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A biomathematical model of human thrombopoiesis under chemotherapy

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Running head: Human Thrombopoiesis Model

Abstract

Intensification of cytotoxic chemotherapy enhances the outcome of several malignancies but is limited by haematotoxicity. While neutropenia and anaemia can be treated with supportive growth factor applications, thrombocytopenia remains a dose-limiting side effect due to the lack of clinically approved pharmaceutical growth factors. Hence, it is necessary to assess the degree of thrombocytopenia of newly designed intensified regimens in the planning phase of a clinical trial.

We present a simple ordinary differential equations model of thrombopoiesis under chemotherapy which maps the dynamics of stem cells, CFU-Mk, megakaryocytes and platelets in spleen and circulation. Major regulatory cytokine of thrombopoiesis is thrombopoietin (TPO) whose production and consumption is explicitly modelled. TPO acts by increasing the number of mitoses of CFU-Mk and increasing the mass and maturation of megakaryocytes. Chemotherapy is modelled by a drug-dose and cell-stage specific acute cell loss.

Most of the cell kinetic parameters of the model were taken from literature. Parameters regarding TPO regulation and chemotherapy toxicity were estimated by fitting the predictions of the model to time series data of platelets received from large clinical data sets of patients under seven different chemotherapies. We obtained a good agreement between model and data for all scenarios. Parameter estimates were biologically plausible throughout. For validation, the model also explains data of TPO and platelet dynamics after thrombopheresis taken from literature.

We used the model to make clinically relevant predictions. Regarding thrombocytopenia we estimated that the CHOP regimen for the treatment of high-grade non-Hodgkins lymphoma can be time-intensified to a cycle duration of 12 days while the time-intensified CHOEP regimen would result in severe cumulative toxicity. We conclude that our proposed model proved validity for both, different chemotherapeutic regimens and thrombopheresis as well. It is useful to assess the thrombocytopenic risk in the planning phase of a clinical trial.

Keywords: Thrombopheresis, Thrombopoietin, TPO

1. Introduction and motivation

Multiagent, multicycle polychemotherapy is a major therapy option for the treatment of several malignancies. Therapy intensification by either escalation of total dose, reduction of time between cycles of therapy or introduction of new cytotoxic agents proved to enhance the outcome of the therapy in several clinical studies (Hodgkin's disease (Diehl *et al.* (2003)), aggressive non-Hodgkin lymphoma (Blayney *et al.* (2003); Pfreundschuh *et al.* (2004a,b); Shipp *et al.* (1995)), breast cancer (Hortobagyi (2001); Minckwitz *et al.* (2005))). However, these therapy intensifications are limited by the haematotoxic side effects induced by the general cytotoxicity of the applied drugs. Although granulotoxicity is considered to be the most critical haematotoxic side effect of chemotherapy, the application of recombinant granulocyte colony-stimulating factor provides an option for an effective supportive treatment of this adverse event (Blayney *et al.* (2005); Crawford (2002); Dale (2003); Kuderer *et al.* (2006); Schwenkglenks *et al.* (2006); Siena *et al.* (2003)).

On the other hand, the recombinant thrombopoietic growth factors Peg-rHuMGDF (pegylated recombinant human megakaryocyte growth and development factor) and rhTPO (recombinant human thrombopoietin) were not carried through intensive practical use in the field of chemotherapy because of observed severe side effects of Peg-rHuMGDF (Kuter & Begley (2002); Schuster *et al.* (2002)). Application of platelet transfusions is also limited because of the risk of infections, reactions of the immune system and other transfusion related side effects. Moreover, the need of platelet transfusion is permanently rising in other fields of medicine such as surgery (Vadhan-Raj *et al.* (1997)). Hence, severe reduction in the number of platelets (thrombocytopenia) remains a major limiting factor of chemotherapy intensifications (Diehl *et al.* (2003); Pfreundschuh *et al.* (2004a); Kuter & Begley (2002); Wunderlich *et al.* (2003)).

In consequence, it is necessary to assess the degree of haematotoxicity of newly designed chemotherapeutic regimens in the forefield of clinical trials. Recently, we established a model of human granulopoiesis under chemotherapy with G-CSF support which allows the quantification of chemotherapeutic agent specific toxicity to bone marrow cell stages (Scholz *et al.* (2005); Engel *et al.* (2004)). This model proved to make precise predictions of the time course of granulocytes under various chemotherapy situations. Therefore, it can be used to optimise therapy with respect to granulotoxicity and can support the planning of clinical trials (Scholz *et al.* (2006)). In the present paper, we aim to construct a similar human model of thrombopoiesis under chemotherapy in order to predict thrombocytopenia of newly developed chemotherapeutic regimens too.

Our approach is by far not the first attempt to model (human) thrombopoiesis. A large variety of mathematical models has been proposed in the literature comprising models for different species (Wichmann (1984); Skomorovski *et al.* (2003)), thrombopoiesis under radiation exposure (Selivanov *et al.* (1986)), high-dose chemotherapy (Obeyesekere *et al.* (2004)), growth factor applications (Harker *et al.* (2000); Jin & Krzyzanski (2004); Skomorovski *et al.* (2003)) or models of certain haematologic disorders (Santillan *et al.* (2000)). So far, none of the existing models were built to explain the time course of platelets under conventional chemotherapy. The purpose of our modelling approach is to construct a model which can directly be compared with clinical data of humans under conventional chemotherapy. We have access to a unique data set of close-meshed platelet time series under different chemotherapy regimens which is essential for this purpose.

2. Model basics

2.1. Modelling approach

It is our major intention to construct a comprehensive, physiological and quantitative model of human thrombopoiesis under chemotherapy. The model should map major identified regulatory mechanisms of thrombopoiesis to provide a deeper insight into this complex biological process. Furthermore, parameters of the model should have a measurable biological equivalent as far as possible. To address these objectives, we construct an ordinary differential equations compartment model on the basis of a set of physiological assumptions. The content of the compartments describe the time dependent relative amount of corresponding cells, cytokines and chemotherapeutic toxicity. We aim to keep the model simple to avoid speculative assumptions or parameters without supportive data.

The model is based on a model of murine thrombopoiesis developed by our group (Kliem (2001)). We aim to translate the major regulatory mechanisms from the murine to the human model by keeping corresponding model equations constant but changing physiological parameters different for mice and humans. Furthermore, we introduce the spleen into the model which has a major function with respect to age-dependent platelet redistribution and sequestration in humans (Freedman & Karpatkin (1975); Gehrman *et al.* (1972); Karpatkin (1972); Wichmann (1984)). The new model also comprises a stem cell compartment which is completely the same as for our model of granulopoiesis (Scholz *et al.* (2005)). Finally, the regulation of cell kinetic parameters such as amplification and transition times and the influence of chemotherapy is modelled in analogy to the granulopoiesis model. This approach guarantees full comparability of both, our model of granulopoiesis and the new model of thrombopoiesis as well.

2.2. Basic model structure and assumptions

Here we describe and discuss the most important biological assumptions and simplifications which lead to the model equations (see also figure 1).

1. The bone marrow is modelled by three compartments: The stem cell compartment S is characterized by self-renewal capability and lineage specification regulated by the demand of lineage-specific bone marrow cell stages (Glauche *et al.* (2007); Wichmann & Loeffler (1985)). The compartment of CFU-Mk CM (colony forming unit of megakaryocytes) summarizes all progenitors and precursors committed to the thrombopoietic lineage but still capable of cell divisions. The compartment MKC summarizes the megakaryocytes which are clearly morphologically distinguishable from the other cells and are characterised by endomitoses.

In fact, cell populations in bone marrow are more a continuum rather than cell stages. We decided to roughly divide this continuum into three compartments comprising a qualitative change in the properties of cells by lineage commitment in CM and loss of cell division capability in MKC . For the same reason, we assume irreversibility of all transitions.

2. Platelet production rate is proportional to the mass of megakaryocytes which again is proportional to the ploidy of megakaryocytes changed by endomitoses.

The process of platelet production by megakaryocytes is not well understood. Therefore, in our model we do not aim to model it in detail. We neglect for example intermediate states of this

process such as proplatelet formation. It is generally believed that ploidy of megakaryocytes is proportional to the megakaryocyte mass (e.g. Corash (1989)). On the other hand, proportionality between megakaryocyte mass and resulting platelet number is less clear. In order to explain the distribution of platelet volumes, biologist failed to prove a clear relation between megakaryocyte mass and platelet volume (Stenberg & Levin (1989)). Hence we assume that the initial platelet volume is roughly constant resulting in a proportionality between megakaryocyte mass and produced platelets. The dynamics of platelet volume is not considered in our model.

