ODE Model of Thrombopoiesis

S. Indumathy\(^1\), S. Rajasekaran\(^2\), S. Balamuralitharan\(^3\)

\(^1\)Research scholar, \(^2\)Professor, Department of Mathematics, B.S. ABDUR RAHMAN UNIVERSITY, Chennai-48, India.
\(^3\)Assistant Professor, Faculty of Engineering and Technology, Department of mathematics, SRM University, Kattankulathur-603202, Tamil Nadu, India.

Abstract—In this paper, we establish ordinary differential equations model of thrombopoiesis which maps the dynamics of stem cells, CFU-Mk, megakaryocytes and platelets in spleen and circulation. The primary cytokine responsible for platelet formation is, thrombopoietin (TPO). TPO acts by stimulating proliferation and differentiation of megakaryocytes precursors, increasing the mass and maturation of megakaryocytes. TP\(^0\) parameters were estimated by fitting the model to time series data of platelets. We obtained a good agreement between model and data.

The model can be used to explore the origin of the rhythmic fluctuations which characterize CT, to predict the dynamics of bone marrow cells stages and endogenous TPO dynamics during chemotherapy. The long term recovery after chemotherapy can also be simulated.

Keywords—Thrombopoiesis, Thrombopoietin (TPO), Compartments, Megakaryocytes, Platelets.

I. INTRODUCTION

The model description as presented here, gives the mathematical and technical details. The paper is divided into 6 sections. Here we derive the model equations for compartments viz. the stem cell compartment \(S\), the CFU-Mk compartment \(M_1\), and the megakaryocyte compartment \(M_2\). We also model the platelet dynamics in spleen and circulation. The general scheme of these equations is that the change of the compartment size is equal to the influx minus the efflux.

A. The bone marrow is modeled by three compartments:

The stem cell compartment \(S\) is characterized by self renewal capability and lineage specifications regulated by the demand of lineage – specific bone marrow cell stages (Glauche et al., 2007:). The compartment \(M_1\) summarizes all progenitors and precursors committed to the thrombopoietic lineage but still capable of cell divisions. The compartment \(M_2\) summarizes the megakaryocyte which are clearly morphologically distinguishable from the other cells and are characterized by endomitoses.

We roughly divide the bone marrow compartment into three compartments comprising a qualitative change in the properties of cells by lineage commitment in \(M_1\) and loss of cell division in \(M_2\). Since the cell population in bone marrow are a continuous process rather than cell stages. For the same reason we assume irreversibility all transitions.

II. BASIC NOTATIONS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Representation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)</td>
<td>Stem cells</td>
</tr>
<tr>
<td>(P)</td>
<td>Self renewal probability</td>
</tr>
<tr>
<td>(P_{fs})</td>
<td>Fraction of cells in active cell cycle</td>
</tr>
<tr>
<td>(t_s)</td>
<td>Cycle time of proliferating cells</td>
</tr>
<tr>
<td>(M_1)</td>
<td>CFU-Mk(colony forming units of megakaryocytes)</td>
</tr>
<tr>
<td>(Z_{M_1})</td>
<td>Function of TPO</td>
</tr>
<tr>
<td>(T_{M_1})</td>
<td>Transit time in CFU-mk compartment</td>
</tr>
<tr>
<td>(M_2)</td>
<td>Megakaryocytes</td>
</tr>
<tr>
<td>(Z_{M_2})</td>
<td>Function of TPO</td>
</tr>
<tr>
<td>(T_{M_2})</td>
<td>Transit time in megakaryocyte compartment</td>
</tr>
<tr>
<td>(P_s)</td>
<td>Platelets in spleen</td>
</tr>
<tr>
<td>(T_p^{sub})</td>
<td>Transit time in platelet subcompartments</td>
</tr>
<tr>
<td>(\theta_c)</td>
<td>Ratio of cells entering directly into circulation</td>
</tr>
<tr>
<td>(P_c)</td>
<td>Platelets in circulation</td>
</tr>
<tr>
<td>(\theta_c^{sc})</td>
<td>Transition of aged platelets from spleen to circulation</td>
</tr>
</tbody>
</table>
III. MODEL DEVELOPMENT

A. S- stem cells

In the model the stem cells are denoted by S. They are characterized by two regulated variables (namely, the self renewal probability 'p' and the fraction of cells in active cell cycle 'Pfs'). For the fraction of stem cells in active cycle, Pfs = 0.15 is assumed for the normal steady state. This implies that 85% of the stem cells are in resting phase. By stimulation all resting cells may be inactivated (Pfs = 1.0) and by suppression 99% of the stem cells may become inactivated (Pfs = 0.01).

