Mathematical Model of Radiation Effects on Thrombopoiesis in Rhesus Macaques and Humans

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Abstract

A mathematical model that describes the effects of acute radiation exposure on thrombopoiesis in primates and humans is presented. Thrombopoiesis is a complex multistage dynamic process with potential differences between species. Due to known differences in cellular radiosensitivities, nadir times, and cytopenia durations, direct extrapolation from rhesus to human platelet dynamics is unrealistic. Developing mathematical models of thrombopoiesis for both humans and primates allows for the comparison of the system's response across species. Thus, data obtained in primate experiments can be extrapolated to predictions in humans. Parameter values for rhesus macaques and humans were obtained either from direct experimental measurements or through optimization procedures using dynamic data on platelet counts following radiation exposure. Model simulations accurately predict trends observed in platelet dynamics: at low radiation doses platelet counts decline after a time lag, and nadir depth is dose dependent. The models were validated using data that was not used during the parameterization process. In particular, additional experimental data was used for rhesus, and accident and platelet donor data was used for humans. The model aims to simulate the average response in rhesus and humans following irradiation. Variation in platelet dynamics due to individual variability can be modeled using Monte Carlo simulations in which parameter values are sampled from distributions. This model provides insight into the time course of the physiological effects of radiation exposure, information which could be valuable for disaster planning and survivability analysis and help in drug development of radiation medical countermeasures.

Keywords: platelet, megakaryocyte, health effects, ordinary differential equation model

1. Introduction

Thrombopoiesis is the process of platelet formation. Platelets are responsible for the coagulation of blood and play a role in immunity (Yeaman, 2010). The thrombopoietic system is highly sensitive to ionizing radiation, primarily due to the effect of radiation on hematopoietic stem cells (HSCs) (Kato et al., 2013). Perturbations to platelet counts, including rapid declines and states of thrombocytopenia, are correlated with lethality (Housing et al., 1993; Akca et al., 2002; Wang et al., 2010). Understanding the dynamics of the thrombopoietic system following radiation exposure can help one predict survivability, understand radiation damage mechanisms, and develop interventions.

Platelet generation is initiated by self-renewing HSCs in the bone marrow. These stem cells differentiate and through a series of mitotic divisions produce megakaryocytes (MKs), the precursors of platelets. As MKs mature, their ploidy increases through a series of endomitoses. Once mature, MKs produce platelets which enter the blood stream. Mathematical models have been

developed to describe how these processes are affected by radiation exposure (Smirnova, 2010, 2012; Graessle, 2000), chemotherapy treatment (Scholz et al., 2010), pegylated recombinant MK growth and development factor (Harker et al., 2000), and thrombopoietin (TPO) (Skomorovski et al., 2003). In addition, we have adapted O. A. Smirnova's radiation injury model to study how burn injury affects thrombopoiesis (Wentz et al., 2014a).

In this study, we use Smirnova's radiation exposure model as a starting point (Smirnova, 2010, 2012). Smirnova's models provide reasonable predictions of the hematopoietic response in humans after acute radiation exposure. However, this work seeks to (1) adapt Smirnova's model to accurately predict thrombopoiesis in rhesus and (2) parameterize the model by incorporating as many well-documented experimentally determined parameters as possible. In order to better correlate certain trends observed with experimental data, we made modifications to the model structure. This new model structure was re-parameterized to predict the platelet response in rhesus and humans following a wide range radiation dose levels. One significant structural change between Smirnova's model and the model here is the addition of transit subcompartments to simulate time delays and introduce an age-structure into the model. Additionally, the model incorporates different

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Table 1: State variables in the human and rhesus thrombopoiesis models.

State Variable	Biological Representation
x_1^{ud}	Undamaged cells in the mitotic compartment X_1
$x_{2I,i}^{ud}$	Undamaged immature MKs in the i^{th} subcompartment of X_{2I}
$x_{2M,i}^{ud}$	Undamaged mature MKs in the i^{th} subcompartment of X_{2M}
$x_{3,i}$	Undamaged circulating platelets in the i^{th} subcompartment of X_3
x_1^d	Damaged cells in the mitotic compartment X_1
x_2^d	Damaged MKs

feedback mechanisms, MK radiosensitivity, and alternate models of radiation damage (see Model Development).

The development of a rhesus model followed by a human model adds model validity for several reasons. First, rhesus data comes from a controlled environment, which eliminates confounding factors such as extensive supportive care treatment and blood transfusions. This also helps one identify structures to include in a model. Observed changes in platelet count are driven only by the insult and physiological response. Developing a rhesus model alongside a human model is also the first step in translating effects from rhesus to humans.

In the sections that follow, we describe a mechanistic model of the effect of acute radiation exposure on thrombopoiesis in rhesus and humans. Extensive supportive care is excluded from this model. Using this model one can simulate, up to 30 days following exposure, radiation-induced perturbations in peripheral platelet dynamics and progenitor cell dynamics.

2. Methods

2.1. Model Development

We adopt a simplified view of the thrombopoietic system, as illustrated in Figure 1, by grouping cells into compartments based on degree of maturity, differentiation, and location in the body (e.g. bone marrow, circulation). Similar to Smirnova (2010), these compartments include the mitotic bone marrow precursor cells (HSCs to megakaryoblasts, X_1), MKs in the bone marrow (X_2), and platelets in circulation (X_3) (see Table 1 for a complete list of state variables and their biological interpretation). Normal transitions among the compartments are indicated by solid arrows at the top of Figure 1, and dotted lines represent homeostatic feedback mechanisms. The effect of radiation on the thrombopoietic system is modeled by the transition of radiosensitive cells into additional compartments that essentially sequester the damaged cells: there is no further maturation or differentiation of these cells, though they continue to modulate homeostatic feedback until they leave the model system through early death.

For the complete list of model equations, see Appendix A.1.

This conceptual model of thrombopoiesis was applied to both non-human primates (NHPs) and humans. NHP data provided key insight into model structure because of the precise experimental conditions that could be obtained in these studies.

2.1.1. Mitotic progenitor compartment

The mitotic progenitor compartment contains early thrombopoietic progenitors in the bone marrow ranging from self-replicating HSCs through megakaryoblasts. Cells in this compartment are capable of dividing and can also become further differentiated, thereby leaving the compartment. The rate of change of concentration of undamaged mitotic progenitors, x_1^{ud} , is given by (Smirnova, 2010)

$$\frac{dx_1^{ud}}{dt} = Bx_1^{ud} - \gamma x_1^{ud} \quad (1)$$

where γ is the constant rate of transition into the X_2 compartment and B is the time-dependent rate of mitotic progenitor repopulation.

To incorporate homeostatic feedback into the repopulation rate B , we assume that B is positively correlated with the amount of a generic stimulatory mediator within the system. In particular, we assume that

$$B = \frac{\alpha}{1 + \frac{K}{I}} \quad (2)$$

where α is the maximum repopulation rate, K is the stimulation constant, and I is the concentration of the generic mediator. Equation 6 is similar to the HSC repopulation rate defined by Smirnova (2010); however, in Smirnova's model the repopulation rate B is negatively correlated with the mediator concentration I (i.e., the mediator is inhibitory). We redefined the mediator in the system such that I is stimulatory because this is consistent with the effect of the principle mediator of thrombopoiesis, TPO (Kaushansky, 2005). Ultimately, the mediator I is intended to represent the combined effect of all biological factors, both inhibitory and stimulatory, that modulate the repopulation rate. These factors include spatial constraints within the bone marrow environment and cytokines.

To close the feedback loop we now need to relate I to the number of cells in our model of the thrombopoiesis system. We therefore assume that all cells in the system, including mitotic progenitors, MKs, and platelets, contribute to the degradation of I . For example, the degradation of I due to an overabundance of X_1 cells represents negative feedback due to bone marrow spatial constraints, and the degradation of I due to X_2 and X_3 cells represents the removal of TPO via receptor interactions. This feedback loop is analogous to that developed by Smirnova (2010) where all cells lead to the generation of the inhibitory mediator.