3. Platelets are released from the bone marrow *MKC* compartment to the peripheral blood. Young platelets (megathrombocytes) were preferentially sequestered in the spleen (*PLS*, Freedman & Karpatkin (1975)). Platelets are age-dependently released from the spleen to the circulating blood (*PLC*, Wichmann (1984)). Finally, platelet survival in circulation is approximately Gamma-distributed (Tsan (1984)).
4. Thrombopoiesis is highly regulated by growth-factor mediated feed-back loops. The most important acting cytokine is thrombopoietin (TPO) which concentration is explicitly modelled in the *TPO* compartment. TPO acts by increasing the amplification of CFU-Mk (Kaushansky *et al.* (2004, 1996)), by increasing the number of endomitoses in megakaryocytes (Ebbe *et al.* (1988); Horie *et al.* (1997); de Sauvage *et al.* (1994)) and by accelerating the maturation of megakaryocytes (Ebbe *et al.* (1966, 1968)).
5. TPO is produced in the liver and the kidneys (Cohen-Solal *et al.* (1996)). The rate of production is assumed to be constant (Cohen-Solal *et al.* (1996); Fielder *et al.* (1996); Kuter *et al.* (1994)). TPO is degraded unspecifically via the kidneys and primarily via specific receptor mediated clearance (Broudy *et al.* (1997); Kuter *et al.* (1994); Li *et al.* (1999); Fielder *et al.* (1996)).
6. A single application of chemotherapeutic drugs induce a first order depletion in each bone marrow cell stage for the duration of one day. We define the ratio of cell loss rate to compartment size as corresponding (constant) specific toxicity parameter of the therapy. This model assumption is based on the usually fast metabolism of the drugs (Bender *et al.* (1977); Busse *et al.* (1997); Sinkule (1984)) and an exponential decay of bone marrow cellularities observed in mice (Lohrmann & Schreml (1982)).
7. The bone marrow damage is reversible. No long-lasting deterioration of haematopoiesis is assumed. That is, the dynamic parameters of the model are not influenced by chemotherapy. This assumption is justified by the moderate doses of conventional chemotherapies resulting in a quick recovery of haematopoiesis (Lohrmann & Schreml (1982)).
8. Drugs applied in combination damage independently of each other. Consequently, the toxicity parameter of a drug combination is the sum of the toxicity parameters of its components. This is justified by different modes of action of cytotoxic drugs applied in combination.

Remark: The assumptions for chemotherapy action are the same as for our former model of granulopoiesis (compare Scholz *et al.* (2005, 2009)).

Additional minor assumptions regarding the modelling of single experiments are explained in the text.

2.3. Regulatory mechanisms

We used the same regulatory functions as in our model of human granulopoiesis under chemotherapy. Here we only sketch the mechanisms for self-consistency. A more detailed description and discussion can be found in Scholz *et al.* (2005).

State variables

The state variables calculated in the model are presented in table 1. In general, the compartment wild card X can be one of the compartments S (stem cells), CM (colony forming unit of megakaryocytes), MKC (megakaryocytes), PLC (platelets in circulation), PLS (platelets in spleen), TPO (thrombopoietin) or the total thrombopoietic bone marrow cellularity $TTB = CM + MKC$ except for the variables regarding proliferation (a , A) which are applicable only for S and CM . The unperturbed thrombopoiesis is modelled by a steady-state for which all state variables are constant.

Self-renewal probability p

According to Wichmann & Loeffler (1985) the self-renewal probability of stem cells is regulated by both, the demand of differentiated cells and stem cells itself:

$$p = 0.1 * \tanh(-\vartheta_S(t) (C_S^{rel}(t) - 1) - \vartheta_{TTB} (C_{TTB}^{rel}(t) - 1)) + 0.5 \quad (1)$$

where

$$\vartheta_S(t) = \begin{cases} \frac{2}{C_S^{rel}(t)^{0.6}} & \text{for } C_S^{rel} \leq 1 \\ 2 & \text{for } C_S^{rel} > 1 \end{cases},$$

ϑ_{TTB} is constant and C_S^{rel} is the content of the stem cell compartment relative to steady-state. The self-renewal probability varies between 0.4 for low numbers of cells committed to thrombopoietic lineage and high numbers of stem cells and 0.6 for low numbers of stem cells. The parameters ϑ_{TTB} and ϑ_S are weighting parameters of the concurrent need of stem cells and committed cells. Since ϑ_S approaches infinity if C_S^{rel} tends to zero, p always tends to 0.6 in case of low stem cell content preventing exhaustion of this essential compartment.

Proliferative fraction a_X

This quantity is only valid for the compartments S and CM . It represents the fraction of cells in cell cycle and is regulated by the bone marrow cellularity. It is a monotone function with a range between a_X^{min} and a_X^{max} . Low bone marrow cellularity cause an increment of a_X . Define

$$x = \omega_{TTB} \ln C_{TTB}^{rel}(t) + \omega_s * \begin{cases} \ln C_S^{rel}(t) & \text{for } C_S^{rel} \leq 1 \\ C_S^{rel}(t) - 1 & \text{for } C_S^{rel} > 1 \end{cases}$$

$$y = -\frac{1}{2 \ln 2} \left(\ln \left(\frac{a_X^{int} - a_X^{max}}{a_X^{min} - a_X^{int}} \right) - \ln \left(\frac{a_X^{nor} - a_X^{max}}{a_X^{min} - a_X^{nor}} \right) \right) x + \frac{1}{2} \ln \left(\frac{a_X^{nor} - a_X^{max}}{a_X^{min} - a_X^{nor}} \right)$$

one obtains

$$a_X = \begin{cases} \frac{a_X^{max} e^{-y} + a_X^{min} e^y}{e^{-y} + e^y} & \text{for } a_X^{min} < a_X^{nor} < a_X^{int} < a_X^{max} \\ a_X^{nor} & \text{for } a_X^{min} = a_X^{nor} = a_X^{int} = a_X^{max} \end{cases} \quad (2)$$

The variable y defines the actual point on the regulatory curve; whereas the variable x represents some kind of weighted logarithmic relative system size. In this context, the proliferative fraction a^{int} corresponds to $x = -\ln 2$ and a^{nor} corresponds to $x = 0$.

Z-function

The Z-function is a sigmoidal function which regulates amplification or transit time between a minimum and a maximum value depending on the concentration of the growth factor TPO.

$$Y(C_{TPO}^{rel}) = \begin{cases} Y^{max} - (Y^{max} - Y^{min}) e^{-\ln\left(\frac{Y^{max}-Y^{min}}{Y^{max}-Y^{nor}}\right) (C_{TPO}^{rel})^{b_Y}} & \text{for } Y^{min} < Y^{nor} < Y^{max} \text{ or } Y^{min} > Y^{nor} > Y^{max} \\ Y^{nor} & \text{for } Y^{min} = Y^{nor} = Y^{max} \end{cases} \quad (3)$$

The parameter b_Y defines the steepness of the Z-function and is therefore called *sensitivity parameter*.

Amplification splitting

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 one compartment. To avoid the introduction of an age-structure, we used the method of amplification splitting derived in Scholz *et al.* (2005). At this, the amplification of a compartment is divided into an amplification of the cell influx into a compartment A_X^{in} and an amplification of the cell efflux of a compartment A_X^{out} . The product of these rates is equal to the overall amplification A_X . Under the assumption that the amplification is uniformly distributed over the transit time, Scholz *et al.* (2005) proved that

$$A_X^{in} = \begin{cases} \frac{A_X - 1}{\ln A_X} & \text{for } A_X \neq 0, \quad A_X \neq 1 \\ \ln 2 & \text{for } A_X = 1 \\ 0 & \text{for } A_X = 0 \end{cases} \quad (4)$$

$$A_X^{out} = \begin{cases} \frac{A_X}{A_X^{in}} & \text{for } A_X \neq 0 \\ 0 & \text{for } A_X = 0 \end{cases} \quad (5)$$

The major effect of amplification splitting is a delayed reaction of the system to changes in amplification rates, in better accordance to the observed behaviour.

Division into subcompartments

In maturing compartments with transit time T we use the technique of dividing the compartment into N equal subcompartments with transit time $\frac{T}{N}$ each. It has been shown that this results in a Gamma-distribution of the length of stay of a cell with expectation T and variance $\frac{T^2}{N}$ (Scholz *et al.* (2005)). Hence, with this approach we model a biologically more realistic condition of maturation which is in between a completely age-independent length of stay ($N = 1$) and a completely deterministic length of stay $N \rightarrow \infty$.

2.4. Determination of parameters

Bone marrow data of human thrombopoiesis are rare which complicates the choice of corresponding model parameters. Some evidence is available for the number of cell divisions, transit times in the compartments or ploidy of megakaryocytes under various stimulating and suppressing conditions. These data provide rough estimates for our regulation parameters Y^{min} , Y^{nor} and Y^{max} . Additionally, the mechanisms of platelet distribution between circulating blood and spleen are well studied allowing a rough choice of corresponding parameters.