The self renewal probability p normally equals to 0.5. This means that on average 50% of the newly formed cells (after mitosis of stem cells) remain in the S compartment. While 50% are lost through differentiation. If p > 0.5, more than 50% of the daughter cells remain stem cells and S increases. The opposite happens if p < 0.5.

P and Pfs are not dependent on each other. Their values depend on the number of stem cells and differentiated bone marrow cells, respectively.

Of those stem cells differentiating, the fraction $\lambda_f$ goes into thrombopoietic cell lineage. While $\lambda_T$ goes thrombopoietic cells. $\lambda_T$ is constant in the model.

In the model, the stem cell compartment is homogeneous and an age structure is not considered.

B. $M_1$. CFU-mk (colony forming units of megakaryocytes)

These cells are the first population of differentiated Thrombopoietic cells. Each cell which enters performs many number of mitotic cell divisions. The cell cycle time is 8hr.

C. $M_2$. Megakaryocytes

After leaving $M_1$, the thrombopoietic cells enter the $M_2$ population. The cells in this population does not undergo mitosis but they undergo endoreduplication i.e., they are characterized by endomitoses.

The megakaryocytes are clearly morphologically distinguishable from the other cells.

D. $P_s$ - Platelets in Spleen Title and Author Details

Platelets are released from the bone marrow $M_2$ compartment to the peripheral blood. Young platelets (Megathrombocytes) were preferentially sequestered in the spleen.

E. $P_c$. Platelets in circulation

Platelets are age dependently released from the spleen to the circulating blood.

IV. MATHEMATICAL MODELING OF THROMBOPOIESIS

In this section we will model the dynamics of all compartments starting with the bone marrow compartments.

A. Stem cell compartment (S)

In this model the stem cells are denoted by S. In the model the stem cell compartment is homogeneous and an age structure is not considered. The model equations for this compartment is obtained from Wichmann and loeffler equations as,

$$\frac{dS}{dt} = (2p-1) * S * \frac{Pfs}{t_s}$$

(1)

Here $Pfs * S$ are proliferative active cells. $t_s$ is the cycle time of proliferating cells. Therefore $S * \frac{Pfs}{t_s}$ cells enter mitosis per unit time.
Doubling gives a factor of 2. Of these cells the fraction \((1-p)\) leaves the stem cell compartment and differentiates, while the fraction \(p\) remains. Thus the \(2*p*S*\frac{Pf_s}{t_s}\) cells replace the \(S*\frac{Pf_s}{t_s}\) stem cells which have entered mitosis, per unit time. This justifies equation (1). The rate of cells differentiating then equals

\[
\frac{dS_{out}}{dt} = 2(1 - p) * S * \frac{Pf_s}{t_s}
\]

(2)

Since the cell divisions are averaged, a distinction between symmetric and asymmetric divisions is not necessary. The normal steady state values for the models are chosen as \(t_s = 8\, \text{hr}, \, Pf_s = 0.15, \, p = 0.5\) (table 1a). The normal steady state compartment value is arbitrarily set to be \(S^* = 1\). Therefore relative and absolute values are identical \((S^* = S)\). \(Pf_s\) and \(p\) are not constant but may vary between 0.01 & 1 and 0.4 & 0.6 respectively. ‘\(Pf_s\)’ and \(p\) are independent of each other.

This is an important feature showing that in the model the process of cell cycling is distinct from the process of self renewal.

