A combined model of human erythropoiesis and granulopoiesis under growth factor and chemotherapy treatment: Supplement material

Sibylle Schirm\textsuperscript{1,2}, Christoph Engel\textsuperscript{1}, Markus Loeffler\textsuperscript{1} and Markus Scholz\textsuperscript{*1,2}

\textsuperscript{1}Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany
\textsuperscript{2}LIFE Research Center of Civilization Diseases, University of Leipzig, Leipzig, Germany

Email: sibylle.schirm@imise.uni-leipzig.de; christoph.engel@imise.uni-leipzig.de; markus.loeffler@imise.uni-leipzig.de; markus.scholz@imise.uni-leipzig.de;

*Corresponding author

A Model Equations

Here we describe all major model variables, mechanisms and equations of the cell kinetic model. An overview of model variables and parameters is shown in table A.1. At first, we describe major model principles and corresponding equations.

A.1 Amplification Splitting

Influx and efflux of cells at one compartment are amplified, so that the product is the over-all amplification ($A_X^\text{in}(t) \cdot A_X^\text{out}(t) = A_X(t)$),

$$A_X^\text{in}(t) = \begin{cases} 
\log 2 & \text{for } A_X \neq 1 \\
0 & \text{for } A_X = 0
\end{cases}$$

(A.1)

$$A_X^\text{out}(t) = \begin{cases} 
\frac{A_X - 1}{\ln 2} & \text{for } A_X 
eq 0, A_X \neq 1 \\
0 & \text{for } A_X = 0
\end{cases}$$

(A.2)

The effect is a delayed reaction of efflux and compartment size to changes in amplification rates. Amplification splitting is modelled for all compartments with amplification.
Table A.1: variables

| quantity  | meaning                                                                 | type/calculation |
|-----------|------------------------------------------------------------------------|-------------------|
| $C_X$     | content of compartment X function of time $t$                          |                   |
| $C_X^{\text{nor}}$ | content of compartment X in steady state (normal value)          | $C_X(0) = C_X^{\text{nor}}$ |
| $C_X^{\text{rel}}$ | content of compartments X relative to normal value | $C_X^{\text{rel}}(t) = \frac{C_X(t)}{C_X^{\text{nor}}}$ |
| $C_X^{\text{in}}$ | influx in compartment X parameter, see above                      |                   |
| $C_X^{\text{out}}$ | efflux from compartment X function of time                        |                   |
| $a_X$     | proliferative fraction in cell compartment X function of state, sometimes constant |                   |
| $A_X$     | amplification in cell compartment X                                  |                   |
| $A_X^{\text{in}}$ | amplification of influx                                              |                   |
| $A_X^{\text{out}}$ | amplification of efflux                                              |                   |
| $n_X$     | average number of mitoses in cell compartment X function of state    | $n_X = ldA_X$     |
| $p$       | self-renewal probability of stem cells function of state             |                   |
| $\tau_X$  | average duration of cell cycle in compartment X function of time, sometimes constant | $\tau_X$ (not regulated) |
| $T_X$     | average transit time of active cells in cell compartment X function of time | $T_X = n_X\tau_X$ |
| $T_X^{\text{tot}}$ | total transit time                                                      |                   |
| $k$       | transition, degradation or toxicity coefficients function of time or parameter |                   |
| $Y^{\text{min}}$ | quantity Y under minimum stimulation parameter to determine the regulatory function of Y |                   |
| $Y_X^{\text{nor}}$ | quantity Y in steady state                                             |                   |
| $Y_X^{\text{int}}$ | quantity Y under intensified stimulation                                |                   |
| $Y_X^{\text{max}}$ | quantify Y under maximum stimulation                                   |                   |
| $b_Y$     | sensitivity of Y under stimulation                                     |                   |

A.2 Regulatory Function

Amplification $A$ and transition time $T$ are regulated between a minimum $Y^{\text{min}}$ and a maximum $Y^{\text{max}}$ by the growth factors EPO or G-CSF according to the following regulatory function:

$$ Y = Z_Y(C_{\text{Cyto}}(t); Y^{\text{min}}, Y_X^{\text{nor}}, Y_X^{\text{max}}, b_Y) $$  \hspace{1cm} (A.3)

$$ Z_Y(C_{\text{Cyto}}) = \begin{cases} 
Y^{\text{max}} - (Y^{\text{max}} - Y^{\text{min}}) e^{-\ln\left(\frac{Y^{\text{max}} - Y^{\text{min}}}{Y^{\text{max}} - Y_X^{\text{nor}}}\right)}(C_{\text{Cyto}})^{b_Y} & \text{for } Y^{\text{min}} < Y_X^{\text{nor}} < Y^{\text{max}} \text{ or } Y^{\text{max}} < Y_X^{\text{nor}} < Y^{\text{min}} \\
Y^{\text{nor}} & \text{for } Y^{\text{min}} < Y_X^{\text{nor}} < Y^{\text{max}} \end{cases} \hspace{1cm} (A.4)$$

where $Y_X^{\text{nor}}$ is the steady state value of amplification or transition time, $C_{\text{Cyto}} \in \{C_{\text{EPO}}^{\text{int}}, C_{\text{GCSF}}^{\text{rel}}\}$ and $b_Y$ is the sensitivity of $Y$ under stimulation (see figure A.2 and [1], p. 69).
Figure 1: Regulatory function. As an example we plot the regulatory function of the amplification in compartment BE, $C_{\text{Cyto}} = \text{EPO concentration } C_{\text{int}}^{\text{EPO}}$.

A.3 Modelling of Delays

Several delays are included into the model such as delayed action of growth factors or chemotherapy. According to [2,3], these delays are modelled by a set of concatenated compartments with first order transitions

\[
\frac{d}{dt} C_X^1 = C_X - D_X C_X^1 \\
\frac{d}{dt} C_X^i = D_X \left( C_X^{i-1} - C_X^i \right) \quad i = 2, \ldots, N_X
\]

where $C_X$ is a quantity to be delayed, $D_X$ is the delay parameter and $N_X$ is the number of delay compartments. The delayed quantity is now defined by

\[
C_X^{\text{del}} = D_X C_X^{N_X}
\]

i.e. as the efflux from the last delay compartment.

As explained in [2,3] this modelling of delays is in between a random, age-independent transition ($N_X = 1$) and a strict "first-in-first-out" kinetic ($N_X \to \infty$). By our modelling, one can mimic both, an expectation and a variance of individual delay times. This is achieved by setting $D_X = T_X/N_X$ where $T_X$ is the desired expectation of the transition time and $N_X$ determines its variance (see [2] for details).
A.4 Chemotherapy

The infusion of chemotherapeutic drugs is modelled by Heaviside functions

\[ \text{CHEMO}^{\text{drug}}(t) = \sum_{i=1}^{N_{\text{cycle}}} (H(t - \tilde{t}_i) - H(t - \tilde{t}_i - t_{\text{inf}}^{\text{CHEMO}})), \]  

(A.5)

where \(N_{\text{cycle}}\) is the number of chemotherapy cycles, \(\tilde{t}_i\) are the time points with application of a specific drug, and \(t_{\text{inf}}^{\text{CHEMO}}\) is the duration of chemotherapy application. The delayed effect of the drugs is modelled by four compartments

\[ \frac{d\Psi_{\text{drug}}^{(i)}}{dt} = \Psi_{\text{drug, out}}^{(i-1)}(t) - k_{\text{Delay}}^{\text{drug}} \cdot \Psi_{\text{drug}}^{(i)}(t), \quad i = 1, \ldots, 4, \]  

(A.6)

with

\[ \Psi_{\text{drug}}^{(0)}(t) = \text{CHEMO}^{\text{drug}}(t), \]
\[ \Psi_{\text{drug, out}}^{(i)}(t) = k_{\text{Delay}}^{\text{drug}} \cdot \Psi_{\text{drug}}^{(i)}(t). \]