On the other hand, no data are available for the sensitivity parameters b_Y , the parameters regarding endogenous TPO regulation and the toxicity parameters of chemotherapy. These parameters were estimated by fitting the predictions of the model simulations to data sets of platelet or TPO dynamics under various scenarios. The fitness function which is minimized during the fitness process is defined as the mean absolute difference between the logarithm of the model prediction and the logarithm of the median of the data for given time points to achieve a good agreement with the interesting nadir phase of platelet counts. Optimisation is performed using evolutionary strategies (Schwefel (1984)). Our fitting procedure is stepwise keeping already identified parameters constant in subsequent fitting steps. First, we estimated the parameters of the endogenous TPO regulation model on the basis of measured TPO dynamics during chemotherapy. Next, we determined the unknown parameters of our cell kinetic model and some toxicity parameters on the basis of platelet dynamics during four simple chemotherapies. Finally, toxicity parameters of more complex chemotherapies were estimated.

We provide a complete list of chosen or fitted cell-kinetic parameters of our model in the appendix of the paper. Estimated toxicity parameters were presented in section 4.2. We also provide confidence limits for all estimates defined by a fitness deterioration of less than 10% compared to optimum.

The data used for model fitting were taken from the literature or were collected by our cooperating clinical study groups. The next section will provide an overview over these data sets.

2.5. Data

TPO serum concentration

Since the thrombopoietic growth factor TPO is a key player in the regulation of thrombopoiesis, we aim to model the dynamics of TPO serum concentrations by construction of a regulation model of endogenous TPO (parameters see table A5). Engel *et al.* (1999) published close meshed-time series of both TPO serum concentrations and platelets for three patients treated with different chemotherapies. The third patient had unusually high starting serum concentrations which are more than ten times higher than for the two other patients. Furthermore, the patient was critically ill (Engel, personal communication). Hence, we decided to discard the data of this patient.

Chemotherapy data

To model the time course of platelets under chemotherapy, we received data of 1644 patients with high-grade non-Hodgkin's lymphoma treated with five different multi-cyclic, multi-drug regimens (CHOP-14, CHOP-21, CHOEP-14, CHOEP-21, high-CHOEP) and 809 patients with Hodgkin's Disease treated with BEACOPP Basis or BEACOPP escalated from our national study groups (*German High Grade*

Non-Hodgkin's-Lymphoma Study Group and *German Hodgkin's Lymphoma Study Group*). The patients were treated in the framework of published clinical studies for which Markus Loeffler was the responsible biostatistician (Pfreundschuh *et al.* (2004a,b, 2008); Diehl *et al.* (2003)). Major myelotoxic drugs used in the regimens were cyclophosphamide (C), doxorubicin (D), vincristine (V), etoposide (E) and procarbazine (P). All other drugs used in the regimens were assumed to be unimportant for thrombotoxicity. Dosing and timing of the drugs and other therapy informations can be found in table 2.

From these data, we constructed time courses of platelet counts by pooling all available patients treated with the same therapy. Since the time points for taking blood samples was not prescribed in the study protocols, we are able to construct time series with daily measurements for all scenarios. The CHO(E)P-regimens were used to determine the unknown cell kinetic parameters of our model (parameters see tables A2, A3 and A4) and the toxicity parameters of the corresponding chemotherapies as well (table 3). In contrast, the other chemotherapies were only used to estimate the toxicity parameters of the new therapies without changing the cell kinetic parameters (table 3). Hence, we obtained a unique set of model parameters valid for all scenarios except for different toxicity parameters to be assumed for different chemotherapies.

Thrombopheresis data

Although the modelling of chemotherapy is our primary focus, we aim to analyse additional experimental data to check, whether the model is able to cover other scenarios than built for. Thrombopheresis seems to us a good candidate since this intervention can simply be modelled by an initial reduction of platelets. Afterwards, the model should be able to predict the resulting dynamics of both platelets and TPO. Three papers reporting platelets and TPO serum concentration dynamics after thrombopheresis were found in the literature (Dettke *et al.* (1998); Wagner *et al.* (2001); Weisbach *et al.* (1999)). We pooled these data on the basis of reported means and standard deviations assuming normal distribution of measurements. A total of 56 donors were pooled, generating a time series of platelets and TPO for the time points 0, 1, 2, 3, 4, and 7 days after donation.

2.6. Simulation

Our model has been programmed with MATLAB 7.5.0 and SIMULINK toolbox (The MathWorks Inc., Natick, MA, USA). Simulations of the model were performed by numerical integration of the equation system using the variable step solver from Adams and Bashford implemented in the SIMULINK toolbox.

3. The model of thrombopoiesis

In this section we derive the model equations for all compartments starting with the bone marrow compartments. The general scheme of these equations is that the change of the compartment size is equal to the (amplified) influx minus the efflux minus the cell loss caused by the chemotherapy.

3.1. Stem cell compartment

The equations for the stem cell compartment have been adopted from Wichmann & Loeffler (1985) without modifications. Without chemotherapy, it describes the balance between stem cell self-renewal and differentiation. Chemotherapy causes a cell loss which is proportional to the compartment size.

$$\frac{d}{dt}C_S = (2p - 1)C_S\frac{a_S}{\tau_S} - \Psi_S C_S \quad (6)$$

$$C_S^{out} = 2(1 - p)C_S\frac{a_S}{\tau_S} \quad (7)$$

Equation (6) is motivated by the fact that a cell which performs a self-renewal division results in one additional stem cell while the other cell divisions result in an output of two committed cells (equation (7)). Since cell divisions are averaged, a distinction between symmetric and asymmetric divisions is not necessary.

For steady-state, we assume $C_S = C_S^{nor} = 1$ that is all model bone marrow cell counts are normalised to one stem cell unit. The function Ψ is the characteristic chemotherapy function. It is a step function which has a value different from zero for one day after the application of a single cytotoxic drug (section 2.2, assumption 6). This value is called the toxicity parameter of the drug. It is specific for different bone marrow cell stages. For multiple drug applications, these step functions are added. Since we assumed independent toxicity of different drugs, the chemotherapy function of a drug combination is equal to the sum of the chemotherapy functions of its components. For example for the CHOEP-21 regimen it reads as follows

$$\Psi_X^{CHOEP-21} = k_X^{CHO} \sum_{i=0}^5 \chi_{[21 * i; 21 * i + 1]} + k_X^E \sum_{i=0}^5 \chi_{[21 * i; 21 * i + 3]}$$

where

$$\chi_A(t) = \begin{cases} 1 & \text{if } t \in A \\ 0 & \text{else} \end{cases}$$

and k_X^{CHO} and k_X^E are the toxicity parameters of the drug combination cyclophosphamide, doxorubicin, vincristine applied at the first day of each therapy cycle and etoposide applied at day 1-3 respectively.

3.2. Compartment of CFU-Mk

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

$$\frac{d}{dt}C_{CM} = A_{CM}^{in} C_S^{out} - \frac{C_{CM}}{T_{CM}} - \Psi_{CM} C_{CM} \quad (8)$$

$$C_{CM}^{out} = A_{CM}^{out} \frac{C_{CM}}{T_{CM}} \quad (9)$$

While A_{CM} is a Z-function of TPO , T_{CM} is assumed to be constant. We adopt the simplification

$$\Psi_{CM} = \Psi_S$$

proposed in Scholz *et al.* (2005). That is, the toxicity of chemotherapy is equal for stem cells and CFU-Mk.

3.3. Compartment of megakaryocytes

Here, amplification of the compartment is to be understood as increased ploidy of cells caused by endomitoses. Both, amplification and maturation time are assumed to be Z-functions of TPO.

$$\frac{d}{dt}C_{MKC} = A_{MKC}^{in}C_{CM}^{out} - \frac{C_{MKC}}{T_{MKC}} - \Psi_{MKC}C_{MKC} \quad (10)$$

$$C_{MKC}^{out} = A_{MKC}^{out} \frac{C_{MKC}}{T_{MKC}} \quad (11)$$

According to our assumption 2, C_{MKC}^{out} can be interpreted as the mass output of the megakaryocyte compartment which is proportional to the number of produced platelets. The size of this proportionality factor is unimportant for our modelling purposes, since we always calculate relative changes of compartment sizes.