Figure 1: **Model of effects of radiation on thrombopoiesis in rhesus and humans.**

Assuming that I is generated at a constant rate, the concentration of I changes according to

$$\frac{dI}{dt} = G - H(x_1^{ud} + x_1^d + \theta_2(x_2^{ud} + x_2^d) + \theta_3 x_3)I \quad (3)$$

where θ_2 and θ_3 represent the relative rate of MK- and platelet-mediated I degradation, respectively (relative to the effect of mitotic progenitors).

The parameters θ_i thus quantify the relative impact of X_i cells on the repopulation rate feedback signal. We calculate θ_2 through optimization and use experimental data to map θ_2 to θ_3 . To construct this mapping, we first note that platelets and MKs regulate TPO concentration through receptor interactions. Specifically, receptors on the membranes of platelets and MKs bind to and engulf TPO, removing it from the system. We therefore use a receptor count ratio to estimate the amount of TPO removed by platelets relative to the amount removed by MKs. In humans, the average TPO receptor count on peripheral and cord blood MKs is approximately 934 (Kuwaki et al., 1998). In contrast, the TPO receptor count on platelets is approximately 30 ± 4 (Broudy et al., 1997). Thus, each MK destroys 934/30 times as much TPO as each platelet, so we assume

$$\theta_3 = 0.03 \cdot \theta_2 \quad (4)$$

In summary, to map θ_2 to θ_3 , we have assumed that (i) platelets and MKs modulate the repopulation rate only through receptor-mediated destruction of TPO, and (ii) the relative amount of TPO degradation due to platelets

and MKs depends only on their TPO receptor count ratio. Finally, although Equation 4 was determined using data in humans, it was assumed to hold for rhesus as well.

Using the same approach as Smirnova (2010), we reduce the feedback model given by Equation 2–3 by assuming that I 's characteristic time scale is much shorter than the time scales over which the cell populations change. Using a quasi-steady-state approximation for I , we assume $dI/dt = 0$ and then solve Equation 3 for I :

$$I = \frac{G}{H(x_1^{ud} + x_1^d + \theta_2(x_2^{ud} + x_2^d) + \theta_3 x_3)} \quad (5)$$

Substituting this expression for I into Equation 2 yields

$$B = \frac{\alpha}{1 + \beta(x_1^{ud} + x_1^d + \theta_2(x_2^{ud} + x_2^d) + \theta_3 x_3)} \quad (6)$$

where $\beta = HK/G$.

β can be determined as a function of kinetic rates and the healthy, steady-state values of x_1^{ud} , x_2^{ud} , and x_3 ($\bar{x}_1^{ud}$, $\bar{x}_2^{ud}$, and $\bar{x}_3$, respectively). Under steady-state conditions, the concentration of mitotic progenitors is constant ($dx_1^{ud}/dt = 0$) and there are no damaged cells. Thus, $B = \gamma$ (see Equation 1) and, $x_i^d = 0$ for $i = 1, 2$. Making these substitutions into Equation 6 yields

$$\gamma = \frac{\alpha}{1 + \beta(\bar{x}_1^{ud} + \theta_2 \bar{x}_2^{ud} + \theta_3 \bar{x}_3)} \quad (7)$$

Rearranging, we see that

$$\beta = \frac{\alpha/\gamma - 1}{\bar{x}_1^{ud} + \theta_2 \bar{x}_2^{ud} + \theta_3 \bar{x}_3} \quad (8)$$

Equation 2 implies that the maximum rate of mitotic progenitor repopulation is equal to α . In Smirnova's model, α is assumed to equal $2.0d^{-1}$ in humans (Smirnova, 2010). Using an exponential growth model, this implies that the time needed for cellular division is

$$T_{div} = \frac{\ln(2)}{2d^{-1}} \cdot \frac{24h}{1d} = 8.3h, \quad (9)$$

which is consistent with the time required for DNA synthesis (Andreeff et al., 2000). Thus, $2.0d^{-1}$ is a biologically reasonable maximum rate of maturation, and we use it in both the human and rhesus models presented here.

Here, the cellular division time is assumed to equal the DNA synthesis time as cell concentrations approach zero. A more accurate method would be to optimize α , using $2.0d^{-1}$ as an upper bound; however, because the parameters α and γ were found to be highly correlated in the optimization, a value for one of these parameters had to be set.

2.1.2. MK compartment

After MKs are produced through stem cell differentiation and mitotic division, the MKs enter a maturation phase characterized by a gradual increase in both mass and ploidy level (Kaushansky, 2005). It is only after MKs have matured that they produce platelets that enter the blood. A time delay, therefore, exists between events that selectively damage HSCs and downstream effects such as perturbations in platelet count. For example, in both rhesus and humans, there is a delay between radiation exposure and decline in the peripheral platelet count (Authier et al., 2013; Bond et al., 1965).

To introduce a maturity structure into the model and represent the MK maturation delay, we divide the MK compartment, X_2 , into n subcompartments. Cells in the first $n/2$ subcompartments, $X_{2I,i}$, are called *immature* MKs, and cells in the second $n/2$ subcompartments, $X_{2M,i}$, are called *mature* MKs. Moreover, as described below, the transition rates among the first $n/2$ subcompartments depend on platelet concentration, so the model essentially describes a state-dependent MK maturation delay.

The model equations for the MK compartment are

$$\frac{dx_{2I,1}^{ud}}{dt} = \gamma x_1^{ud} - n\delta x_{2I,1}^{ud} \quad (10)$$

$$\frac{dx_{2I,i}^{ud}}{dt} = n\delta x_{2I,i-1}^{ud} - n\delta x_{2I,i}^{ud} \quad (i = 2, 3, \dots, n/2) \quad (11)$$

$$\frac{dx_{2M,1}^{ud}}{dt} = n\delta x_{2I,n/2}^{ud} - n\delta_0 x_{2M,1}^{ud} \quad (12)$$

$$\frac{dx_{2M,i}^{ud}}{dt} = n\delta_0 x_{2M,i-1}^{ud} - n\delta_0 x_{2M,i}^{ud} \quad (i = 2, 3, \dots, n/2) \quad (13)$$

where $x_{2I,i}$ and $x_{2M,i}$ for $i = 1, 2, \dots, n/2$ are state variables that represent subcompartment i in the immature and mature MK compartments, respectively. γx_1^{ud} represents the

Figure 2: **Feedback effect of platelets on MK transit time.** As the platelet blood concentration x_3 increases, the immature MK transit time (τ_{2I}) increases while the mature MK transit time (τ_{2M}) remains constant. τ_{min} represents the minimum MK transit time, τ_{max} represents the maximum MK transit time, and τ_0 is the transit time when $x_3 = \bar{x}_3$. ($\tau_{2I} = 1/2\delta$, $\tau_{2M} = 1/2\delta_0$.)

influx from the X_1 compartment, δ_0^{-1} is the expected MK transit time under healthy, steady-state conditions, and δ is a variable rate that determines how the transit time through the immature MK subcompartments changes in response to perturbations in the platelet concentration.

We have thus introduced a second feedback mechanism, represented by the rate δ , whereby the platelet concentration x_3 modulates maturation rate in the $X_{2I,i}$ subcompartments (see Figure 1). In Smirnova's 2010 model the rate of MK maturation is not variable and there is instead an amplification factor which is dependent on platelet concentration x_3 . The revised feedback mechanism used here is based on a review of experimental data analyzing TPO and platelet dynamics. In particular, TPO is known to affect MK maturation; however, TPO does not affect the formation of platelets from the MK cytoplasm (Kaushansky, 2005). Following thrombophoresis in humans, platelet counts return to normal levels at the expected rate for the first 3–4 days given known production rates (Sullivan et al., 1977). However, after the fourth day following thrombophoresis, there is a subsequent increase in the platelet production rate, suggesting a negative feedback effect of platelet concentration on the maturation rate of early MKs. It is for these reasons that we assume platelet concentration affects the immature MK maturation rate, but not the transit time through the X_{2M} compartment (see Figure 2).