The output-function \(\Psi_{\text{drug, out}}^{(4)}(t)\) is multiplied by the toxicity parameters of the single compartments \(k_{S}^{\text{drug}}, k_{\text{CG}}^{\text{drug}}, k_{\text{PGB}}^{\text{drug}}, k_{\text{MGB}}^{\text{drug}}, k_{\text{BE}}^{\text{drug}}, k_{\text{CE}}^{\text{drug}}, k_{\text{PEB}}^{\text{drug}}, k_{\text{MEB}}^{\text{drug}},\) and \(k_{\text{RET}}^{\text{drug}}\) respectively. If multiple cytotoxic drugs are applied, corresponding toxicity functions are added resulting in an overall toxic effect \(\Psi_X\) which is cell stage and chemotherapy specific. In complete analogy to our former work [3,4], the effect of chemotherapy is introduced to the balance equations of the bone marrow cell compartments by a first-order loss term. Hence, the schematic compartment equation has the form

\[ \frac{d}{dt}C_X = A_{\text{in}}^{\text{in}} \cdot C_{X_{\text{in}}}^{\text{in}} - C_X^{\text{out}} - \Psi_X \cdot C_X. \]

In clinical practice often only leukocytes are available. We calculate the leukocyte count as the sum of lymphocytes and granulocytes. To avoid a full model of lymphopoiesis, we modelled the reduced lymphocyte count under chemotherapy by an exponential function of the corresponding toxicity function.

\[ C_{\text{WBC}}(t) \approx c_{\text{LY}} \exp(-\Psi_{\text{LY}}(t)) + c_{\text{GRA}} \frac{C_{\text{GRA}}(t)}{C_{\text{GRA}}^{\text{norm}}} \]  

(A.7)

where \(c_{\text{LY}} = 3000\) cells per \(\mu l\) and \(c_{\text{GRA}} = 4000\) cells per \(\mu l\) are the normal concentrations of lymphocytes and granulocytes respectively. \(\Psi_{\text{LY}}\) is the toxicity function for lymphocytes defined in analogy to the toxicity functions of bone marrow cell stages (see above).
A.5 Stem cell compartment S

Cells differentiating into granulopoietic or erythropoietic lineages originate from the same stem cell compartment. We adopted the corresponding stem cell model of Loeffler & Wichmann [1]. The output of the stem cell compartment is splitted into red or white cell lines under the assumption that 15% of the released cells differentiate into red blood cells ($\alpha_E = 0.15$), and 80% into the white blood cell line ($\alpha_G = 0.8$). The stem cell compartment $S$ has self-renewal capability. Under steady state conditions, 50% of the stem cells remain in this compartment, and 50% differentiate into red or white blood cell lineages. Hence, the stem cell compartment equation is

$$\frac{d}{dt} C_S = (2p - 1)C_S \frac{a_S}{\tau_S} \quad \text{(A.8)}$$

and

$$C_{S}^{\text{out}} = 2(1 - p)C_S \frac{a_S}{\tau_S}, \quad \text{(A.9)}$$

where $a_S$ is the proliferative fraction, $\tau_S$ is the average duration of a cell cycle, and $p$ the self-renewal probability of stem cells.

The self renewal probability $p$ is regulated by a competition of the stem cells ($C_{S}^{\text{rel}}(t)$), the granulopoietic ($C_{G}^{\text{rel}}(t)$), and the erythropoietic ($C_{E}^{\text{rel}}(t)$) bone marrow cells:

$$p = p(C_{S}^{\text{rel}}(t), C_{E}^{\text{rel}}(t), C_{G}^{\text{rel}}(t), p_S, \vartheta_E, \vartheta_G, \vartheta_S(t)),$$

where the parameters $\vartheta_E = -2, \vartheta_G = -8$, and $\vartheta_S(t)$ are hypothetical weighting factors representing the strength of the influence of the bone marrow cells $C_{S}^{\text{rel}}(t) = C_S(t), C_{E}^{\text{rel}}(t) = \frac{C_{BE}(t) + C_{CE}(t) + C_{PEB}(t) + C_{MEB}(t)}{C_{BE} + C_{CE} + C_{PEB} + C_{MEB}}$, and $C_{G}^{\text{rel}}(t) = \frac{C_{BG}(t) + C_{PGB}(t) + C_{MGB}}{C_{BG} + C_{PGB} + C_{MGB}}$. It is assumed that

$$p_S = p^\text{nor} - p^\text{min} = p^\text{max} - p^\text{nor},$$

$$\vartheta_S(t) = \begin{cases} \frac{2}{C_{S}^{\text{rel}}(t)^{\vartheta}} & \text{for } C_{S}^{\text{rel}}(t) \leq 1 \\ 2 & \text{for } C_{S}^{\text{rel}}(t) > 1 \end{cases}$$

$$p = p_S \tanh \left( -\vartheta_S(t)(C_{S}^{\text{rel}}(t) - 1) - \vartheta_E(C_{E}^{\text{rel}}(t) - 1) - \vartheta_G(C_{G}^{\text{rel}}(t) - 1) \right) + 0.5,$$

where the steady state value $p^\text{nor} = \frac{1}{2}$. Thus, for the initial conditions it holds that

$$C_S(0) = C_S^{\text{nor}} = 1 \quad \text{(A.10)}$$

$$C_{S}^{\text{out}}(0) = C_{S}^{\text{out,nor}} = 2(1 - p^\text{nor})C_S^{\text{nor}} \frac{a_S^{\text{nor}}}{\tau_S}, \quad \text{(A.11)}$$

The proliferative fraction $a_S$ can be interpreted as the percentage of cells which are currently in cell cycle. The proliferative fractions $a_X$ of the compartments S, BE and CG are regulated by the haematopoietic bone
marrow system $C_S^{rel}(t)$ and $C_G^{rel}(t)$ or $C_E^{rel}(t)$:

$$a_X = a_X \left(C_S^{rel}(t), C_E^{rel}(t), C_G^{rel}(t), a_X^{\text{min}}, a_X^{\text{nor}}, a_X^{\text{int}}, a_X^{\text{max}}, \omega_E, \omega_G, \omega_S\right).$$

The parameters $\omega_E = 0.3, \omega_G = 0.1$ and $\omega_S = 1$ are weighting factors. They represent the strengths of the influence of stem cells, erythropoietic and granulopoietic cells on the proliferative fraction of BE, CG and S.

With

$$x = \omega_E \ln C_E^{rel}(t) + \omega_G \ln C_G^{rel}(t)$$

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

the proliferative fraction is given by

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

where $X$ is one of the compartments S, BE, or CG. It is a monotone function with ranges between $a_X^{\text{min}}$ and $a_X^{\text{max}}$. Low cell numbers in the bone marrow compartments cause a higher demand of proliferating cells and therefore a larger proliferative fraction $a_X$. The value of $y$ defines the actual point on the regulatory curve.

The variable

$x$ is a measure of the total bone marrow content. It is calculated as a weighted sum of the logarithms of the relative counts of stem cells, erythropoietic cells and granulopoietic cells. If any cell counts tend to zero, $x$ tends to minus infinity, and with it, $a$ becomes maximal. Parameter values $a^{\text{int}}$ corresponds to $x = -\ln 2$ and $a^{\text{nor}}$ corresponds to $x = 0$ (see figure 2).

**A.6 Erythropoiesis**

**Compartment BE**

The model equations of BE are similar to [4], but now the additional influence of the granulopoietic cell lineage on the proliferative fraction in BE is taken into account.

$$\frac{d}{dt} C_{BE} = \alpha_E C_S^{\text{out}} A_{BE} - C_{BE} \frac{a_{BE}}{T_{BE}} - \Psi_{BE} \cdot C_{BE}$$

$$C_{BE}^{\text{out}} = C_{BE} A_{BE} \frac{a_{BE}}{T_{BE}}$$
Figure 2: Regulation of the proliferative fraction - dependence on normalised stem cell count.

