In-labeled platelets and homologous ^{51}Cr-labeled platelets differ, *Blood* **67** (1), 86–92, (1986).
31. A. du P. Heyns, M.G. Lötter, P.N. Badenhorst, O.R. van Reenen, H. Pieters, P.C. Minnaar and F.P. Retief, Kinetics, distribution and sites of destruction of ^{111}Indium-labelled human platelets, *British J. of Haematology* **44**, 269–280, (1980).
32. H. Louwes, E. Vellenga, E.J. Houwerzijl, J.Th.M. de Wolf, Effects of prednisone and splenectomy in patients with idiopathic thrombocytopenic purpura: Only splenectomy induces a complete remission, *Ann. Hematol.* **80**, 728–732, (2001).
33. S. Savolainen, K. Liewendhal, M.T. Syrjälä and J. Gripenberg, Platelet splenic transit times in idiopathic thrombocytopenic purpura. Compartmental vs. non-compartmental model, *Int. J. Hematol.* **55**, 81–87, (1992).
34. International Committee for Standardization in Hematology, Panel on Diagnostic Applications of Radionuclides, Recommended method for Indium-111 platelet survival studies, *J. Nucl. Med.* **29**, 564–566, (1988).

35. The Panel on Diagnostic Application of Radioisotopes in Hematology, International Committee for Standardization in Hematology, Recommended methods for radioisotope platelet survival studies, *Blood* **50** (6), 1137–1144, (1977).
36. I. Branehög, A. Weinfeld and B. Roos, The exchangeable splenic platelet pool studied with epinephrine infusion in idiopathic thrombocytopenic purpura and in patients with splenomegaly, *British J. of Haematology* **25**, 239–248, (1973).
37. D.G. Luenberger, *Introduction to Dynamic Systems, Theory, Models, and Applications*, John Wiley and Sons, New York, (1979).