We assume this effect depends only on the platelet concentration. However, the mechanism may involve TPO which can be degraded by MKs. Although, the MK con-

centration could ultimately affect transit time through the X_{2I} compartment, this potential mechanism is not included in our model. This was due to the lack of available data on the contribution of MKs to this mechanism.

To complete the description of the second feedback loop we must now define how the rate δ depends on the platelet concentration x_3 . In other words, we need to define how the immature MK transit time τ_{2I} depends on x_3 . First, the MK compartment *total* transit time function $(\tau_{2M} + \tau_{2I})(x_3)$ should have the following attributes (see Figure 2): (1) $(\tau_{2M} + \tau_{2I})(\bar{x}_3) = \tau_0$, i.e., at steady-state, the transit time through all n MK subcompartments should be τ_0 , (2) as the platelet concentration approaches zero, $(\tau_{2M} + \tau_{2I})$ should approach a minimum value τ_{min} , and (3) as the platelet concentration approaches infinity, $(\tau_{2M} + \tau_{2I})$ should approach a maximum value τ_{max} . The values of $\tau_0 = 1/\delta_0$, τ_{min} , and τ_{max} correspond to experimental measurements of steady-state, minimum, and maximum MK maturation times (respectively).

Next, we allocate a fixed portion of the MK total transit time to the X_{2M} compartment: $\tau_{2M}(x_3) \equiv \tau_0/2$ (and therefore we assume $\tau_{min} > \tau_0/2$; see Figure 2). Given this fixed value of τ_{2M} , the above three criteria for the function $(\tau_{2M} + \tau_{2I})(x_3)$ imply the following three criteria for the function $\tau_{2I}(x_3)$: (1') $\tau_{2I}(\bar{x}_3) = \tau_0/2$, i.e., at steady-state, the transit time through the $n/2$ $X_{2I,i}$ subcompartments should be $\tau_0/2$, (2') as the platelet concentration approaches zero, τ_{2I} should approach a minimum value $\tau_{2I}^{min} = \tau_{min} - \tau_0/2$, and (3') as the platelet concentration approaches infinity, τ_{2I} should approach a maximum value $\tau_{2I}^{max} = \tau_{max} - \tau_0/2$. To model a sigmoidal response that satisfies (1'), (2'), and (3'), we define

$$\tau_{2I}(x_3) = \left(\frac{1}{\tau_{2I}^{max}} + \left(\frac{1}{\tau_{2I}^{min}} - \frac{1}{\tau_{2I}^{max}} \right) \left(\frac{\frac{1}{\tau_0/2} - \frac{1}{\tau_{2I}^{max}}}{\frac{1}{\tau_{2I}^{min}} - \frac{1}{\tau_{2I}^{max}}} \right)^{\lambda} \left(\frac{x_3}{\bar{x}_3} \right)^{\lambda} \right) \quad (14)$$

where λ determines the feedback strength and $\bar{x}_3$ is the concentration of platelets under healthy, steady-state conditions. In Figure 2 the MK compartment transit time is plotted using hypothetical values for τ_0 , τ_{min} , τ_{max} , and λ . This feedback function was adapted from Scholz et al. (2010), in which a similar function was used to describe how TPO increases the maturation rate of progenitor cells. Finally, returning to defining how the rate δ depends on the platelet concentration x_3 , there are $n/2$ $X_{2I,i}$ subcompartments, so we set $1/n\delta$ equal to $\tau_{2I}/(n/2)$ (see Equations 10–11). In other words, we define

$$\delta(x_3) = \frac{1}{2\tau_{2I}(x_3)} \quad (15)$$

Values for the parameters τ_{max} and τ_{min} were determined by assuming $\tau_0/4 \leq \tau_{2I} \leq 3\tau_0/4$. Under this assumption, $\tau_{max} = 5\tau_0/4$ and $\tau_{min} = 3\tau_0/4$. Though there is little experimental data that supports our assumption regarding τ_{2I} , we note that it has been observed that when

92% of platelets were removed from the circulation of rats, the MK maturation time decreased to 62–85% of control values (Ebbe et al., 1968). This provides some validation for setting the minimum MK transit time equal to 75% of normal. However, the same study notes that sustained transfusion-induced thrombocytosis did not result in a suppressed MK maturation rate in rats. Thus, verifying whether thrombocytosis reduces MK maturation rate requires future experimental work.

2.1.3. Platelet compartment

The platelet compartment consists of all platelets in the blood stream. The platelet compartment is divided into m subcompartments to give it a maturity structure and to generate more biologically realistic transit time distributions (Murphy and Francis, 1971). This is an alteration to Smirnova's 2010 model in which there is only one platelet compartment. Fitting human platelet data to gamma functions suggests a value for m of 7 or 11 (Dowling et al., 2010; Scholz et al., 2010). Here, 9, the midpoint of that range, was chosen for m in the human model, and it was assumed to be the same in the rhesus model. The concentration of platelets in each subcompartment changes with time according to

$$\frac{dx_{3,1}}{dt} = \sigma n \delta_0 x_{2M,n/2}^{ud} - m\psi x_{3,1} \quad (16)$$

$$\frac{dx_{3,i}}{dt} = m\psi x_{3,i-1} - m\psi x_{3,i} \quad (i = 2, 3, \dots, m) \quad (17)$$

where $x_{3,i}$ represents the concentration of platelets in the platelet subcompartment i . $n\delta_0 x_{2M,n/2}^{ud}$ is the efflux from the MK compartment and σ is an amplification factor. $\bar{\sigma}^1$ represents the number of platelets produced per MK, which is approximately 3000 in humans and assumed to be the same in rhesus (Deutsch and Tomer, 2013). In humans, the lifespan of a platelet is approximately 9 days (Schmitt et al., 2001; Mezzano et al., 1982; Kaushansky, 2005; Finch et al., 1977). Thus, in the human model the value of ψ was set to $1/9$ or 0.11 d^{-1} . In rhesus, fitting platelet decay to a gamma distribution led to an expected platelet lifespan of 5.5 d (Harker et al., 1997), leading to $\psi = 0.18 \text{ d}^{-1}$.

2.1.4. Radiation damage

Following radiation exposure, we assume cells instantaneously transition into the damaged compartments. In a real-life scenario, acute radiation exposure would occur over a certain time interval of minutes/hours causing damage during this entire interval. However, because the model is intended to capture a lower resolution of response (i.e., days), we can assume that acute exposure is instantaneous. Thus, the proportion of cells damaged is purely dependent on the total dose received and not the dose rate. The input dose to the model is intended to be a gamma free-in-air dose. Once cells become damaged they stop the maturation process and decay at a fixed rate. In

our model, mitotic progenitors and MKs are radiosensitive, while platelets are assumed to be radioresistant (Greenberg et al., 1968). This is in contrast to Smirnova’s 2010 thrombopoiesis model, in which MKs are radioresistant.

Damaged cells are assumed to die during interphase or the next mitosis through either necrotic or apoptotic pathways. In Smirnova’s thrombopoiesis model there are two damaged compartments from which cells decay at different rates (Smirnova, 2010). However, we have simplified this model by using only one damaged compartment. Based on the platelet dynamic data collected, including more than one compartment did not significantly improve optimizations. The rate of decay μ from the damaged compartment was determined using the rates of decay from the two damaged compartments in Smirnova’s original model which she obtained from the literature. Specifically the reciprocal of these rates (0.16d and 2.0d) were added together and divided by 2 to find the average of the expected lifespan. μ was then set as the reciprocal of this value ($\mu = 1.0d^{-1}$).