Cell stages $C_E$ and $C_G$ were set to normal values. The graph has the same shape if these quantities are varied instead of $C_S$. Parameter settings: $a_S^{\min} = 0.01, a_S^{\text{nor}} = 0.15, a_S^{\text{int}} = 0.45, a_S^{\max} = 1$.

with the initial values

\[
C_{BE}(0) = C_{BE}^{\text{nor}} = \alpha_E C_S^{\text{nor}} A_{BE}^{\text{nor}} T_{BE}^{\text{nor}} / a_{BE}^{\text{nor}}
\]

\[
C_{BE}^{\text{out, nor}} = C_{BE}^{\text{nor}} A_{BE}^{\text{nor}} T_{BE}^{\text{nor}} / a_{BE}^{\text{nor}} = \alpha_E C_S^{\text{out, nor}} A_{BE}^{\text{nor}}
\]

where $\alpha_E = 0.15$ is the proportion of cells differentiating into erythropoietic cell lineage [1].

**Compartment CE**

\[
A_{CE} = Z(C_{EPO}^{\text{int}})
\]

\[
\frac{d}{dt} C_{CE} = C_{CE}^{\text{out}} A_{CE}^{\text{nor}} - \frac{C_{CE}}{T_{CE}} - \Psi_{CE} \cdot C_{CE}
\]

\[
C_{CE}^{\text{out}} = C_{CE} A_{CE}^{\text{nor}} T_{CE}
\]

The initial values are

\[
C_{CE}(0) = C_{CE}^{\text{nor}} = C_{BE}^{\text{nor}} A_{CE}^{\text{nor}} T_{CE}^{\text{nor}}
\]

\[
C_{CE}^{\text{out, nor}} = C_{CE}^{\text{nor}} A_{CE}^{\text{nor}} T_{CE}^{\text{nor}}
\]

The amplification and transit time in the compartment CE are regulated by the growth factors EPO and G-CSF. This is modelled by regulatory functions acting on proliferation rate and transition time in the
compartment CE. The regulatory function of amplification is regulated by the internalised EPO \( Z_{A_CE} \left( C_{EPO}^{int} \right) \). The regulatory function of the transition time is also regulated by internalised EPO, \( Z_{T_CE} \left( C_{EPO}^{int} \right) \). But, it is additionally multiplied by a regulatory function regulated by G-CSF (\( F_{GCSF}(t) \)), mimicking the G-CSF effect on CE. In summary, amplification and transition time in CE are calculated by

\[
A_{CE} = Z_{A_CE} \left( C_{EPO}^{int} \right) \quad (A.13)
\]

\[
T_{CE} = Z_{T_CE} \left( C_{EPO}^{int} \right) \cdot F_{T_{GCSF}}(t). \quad (A.14)
\]

with

\[
F_{T_{GCSF}}(t) = \omega_P(t) \cdot Z_{T_{PEG}}(t) + (1 - \omega_P(t)) \cdot Z_{T_{Fil}}(t), \quad (A.15)
\]

where \( Z_{T_{PEG}}(t) \) and \( Z_{T_{Fil}}(t) \) are the regulation functions of the growth factors endogenous G-CSF and Filgrastim on one hand and Pegfilgrastim on the other hand (equation A.4), \( 0 \leq \omega_P(t) \leq 1 \) is the weighting factor to model the superimposing effect of concurrent Filgrastim or endogenous G-CSF, and Pegfilgrastim (see [3]), and \( C_{EPO}^{int} \) is the internalised EPO (see [4]):

\[
\omega_P = Z_{\omega_P} \left( \frac{C_{GCSF}^{rel,peg}}{C_{GCSF}^{rel,fil}} \right) \quad (A.16)
\]

with \( \omega_{P}^{\text{min}} = 0 \) and \( \omega_{P}^{\text{max}} = 1 \)

**Compartment PEB**

\[
A_{PEB} = Z( C_{EPO}^{int} )
\]

\[
\frac{d}{dt} C_{PEB} = C_{CE} A_{PEB} - \frac{C_{PEB}}{T_{PEB}} - \Psi_{PEB} \cdot C_{PEB}
\]

\[
C_{PEB}^{out} = C_{PEB} \frac{A_{PEB}^{out}}{T_{PEB}}
\]

The initial values are

\[
C_{PEB}(0) = C_{PEB}^{nor} = C_{CE}^{nor} A_{PEB}^{nor} T_{PEB}^{nor}
\]

\[
C_{PEB}^{out}(0) = C_{PEB}^{out,nor} = C_{CE}^{out,nor} A_{PEB}^{nor}.
\]
**Compartment MEB**

The maturation is modelled by splitting MEB into $N_{MEB} = 15$ subcompartments, without amplification.

\[
T_{MEB} = Z(C_{EPO}^{\text{int}})
\]

\[
C_{MEB} = \sum_{i=1}^{N_{MEB}} C_{MEB_i}
\]

\[
\frac{d}{dt} C_{MEB_i} = C_{\text{PEB}} - C_{MEB_i} \frac{N_{MEB}}{T_{MEB}} - \Psi_{MEB} \cdot C_{MEB_i}, \quad i = 2, \ldots, N_{MEB}
\]

\[
\frac{d}{dt} C_{MEB_1} = C_{\text{PEB}} - C_{MEB_1} \frac{N_{MEB}}{T_{MEB}} - \Psi_{MEB} \cdot C_{MEB_1}
\]

\[
C_{\text{out}}^{\text{PEB}} = C_{\text{out}}^{\text{MEB}_1} = \sum_{i=1}^{N_{MEB}} C_{\text{out}}^{\text{MEB}_i}, \quad i = 1, \ldots, N_{MEB}
\]

The initial values are

\[
C_{MEB}(0) = C_{\text{nor}}^{\text{MEB}} = C_{\text{PEB}}^{\text{nor}} \frac{T_{\text{nor}}^{\text{MEB}}}{T_{MEB}}
\]

\[
C_{\text{MEB}_i}(0) = C_{\text{nor}}^{\text{MEB}_i} = C_{\text{PEB}}^{\text{nor}} \frac{T_{\text{nor}}^{\text{MEB}_i}}{N_{MEB}}, \quad i = 1, \ldots, N_{MEB}
\]

\[
C_{\text{out}}^{\text{MEB}_i}(0) = C_{\text{nor}}^{\text{MEB}_i} = C_{\text{MEB}}^{\text{nor}} \frac{T_{\text{nor}}^{\text{MEB}_i}}{T_{MEB}} = C_{\text{out}}^{\text{nor}}^{\text{MEB}_i}, \quad i = 1, \ldots, N_{MEB}
\]

\[
C_{\text{out}}^{\text{MEB}}(0) = C_{\text{nor}}^{\text{MEB}} = C_{\text{MEB}}^{\text{nor}} = C_{\text{out}}^{\text{nor}}
\]

**Compartment RET**

\[
T_{RET} = T_{MEB}^{\text{nor}} + T_{RET}^{\text{nor}} - T_{MEB}
\]

\[
\frac{d}{dt} C_{RET} = C_{\text{out}}^{\text{MEB}} - C_{RET} \frac{T_{\text{nor}}^{\text{RET}}}{T_{RET}} - \Psi_{RET} \cdot C_{RET}
\]

\[
C_{\text{out}}^{\text{RET}} = \frac{C_{RET}}{T_{RET}}
\]

\[
C_{RET}(0) = C_{\text{nor}}^{\text{RET}} = C_{\text{MEB}}^{\text{nor}} \frac{q_{RET}}{1-q_{RET}}
\]

\[
C_{\text{out}}^{\text{RET}}(0) = C_{\text{nor}}^{\text{RET}} = C_{\text{out}}^{\text{nor}}^{\text{RET}}
\]

\[
T_{\text{nor}}^{\text{RET}} = \frac{C_{\text{out}}^{\text{RET}}}{C_{\text{RET}}^{\text{nor}}} = \frac{q_{RET}}{1-q_{RET}} \left(1 - s_{\text{ERY}}^{\text{nor}} T_{\text{ERY}_{\text{rd}}} + s_{\text{ERY}}^{\text{nor}} T_{\text{ERY}_{\text{age}}}ight).
\]

$q_{RET}$ is the proportion of reticulocytes to the total number of red blood cells in steady state. $s_{\text{ERY}}^{\text{nor}}, T_{\text{ERY}_{\text{rd}}}$, and $T_{\text{ERY}_{\text{age}}}$ were explained in the next section.