3.4. Platelets in spleen and circulation

The platelet compartments in spleen and circulation are divided into n subcompartments to model the age structure of these compartments (see section 2.2. and assumption 3). The transition time in each of these subcompartments is $T_{PL}^{sub} = \frac{T_{PL}}{n}$. Since young platelets are preferentially sequestered in the spleen, we assume a direct influx of platelets from bone marrow to both, spleen and circulation as well. The ratio of cells entering directly into circulation is denoted as k_{circ} . Hence, the balance equations for the first platelet subcompartments are

$$\frac{d}{dt}C_{PLC_1} = k_{circ}C_{MKC}^{out} - \frac{C_{PLC_1}}{T_{PL}^{sub}} + k_1^{sc}C_{PLS_1} \quad (12)$$

$$\frac{d}{dt}C_{PLS_1} = (1 - k_{circ})C_{MKC}^{out} - \frac{C_{PLS_1}}{T_{PL}^{sub}} - k_1^{sc}C_{PLS_1} \quad (13)$$

where k_i^{sc} denote the transition of aged platelets from spleen to circulation. For the following subcompartments one obtains analogously

$$\frac{d}{dt}C_{PLC_i} = \frac{C_{PLC_{i-1}}}{T_{PL}^{sub}} - \frac{C_{PLC_i}}{T_{PL}^{sub}} + k_i^{sc}C_{PLS_i} \quad (14)$$

$$\frac{d}{dt}C_{PLS_i} = \frac{C_{PLS_{i-1}}}{T_{PL}^{sub}} - \frac{C_{PLS_i}}{T_{PL}^{sub}} - k_i^{sc}C_{PLS_i} \quad \text{for } i = 2, 3, \dots, n \quad (15)$$

The steady state conditions of equations (12)-(15) read as follows:

$$C_{PLC_1}^{nor} = (k_{circ} + k_1^{sc} T_{PL}^{sub}) \frac{T_{PL}^{sub} C_{MKC}^{out,nor}}{1 + k_1^{sc} T_{PL}^{sub}} \quad (16)$$

$$C_{PLS_1}^{nor} = (1 - k_{circ}) \frac{T_{PL}^{sub} C_{MKC}^{out,nor}}{1 + k_1^{sc} T_{PL}^{sub}} \quad (17)$$

$$C_{PLC_i}^{nor} = C_{PLC_{i-1}}^{nor} + k_i^{sc} T_{PL}^{sub} \frac{C_{PLS_{i-1}}^{nor}}{1 + k_i^{sc} T_{PL}^{sub}} \quad (18)$$

$$C_{PLS_i}^{nor} = \frac{C_{PLS_{i-1}}^{nor}}{1 + k_i^{sc} T_{PL}^{sub}} \quad \text{for } i = 2, 3, \dots, n \quad (19)$$

The next aim is to define the transition coefficients k_i^{sc} . The underlying observation is that in steady-state the spleen contains approximately one third of all platelets (Freedman *et al.* (1977)). The preferred sequestration of young platelets in the spleen is modelled by an age-dependent linearly increasing proportion g of platelets in circulation. Under the restriction on the total platelet distribution, one obtains

$$g(t) = 2(g - g_1)t + g_1 \quad (20)$$

where $g = \frac{2}{3}$ and g_1 is a free parameter to be determined later (see figure 2). Setting $g_i = g \left(\frac{i-1}{n-1} \right)$ and $G_i = \frac{C_{PLC_i}^{nor}}{C_{PLS_i}^{nor}} = \frac{g_i}{1-g_i}$ after some calculations it follows from the steady-state conditions (16-19) that

$$k_1^{sc} = \frac{g_1 - k_{circ}}{T_{PL}^{sub} (1 - g_1)} \quad (21)$$

$$k_i^{sc} = \frac{G_i - G_{i-1}}{T_{PL}^{sub} (G_{i-1} + 1)} \quad \text{for } i = 2, 3, \dots, n \quad (22)$$

Since $g(t)$ must be a percentage for $t \in [0, 1]$, from (20) and (21) it can be derived that

$$g_1 > \max \left\{ \frac{1}{3}, k_{circ} \right\}$$

Since the platelet counts were calculated relative to a single stem cell, C_{PLC}^{rel} must be multiplied with a constant C_{PLC}^0 of normal platelet counts in order to make comparisons with data.

3.5. Regulation model of endogenous TPO

According to our assumption 5, the endogenous TPO serum concentration is regulated by a constant production rate α , an unspecific first order elimination with transit time T_{TPO} and a specific saturable elimination via a Michaelis-Menten kinetic with Michaelis constant k_m . Since this elimination is mediated by TPO receptors, the saturation constant of this elimination term is a weighted sum of megakaryocytes and circulating platelets. Hence, the balance equation for TPO has the form

$$\frac{d}{dt} C_{TPO}^{rel} = \alpha - \frac{C_{TPO}^{rel}}{T_{TPO}} - (w_{MKC} C_{MKC}^{rel} + w_{PLC} C_{PLC}^{rel}) \frac{C_{TPO}^{rel}}{k_m + C_{TPO}^{rel}} \quad (23)$$

with the initial condition $C_{TPO}^{rel}(0) = 1$. Hence, the relative production rate α can be calculated given the other parameters

$$\alpha = \frac{1}{T_{TPO}} + \frac{w_{MKC} + w_{PLC}}{k_m + 1}$$

4. Model results

4.1. TPO serum concentrations during chemotherapy

First, we determined the parameters of our regulation model of TPO (section 3.5.). Therefore, we fitted equation (23) to the time series of TPO serum concentrations of two patients under therapy (Engel *et al.* (1999)). Since time series of both, platelets and megakaryocytes are required in order to calculate the specific degradation, we imprinted the time series of platelets to equation (23) by interpolating the observed data. Megakaryocytes were not directly observed. We generated a time series of relative megakaryocyte counts by assuming a time delay t_{MKC} between the relative megakaryocyte and platelet dynamics. Hence, we imprinted both the original interpolated platelet data and a time shifted version of it into the model. Fitting resulted in a good agreement of data and model (see figure 3). Parameter estimates can be found in the appendix and were used without changes for all subsequent modelling steps. Since in the full model, the megakaryocytes are directly modelled, the parameter t_{MKC} is not used for the final model.

We estimated that the unspecific elimination is almost neglectable under steady-state conditions (see appendix, unspecific elimination rate: 0.05h^{-1} , specific elimination rate: 3.65h^{-1}). Furthermore, the ratio of megakaryocyte and platelet TPO receptor mediated clearance is estimated to be approximately 1:1.8. Hence, contribution of platelets to specific degradation is almost 65%.

4.2. Platelet dynamics during chemotherapy

Calibration of the model

Time courses of platelet dynamics under the chemotherapies CHO(E)P-14/21 were used to determine both, the unknown parameters of the cell-kinetic model and the toxicity parameters of the chemotherapies as well. We used these therapies for model fitting because of the relatively simple structure of the corresponding chemotherapy characteristic function which reduces the number of toxicity parameters to be estimated. Results of data fitting are shown in figure 4. Cell-kinetic parameter estimates can be found in the appendix. Toxicity parameters can be found in table 3. We obtained a good fit of all chemotherapy data.

Testing the cell-kinetic model and chemotherapy model assumptions on the basis of further chemotherapy data

To test the identified cell-kinetic model and corresponding chemotherapy model assumptions, we used the data of three more complex chemotherapies BEACOPP Basis, BEACOPP escalated and high-CHOEP. All cell kinetic parameters identified in the last step and the chemotherapy model assumptions as well were kept constant. But toxicity parameters of the new drugs or drug combinations must be estimated. Some of the drugs such as procarbazine and vincristine are used in different regimens with the same dose compelling the same toxicity parameters. Toxicity parameters for etoposide $100\frac{\text{mg}}{\text{m}^2}$ was estimated for CHOEP and BEACOPP Basis separately since patients treated with CHOEP were significantly older. In some cases, the toxicity parameter for megakaryocytes could not be estimated because of an almost extinction of this compartment. In these cases, we set the toxicity parameter equals 0.3 which means almost infinite toxicity (see table 3). Patients treated with BEACOPP Basis or

BEACOPP escalated chemotherapies showed increased platelet counts at the beginning of the therapy probably due to tumour cytokine activity. Therefore, we decided to increase the starting values of the *PLC* and *PLS* compartment by 40%.

Simulations of the three new regimens revealed a good agreement between model and data (see figure 4). All toxicity parameter estimates are plausible. We estimated that both procarbazine and vincristine have low thrombotoxicity according to clinical experiences. Etoposide $100\frac{mg}{m^2}$ is more toxic in elderly patients than in young patients (Ziepert *et al.* (2008)). The drug combination C650+D25 is less toxic than C1250+D35. There is a clear dose-toxicity relation for etoposide in young patients (see table 3, rows 7-9). Comparing the estimates for k_S between our models of granulopoiesis (Scholz *et al.* (2005)) and thrombopoiesis, reveals that the toxicity relations between drugs and drug doses are preserved and that the estimates are in the same order of magnitude.

4.3. Platelet and TPO dynamics after thrombopheresis

To test whether our model is valid also for other situations than chemotherapy, we compared data of platelet and TPO dynamics after thrombopheresis with our model predictions. Thrombopheresis was simply modelled by a reduction of the initial value of the circulating platelet compartment by 30% compared to normal. All other parameters were kept constant. Model dynamics fit well to the pooled literature data of TPO and platelets (see figure 5). We predict a quick increment of TPO serum concentrations shortly after thrombopheresis which is not observed in the data but can also not be excluded due to the wide spacing of sample times.