To model cell survivability following radiation exposure, we use the single-target, multi-hit model of radiation damage (Joiner, 2009). In this model, cells have multiple targets which must all be hit by radiation for a cell to become damaged. The fraction of surviving cells S following acute radiation dose D is

$$S_i = 1 - (1 - e^{-D/D_i^0})^{n_i} \quad (18)$$

where $i = 1, 2$ (S_1 is the undamaged proportion of mitotic progenitors and S_2 is the undamaged proportion of MKs). D_i^0 is the dose at which there is a 37% probability that a specific target is not hit and n_i is the number of targets per cell. Thus, as D_i^0 increases the cell becomes less radiosensitive, and as n_i increases there is a larger shoulder in the dose response curve, meaning at lower doses each cell’s likelihood of becoming damaged is small.

Data from *in vitro* experiments on MK colony forming units (CFU-MKs) following radiation exposure was used to estimate mitotic cell damage *in vivo*. Here we assume that CFU-MK radiosensitivity represents the radiosensitivity of all mitotic progenitors. In humans cells, the D_1^0 and n_1 values based on CFU-MK experiments when stimulated with only TPO were 0.79 Gy and 1, respectively (Kashiwakura et al., 2000). In rhesus, due to a lack of experimental data we assume n_1 is equal to the value in humans. Using a study on cynomolgus monkeys, D_1^0 was determined to equal 1.18 Gy in the rhesus model (Hrodin et al., 2007) (it was assumed that cynomolgus and rhesus monkey cells have similar radiosensitivities). Besides *in vitro* versus *in vivo*, one source of error with these assumptions is that more attenuation of the radiation is likely to occur in *in vivo* situations before the radiation hits the mitotic progenitors in the bone marrow.

In humans, at low radiation doses there is a significant delay in platelet decline relative to the exposure, which does not happen at doses greater than approximately 5 Gy (Hempelmann et al., 1952; Andrews et al., 1961; Bond

et al., 1965; Jammet et al., 1959; Yarmonenko, 1988; Baranov et al., 1994; Miller et al., 1958). This suggests MKs are becoming damaged only at high radiation doses which is in agreement with other studies showing MKs are more radioresistant than other bone marrow cells (Heylmann et al., 2014). Thus, we set n_2 to a value greater than 1 to simulate the lack of damage at low radiation doses while D_2^0 was optimized. Both n_2 and D_2^0 were not simultaneously included in the optimization because there was a high collinearity between these two parameters. Multiple combinations of n_2 and D_2^0 resulted in the same model likelihood. The number of hits required to kill a MK was set to 4 ($n_2 = 4$) in both the human and rhesus models after incrementally testing integers less than 4. It was determined this was adequate for capturing the early dose response.

2.2. Data Collection

Data for optimization and subsequent validation of the model were obtained from experimental animal studies and human case studies. Data for the rhesus optimizations was obtained from well-controlled studies performed in rhesus macaques exposed to various levels of radiation (Basile et al., 2012; Gluzman-Poltorak et al., 2014a,b; Authier et al., 2013; Neumedicines, Inc.). Data for the human optimizations was obtained from Hempelmann et al. (1952); Andrews et al. (1961); Bond et al. (1965); Jammet et al. (1959); Yarmonenko (1988); Baranov et al. (1994); Miller et al. (1958). Tables B4 and B5 provide a summary of the radiation data used in optimizing the rhesus and human model, respectively. Information on the reference, radiation source, dose, and baseline control values is given for all optimization data. For human case studies, dose information was often presented in the literature as a range. In these cases, the midpoint of the dose range was used for optimization and subsequent comparison.

All the data were normalized by baseline control values. If multiple pre-radiation baseline values were obtained, the average of the baseline values was used. Each individual’s observational dataset was normalized by the baseline value specific to that individual prior to optimization. In some cases, pre-radiation values for human subjects were not available. When this occurred, the mean of up to four data points collected within 3 days of radiation exposure was used as the baseline. The assumption with this calculation is that the platelet values do not change significantly within the first three days of radiation exposure. Of the 12 subjects whose baseline values were calculated using this method, 9 values are within the normal range observed in humans of $140 - 440 \cdot 10^3 \mu L^{-1}$ (Valentin, 2002), one of the values is larger than this range, and two of the values are lower. If no data was collected within three days of exposure, the baseline value was set equal to the mean platelet concentration observed in humans ($250 \cdot 10^3 \mu L^{-1}$; Valentin (2002)).

Data from 254 rhesus macaques with doses ranging from 4 to 12.1 Gy were included in the optimization of the

rhesus model while 17 human case studies with doses ranging from 0.12 to 12.5 Gy were included in the optimization of the human thrombopoiesis model. Human optimization data were carefully selected in order to represent a range of doses (0.12-12.5 Gy) and minimize the uncertainty and confounding factors affecting the data. Thus, studies included in the optimization had the most accurate dose estimates, minimal treatment, and relatively uniform and acute gamma exposures. Radiotherapy studies involving cancer patients where the cancer was not related to hematopoiesis were also given priority because many subjects from these studies had baseline platelet count recordings.

2.3. Parameter Optimization and Confidence Interval Calculations

To optimize parameters, quantify parameter uncertainty, and assess model identifiability we used nonlinear least squares curve fitting and Markov Chain Monte Carlo sampling. All ordinary differential equation (ODE) simulations, optimization procedures, and parameter confidence interval calculations were performed using R v3.0.0 (R Core Team, 2013).

First, to ensure equal weighting of residuals from different data sets, data values were normalized by scaling each value by baseline control values. An optimized parameter set p_{LM} was then obtained using the Levenberg-Marquardt algorithm (Mor, 1978) implemented in the modCost and modFit tools from the FME package (Soetaert and Petzoldt, 2010). As part of this process, solution curves for Equations 1, 10–13, 16–17 were calculated using the ode function from the deSolve package (Soetaert et al., 2010).

Next, using the parameter set p_{LM} to initialize a Markov Chain, the Markov Chain Monte Carlo (MCMC) method with the adaptive Metropolis algorithm was used (Laine, 2008; Haario et al., 2001) to estimate 95% confidence intervals for parameters. This algorithm was performed in R using modMCMC, a function of the FME library. Finally, to determine whether the models were identifiable the collinearity value was determined using the collin function from the FME package in R (Brun et al., 2001).

In the material that follows, ranges given for optimized parameters represent 95% confidence interval obtained from this MCMC analysis.

3. Results and Discussion

3.1. Mathematical model of thrombopoiesis reproduces observed trends in platelet dynamics following acute radiation exposure in rhesus and humans

The rhesus and human thrombopoiesis models were optimized using platelet dynamic data from rhesus and humans following radiation exposure. The finalized parameter values for the model are shown in Table 2. Both the rhesus and human thrombopoiesis models accurately

capture dose-dependent trends observed following acute radiation exposure. Figure 3 shows the thrombopoiesis model simulations at increasing radiation dose levels for both rhesus and humans and compares simulations to select experimental and observational optimization data. All other comparisons between model simulations and optimization data are given in Figure B1 for the rhesus model and in a publicly available technical report for the human model (Wentz et al., 2014b). The purpose of these comparisons is to verify that trends observed in the data are reflected by the models. To further assess the fit of the model, a plot of the model predictions compared with the observed data used in the optimization is given for both rhesus and humans (Figure 4). Figure 3 shows that at low acute radiation doses, there is a plateau phase prior to a decrease in platelet count. The duration of this phase represents the time needed for MK maturation. In rhesus this plateau phase is shorter suggesting a faster MK maturation time in rhesus compared with humans. This is also reflected in the optimized value for δ_0 which leads to an expected MK maturation time of 3.8 (3.7-4.0) days in rhesus and 16.7 (14-20) days in humans. This predicted value for the human MK maturation time is somewhat larger than the values given by other studies and mathematical models which range from 4 to 10 days (Smirnova, 2010; Bond et al., 1965; Scholz et al., 2010); however, a larger expected MK maturation time was necessary to capture the duration of the plateau in platelet counts following radiation exposure which in some studies lasted more than 20 days. Therefore, it is possible that in our model we effectively include in the MK compartment some MK progenitors which show similar radiosensitivity patterns as MKs (i.e. some precursors are also not damaged at low radiation doses). Smirnova used the notion of an abortive rise rather than an MK maturation delay to simulate the plateau (Smirnova, 2010). In this phenomenon, a proportion of damaged cells reproduce and behave normally for a certain time period prior to apoptosis (Bond et al., 1965). However, in this version of the model an immediate decrease in platelet counts is still observed at low doses which is not supported by experimental data. Thus, we decided that adding a MK maturation delay was more supported by biological data. In reality, both these processes may be interplaying and causing the observed response.