**Compartment ERY**

The compartment ERY is split into the compartments "RANDOM" and "AGE". In steady state, most erythrocytes die dependent on age. The age dependent reduction is modelled by divisions into subcompart-
ments.

Under stimulation, the depletion is more randomly (i.e. exponential decay, see [5]). Hence, the influxes into the compartments "RANDOM" and "AGE" are regulated by the factor \( s_{ERY} \), which depends on the bone marrow output of the reticulocytes. \( T_{ERY\text{\_rand}} \) and \( T_{ERY\text{\_age}} \) are transition times in the subcompartments "RANDOM" and "AGE". (See [1, 2, 5, 6].)

\[
s_{ERY} = \exp \left( \left( \frac{C_{out\text{\_RET}}}{C_{out\text{\_nor}}} \right)^{2} \ln s_{nor} \right)
\]

\[
C_{ERY} = C_{ERY\text{\_age}} + C_{ERY\text{\_rand}}
\]

\[
C_{ERY\text{\_age}} = \sum_{i=1}^{N_{ERY}} C_{ERY\text{\_age}_{i}}
\]

\[
\frac{d}{dt}C_{ERY\text{\_age}_{1}} = s_{ERY}C_{out\text{\_RET}} - \frac{C_{ERY\text{\_age}_{1}}}{T_{ERY\text{\_age}}} N_{ERY}
\]

\[
\frac{d}{dt}C_{ERY\text{\_age}_{i}} = C_{out\text{\_age}_{i-1}} - C_{out\text{\_age}_{i-1}} - C_{out\text{\_age}_{i}}, \quad i = 2, \ldots, N_{ERY}
\]

\[
\frac{d}{dt}C_{ERY\text{\_rand}} = \left( 1 - s_{ERY} \right)C_{out\text{\_RET}} - \frac{C_{ERY\text{\_rand}}}{T_{ERY\text{\_rand}}} \frac{1}{N_{ERY}}
\]

with initial conditions

\[
C_{ERY}(0) = C_{nor\text{\_ERY}} = C_{nor\text{\_ERY\text{\_age}}} + C_{nor\text{\_ERY\text{\_rand}}}
\]

\[
C_{ERY\text{\_age}}(0) = C_{nor\text{\_ERY\text{\_age}}} = \sum_{i=1}^{N_{ERY}} C_{nor\text{\_ERY\text{\_age}_{i}}} = s_{nor\text{\_ERY}}C_{out\text{\_nor}\text{\_RET}} T_{ERY\text{\_age}}
\]

\[
C_{ERY\text{\_age}_{1}}(0) = C_{nor\text{\_ERY\text{\_age}_{1}}} = s_{nor\text{\_ERY}}C_{out\text{\_nor}\text{\_RET}} T_{ERY\text{\_age}}
\]

\[
C_{ERY\text{\_age}_{i}}(0) = C_{nor\text{\_ERY\text{\_age}_{i}}} = C_{out\text{\_nor}\text{\_RET}} T_{ERY\text{\_age}} \quad i = 2, \ldots, N_{ERY}
\]

\[
C_{out\text{\_age}_{i}}(0) = C_{nor\text{\_ERY\text{\_age}_{i}}} = s_{nor\text{\_ERY}}C_{out\text{\_nor}\text{\_RET}} T_{ERY\text{\_age}}
\]

\[
C_{ERY\text{\_rand}}(0) = C_{nor\text{\_ERY\text{\_rand}}} = \left( 1 - s_{ERY} \right)C_{out\text{\_nor}\text{\_RET}} T_{ERY\text{\_rand}}
\]
Endogenous production of EPO

According to [6, 7], the endogenous production of EPO (EPO$_{\text{prod}}$) is assumed to depend on the oxygen partial pressure in the kidneys and the number of circulating red blood cells

$$EPO_{\text{prod}} = P_{\text{endo max}} e^{-b_{\text{EPO}} f}, \quad \text{where } EPO_{\text{prod}}(0) = 1 \quad \text{and } f = \frac{P'_O}{P_{\text{nor} O}_2}$$

$$P'_O = P_{50} \cdot \left( \frac{S'_{O_2}}{100 - S'_{O_2}} \right)^{\gamma} \quad \text{(Hill equation)}$$

$$S'_O = \frac{100}{\left( \frac{P_{50}}{P_{\text{nor} O}_2} \right) + 1} - \Delta SO_2 \cdot \frac{RET_{\text{nor}} + ERY_{\text{nor}}}{C_{\text{RET}} + C_{\text{ERY}}}$$

$$S'_{O_2} = \frac{100}{\left( \frac{P_{50}}{P_{\text{nor} O}_2} \right) + 1} - \Delta SO_2$$

$$P'_{O_2} = P_{50} \cdot \left( \frac{S'_{O_2}}{100 - S'_{O_2}} \right)^{\gamma}$$

The variables are explained in Table A.2. For further explanation and justification, see [4, 6, 7].

| quantity | meaning | type/calculation |
|----------|---------|------------------|
| $P'_O$  | kidney tissue oxygen tension | function of time [6, 7] |
| $P'_{O_2}$ | kidney tissue oxygen pressure, normal value | [6, 7] |
| $S'_O$  | percent saturation of hemoglobin | function of time [6, 7] |
| $S'_{O_2}$ | normal value of percent saturation of hemoglobin | constant [6, 7] |
| $P_{50}$ | partial oxygen pressure corresponding to $S'_{O_2} = 50\%$ | 26.5 mm Hg [6, 7] |
| $P'_{A_2}$ | arterial oxygen pressure, normal value | 97 mm Hg [6, 7] |
| $\Delta SO_2$ | desaturation of HB (arteriovenous difference), normal value | 20 % [6, 7] |
| $\gamma$ | Hills coefficient, describes the slope of the curve | 2.65 [6, 7] |
| $P_{\text{endo max}}$ | maximum production | 200 (set) [6, 7] |
| $b_{\text{EPO}}$ | sensitivity of EPO$_{\text{prod}}$ to changes in $P'_O$ | $\ln 200$ (set) [6, 7] |

Exogenous EPO Application

In our model, we use simple pulse functions EPO$_{\text{inj}}$ for intravenous injections. Regarding subcutaneous injections, the model adapted from [8] includes direct absorption from the subcutaneous tissue into the bloodstream, or indirect through the lymphatic system. In both processes, a time delay is assumed. A loss of EPO is included at the injection site ($k^F$) and in the lymphatic system ($k^L$). The structure of this
injection model is described in detail in [4, 8]. The model equations read as follows: The general EPO injection function $EPO_{\text{inj}}(t)$ is modelled by a sum of pulse functions

$$EPO_{\text{inj}}(t) = \frac{EPO_{\text{dose}}}{EPO_{\text{tinf}}} \sum_{i=1}^{N} (Hv(t - \tilde{t}_i) - Hv(t - \tilde{t}_i - EPO_{\text{tinf}})),$$

where (A.17)

$$Hv(t) = \begin{cases} 0 : t \leq 0 \\ 1 : t > 0 \end{cases}.$$  

(A.18)

is the Heaviside-function, $\tilde{t}_i$ are time points at which EPO at dose $EPO_{\text{dose}}$ is administered. The injection time $EPO_{\text{tinf}}$ is set to five minutes, and $EPO_{\text{dose}}$ is the administered dose in IU/kg. The dynamics of the EPO concentration in the subcutaneous tissue $C_{\text{SC}EPO}(t)$ is described by:

$$\frac{d}{dt} C_{\text{SC}EPO}(t) = EPO_{\text{inj}}(t) - C_{\text{SC}EPO}(t) \cdot (k_a^F + k_{FL} + k_e^F),$$

(A.19)

where $k_a^F$ is the absorption constant for the direct influx into the central compartment, $k_e^F$ is a loss term at injection site, and $k_{FL}$ is the absorption constant of the lymphatic system. The efflux from the subcutaneous tissue into the peripheral blood is delayed by four delay compartments, i.e.