B. CFU-Mk compartment (\(M_1\))

The efflux of the stem cell compartment is the influx of the CFU – Mk compartment.

\[
\frac{dM_1}{dt} = Z_{M_1}^{in} S_{out} - \frac{M_1}{T_{M_1}}
\]

(3)

\[
M_{out} = Z_{M_1}^{out} \frac{M_1}{T_{M_1}}
\]

(4)

\[
Z_{M_1} = Z_{M_1}^{in} * Z_{M_1}^{out} = 2^{\alpha_{M_1}}
\]

(5)

While \(Z_{M_1}\) is a function of TPO, \(T_{M_1}\) is assumed to be constant. Equation (3) indicate that the efflux from the preceding compartment \(S_{out}\), is amplified by \(Z_{M_1}^{in}\) as soon as the cells enter \(M_1\). Immediately before they leave compartment \(M_1\) they are amplified by \(Z_{M_1}^{out}\). Since the amplification in cell compartments is regulated by TPO, fluctuations in TPO concentrations result in immediate changes of the amplification rate. On the other hand, amplification is distributed over the transit time of a cell in the compartment.
The amplification of a compartment is divided into an amplification of the cell influx into a compartment $Z_{M_i}^{in}$ and an amplification of the cell efflux of a compartment $Z_{M_i}^{out}$. The product of these rates is equal to the overall amplification $Z_{M_i}$. Under the assumption that the amplification is uniformly distributed over the transit time, Scholz et al, (2005) proved that

$$Z_{M_i}^{in} = \begin{cases} \frac{Z_{M_i} - 1}{IdZ_{M_i}} & \text{for } Z_{M_i} \neq 0, Z_{M_i} \neq 1 \\ \ln 2 & \text{for } Z_{M_i} = 1 \end{cases}$$

$$Z_{M_i}^{out} = \frac{Z_{M_i}^{in}}{Z_{M_i}}$$

C. Megakaryocytes ($M_2$)

In this compartment amplification indicates the increased ploidy of cells caused by endomitoses. Both amplification and maturation time are assumed to be $z$ – functions of TPO.

$$\frac{dM_i}{dt} = Z_{M_i}^{in} M_{2,m} - \frac{M_i}{T_{M_i}}$$  (6)

$$M_{2,m} = Z_{M_i}^{out} M_i \frac{T_{M_i}}{T_{M_i}}$$  (7)

All the variables in equations (6) and (7) have same effect as the variables in the previous compartment.

D. Platelets in spleen and circulations ($P_s$ & $P_c$)

The platelet compartments in spleen and circulation are divided into $n$ sub compartments to model the age structure of these compartments. The transition time in each of these sub compartments is $T_{P_i}$ and $T_P$. We assume that there is a direct influx of platelets from bone marrow to both, spleen and circulation. The ratio of cells entering directly into circulation is denoted by $\theta_i$. Hence the balance equations for the first platelet sub compartments are:

$$\frac{dP_{i1}}{dt} = \theta_c * M_{2,m} - \frac{P_{i1}}{T_{P_i}}$$  (8)

$$\frac{dP_{i1}}{dt} = (1 - \theta_c) * M_{2,m} - \frac{P_{i1}}{T_{P_i}}$$  (9)

Where $\theta_i^{sc}$ denote the transitions of aged platelets from spleen to circulation.

For the following subcompartments we obtain,

$$\frac{dP_{i2}}{dt} = \frac{P_{i1}}{T_{P_i}} - \frac{P_{i2}}{T_{P_i}}$$  (10)

$$\frac{dP_{i2}}{dt} = \frac{P_{i1}}{T_{P_i}} - \frac{P_{i2}}{T_{P_i}}$$  (11)

The steady state conditions of equations (8) - (11) are as follows:

$$P_{i1}^{sc} = (\theta_c + \theta_i^{sc}) \frac{T_{P_i} + M_{2,m}^{sc}}{1 + \theta_i^{sc} T_{P_i}}$$  (12)

$$P_{i2}^{sc} = (1 - \theta_c) \frac{T_{P_i} + M_{2,m}^{sc}}{1 + \theta_i^{sc} T_{P_i}}$$  (13)

$$P_{i3}^{sc} = P_{i2}^{sc} + \theta_i^{sc} \frac{T_{P_i} + P_{i3}^{sc}}{1 + \theta_i^{sc} T_{P_i}}$$  (14)

$$P_{i1}^{sc} = \frac{P_{i1}^{sc}}{1 + \theta_i^{sc} T_{P_i}}$$  for $i = 1, 2, 3, ..., n$  (15)