4.4. Model predictions

The model can be used to make clinical relevant predictions for which no data are available so far. By model simulations, we calculated for example the time course of megakaryocytes, platelets and TPO serum concentrations after CHOP-14 and high-CHOEP chemotherapy (see figure 6). We estimated that the time courses of TPO serum concentrations and platelets are strongly inversely correlated. Platelets in spleen fluctuate more heavily than the circulating pool. The course of megakaryocytes is time-shifted compared to circulating platelets by a time-shift of approximately four to seven days. We estimated that the thrombopoietic system reaches steady state approximately six weeks after the last cycle of CHOP-14 therapy and 12 weeks after the last cycle of high-CHOEP therapy.

Next, we performed model simulations after setting the initial value of the relative TPO compartments to high values. This situation is to some extent comparable with an intravenous injection of TPO to healthy subjects. We performed simulations with four different initial values of $C_{TPO}^{rel}(0)$ which are 1000, 2000, 4000, and 8000 (see figure 7). Peak platelets occurred always at day 12 and the number of platelets was increased by 83%, 104%, 127% and 152% respectively.

Finally, we analysed the thrombotoxicity of regimens not yet tested in clinical practice. It has been shown that time intensification of regimens led to improved outcome of the therapy of aggressive non-Hodgkin's lymphoma (Pfreundschuh *et al.* (2004a,b)). Both, CHOP-21 and CHOEP-21 proved to be inferior compared to their time intensified analogs CHOP-14 and CHOEP-14. By a further reduction of the distances between cytotoxic drug applications up to 12 days, we simulated the experimental regimens CHOP-12 and CHOEP-12. We estimated that CHOP-12 should be tolerable regarding

thrombotoxicity while CHOEP-12 would result in a severe cumulative toxicity which is probably not tolerable without further supportive care (see figure 8).

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5. Discussion

In the present paper, we constructed a biomathematical ordinary differential equations model of human thrombopoiesis under chemotherapy which is able to explain the time course of platelets of patients under seven different chemotherapies, the TPO dynamics for two patients under chemotherapy and platelet and TPO dynamics after thrombopheresis. Based on prespecified toxicity parameters of the therapy, the model can predict resulting platelet dynamics in order to assess the thrombocytopenic risk.

Since our proposed model is not the first mathematical model of human thrombopoiesis, we compare our approach with existing models in the literature. Wichmann (1984) proposed differential equations models of murine and human thrombopoiesis but without chemotherapy and under assumption of a demand-specific production of TPO. Selivanov *et al.* (1986) modelled thrombopoiesis under radiation exposure. Santillan *et al.* (2000) constructed an age-structured partial differential equations model which explains cyclic thrombocytopenia. Harker *et al.* (2000) constructed a pharmacokinetic and pharmacodynamic model of the pharmaceutical derivative Peg-MGDF (pegylated megakaryocyte growth and development factor). Skomorovski *et al.* (2003) developed a model of thrombopoiesis in mice and monkeys which has a similar compartment structure as our model. This model is based on a delay difference equation system and was validated on the basis of several experimental data. Obeyesekere *et al.* (2004) constructed a combined differential equations model of granulopoiesis and thrombopoiesis to simulate the recovery of both lineages after high-dose chemotherapy with stem cell transplantation. Jin & Krzyzanski (2004) proposed a pharmacokinetic model of TPO application. So far, none of these models were built to simulate the time course of platelets under conventional chemotherapy. A novelty of our modelling approach is the explanation of close-meshed platelet time courses during different chemotherapies on the basis of a unique parameter set which allows predictions for yet untested regimens.

The present model maps the basic regulatory mechanisms of bone marrow thrombopoiesis and the dynamics of platelets redistribution between spleen and circulation. Bone marrow thrombopoiesis is modelled by the three major cell compartments; stem cells, CFU-Mk and megakaryocytes. The stem cell compartment and its regulation has been adopted from other haematopoiesis models of our group (Wichmann & Loeffler (1985); Kliem (2001); Scholz *et al.* (2005, 2009)). We assumed a proportionality between megakaryocyte ploidy and platelet production (Corash (1989); Stenberg & Levin (1989)). For simplicity, we neglected proplatelet formation and regulation of the volume of platelets since both processes are still not well understood (Geddis (2009)).

In humans, the spleen is important for sequestration and maturation of platelets which is modelled by an age-dependent release of platelets from spleen to circulation (Freedman & Karparkin (1975); Wichmann (1984)). Finally, platelets are age-dependently removed from the plasma (Tsan (1984)).

The major regulating cytokine TPO was explicitly modelled. All other cytokines are neglected due to lack of data. TPO is known to have several modes of action on thrombopoiesis, which are increased amplification of CFU-Mk, increased endomitosis of megakaryocytes and accelerated maturation of megakaryocytes (Ebbe *et al.* (1966, 1968, 1988); Horie *et al.* (1997); Kaushansky *et al.* (2004, 1996); de Sauvage *et al.* (1994)). No direct effect of TPO to stem cells is assumed (Kaushansky (1997)) but we modelled an indirect feedback by the demand of differentiated cells regulating the self-renewal probability (see section 2.3.). We proposed a model of endogenous TPO regulation which is based on

a constant production rate, an unspecific first order elimination and a saturable specific elimination via receptors of megakaryocytes and platelets (Broudy *et al.* (1997); Cohen-Solal *et al.* (1996); Fielder *et al.* (1996); Kuter *et al.* (1994); Li *et al.* (1999); Mukai *et al.* (1996); Stefanich *et al.* (1997)). Some controversial discussions appeared with respect to TPO regulation. The theory of consumption assumes a constant TPO production while the TPO level is regulated by specific elimination (Fielder *et al.* (1996); Kuter *et al.* (1994)). An alternative theory is that there is a demand-specific production of TPO (McCarty *et al.* (1995)). However, the theory of consumption is more widely accepted. In view of the relative scarcity of dynamic TPO data in men, our model of endogenous TPO regulation has been kept as simple as possible. Since endogenous TPO levels show a high degree of heterogeneity between individuals, we decided to model only relative TPO levels. The dynamics of relative TPO levels appear to be more homogeneous than the dynamics of absolute levels (Nichol *et al.* (1995); Engel *et al.* (1999)).

Chemotherapy is modelled by a drug and cell stage specific cell kill (toxicity parameter) with a duration of one day. The assumptions for chemotherapy modelling are the same as for our model of granulopoiesis under chemotherapy and are discussed there in detail (Scholz *et al.* (2005, 2009)). The assumption with respect to the duration of chemotherapy action is based on the fact that the metabolism of the cytotoxic drugs is usually fast. It is a less critical model assumption since other durations would also work fine but would require re-estimation of the toxicity parameters (not shown). Hence, the assumed duration of one day simply normalises the toxicity parameter estimates.

Because of the simplicity of the model, most of the cell-kinetic parameters can be chosen from literature data. On the other hand, parameters of the model of endogenous TPO regulation and the toxicity parameters must be estimated. This is performed by a stepwise fitting process optimizing the agreement between model and data. First, the parameters of the TPO regulation model were determined by imprinting observed platelet dynamics of two patients under chemotherapy (Engel *et al.* (1999)) into the model and fitting the resulting TPO dynamics to observed TPO serum concentrations. Hence, estimation of TPO regulation parameters was based on a model which was not fully independent of data. Alternatively, one could try to estimate the TPO regulation parameters simultaneously with the unknown parameters of the cell-kinetic model. However this would require a much larger data set of both, platelets and TPO dynamics after chemotherapy or other interventions. Modelling of individual time courses of platelets is not possible at the current state of our model, since both, chemotherapy toxicity and platelet counts are affected by a large set of random factors not considered by our thrombopoiesis model. Our model is accurate only for averaged time courses of platelets. On the other hand, the correlation between platelets and TPO serum concentration is very strong (Engel *et al.* (1999)) and appears to be robust against random effects which allows the estimation of the required TPO regulation model parameters. All parameter estimates of the endogenous TPO regulation model are very plausible. The estimated ratio of contributions of megakaryocytes and platelets to TPO degradation was 1:1.8 in steady-state. It is believed that a single megakaryocyte produces approximately 1400 platelets (Stenberg & Levin (1989)). Furthermore, ratio of TPO receptor density of platelets and megakaryocytes was estimated to be 30:48,000 (Broudy *et al.* (1997)). Finally, the life span of platelets and megakaryocytes is approximately 240h and 144h respectively (Dassin *et al.* (1978); Finch *et al.* (1977); Karpatkin (1972); Schmitt *et al.* (2001)). Hence, by these data the contribution of the two cell stages to TPO consumption can be estimated as 1:1.5 which is in good

agreement with our parameter estimates. On the other hand, almost all of the above parameters taken from literature are only roughly known. According to literature, we estimated that the unspecific degradation of TPO plays a minor role under steady-state conditions (Broudy *et al.* (1997); Fielder *et al.* (1996); Kuter *et al.* (1994); Li *et al.* (1999)). Since megakaryocyte dynamics were not available for the two patients, we imprinted a time shifted platelet curve instead of the megakaryocyte curve. The shift parameter was 130h which roughly fits to the predicted dynamics of the complete model (figure 6). Finally, the TPO regulation model correctly predicts the time course of TPO after thrombopheresis (section 4.3.). Additionally, the results of our model of endogenous TPO regulation are also plausible in view of other data sets in the literature such as patients with megakaryocytic hypoplasia or after high-dose chemotherapy (Emmons *et al.* (1996); Nichol *et al.* (1995)). But modelling these data requires additional model assumptions which are not in the focus of our present paper (results not shown). Although fitted to only a few data sets, we conclude that the proposed simple model of endogenous TPO regulation is plausible in view of many other findings in literature.