$$\frac{d}{dt} C_{\text{EPO}Fout}^{(i)}(t) = C_{\text{EPO}Fout}^{(i-1)}(t) - k_{\text{Delay}}^F \cdot C_{\text{EPO}F}^{(i)}(t), \quad i = 1, \ldots, 4,$$

(A.20)

with the settings

$$C_{\text{EPO}Fout}^{(0)}(t) = C_{\text{SC}EPO}(t) \cdot k_a^F,$$

and

$$C_{\text{EPO}Fout}^{(i)}(t) = k_{\text{Delay}}^F \cdot C_{\text{EPO}F}^{(i)}(t), \quad i = 1, \ldots, 4.$$

$C_{\text{EPO}Fout}^{(4)}(t)$ enters the central EPO compartment. Analogously, the lymphatic absorption is modelled by a delay function with four compartments:

$$\frac{d}{dt} C_{\text{EPO}Lout}^{(i)}(t) = C_{\text{EPO}Lout}^{(i-1)}(t) - k_{\text{Delay}}^L \cdot C_{\text{EPO}L}^{(i)}(t), \quad i = 1, \ldots, 4,$$

(A.21)

$$C_{\text{EPO}Lout}^{(0)}(t) = C_{\text{SC}EPO}(t) \cdot k_{FL},$$

$$C_{\text{EPO}Lout}^{(i)}(t) = k_{\text{Delay}}^L \cdot C_{\text{EPO}L}^{(i)}(t), \quad i = 1, \ldots, 4,$$

where $C_{\text{EPO}Lout}^{(4)}(t)$ enters the central compartment. Thus, EPO dynamics in the lymphatic compartment $C_{\text{EPO}L}$ are given by

$$\frac{d}{dt} C_{\text{EPO}L}(t) = C_{\text{EPO}Lout}^{(4)}(t) - C_{\text{EPO}L}(t) \cdot (k_a^L + k_e^L),$$

(A.22)

$$C_{\text{EPO}L}(0) = 0.$$
where $k_a^L$ is the absorption constant of the transition between the lymphatic and the central compartment and $k_e^L$ is a loss term. Summarising the effluxes of the direct and the lymphatic way of absorption yields

$$EPO^{\text{exogen}}(t) = C_{\text{EPO}}^L(t) \cdot k_a^L + C_{\text{EPO, Ecent}}^L(t),$$  \hfill (A.23)

for subcutaneously administered EPO and

$$EPO^{\text{exogen}}(t) = EPO^{\text{inj}}(t).$$  \hfill (A.24)

for intravenous injections.

**Central EPO Compartment**

Dynamics of Erythropoietin in central compartment (circulation) is modelled in the following way (see [1, 4, 9]):

$$\frac{dC_{\text{EPO}}^{\text{cent}}}{dt} = P_{\text{EPO}}^{\text{endo}}(t) - k_{\text{on}} \cdot R(t) \cdot C_{\text{EPO}}^{\text{cent}}(t) + k_{\text{off}} \cdot C_{\text{EPO}}^{\text{rb}}(t) - k_{\text{cl}} \cdot C_{\text{EPO}}^{\text{cent}}(t)$$

$$- k_{12} \cdot C_{\text{EPO}}^{\text{cent}}(t) + k_{21} \cdot C_{\text{peri}}^{\text{EPO}}(t) + EPO^{\text{exogen}}(t),$$  \hfill (A.25)

with

$$P_{\text{EPO}}^{\text{endo}}(t) = (C_{\text{EPO}}^{\text{cent}}(0) \cdot k_{\text{cl}} - C_{\text{EPO}}^{\text{rb}}(0) \cdot k_{\text{off}} + k_{\text{on}} \cdot R(0) \cdot C_{\text{EPO}}^{\text{cent}}(0) \cdot \text{EPO}_{\text{prod}},$$  \hfill (A.26)

where EPO$_{\text{prod}}$ equals one in steady state, so that equation A.25 equals zero.

The peripheral compartment and the EPO-receptor complex are described by

$$\frac{dC_{\text{EPO}}^{\text{peri}}}{dt} = k_{12} \cdot C_{\text{EPO}}^{\text{cent}}(t) - k_{21} \cdot C_{\text{EPO}}^{\text{peri}}(t)$$

$$\frac{dC_{\text{EPO}}^{\text{rb}}}{dt} = k_{\text{on}} \cdot R(t) \cdot C_{\text{EPO}}^{\text{cent}}(t) - (k_{\text{off}} + k_{\text{int}}) \cdot C_{\text{EPO}}^{\text{rb}}(t).$$

The dynamics of the EPO receptors $R$ is determined on the basis of the bone marrow content of the cell kinetic model, namely the compartments $C_{\text{BE}}$, $C_{\text{CE}}$, $C_{\text{PEB}}$, $C_{\text{MEB}}$, and $C_{\text{RET}}$ [4].

To account for different receptor densities of erythropoietic bone marrow cells we introduced weighting factors $w_{\text{RET}}$, $w_{\text{MEB}}$, $w_{\text{PEB}}$, $w_{\text{CE}}$, and $w_{\text{BE}}$. CFU-E have the highest weighting factor due to the highest number of EPO receptors observed [10]: $w_{\text{BE}} \leq w_{\text{CE}}$. The receptor density declines with further maturation: $w_{\text{RET}} \leq w_{\text{MEB}} \leq w_{\text{PEB}} \leq w_{\text{CE}}$. Hence

$$\frac{dR}{dt} = k_{\text{off}} \cdot C_{\text{EPO}}^{\text{rb}}(t) - k_{\text{on}} \cdot R(t) \cdot C_{\text{EPO}}^{\text{cent}}(t) - k_{\text{deg}} \cdot R(t) + k_{\text{syn}} \cdot R_{\text{rel}}^{\text{rel}}(t)$$  \hfill (A.27)
where \( R_{rel}(t) = w_{RET} \cdot C_{RET} + w_{MEB} \cdot C_{MEB} + w_{PEB} \cdot C_{PEB} + w_{CE} \cdot C_{CE} + w_{BE} \cdot C_{BE} \) is the number of EPO receptors relative to steady-state \([4]\).

The initial values are derived from steady-state conditions

\[
C_{EPO}^{\text{rb}}(0) = \frac{k_{\text{on}}}{k_{\text{off}} + k_{\text{int}}} \cdot R(0) \cdot C_{\text{cent}}^{EPO}(0)
\]

\[
P_{\text{endo}}^{EPO}(0) = C_{EPO}^{\text{rb}}(0) \cdot k_{\text{cl}} - C_{EPO}^{\text{rb}}(0) \cdot k_{\text{off}} + k_{\text{on}} \cdot R(0) \cdot C_{EPO}(0)
\]

\[
P_{\text{peri}}^{EPO}(0) = \frac{k_{12}}{k_{21}} \cdot C_{EPO}^{\text{cent}}(0)
\]

where \( C_{\text{cent}}^{EPO}(0) = EPO_{\text{serum}} \cdot EPO_{Vc} \), \( EPO_{\text{serum}} = 15 \text{ IU/l} \) is the basic level of endogenous EPO, and \( EPO_{Vc} \) denotes the distribution volume of EPO \([9]\). According to \([9]\), we set \( R(0) = 64.31 \) and from equation A.27 it follows that \( k_{\text{syn}} = k_{\text{deg}} \cdot R(0) + k_{\text{int}} \cdot C_{EPO}^{\text{rb}}(0) \). The relative internalised EPO \( C_{\text{EPO,int}}^{\text{rel}} \) is used as argument of the regulatory functions regulated by EPO:

\[
C_{EPO,int}(t) = C_{EPO}^{\text{rb}}(t) \cdot k_{\text{int}}
\]

\[
C_{EPO,int}^{\text{rel}}(t) = \frac{C_{EPO,int}(t)}{C_{EPO,int}(0)}.
\]

### A.7 Granulopoiesis

Here we present model equations of our granulopoiesis model (see also \([3]\)). Initial conditions are derived again from steady-state conditions.