As the radiation dose increases, the plateau phase diminishes in the human model but remains in the rhesus model. This behavior is in agreement with platelet dynamic data. The radiation threshold for induction of MK damage is lower in humans than in rhesus, leading to the observed differences between the model predictions. The increased sensitivity is reflected by the optimized value of D_2^0 which is 2.77 (2.59-2.93) Gy in the human model and approaches the upper bound of 50 Gy in the rhesus model, implying that rhesus MKs are radioresistant. MK radiosensitivity was engineered into the model as the hypothesized cause for the elimination of the plateau phase at higher doses. The inclusion of MK radiosensitivity is

Table 2: Parameter values for thrombopoiesis model

Parameter	Description	Rhesus		Human	
		Value	Source	Value	Source
α	Maximum rate of mitotic progenitor cell repopulation	$2.0d^{-1}$	$\rightarrow$	$2.0d^{-1}$	Assumed
γ	Rate of mitotic progenitor cell maturation	$0.06d^{-1}$	Optimized	$0.26d^{-1}$	Optimized
δ_0	Rate of MK maturation when system is at equilibrium	$0.26d^{-1}$	Optimized	$0.06d^{-1}$	Optimized
ψ	Rate of platelet decay	$0.18d^{-1}$	Harker et al. (1997)	$0.11d^{-1}$	Mezzano et al. (1982); Finch et al. (1977)
n	Number of MK subcompartments	10	Assumed	10	Assumed
m	Number of platelet subcompartments	9	$\rightarrow$	9	Dowling et al. (2010); Scholz et al. (2010)
θ_2	Decay rate of mediator due to x_2 cells relative to decay rate due to x_1 cells	0.03	Optimized	0.006	Optimized
θ_3	Decay rate of mediator due to x_3 cells relative to decay rate due to x_1 cells	$0.03 \cdot \theta_2$	$\rightarrow$	$0.03 \cdot \theta_2$	Kuwaki et al. (1998); Broudy et al. (1997)
τ_{max}	Maximum MK maturation time	$5/(\delta_0 \cdot 4)$	Assumed	$5/(\delta_0 \cdot 4)$	Assumed
τ_{min}	Minimum MK maturation time	$3/(\delta_0 \cdot 4)$	Assumed	$3/(\delta_0 \cdot 4)$	Assumed
λ	Strength of x_3 feedback on immature MK maturation	7.32	Optimized	3.5	Optimized
σ	Number of platelets per MK	3000	$\rightarrow$	3000	Smirnova (2010); Deutsch and Tomer (2013)
D_1^0	Determines fraction of x_1 targets that are hit by radiation at dose D	1.18 Gy	Hrodin et al. (2007)	0.79 Gy	Kashiwakura et al. (2000)
n_1	Number of targets per x_1 cell	1	$\rightarrow$	1	Kashiwakura et al. (2000)
D_2^0	Determines fraction of x_2 targets that are hit by radiation at dose D	49.20 Gy	Optimized	2.77 Gy	Optimized
n_2	Number of targets per x_2 cell	4	Assumed	4	Assumed
μ	Rate of damaged cell death	$1.0d^{-1}$	$\rightarrow$	$1.0d^{-1}$	Smirnova (2010)

$\rightarrow$ assumed to equal value in human model

supported by experimental *in vitro* data in human cells (Monzen et al., 2009). However, further experiments are warranted to both validate this proposed mechanism and explain the differences in MK radiosensitivity across species.

Our model successfully reproduces the platelet count nadirs, which occur within 10 to 20 days following radiation exposure for the rhesus model and 20 to 30 days following radiation exposure for the human model. The difference in time of nadir is due to species-dependent MK maturation times and platelet lifespans. The longer platelet lifespan and MK maturation time in humans leads to a later nadir than that seen in rhesus.

The recovery characteristics of the model are affected by a combination of parameters. In the human model, platelet recovery is characterized by a distinct rebounding during which the platelet concentration increases above normal pre-radiation levels which is in agreement with data from exposed individuals. This rebound is not observed in the rhesus model. This is partially due to the larger value of γ in the human model ($0.26d^{-1}$) compared with the rhesus model ($0.06d^{-1}$). When γ was reduced in the human model, the rebound was not observed. The accelerated recovery in the human model compared with the rhesus model could also be the result of treatment confounding the results.

It is clear from these comparisons that while both models perform very well, the rhesus model fits experimental results better than the human model. This is to be ex-

pected since the animal data is collected under more controlled and precise experimental conditions. Additional sources of uncertainty and variability in human observational data that do not exist in the rhesus experimental data include uncertainty in the estimated dose, other dose types (neutron and internal contamination), protracted effects (i.e. lower dose rate over longer durations), non-uniformity of the exposure, treatment, and inter-individual variability. Some subjects with a higher estimated radiation dose have a less intense response than subjects with lower radiation doses. For example, the 2.6 Gy case study from Goans (2012) had a lower normalized thrombocyte nadir when compared with the 3.51 Gy Vinca case study B (Jammet et al., 1959; Pei, 2012). This inconsistency could arise from individual variability in the response to radiation or result from uncertainty in the reported dose. Such discrepancies in the case study data help explain why some of the model predictions vary significantly from observational data.

In some case studies included in the optimizations, treatment details were not provided (Goans, 2012; Yarmenko, 1988). When comparing simulations to data from subjects that had known treatment, earlier recovery than that predicted by the model was observed (Math et al., 1964). Thus, treatment may have large effects on the thrombopoietic system, and uncertainties in treatment could be affecting model comparisons as well as resulting optimized parameter values. Partial body exposures also re-

Figure 3: **Thrombopoiesis model matches observed trends.** Top Left: Rhesus thrombopoiesis simulations at increasing dose levels. Top Right: Rhesus data following 7 Gy irradiation (data obtained from Gluzman-Poltorak et al. (2014a) and Neumedicines, Inc.) overlaid on thrombopoiesis simulations (includes range based on sampling of parameter values from MCMC analysis). Bottom Left: Human thrombopoiesis simulations at increasing dose levels. Bottom Right: Human case study data (Mettler et al., 2001; Yarmonenko, 1988) overlaid on thrombopoiesis simulations.

sult in deviations from the simulation predictions (Subject K from Yarmonenko (1988)). For both treatment and

partial body exposure, more analyses would need to be conducted to determine if deviations from the model are

Figure 4: **Assessing the quality of the rhesus and human models by comparing observations used for optimization with model predictions.** Left Panel: Rhesus model/data (Basile et al., 2012; Gluzman-Poltorak et al., 2014a,b; Authier et al., 2013; Neumedicines, Inc.); Right Panel: Human model/data (Hempelmann et al., 1952; Andrews et al., 1961; Bond et al., 1965; Jammet et al., 1959; Yarmonenko, 1988; Baranov et al., 1994; Miller et al., 1958).

also in part due to other factors such as dose uncertainty, individual variability, and model structure error.

Given the inherent uncertainties and variability in available human radiation accident data, the degree of accuracy achieved by the presented model is quite remarkable.

3.2. Validation of thrombopoiesis model using platelet dynamic data and compartment concentrations

The thrombopoiesis models were validated using three independent techniques. First, model outputs were compared to platelet dynamic data from rhesus and human radiation exposures not used in the optimizations (Rhesus: Haigh and Paterson (1956); Farese et al. (1993); Burdelya et al. (2008); Gluzman-Poltorak et al. (2014b); Human: Hempelmann et al. (1952); Bond et al. (1965); Hirama et al. (2003); Stavem et al. (1985); Mettler et al. (2001); Mettler (2001)). Second, model output was compared to platelet dynamic data from thrombopheresis patients (Lasky et al., 1981; Weisbach et al., 1999; Sullivan et al., 1977). Third, the relative compartment sizes calculated using experimental data were compared to the relative compartment sizes calculated using model parameters.