After specification of the TPO regulatory model, we estimated unknown cell-kinetic parameters by fitting the model to the time course of platelets in patients under CHOP or CHOEP therapy. This also requires the estimation of the toxicity parameters of the therapies. As a result, we received a unique setting of the cell-kinetic parameters and parameters regarding TPO regulation which is valid for all scenarios considered.

In the next step, the model was applied to more complex chemotherapies extending the set of toxicity parameter estimates but preserving all other model parameters and assumptions. Agreement of model and data was fine for all regimens considered. Furthermore, estimates of toxicity parameters fit well to corresponding estimates obtained with our model of granulopoiesis under chemotherapy (compare Scholz *et al.* (2005)). On the other hand, the toxicity parameter for the megakaryocyte compartment could not be estimated with high accuracy in some cases for which an almost complete extinction of the megakaryocyte compartment is predicted (see table 3). Finally, the model was validated with data of TPO and platelet time courses after thrombopheresis which is modelled by a reduction of initial platelet counts.

The model can be used to make clinically relevant predictions. We demonstrated this by three examples. One could predict for example, the dynamics of bone marrow cell stages and endogenous TPO dynamics during chemotherapy. Additionally, the long term recovery after chemotherapy could be simulated. More interestingly, we simulated high initial levels of TPO which is comparable to intravenous TPO injections. The results are in rather good qualitative and quantitative agreement with data of Vadhan-Raj *et al.* (1997). However, modelling exogenous TPO injections require a detailed model of pharmacokinetics of TPO derivatives which was not in the scope of our current model state. In our opinion, data base is still too small to perform such a modelling but it is planned when better data of clinically relevant TPO derivatives are available in the future. Finally, one could make predictions for regimens not yet tested in clinical practise in order to assess the thrombocytopenic risk in the planning phase of a clinical trial. We estimated for example that a further time intensification of CHOP therapy up to 12 days might be feasible regarding thrombocytopenia. In contrast, the same time intensification for the CHOEP regimen might result in severe cumulative thrombocytopenia making the regimen unfeasible for the majority of patients. Other application scenarios might be regarding individual risk factors of thrombocytopenia and corresponding stratified risk assessment of therapies

(compare Scholz *et al.* (2006)).

The presented model of thrombopoiesis is only one step in our systems-biological approach to quantitatively describe haematopoiesis. Several extensions are planned in the future. At first, we perform a set of mice experiments to better understand bone marrow dynamics after chemotherapy applications. Insights from the mouse model will be used to refine our assumptions regarding chemotherapy actions. Furthermore, at the current model state we did not modelled exogenous TPO applications since clinically relevant pharmaceutical TPO derivatives are not available so far. However, there are several ongoing activities to develop and improve pharmaceutical TPO derivatives. When becoming clinically approved, we aim to extend our model by a pharmacokinetic model of exogenous TPO applications in order to make predictions about optimal use of the pharmaceutical derivatives as demonstrated for G-CSF optimisation using our granulopoiesis model (Scholz *et al.* (2009), ongoing).

Our models of granulopoiesis, erythropoiesis and thrombopoiesis are based on the same stem cell compartment. By using a model of lineage commitment proposed recently (Glauche *et al.* (2007)) we aim to combine our lineage models into one comprehensive model in the future. This combined model will allow the simulation of all haematotoxic side effects of chemotherapy in parallel and would be an excellent tool for risk assessment and optimisation of growth factor applications in the planning phase of clinical trials.

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A. Appendix - parameter settings

A.1. Stem cell compartment

Parameters of this compartment were taken from Wichmann & Loeffler (1985) without modification. Hence, the regulation of this compartment is identical to Scholz *et al.* (2005).

parameter	Value/ estimate	confidence of estimate	source/remark
a_S^{min}	0.01	-	Wichmann & Loeffler (1985)
a_S^{nor}	0.15	-	Wichmann & Loeffler (1985)
a_S^{int}	0.45	-	Wichmann & Loeffler (1985)
a_S^{max}	1	-	Wichmann & Loeffler (1985)
τ_S	8h	-	Wichmann & Loeffler (1985)
ω_S	1	-	Wichmann & Loeffler (1985)
ω_{TTB}	0.4	-	Wichmann & Loeffler (1985), $\omega_{TTB} \doteq \omega_E + \omega_G$
ϑ_{TTB}	-10	-	Wichmann & Loeffler (1985), $\vartheta_{TTB} \doteq \vartheta_E + \vartheta_G$

A.2. CFU-Mk compartment

parameter	Value/ estimate	confidence of estimate	source/remark
A_{CM}^{min}	2.42	1.55 – 2.56	fitted
A_{CM}^{nor}	2.67	2.52 – 3.83	fitted
A_{CM}^{max}	240	153 – 1120	fitted
b_{ACM}	2.74	2.38 – 4.02	fitted
T_{CM}^{nor}	630h	299h – 903h	fitted, T_{CM} is constant

A.3. Megakaryocyte compartment

parameter	Value/ estimate	confidence of estimate	source/remark
A_{MKC}^{min}	4	-	Harker (1971)
A_{MKC}^{nor}	8	-	Corash (1989); Harker (1971)
A_{MKC}^{max}	16	-	Harker (1971)
b_{AMKC}	0.047	0 – 0.42	fitted
T_{MKC}^{min}	96h	-	Wichmann & Loeffler (1985)
T_{MKC}^{nor}	144h	-	Dassin <i>et al.</i> (1978); Finch <i>et al.</i> (1977); Miyazaki <i>et al.</i> (1999)
T_{MKC}^{max}	168h	-	Wichmann & Loeffler (1985)
b_{TMKC}	1.5	> 0.68	fitted

A.4. Platelet compartments

parameter	Value/ estimate	confidence of estimate	source/remark
q	0.67	-	Freedman <i>et al.</i> (1977)
g_1	0.34	-	set
k_{circ}	0.33	0.07 – 0.34	fitted
n	7	5 – 11	fitted
T_{PL}	240h	-	Begemann & Rastetter (1993); Schmitt <i>et al.</i> (2001)
C_{PLC}^0	$275 * 10^9 l^{-1}$	-	Begemann & Rastetter (1993); Schmitt <i>et al.</i> (2001), required for the comparison of relative model platelet dynamics and absolute platelet counts

A.5. TPO regulation parameters

parameter	Value/ estimate	confidence of estimate	source/remark
α	3.7	-	derived from steady-state condition of equation (19)
T_{TPO}	20h	12h – 32h	fitted
k_m	0.75	0.64 – 1.21	fitted
w_{MKC}	$2.26h^{-1}$	$1.72h^{-1} - 2.43h^{-1}$	fitted
w_{PLC}	$4.12h^{-1}$	$4.03h^{-1} - 4.39h^{-1}$	fitted
t_{MKC}	130h	85h – 151h	fitted, only relevant for TPO regulation model fitting

Tables and figures

Tables

quantity	meaning	type
C_X	(normalised) content of compartment X	function of time t
C_X^{nor}	content of compartment X in steady state (normal value)	constant, obtained by steady-state condition
C_X^{rel}	content of compartments X relative to normal value	$C_X^{rel}(t) = C_X(t)/C_X^{nor}$
C_X^{in}	influx in compartment X	function of time
C_X^{in-nor}	normal influx	constant, see above
C_X^{out}	efflux from compartment X	function of time
$C_X^{out-nor}$	normal efflux	constant, see above
n	number of age-compartements in <i>PLC</i> and <i>PLS</i> respectively	parameter
a_X	proliferative fraction in cell compartment X	function of state, sometimes constant
A_X	amplification in cell compartment X	"
A_X^{in}	amplification of influx (see amplification splitting)	"
A_X^{out}	amplification of efflux (see amplification splitting)	"
p	self-renewal probability of stem cells	function of state
α	endogenous production of <i>TPO</i>	"
τ_X	average duration of cell cycle in compartment X	function of time, sometimes constant
T_X	average transit time in cell compartment X	"
k	transition or toxicity coefficients	functions of time or parameter
ω, ϑ	weighting parameters	parameter
k_M	Michaelis-Menten saturation parameter	constant
Y^{min}	quantity Y under minimum stimulation (here Y is either T_X or A_X)	parameter to determine the regulatory function of Y
Y^{nor}	quantity Y in steady state	"
Y^{int}	quantity Y under intensified stimulation	"
Y^{max}	quantify Y under maximum stimulation	"
b_Y	sensitivity of Y under stimulation	"
Ψ_X	characteristic chemotherapy function of compartment X	given function of time