**Compartment CG**

The model equations of CG are similar to \([3]\). The influence of red blood cell line on the proliferative fraction is modelled in analogy to \([1]\).

\[
A_{CG} = Z_{A_{CG}} \left( C_{\text{cent}}^{\text{GCSF}, \text{rel}} \right)
\]

\[
T_{CG} = Z_{T_{CG}} \left( C_{\text{cent}}^{\text{GCSF}, \text{rel}} \right)
\]

\[
\frac{d}{dt} C_{CG} = \alpha_{G} C_{S} C_{CG} - C_{CG} \frac{a_{CG}}{T_{CG}} - k_{CG} \Psi_{CG} C_{CG}
\]

(A.28)

where \( a_{CG} \) is the proliferative fraction and \( \alpha_{G} = 0.8 \) is the part of cells differentiating into the white blood cell line \([1]\). The amplification \( A_{CG} \) and the transit time \( T_{CG} \) are regulated by the concentration of G-CSF in the central compartment.
Compartment PGB

\[
\begin{align*}
A_{\text{PGB}} &= Z_{A_{\text{PGB}}} \left( C_{\text{GCSF}}^{\text{cent rel del}} \right) \\
T_{\text{PGB}} &= Z_{T_{\text{PGB}}} \left( C_{\text{GCSF}}^{\text{cent rel del}} \right) \\
\frac{d}{dt} C_{\text{PGB}} &= C_{\text{out}} C_{\text{PGB}} - \frac{C_{\text{PGB}}}{T_{\text{PGB}}} - k_{\text{PGB}} \Psi_{\text{PGB}} C_{\text{PGB}} \\
C_{\text{out}} &= A_{\text{PGB}} \frac{C_{\text{PGB}}}{T_{\text{PGB}}}
\end{align*}
\]

(A.29) (A.30) (A.31) (A.32)

Compartment MGB

This compartment is divided into three compartments denoted as \( G_4, G_5 \) and \( G_6 \). The compartments are again divided into \( N_X \) subcompartments to model the maturation process by a delay. In these subcompartments, the effect of postmitotic apoptosis is also implemented [2, 11] by introducing a postmitotic amplification denoted again as \( A \). It holds that \( A \leq 1 \) for all subcompartments.

\[
\begin{align*}
C_{\text{MGB}} &= C_{G_4} + C_{G_5} + C_{G_6} \\
C_{\text{out}}^{\text{MGB}} &= C_{\text{out}}^{\text{G_6}} \\
A_{G_4} &= Z_{A_{G_4}} \left( C_{\text{GCSF}}^{\text{cent rel del}} \right) \\
T_{G_4} &= Z_{T_{G_4}} \left( C_{\text{GCSF}}^{\text{cent rel del}} \right) \\
C_{G_4} &= \sum_{i=1}^{N_{G_4}} C_{G_4 i}
\end{align*}
\]

(A.33) (A.34) (A.35) (A.36) (A.37)

\[
\begin{align*}
\frac{d}{dt} C_{G_4 1} &= C_{\text{out}} - C_{G_4 1} \frac{N_{G_4}}{T_{G_4}} - k_{\text{MGB}} \Psi_{\text{MGB}} C_{G_4 1} \\
\frac{d}{dt} C_{G_4 i} &= C_{\text{out}} C_{G_4 (i-1)} - C_{G_4 i} \frac{N_{G_4}}{T_{G_4}} - k_{\text{MGB}} \Psi_{\text{MGB}} C_{G_4 i}, \quad i = 2, \ldots, N_{G_4} \\
C_{\text{out}}^{\text{G_4 i}} &= A_{G_4} C_{G_4} \frac{N_{G_4}}{T_{G_4}}, \quad i = 1, \ldots, N_{G_4} \\
C_{\text{out}}^{\text{G_4}} &= C_{\text{out}}^{\text{G_4} N_{G_4}}
\end{align*}
\]

(A.38) (A.39) (A.40) (A.41)

The total postmitotic amplification \( A_{G_4} \) is equally distributed over all subcompartments in which there is postmitotic amplification, e.g. if there is postmitotic amplification in all subcompartments, it holds that 

\[
A_{G_4 i} = A_{G_4}^{1/N_{G_4}}.
\]

For \( G_5 \) and \( G_6 \) the equations are completely analogous to (A.35)–(A.41) if one replaces PGB by G4 and G5 respectively. In the present form of our model, postmitotic amplification is restricted to G6.
Compartment GRA

\[ \frac{d}{dt} C_{\text{GRA}} = C_{\text{MGB}} - C_{\text{GRA}} \cdot \frac{1}{T_{\text{GRA}}} \]  
(A.42)

\[ T_{\text{GRA}} = T_{\text{nor}}^{\text{GRA}} (1 + T_{\text{GRA}}^{\text{Pred}} \Psi_{\text{Pred}}) \]  
(A.43)

where \( \Psi_{\text{Pred}} \) is the characteristic function of Prednisone applications modelled as a step-function which is equal to one for the duration of one day after Prednisone application.

Granulopoietic cells

\[ C_G = C_{\text{CG}} + C_{\text{PGB}} + C_{\text{MGB}} \]  
(A.44)

G-CSF

According to [2], the relative G-CSF production \( P^{\text{endo}}_{\text{GCSF}} \) is a regulatory function of the relative content of segmented granulocytes in bone marrow and granulocytes in circulation.

\[ P^{\text{endo}}_{\text{GCSF}} = Z \left( \frac{\omega_{\text{G}} C_{\text{G}}}{\omega_{\text{G}} + \omega_{\text{GRA}} C_{\text{GRA}}} \right), \]  
(A.45)

where \( \omega_{\text{G}} \) and \( \omega_{\text{GRA}} \) are weighting parameters and \( P^{\text{endo}}_{\text{por}} = 1 \).

The G-CSF injection function reads as follows:

\[ P^{\text{exo}}_{\text{GCSF}} = \sum_{i=1}^{L} d_{\text{GCSF}}(t_i) \frac{Hv(t - t_i) - Hv(t - t_i - t_{\text{inf}})}{t_{\text{inf}}} \]  
(A.46)

where \( Hv(t) \) is the Heaviside-function (equation A.18), \( t_i \geq 0 \) (\( i = 1, \ldots, L \)) are the time points of G-CSF injections and \( d_{\text{GCSF}}(t_i) \) are the corresponding doses (in \( \mu\text{g} \)). The injection time \( t_{\text{inf}} \) is set to 5s. The injection function is specific for each G-CSF derivative (details see [3]).

The subcutaneous compartment is divided into two subcompartments \( sc_1 \) and \( sc_2 \) where the efflux of the first compartment is the influx to the second compartment. G-CSF is applied to the first subcompartment (second term of A.47). In the first subcompartment there is a dose-dependent loss of G-CSF modelled by a Michaelis-Menten kinetic (third term of A.47). For Filgrastim injections it holds that

\[ \frac{d}{dt} C_{\text{GCSF}}^{sc_1} = P^{\text{exo}}_{\text{GCSF}} - k_{sc} C_{\text{GCSF}}^{sc_1} - \frac{v_{\text{max}} C_{\text{GCSF}}^{sc_1}}{k_m + C_{\text{GCSF}}^{sc_1}} \]  
(A.47)

\[ \frac{d}{dt} C_{\text{GCSF}}^{sc_2} = k_{sc} ^F (C_{\text{GCSF}}^{sc_1} - C_{\text{GCSF}}^{sc_2}) \]  
(A.48)

with the initial values \( C_{\text{GCSF}}^{sc_1}(0) = C_{\text{GCSF}}^{sc_2}(0) = 0 \). For Pegfilgrastim injections the first term of the right-hand side of A.47 is substituted by \( P^{\text{exo}}_{\text{GCSF}}^{\text{peg}} \). Likewise, the Filgrastim parameters \( k_{sc} ^F, v_{\text{max}} ^F \) and \( k_m ^F \) are substituted by corresponding Pegfilgrastim parameters.