Select results of the validation comparing model output with platelet dynamic data following irradiation not included in the optimization are shown in Figure 5. An observed verse predicted comparison for all the radiation validation data is shown in Figure 6. Similar to the optimization results, the models are able to accurately predict

the observed trends in platelet concentration following radiation exposure.

The thrombopheresis validation results are shown in Figure 7. In thrombopheresis a certain percentage of platelets is removed from the blood stream. We can initialize the value of x_3 in our model using this percentage, where we assume (1) an equal fraction of platelets is removed from each age dependent platelet sub-compartment and (2) the removal of platelets is instantaneous. In one study, thrombopheresis was performed twice. To simulate this, we initialized the value of x_3 according to the first thrombopheresis and manually altered x_3 at the time of the second thrombopheresis without changing the values of the other state variables. This validation helps to confirm that the kinetic rates of cell maturation and feedback are correct in the model. In four separate studies, two of which had mean data from multiple subjects, the model is able to accurately predict the platelet count recovery following platelet removal. These comparisons reassure us that the kinetic parameters obtained from the literature and through optimization are accurate.

To further validate the thrombopoiesis model, the relative compartment sizes under steady-state conditions are calculated using model parameters and compared to compartment sizes predicted using experimental data. For the calculation of the relative compartment sizes using parameter values see the Appendix A.2. To perform this comparison, the total number of platelets and MKs was determined as a function of kg body weight. Table 3 compares

Figure 5: **Thrombopoiesis model accurately predicts trends in data not used for optimization.** Left: Rhesus validation data following 7 Gy irradiation (Gluzman-Poltorak et al., 2014b). Right: Human case studies reserved for validation compared to thrombopoiesis model simulation at specified doses.

Figure 6: **Assessing the quality of the rhesus and human models by comparing observations used for validation with model predictions.** Left Panel: Rhesus model/data (Haigh and Paterson, 1956; Farese et al., 1993; Burdelya et al., 2008; Gluzman-Poltorak et al., 2014b); Right Panel: Human model/data (Hempelmann et al., 1952; Bond et al., 1965; Hiramata et al., 2003; Stavem et al., 1985; Mettler et al., 2001; Mettler, 2001).

Figure 7: **Thrombopoiesis model overlaid on thrombopheresis data.** Top left: Data from Lasky et al. (1981), the number above each data point specifies the number of subjects (mean $\pm$ SEM). Top right: Data from Weisbach et al. (1999), data points from 22 subjects (mean $\pm$ SD). Bottom left: Individual data from Sullivan et al. (1977). Bottom right: Individual data from Sullivan et al. (1977), subject underwent two platelet removal procedures.

the relative size of the platelet and MK compartments as determined with experimental predictions and model parameters. For the human model, the model prediction is

approximately equal to the experimental prediction. For rhesus, the model prediction of the ratio of platelets to MKs appears greater than the experimental prediction.

However, the errors on some of the variables are not available (see Table 3); therefore, the true range for the experimental prediction cannot be calculated. Furthermore, the value of platelets produced per MK, σ , is set to 3000; however, some sources suggest that this value can range from 1000 to 3000 (Deutsch and Tomer, 2013). Based on this range of uncertainty, the model prediction is in reasonable agreement with the experimental prediction.

3.3. Simulations are Consistent with METREPOL and UNSCEAR

Medical Treatment Protocols for Radiation Accident Victims as a Basis for a Computerised Guidance System (METREPOL) provides an assessment of radiation injury severity based upon the hematopoietic response in humans (Fliedner et al., 2001). This severity ranking system was developed by an international group of selected experts and is based on both experimental data and the analysis of data from radiation victims. There are four possible severity grades (H1: Mild damage; H2: Moderate damage; H3: Severe damage; H4: Fatal damage) which are not based on radiation dose but on the ensuing symptoms.

To verify that our human thrombopoiesis model is in agreement with the predicted hematopoietic responses from METREPOL, we developed overlays of our model on the METREPOL predictions for the H2 and H3 severity levels (Figure 8). For an accurate comparison, the thrombopoietic model output is shown for the normal range of blood cell counts as given in the METREPOL report (Fliedner et al., 2001). Thrombopoiesis simulations for 4 and 7 Gy correlate well with METREPOL H2 and H3 severity categories as shown in Figure 8. Overall, the model predictions match the trends given by METREPOL. The platelet recovery predicted by our model is slightly faster and leads to an overshoot not predicted in the METREPOL hematopoietic response; however, this overshoot is observed in several of the individual case studies examined in our work (See Figure 3).

In a second set of expert predictions, Annex G of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1988 report presents a schematic

picture of the average time course of blood cell counts deduced from accidental human exposures (UNSCEAR, 1988). Figure 9 shows a comparison of our human thrombopoiesis model output with this expert prediction. The UNSCEAR report presents the predicted blood cell responses at doses ranging from 0 to 20 Gy divided into four groups. Therefore, we plot our hematopoietic model outputs as a shaded region based on each dose range and overlay the response predicted by UNSCEAR. Although the model is not in exact agreement with the UNSCEAR predictions, the general trends are supported and the dose response matches fairly well. Our model predicts a slightly faster recovery than expert predictions.

3.4. Application of model: Prediction of treatment requirements

One example application of the model is to predict treatment requirements of a population following a nuclear event. The purpose of the human thrombopoiesis model is to capture the average platelet dynamics following radiation exposure. By running Monte Carlo simulations, we can predict the response distribution for a large population and, in turn, predict treatment requirements. As a simplified example, we assume the one source of variability in the population is the initial platelet concentration and run a Monte Carlo simulation to simulate the platelet response in 400 individuals following a set dose of 6 Gy (Figure 10). Using this response distribution, we can predict the number of transfusions required only once per individual as a function of time following the exposure where we assume transfusions are required when platelet levels decline below $20 \cdot 10^3$ cells per μL .

Although this is clearly a simplified example, it provides the framework for how a model of thrombopoiesis following radiation exposure can be used to assist in disaster preparedness. Other endpoints, such as survivability can also be examined. The depth of the platelet nadir and the rate of decline have been correlated with the probability of survival (Housinger et al., 1993; Akca et al., 2002; Wang et al., 2010). Thus, similar approaches could be used in which distributions for other features (i.e., nadir, initial

Table 3: Comparison of model and experimental prediction of relative size of platelet and MK compartment.

	Rhesus	Human
BMC ($10^{10}/kg$)	2.4 (Pegg, 1966)	2 (Valentin, 2002)
MK (% of BMC)	0.03 (Usacheva and Raeva, 1963)	0.04 ± 0.01 (Levine, 1980)
Plts in Blood ($10^3/\mu L$)	373.66 ± 92.62 (Usacheva and Raeva, 1963)	250 (Valentin, 2002)
Blood Volume (mL/kg)	54 (Drexel University College of Medicine, 2011)	67.5 ± 3.5 (Starr and Taggart, 1989; World Book Inc. Staff, 1998)
Predictions (Plts/MK)		
Experimental*	2802 ± 695	2109 ± 539
Model**	4333	1636

BMC: Bone Marrow Cells

Plts: Platelets

*Experimental Prediction=Platelets in Blood $\cdot$ Blood Volume/(BM Cells $\cdot$ MK/100)

**For model prediction calculation see Appendix A.2.

Figure 8: Comparison of thrombopoiesis model output to METREPOL predictions (Fliedner et al., 2001).

Figure 9: Comparison of thrombopoiesis model output to expert predictions. Model output shown as shaded region for each dose range and expert predictions from UNSCEAR report shown as solid/dashed lines (UNSCEAR, 1988) .

rate of decline, duration of cytopenia) are analyzed as a function of radiation dose using Monte Carlo simulations. Future work would involve correlating model outputs with survival.