Table 1: State variables of the thrombopoiesis model

regimen	no. of patients (measurements)	C dose [$\frac{mg}{m^2}$] (time)	D dose [$\frac{mg}{m^2}$] (time)	V dose [mg] (time)	E dose [$\frac{mg}{m^2}$] (time)	P dose [$\frac{mg}{m^2}$] (time)	no. of cycles (duration)
CHOP-21	370 (5451)	750 (d1)	50 (d1)	2 (d1)	-	-	6 (d21)
CHOP-14	360 (5217)	750 (d1)	50 (d1)	2 (d1)	-	-	6 (d14)
CHOEP-21	368 (6596)	750 (d1)	50 (d1)	2 (d1)	100 (d1-3)	-	6 (d21)
CHOEP-14	373 (6074)	750 (d1)	50 (d1)	2 (d1)	100 (d1-3)	-	6 (d14)
BEACOPP-Basis	429 (11525)	650 (d1)	25 (d1)	2 (d8)	100 (d1-3)	100 (d1-7)	8 (d21)
BEACOPP-escalated	380 (12873)	1250 (d1)	35 (d1)	2 (d8)	200 (d1-3)	100 (d1-7)	8 (d21)
high-CHOEP	173 (3717)	1400 (d1)	32.5 (d1-2)	2 (d1)	175 (d1-3)	-	6 (d21)

Table 2: Chemotherapy schedules, number of patients and measurements eligible for modelling

drug or drug combination	regimen	estimate of k_S	confidence of k_S	estimate of k_{MKC}	confidence of k_{MKC}
C750+D50+V2 (elderly)	CHO(E)P-14/21	0.191	0.157 – 0.207	0.034	0.010 – 0.103
E100 (elderly)	CHOEP-14/21	0.042	0.035 – 0.046	0.049	0.015 – 0.223
C650+D25	BEACOPP-Basis	0.071	0.000 – 0.172	0.000	0.000 – 0.019
C1250+D35	BEACOPP-escalated	0.144	0.105 – 0.160	0.300	≥ 0
D32.5	high-CHOEP	0.078	0.059 – 0.083	0.300	≥ 0
C1400	high-CHOEP	0.115	0.073 – 0.125	0.300	≥ 0
E100	BEACOPP-Basis	0.019	0.000 – 0.051	0.009	0.001 – 0.016
E175	high-CHOEP	0.038	0.026 – 0.042	0.300	≥ 0
E200	BEACOPP-escalated	0.063	0.052 – 0.068	0.300	≥ 0
P100	BEACOPP-Basis/escalated	0.011	0.006 – 0.014	0.000	0.000 – 0.016
V2	BEACOPP-Basis/escalated, high-CHOEP	0.001	0.000 – 0.018	0.300	≥ 0

Table 3: Toxicity parameters and confidence limits for different cytotoxic drugs or drug combinations. The first two estimates are for therapies of patients with a markedly higher median age compared to patients treated with one of the other regimens.

Figures

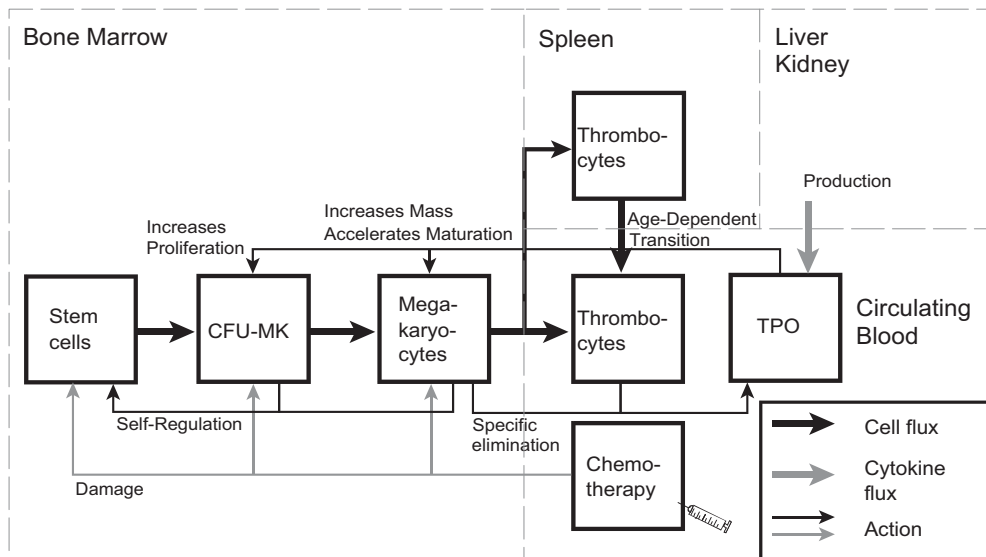


Figure 1: Basic structure of the human cell-kinetic thrombopoiesis model

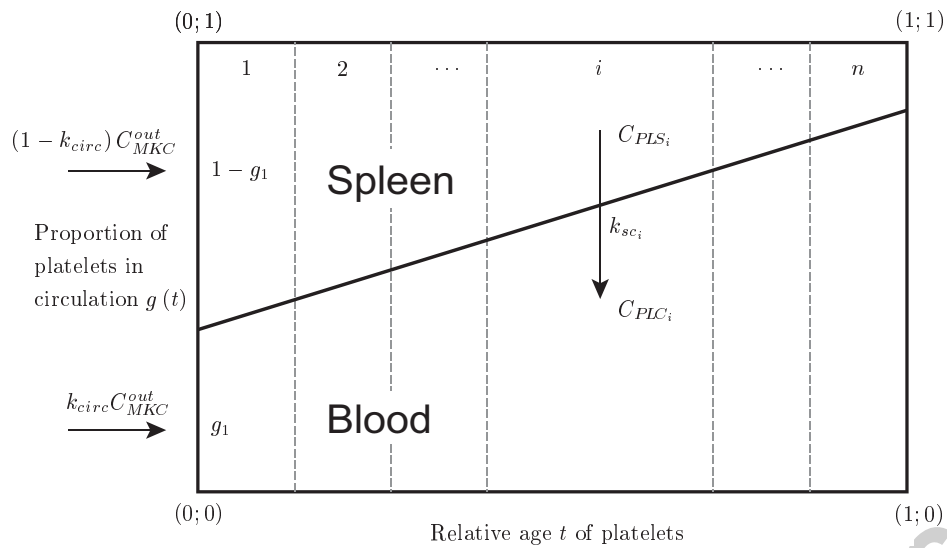


Figure 2: Schematic structure of age-dependent platelet dynamics in spleen and circulation. Vertical lines correspond to the age compartments.

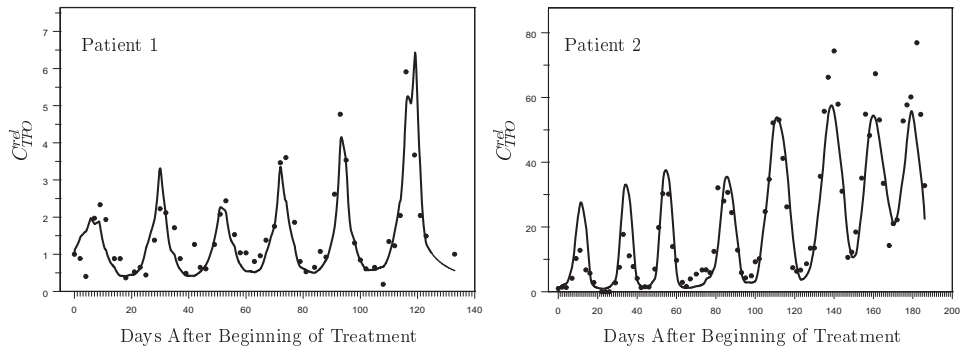


Figure 3: Comparison of TPO time courses (dots) and predictions of the TPO regulation model (solid lines) for two patients treated with chemotherapy.