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For Filgrastim injections it holds that

\[
\frac{dC_{\text{cent}}^{\text{GCSF}}}{dt} = P_{\text{GCSF}}^{\text{ref}} + P_{\text{endo}}^{\text{GCSF}} + k_F^{\text{cent}} C_{\text{cent}}^{\text{GCSF}} - k_u^{\text{cent}} C_{\text{cent}}^{\text{GCSF}} - k_F^{\text{sc}} C_{\text{sc}}^{\text{GCSF}}(A.49)
\]

The balance equation A.49 contains the following terms: \(P_{\text{GCSF}}^{\text{ref}}\) is the endogenous production, \(P_{\text{endo}}^{\text{GCSF}}\) is the intravenous injection, \(k_F^{\text{cent}} C_{\text{cent}}^{\text{GCSF}}\) is the influx from the subcutaneous compartment, \(k_u^{\text{cent}} C_{\text{cent}}^{\text{GCSF}}\) is the unspecific elimination, \(k_F^{\text{sc}} C_{\text{sc}}^{\text{GCSF}}\) is the influx from the peripheral compartment and \(v_{\text{GRA}}^{\text{max}} C_{\text{cent}}^{\text{GCSF}}\) is the specific elimination. The corresponding equation for Pegfilgrastim is the same except for the endogenous production, which is zero, the intravenous injection function which is substituted by \(P_{\text{exo}}^{\text{peg}}\), the parameters and the initial value which is again zero.

With \(C_{\text{cent}}^{\text{GCSF}}(0) = C_{\text{GCSF}}^{\text{nor}} = V_F D C_{\text{cent}}^{\text{ref}}\), the parameter \(P_{\text{GCSF}}^{\text{ref}}\) can be calculated from the steady-state conditions \(P_{\text{endo}}^{\text{GCSF}}(0) = 1, P_{\text{exo}}^{\text{GCSF}}(0) = 0\) and \(-k_F^{\text{sc}} C_{\text{cent}}^{\text{GCSF}}(0) + k_F^{\text{per}} C_{\text{per}}^{\text{GCSF}}(0) = 0:\)

\[
P_{\text{GCSF}}^{\text{ref}} = V_F D C_{\text{cent}}^{\text{ref}} \left( k_u + \frac{v_{\text{GRA}}^{\text{max}}}{k_m^{\text{GRA}} + C_{\text{cent}}^{\text{GCSF}}} \right), \quad (A.50)
\]

where \(V_F\) is the distribution volume and \(C_{\text{cent}}^{\text{GCSF}}^{\text{ref}}\) is the reference G-CSF serum concentration.

For both G-CSF derivatives, we have transitions between central and peripheral compartment:

\[
\frac{dC_{\text{per}}^{\text{GCSF}}}{dt} = k_c^{\text{per}} C_{\text{cent}}^{\text{GCSF}} - k_p^{\text{per}} C_{\text{per}}^{\text{GCSF}} \quad \text{(A.51)}
\]

\[
C_{\text{per}}^{\text{GCSF}}(0) = C_{\text{per}}^{\text{nor}} = V_D \left( k_p^{\text{per}} C_{\text{per}}^{\text{GCSF}}^{\text{ref}} \right) \quad \text{(A.52)}
\]

where the parameters \(k_c, k_p\) and \(V_D\) are specific for Filgrastim and Pegfilgrastim respectively. To model the competition of Pegfilgrastim and endogenous G-CSF with respect to receptor binding, the regulatory functions of Pegfilgrastim and Filgrastim were again combined using the weighting factor \(\omega_p\) defined in equation A.16:

\[
Z_Y = \omega_p \cdot Z_Y \left( C_{\text{GCSF}}^{\text{cent,rel,del,peg}} \right) + (1 - \omega_p) \cdot Z_Y \left( C_{\text{GCSF}}^{\text{cent,rel,del,fil}} \right)
\]

where \(Y\) is an arbitrary quantity regulated by G-CSF such as transition times or amplifications. For all these quantities we assumed the same regulatory function of the weighting parameter \(\omega_p\).

### A.8 Parameters

Here, we present all parameters of the model, their values, and how they were determined. In table A.3 we present general parameters of the cell kinetic model of granulopoiesis.
### Table A.3: G-CSF PK/PD parameters

| parameter | meaning                                                                 | value       |
|-----------|--------------------------------------------------------------------------|-------------|
| $\alpha_G$ | percentage of stem cells differentiating to myeloid cells               | 0.8         |
| $\alpha_E$ | percentage of stem cells differentiating to erythroid cells             | 0.15        |
| $S_{\text{nor}}$ | normal value of stem cells                                                | 1           |
| $\tau_S$ | duration of cell cycle                                                   | 8 [1], p. 70 |
| $p_{E}$ | self-renewal probability                                                 | 0.1 [1], p. 70 |
| $a_{\min}$ | proliferative fraction under minimal stimulation                          | 0.01 [1], p. 70 |
| $a_{\text{nor}}$ | proliferative fraction under normal stimulation                        | 0.15 [1], p. 70 |
| $a_{\text{int}}$ | proliferative fraction under intensified stimulation                     | 0.45 [1], p. 70 |
| $a_{\max}$ | proliferative fraction under maximal stimulation                          | 1 [1], p. 70 |
| $w_E$ | weighting parameter $E$ for regulation of $a$                             | 0.3 [1], p. 70 |
| $w_S$ | weighting parameter $S$ for regulation of $a$                             | 1 [1], p. 70 |
| $p_{E}$ | weighting parameter $E$ for regulation of $p$                             | -2 [1], p. 70 |
| $p_{G}$ | weighting parameter $G$ for regulation of $p$                             | -8 [1], p. 70 |
| $N_{G4}$ | number of subcompartments in $G4$                                         | 5 set       |
| $N_{G5}$ | number of subcompartments in $G5$                                         | 5 set       |
| $N_{G6}$ | number of subcompartments in $G6$                                         | 5 set       |
| $a_{\text{min}}$ | proliferative fraction under minimal stimulation                          | 0.1205 fitted |
| $a_{\text{nor}}$ | proliferative fraction under normal stimulation                        | 0.1252 fitted |
| $a_{\text{int}}$ | proliferative fraction under intensified stimulation                     | 0.8340 fitted |
| $w_{G\text{GRA}}$ | influence of $G\text{GRA}$ on G-CSF production                          | 1 set [12] |
| $w_{G6}$ | influence of $G6$ on G-CSF production                                      | 0.2 set [12] |
| $P_{\text{endo} \text{max}}$ | maximal G-CSF production                                                 | 257.5 fitted |
| $P_{\text{endo} \text{nor}}$ | normal G-CSF production                                                  | 1 set       |
| $P_{\text{endo} \text{min}}$ | minimal G-CSF production                                                 | 0.3179 fitted |
| $p_{GCSF}$ | sensitivity parameter of G-CSF production                                | 0.0220 fitted |
| $T_{\text{nor} \text{GRA}}$ | transition time of granulocytes                                         | 5.576 fitted |
| $T_{\text{pred} \text{GRA}}$ | prolongation of $T_{\text{GRA}}$ under Prednisone                       | 0.4659 fitted |

In Table A.4 we present parameters of the granulopoiesis model which are assumed to be different for Filgrastim and Pegfilgrastim respectively. Note that for endogenous G-CSF, we assumed the same parameter setting as for Filgrastim.