4. Conclusion

We have developed a model of thrombopoiesis following acute radiation exposure in rhesus macaques and humans that provides realistic predictions on platelet dynamics, capturing specific dose-dependent trends. While large variances exist in human case study data, the goal of the model is to capture the average response within a population. This model can eventually be used to assist in disaster preparedness. Furthermore, the mechanistic models allow us to extrapolate experimental observations in rhesus to predict effects in humans.

Throughout model development, several assumptions were made regarding parameter values due to a lack of experimental data. Future work would involve replacing these assumed values with empirically derived values as more data becomes available. This would enhance the biological meaning of the parameter values, and, in turn, allow more accurate predictions of how perturbations to biological kinetic rates would effect the system.

Figure 10: **Estimation of population treatment requirements following 6 Gy radiation exposure.** Left: 400 simulations for which each simulation used a baseline platelet count randomly sampled from a log normal distribution describing platelet concentration in healthy humans based on a 95% confidence interval of $140\text{--}250 \text{ cells } 10^3 \mu\text{L}^{-1}$ (Valentin, 2002). Right: Histogram of transfusions needed as a function of time, assuming one transfusion per patient for platelet counts $\leq 20 \text{ cells } 10^3 \mu\text{L}^{-1}$.

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Appendix A

A.1 Equations for mathematical model

We assume that the thrombopoietic system is at a steady-state before radiation exposure: for $t < 0$, $x_1^{ud}(t) = \bar{x}_1^{ud}$, $x_2^{ud}(t) = \bar{x}_2^{ud}$, and $x_3(t) = \bar{x}_3$, where $\bar{x}_1^{ud}$, $\bar{x}_2^{ud}$, and $\bar{x}_3$ are the steady-state cell concentrations in the X_1 , X_2 , and X_3 compartments, respectively. Following acute exposure, we assume that radiosensitive cells in the X_1 and X_2 compartments instantaneously transition at time $t = 0$ into their respective “damaged” compartments:

$$x_1^{ud}(0) = \bar{x}_1^{ud} \left(1 - (1 - e^{-D/D_1^0})^{n_1} \right) \quad (\text{A.1})$$

$$x_{2I,i}^{ud}(0) = \frac{\bar{x}_2^{ud}}{n} \left(1 - (1 - e^{-D/D_2^0})^{n_2} \right) \quad (i = 1, 2, \dots, n/2) \quad (\text{A.2})$$

$$x_{2M,i}^{ud}(0) = \frac{\bar{x}_2^{ud}}{n} \left(1 - (1 - e^{-D/D_2^0})^{n_2} \right) \quad (i = 1, 2, \dots, n/2) \quad (\text{A.3})$$

$$x_{3,i}(0) = \frac{\bar{x}_3}{m} \quad (i = 1, 2, \dots, m) \quad (\text{A.4})$$

$$x_1^d(0) = \bar{x}_1^{ud} \left(1 - e^{-D/D_1^0} \right)^{n_1} \quad (\text{A.5})$$

$$x_2^d(0) = \bar{x}_2^{ud} \left(1 - e^{-D/D_2^0} \right)^{n_2} \quad (\text{A.6})$$

where D is the radiation dose. The cell concentration values given in Eq. A.1–A.6 are then used as initial conditions for the following differential equation that describes the dynamics of mitotic progenitor repopulation, megakaryocyte maturation, and platelet decay (where we have used dot notation to represent time derivatives):

$$\dot{x}_1^{ud} = Bx_1^{ud} - \gamma x_1^{ud} \quad (\text{A.7})$$

$$\dot{x}_{2I,1}^{ud} = \gamma x_1^{ud} - n\delta x_{2I,1}^{ud} \quad (\text{A.8})$$

$$\dot{x}_{2I,i}^{ud} = n\delta x_{2I,i-1}^{ud} - n\delta x_{2I,i}^{ud} \quad (i = 2, 3, \dots, n/2) \quad (\text{A.9})$$

$$\dot{x}_{2M,1}^{ud} = n\delta x_{2I,n/2}^{ud} - n\delta_0 x_{2M,1}^{ud} \quad (\text{A.10})$$

$$\dot{x}_{2M,i}^{ud} = n\delta_0 x_{2M,i-1}^{ud} - n\delta_0 x_{2M,i}^{ud} \quad (i = 2, 3, \dots, n/2) \quad (\text{A.11})$$

$$\dot{x}_{3,1} = \sigma n\delta_0 x_{2M,n/2}^{ud} - m\psi x_{3,1} \quad (\text{A.12})$$

$$\dot{x}_{3,i} = m\psi x_{3,i-1} - m\psi x_{3,i} \quad (i = 2, 3, \dots, m) \quad (\text{A.13})$$

$$\dot{x}_i^d = -\mu x_i^d \quad (i = 1, 2) \quad (\text{A.14})$$

where

$$B = \frac{\alpha}{1 + \beta (\theta_1(x_1^{ud} + x_1^d) + \theta_2(x_2^{ud} + x_2^d) + \theta_3 x_3)} \quad (\text{A.15})$$

$$x_2^{ud} = \sum_{i=1}^{n/2} x_{2I,i}^{ud} + x_{2M,i}^{ud} \quad (\text{A.16})$$

$$x_3 = \sum_{i=1}^m x_{3,i} \quad (\text{A.17})$$

$$\delta = \frac{1}{2\tau_{2I}} \quad (\text{A.18})$$

$$\tau_{2I} = \left(\frac{1}{\tau_{2I}^{max}} + \left(\frac{1}{\tau_{2I}^{min}} - \frac{1}{\tau_{2I}^{max}} \right) \left(\frac{\frac{1}{\tau_0/2} - \frac{1}{\tau_{2I}^{max}}}{\frac{1}{\tau_{2I}^{min}} - \frac{1}{\tau_{2I}^{max}}} \right)^{\left(\frac{x_3}{\bar{x}_3} \right)^\lambda} \right)^{-1} \quad (\text{A.19})$$

where $\tau_0 = 1/\delta_0$, $\tau_{2I}^{min} = \tau_{min} - \tau_0/2$, and $\tau_{2I}^{max} = \tau_{max} - \tau_0/2$. Note that if $\tau_{max} = \tau_{min} = \tau_0$, the subcompartment model given by Eq. A.8–A.13, A.16, A.17 can be viewed as the result of applying the Linear Chain Trick (MacDonald, 1978) to the distributed delay model

$$\dot{x}_{2I}^{ud} = \gamma x_1^{ud} - F \quad (\text{A.20})$$

$$\dot{x}_{2M}^{ud} = F - J \quad (\text{A.21})$$

$$\dot{x}_3 = \sigma J - K \quad (\text{A.22})$$

$$x_2^{ud} = x_{2I}^{ud} + x_{2M}^{ud} \quad (\text{A.23})$$

where

$$F(t) = \int_{-\infty}^t \gamma x_1^{ud}(\tau) g(t - \tau; n/2, n\delta_0) d\tau \quad (\text{A.24})$$

$$J(t) = \int_{-\infty}^t F(\tau) g(t - \tau; n/2, n\delta_0) d\tau \quad (\text{A.25})$$

$$K(t) = \int_{-\infty}^t \sigma J(\tau) g(t - \tau; m, m\psi) d\tau \quad (\text{A.26})$$

and $g(x; a, b)$ is the density of the gamma distribution with expectation a/b and variance $\frac{a}{b^2}$. However, if $\tau_{max} \neq \tau_0$ or $\tau_{min} \neq \tau_0$ and the system is not in a steady-state, then δ is time dependent, in which case we cannot use the Linear Chain Trick to derive the subcompartment model given above. Nevertheless, Eq. A.20–A.22 provide motivation for Eq. A.8–A.13.