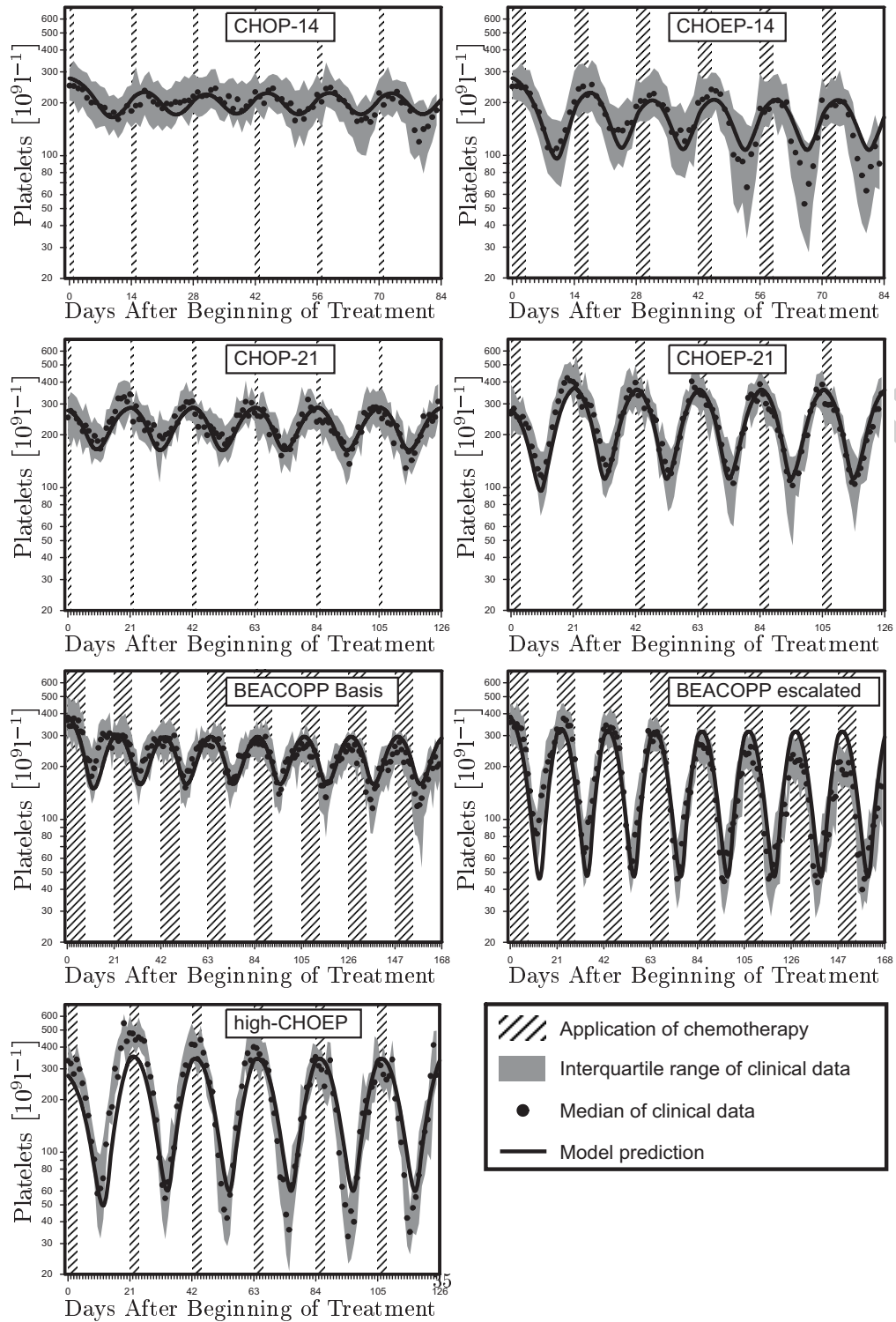


Figure 4: Comparison of platelet time courses and model prediction for 7 different chemotherapies. The CHO(E)P therapies were used for calibrating the cell kinetic model while for the other therapies only toxicity parameters were estimated.

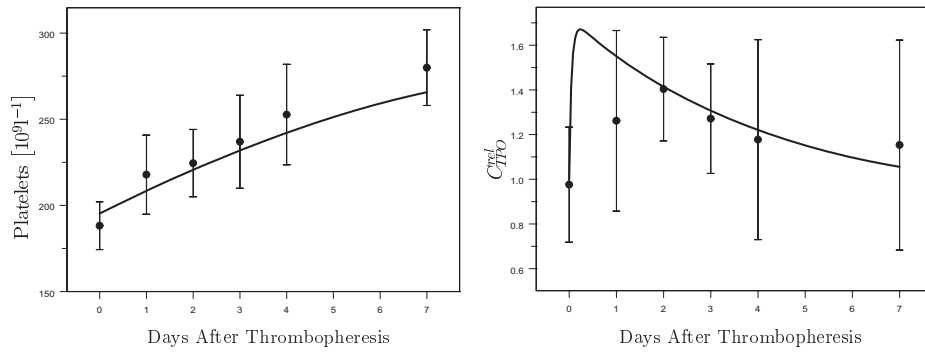


Figure 5: Comparison of platelet and TPO time courses after thrombopheresis and corresponding model prediction. Bars indicate $\pm 0.674SD$ which is equivalent to the interquartile range of normally distributed quantities.

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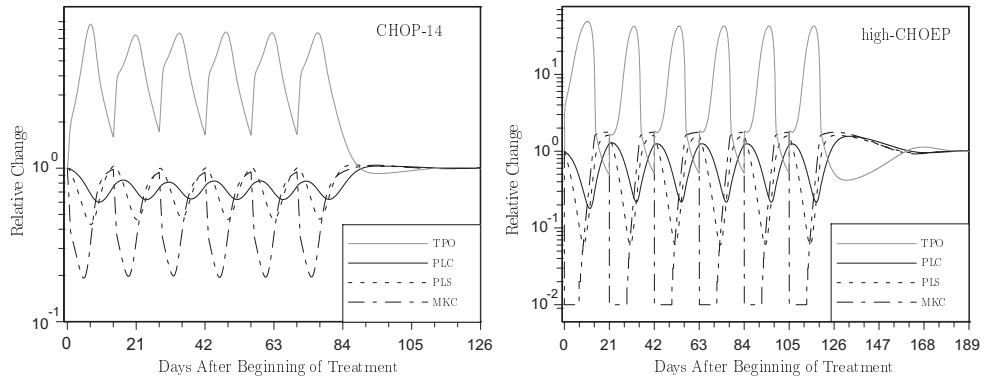


Figure 6: Simulated dynamics of TPO, platelet and megakaryocyte compartments under CHOP-14 and high-CHOEP chemotherapy. In the high-CHOEP scenario, the content of MKC drops to zero, which was cutted to 0.01 in our figure.

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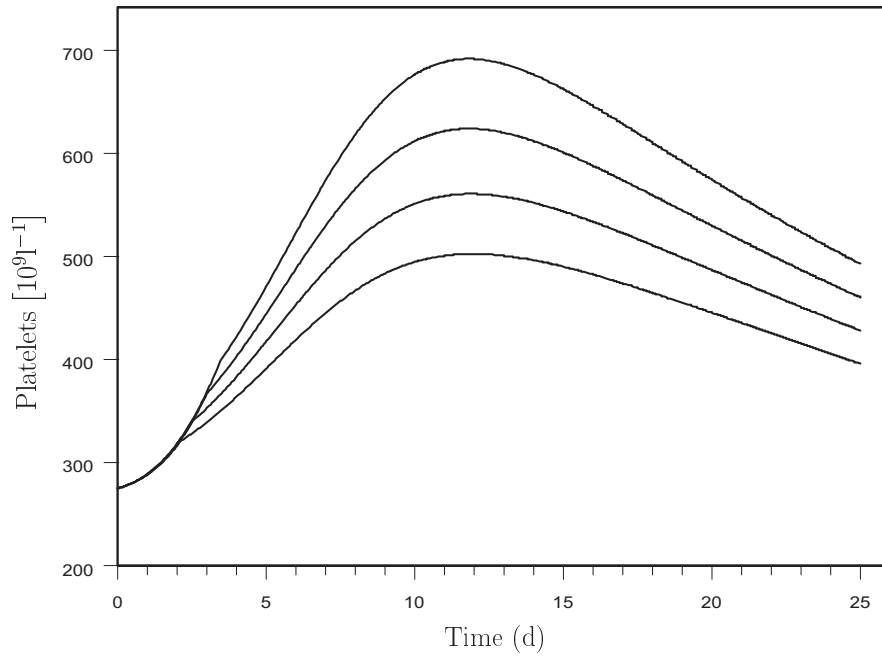


Figure 7: Model simulation of elevated initial relative TPO levels ($C_{TPO}^{rel}(0) = 1000, 2000, 4000$ and 8000 respectively)



Figure 8: Predicted time course of platelets during the two simulated time-intensified chemotherapies CHOP-12 and CHOEP-12.