V. RESULTS

![Platelet dynamics in spleen and circulation](image)

platelet dynamics in spleen and circulation

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Table 1a: Stem Cell Compartment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value used</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P$</td>
<td>0.5</td>
<td>Wichmann and Loeffler (1985)</td>
</tr>
<tr>
<td>$S$</td>
<td>1</td>
<td>Wichmann and Loeffler (1985)</td>
</tr>
<tr>
<td>$P_{fs}$</td>
<td>0.15</td>
<td>Wichmann and Loeffler (1985)</td>
</tr>
<tr>
<td>$t_s$</td>
<td>8 hr</td>
<td>Wichmann and Loeffler (1985)</td>
</tr>
<tr>
<td>$S_{out}$</td>
<td>0.1875</td>
<td>Calculated from eqn (2)</td>
</tr>
</tbody>
</table>

Table 1b: CFU-Mk Compartment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value used</th>
<th>Confidence interval</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z_{M_1}$</td>
<td>2.65</td>
<td>2.52-3.83</td>
<td>Harker (1971)</td>
</tr>
<tr>
<td>$Z_{in}^{M_1}$</td>
<td>1.6930</td>
<td>--</td>
<td>Calculated from eqn (5a)</td>
</tr>
<tr>
<td>$Z_{out}^{M_1}$</td>
<td>1.5653</td>
<td>--</td>
<td>Calculated from eqn (5b)</td>
</tr>
<tr>
<td>$M_1$</td>
<td>0.0734</td>
<td>--</td>
<td>Calculated from eqn (3)</td>
</tr>
<tr>
<td>$T_{M_1}$</td>
<td>630 hr</td>
<td>299-903 hr</td>
<td>Harker (1971)</td>
</tr>
<tr>
<td>$M_{1out}$</td>
<td>$2.9549 \times 10^{-5}$</td>
<td>--</td>
<td>Calculated from eqn (4)</td>
</tr>
</tbody>
</table>

Table 1c: Megakaryocyte Compartment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value used</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z_{M_2}$</td>
<td>8</td>
<td>Harker (1971)</td>
</tr>
<tr>
<td>$Z_{in}^{M_2}$</td>
<td>3.3664</td>
<td>Calculated from eqn (5a) by replacing the suffix 1 as 2</td>
</tr>
<tr>
<td>$Z_{out}^{M_2}$</td>
<td>2.3764</td>
<td>Calculated from eqn (5b) by replacing the suffix 1 as 2</td>
</tr>
<tr>
<td>$M_2$</td>
<td>0.0066</td>
<td>Calculated from eqn (6)</td>
</tr>
<tr>
<td>$T_{M_2}$</td>
<td>144</td>
<td>Dassin et al (1978)</td>
</tr>
<tr>
<td>$M_{2out}$</td>
<td>$1.089 \times 10^{-4}$</td>
<td>Calculated from eqn (7)</td>
</tr>
</tbody>
</table>

VI. DISCUSSIONS

First we determined the parameters of our model of Thrombopoiesis. We evaluated all the parameters outside the negative feedback function. Time courses of platelet dynamics were used to determine the unknown parameters of the cell kinetic model. Results of data fitting are shown in fig.2 and fig.3. All the parameters that are estimated are given in the Table 1a,b,c.

Our model maps the basic regulatory mechanisms of bone marrow thrombopoiesis and the dynamics of platelets redistribution between spleen and circulation. Bone marrow Thrombopoiesis is modeled by the three major cell compartments: Stem cells, CFU-Mk and megakaryocytes. We assumed a proportionality between megakaryocyte poidy and platelet production (Corash, 1989, Stenberg and Lenin, 1989). For simplicity, we neglected proplatelet formation and regulation of the volume of platelets since both processes are still not well understood.

The spleen which is important for sequestration and maturation of platelets is modeled by an age-dependent release of platelets from spleen to circulation. Finally, platelets are age-dependently removed from the plasma (Tsan, 1984). In this paper, we constructed an ordinary differential equations model of thrombopoiesis which is able to explain the time course of platelets. We obtained a good agreement between the model and biological fact.
REFERENCES