A.2 Model predictions for relative compartment sizes

When the system is at healthy, steady-state conditions, $x_1^{ud} = \bar{x}_1^{ud}$, $x_{2I,i}^{ud} = \bar{x}_{2I,i}^{ud}$, $i = 1, 2, \dots, n/2$, $x_{2M,i}^{ud} = \bar{x}_{2M,i}^{ud}$, $i = 1, 2, \dots, n/2$, $x_{3,i} = \bar{x}_{3,i}$, $i = 1, 2, \dots, m$, and Eq. 8-13 of Appendix A.1 imply

$$0 = \gamma \bar{x}_1^{ud} - n\delta \bar{x}_{2I,1}^{ud}$$

$$0 = n\delta \bar{x}_{2I,i-1}^{ud} - n\delta \bar{x}_{2I,i}^{ud} \quad (i = 2, 3, \dots, n/2)$$

$$0 = n\delta \bar{x}_{2I,n/2}^{ud} - n\delta_0 \bar{x}_{2M,1}^{ud}$$

$$0 = n\delta_0 \bar{x}_{2M,i-1}^{ud} - n\delta_0 \bar{x}_{2M,i}^{ud} \quad (i = 2, 3, \dots, n/2)$$

$$0 = \sigma n\delta_0 \bar{x}_{2M,n/2}^{ud} - m\psi \bar{x}_{3,1}$$

$$0 = m\psi \bar{x}_{3,i-1} - m\psi \bar{x}_{3,i} \quad (i = 2, 3, \dots, m)$$

Moreover, under steady-state conditions $\delta = \delta_0$, so we must have

$$\bar{x}_{2I,1}^{ud} = \bar{x}_{2I,2}^{ud} = \dots = \bar{x}_{2I,n/2}^{ud} = \bar{x}_{2M,1}^{ud} = \bar{x}_{2M,2}^{ud} = \dots = \bar{x}_{2M,n/2}^{ud}$$

$$\bar{x}_{3,1} = \bar{x}_{3,2} = \dots = \bar{x}_{3,m}$$

and

$$\frac{\bar{x}_{2I,1}^{ud}}{\bar{x}_1^{ud}} = \frac{\gamma}{n\delta_0}$$

$$\frac{\bar{x}_{3,1}}{\bar{x}_{2M,n/2}^{ud}} = \frac{\sigma n\delta_0}{m\psi}$$

Equations A.16 and A.17 thus imply that, under steady-state conditions, $\bar{x}_2^{ud} = n\bar{x}_{2I,1}^{ud} = n\bar{x}_{2M,n/2}^{ud}$ and $\bar{x}_3 = m\bar{x}_{3,1}$, so under steady-state conditions the relative compartment sizes in humans are

$$\frac{\bar{x}_2^{ud}}{\bar{x}_1^{ud}} = \frac{\gamma}{\delta_0} = \frac{0.26}{0.06} = 4.3$$

$$\frac{\bar{x}_3}{\bar{x}_2^{ud}} = \frac{\sigma \delta_0}{\psi} = \frac{3000 \cdot 0.06}{0.11} = 1636$$

$$\frac{\bar{x}_3}{\bar{x}_1^{ud}} = \frac{\sigma \gamma}{\psi} = \frac{3000 \cdot 0.26}{0.11} = 7091$$

and the relative compartment sizes in rhesus are

$$\frac{\bar{x}_2^{ud}}{\bar{x}_1^{ud}} = \frac{\gamma}{\delta_0} = \frac{0.06}{0.26} = 0.23$$

$$\frac{\bar{x}_3}{\bar{x}_2^{ud}} = \frac{\sigma \delta_0}{\psi} = \frac{3000 \cdot 0.26}{0.18} = 4333$$

$$\frac{\bar{x}_3}{\bar{x}_1^{ud}} = \frac{\sigma \gamma}{\psi} = \frac{3000 \cdot 0.06}{0.18} = 1000$$

Appendix B

B.1 Optimization Data and Model Predictions

Table B4 and B5 provide a summary of the data used to optimize the thrombopoiesis model in rhesus and humans, respectively. Figure B1 provides comparisons of the rhesus optimization data with the model predictions (a comparison of the model with the 7 Gy optimization data is shown in Figure 3). Comparisons of the human optimization data with model predictions is given in a publicly available technical report (Wentz et al., 2014b).

Table B4: Optimization data summary for rhesus thrombopoiesis model

Study/Ref.	Dose-rate (cGy/min)	Dose (Gy)	Number	Baseline ($10^3 \mu L^{-1}$)
Data obtained from Neumedicines	60	5.7	15	456.34
Data obtained from Neumedicines	60	6.0	12	454.63
Data obtained from Neumedicines	60	6.3	15	496.87
Data obtained from Neumedicines	60	6.6	15	509.90
Basile et al. (2012)	60	6.7	8	456.00
Data obtained from Neumedicines	60	6.9	16	474.85
Gluzman-Poltorak et al. (2014a); Data obtained from Neumedicines	60	7.0	32	416.92
Data obtained from Neumedicines	60	7.2	11	467.23
Data obtained from Neumedicine	60	7.4	10	431.50
Authier et al. (2013)	43.6-57.9	4.0	30*	411.73
Authier et al. (2013)	43.6-57.9	6.0	30*	429.16
Authier et al. (2013)	43.6-57.9	6.34	30*	418.06
Authier et al. (2013)	94.8	12.1	30*	396.81

All rhesus monkeys were irradiated using a Cobalt-60 source.

*The number of animals per group is assumed to be 30 based on a total of 120 animals for the entire study as reported in the reference.

Table B5: Optimization data summary for human thrombopoiesis model

Incident/Subject	Ref.	Dose (Gy)	Baseline ($10^3 \mu L^{-1}$)
Los Alamos 1945-2	Hempelmann et al. (1952)	0.12	819.26 ^a
UT CARL 1971	Andrews et al. (1961)*	2.6	350.63 ^a
Argonne 1952-I	Bond et al. (1965)	1.5	111.23 ^a
Y-12 1958-B	Andrews et al. (1961)*	2.97	161.25 ^a
Y-12 1958-C	Andrews et al. (1961)*	3.73	181.25 ^a
Y-12 1958-A	Bond et al. (1965)	4.02	289.56 ^a
Vinca 1958-B	Jammet et al. (1959)	3.51	210.31 ^a
Vinca 1958-H	Jammet et al. (1959)	4.37	233.73 ^a
Vinca 1958-M	Jammet et al. (1959)	5.74	219.88 ^a
Vinca 1958-G	Jammet et al. (1959)	5.35	250.00 ^b
Vinca 1958-D	Jammet et al. (1959)	5.40	250.00 ^b
Vinca 1958-V	Jammet et al. (1959)	6.11	221.29 ^a
Yarmonenko 1988-Z	Yarmonenko (1988)	9.8	140.21 ^a
Nesvizh 1991	Baranov et al. (1994)	12.5	106.75 ^a
Cancer patients 1958-mean of 18 ^c	Miller et al. (1958)	1.0	197.25 ^d
Cancer patients 1958-mean of 12 ^c	Miller et al. (1958)	1.5	234.25 ^d
Cancer patients 1958-mean of 30 ^c	Miller et al. (1958)	2.0	155.75 ^d

Radiation exposure studies used for optimization of the human thrombopoiesis model, including the reference for the data (Ref.) the approximate radiation dose, and the estimated baseline peripheral thrombocyte concentration.

^aMean of up to four data points collected within 3 days of radiation exposure

^bMean platelet concentration observed in humans Valentin (2002)

^cSubjects had non hematopoietic cancer and there was no mention of any pre-treatment in the source documentation.

^dMean of pre-radiation data points

*Data provided by Ron Goans

Figure B1: Thrombopoiesis model overlaid on rhesus optimization data not shown in paper. Optimized simulation (red dashed line) shown along with range (black lines) based on sampling of parameter values from MCMC analysis.

Figure B1: (cont.) Thrombopoiesis model overlaid on rhesus optimization data not shown in paper. Optimized simulation (red dashed line) shown along with range (black lines) based on sampling of parameter values from MCMC analysis.