### Table A.4: G-CSF pharmacokinetic and -dynamic parameters

| parameter | meaning                                                      | value       |
|-----------|--------------------------------------------------------------|-------------|
| $k_F^{sc}$ | subcutaneous absorption                                     | 0.1613 fitted |
| $k_F^{GCSF}$ | Michaelis-Menten constant of subcutaneous elimination       | 34.68 fitted |
| $v_{\text{max}}$ | Maximum of subcutaneous elimination                        | 67.27 fitted |
| $k_F^u$ | unspecific elimination                                      | 0.4408 fitted |
| $k_{G4}^{12}$ | transition central to peripheral                            | 0.0001 fitted |
| $k_{G5}^{21}$ | transition peripheral to central                            | 0.3564 indeterminable |
| $V_{D_F}$ | distribution volume                                         | 1.156 fitted |
| $v_{\text{GRA} \text{F}}^{\max}$ | Maximum of specific elimination                          | 4.769 fitted |
| **Parameter** | **Description** | **Value** | **Fit Type** |
|---------------|-----------------|-----------|--------------|
| $k_{19}^{GRA}$ | Michaelis-Menten constant of specific elimination | 22.38 | fitted |
| $T_{CG, min}$ | transition time in CG under minimal stimulation | 82.02 | fitted |
| $T_{CG, nor}$ | transition time in CG under normal stimulation | 78.19 | fitted |
| $T_{CG, max}$ | transition time in CG under maximal stimulation | 286.3 | fitted |
| $h_{CG}$ | sensitivity of transition time in CG | 0.5901 | fitted |
| $A_{CG, min}$ | amplification in CG under minimal stimulation | 0.9101 | fitted |
| $A_{CG, nor}$ | amplification in CG under normal stimulation | 104.6 | fitted |
| $A_{CG, max}$ | amplification in CG under maximal stimulation | 206.2 | fitted |
| $A_{PGB, b}$ | sensitivity of transition time in PGB | 0.0241 | fitted |
| $A_{PGB, min}$ | amplification in PGB under minimal stimulation | 1.307 | fitted |
| $A_{PGB, nor}$ | amplification in PGB under normal stimulation | 61.20 | fitted |
| $A_{PGB, max}$ | amplification in PGB under maximal stimulation | 814.7 | fitted |
| $A_{PGB, b}$ | sensitivity of amplification in PGB | 0.7212 | fitted |
| $T_{PGB, min}$ | transition time in PGB under minimal stimulation | 4.640 | fitted |
| $T_{PGB, nor}$ | transition time in PGB under normal stimulation | 40.89 | fitted |
| $T_{PGB, max}$ | transition time in PGB under maximal stimulation | 217.1 | fitted |
| $b_{PGB, b}$ | sensitivity of transition time in PGB | 0.1041 | fitted |
| $A_{G4, b}$ | postmitotic amplification in G4 | 1 | set |
| $T_{G4, min}$ | transition time in G4 under minimal stimulation | 119.2 | fitted |
| $T_{G4, nor}$ | transition time in G4 under normal stimulation | 11.37 | fitted |
| $T_{G4, max}$ | transition time in G4 under maximal stimulation | 3.93 | fitted |
| $b_{G4, b}$ | sensitivity of transition time in G4 | 0.3661 | fitted |
| $A_{G5, b}$ | postmitotic amplification in G5 | 1 | set |
| $T_{G5, min}$ | transition time in G5 under minimal stimulation | 48.3 | fitted |
| $T_{G5, nor}$ | transition time in G5 under normal stimulation | 37.00 | fitted |
| $T_{G5, max}$ | transition time in G5 under maximal stimulation | 4.64 | fitted |
| $b_{G5, b}$ | sensitivity of transition time in G5 | 0.4588 | fitted |
| $A_{G6, min}$ | postmitotic amplification in G6 under minimal stimulation | 0.2005 | fitted |
| $A_{G6, nor}$ | postmitotic amplification in G6 under normal stimulation | 0.2488 | fitted |
| $A_{G6, max}$ | postmitotic amplification in G6 under maximal stimulation | 0.8495 | fitted |
| $A_{G6, b}$ | sensitivity of postmitotic amplification in G6 | 0.5034 | fitted |
| $T_{G6, min}$ | transition time in G6 under minimal stimulation | 140.9 | fitted |
| $T_{G6, nor}$ | transition time in G6 under normal stimulation | 82.02 | fitted |
| $T_{G6, max}$ | transition time in G6 under maximal stimulation | 41.38 | fitted |
| $b_{G6, b}$ | sensitivity of transition time in G6 | 0.5260 | fitted |

### Pegfilgrastim

| **Parameter** | **Description** | **Value** | **Fit Type** |
|---------------|-----------------|-----------|--------------|
| $k_{F}$ | subcutaneous absorption | 0.1071 | fitted |
| $k_{sc}$ | Michaelis-Menten constant of subcutaneous elimination | 5.456 | fitted |
| $v_{max}^{sc}$ | Maximum of subcutaneous elimination | 16.50 | fitted |
| $k_{u}$ | unspecific elimination | 0.0874 | fitted |
| $v_{max}^{GRA}$ | Maximum of specific elimination | 5.159 | fitted |
| $k_{19}^{GRA}$ | Michaelis-Menten constant of specific elimination | 30.82 | fitted |
| $V_{D}$ | distribution volume | 4.091 | fitted |
| $k_{12}^{P}$ | transition central to peripheral | 0.0746 | fitted |
| $k_{P1}$ | transition peripheral to central | 0.5475 | fitted |
| $\omega_{min}^{P}$ | minimum of weighting function | 0 | set |
| $\omega_{max}^{P}$ | maximum of weighting function | 1 | set |
| $\omega_{P}$ | value of weighting function for 1µg Pegfilgrastim | 0.4994 | fitted |
| $A_{CG, min}$ | transition time in CG under minimal stimulation | 4.210 | fitted |
Next we present parameters of the cell kinetic model of erythropoiesis not presented in table A.3 and which do not depend on the kind of EPO derivative or their mode of application (table A.5).

A number of parameters depending on EPO derivative but not on mode of application is presented in table A.6.

| Parameter | Description | Value | Type |
|-----------|-------------|-------|------|
| $A_{\text{nor}}^{\text{CGP}}$ | Transition time in CG under normal stimulation | 356.7 | fitted |
| $A_{\text{max}}^{\text{CGP}}$ | Transition time in CG under maximal stimulation | 668.7 | fitted |
| $A_{b}^{\text{CGP}}$ | Sensitivity of transition time in CG | 0.1026 | fitted |
| $T_{\text{min}}^{\text{CGP}}$ | Amplification in CG under minimal stimulation | 0.8480 | fitted |
| $T_{\text{nor}}^{\text{CGP}}$ | Amplification in CG under normal stimulation | 1.687 | fitted |
| $T_{\text{max}}^{\text{CGP}}$ | Amplification in CG under maximal stimulation | 57.60 | fitted |
| $T_{b}^{\text{CGP}}$ | Sensitivity of amplification in CG | 0.0396 | fitted |
| $A_{\text{min}}^{\text{PGBP}}$ | Amplification in PGB under minimal stimulation | 0.0669 | fitted |
| $A_{\text{nor}}^{\text{PGBP}}$ | Amplification in PGB under normal stimulation | 24.54 | fitted |
| $A_{\text{max}}^{\text{PGBP}}$ | Amplification in PGB under maximal stimulation | 47.00 | fitted |
| $A_{b}^{\text{PGBP}}$ | Sensitivity of amplification in PGB | 0.3266 | fitted |
| $T_{\text{min}}^{\text{PGBP}}$ | Transition time in PGB under minimal stimulation | 0.7558 | fitted |
| $T_{\text{nor}}^{\text{PGBP}}$ | Transition time in PGB under normal stimulation | 24.66 | fitted |
| $T_{\text{max}}^{\text{PGBP}}$ | Transition time in PGB under maximal stimulation | 24.69 | fitted |
| $T_{b}^{\text{PGBP}}$ | Sensitivity of transition time in PGB | 0.1180 | fitted |
| $A_{\text{nor}}^{\text{G4PCR}}$ | Postmitotic amplification in G4 | 0.3266 | fitted |
| $T_{\text{min}}^{\text{G4PCR}}$ | Transition time in G4 under minimal stimulation | 152.8 | fitted |
| $T_{\text{nor}}^{\text{G4PCR}}$ | Transition time in G4 under normal stimulation | 14.19 | fitted |
| $T_{\text{max}}^{\text{G4PCR}}$ | Transition time in G4 under maximal stimulation | 4.168 | fitted |
| $T_{b}^{\text{G4PCR}}$ | Sensitivity of transition time in G4 | 0.2246 | fitted |
| $A_{\text{nor}}^{\text{G5PCR}}$ | Postmitotic amplification in G5 | 0.3213 | fitted |
| $T_{\text{min}}^{\text{G5PCR}}$ | Transition time in G5 under minimal stimulation | 152.8 | fitted |
| $T_{\text{nor}}^{\text{G5PCR}}$ | Transition time in G5 under normal stimulation | 14.19 | fitted |
| $T_{\text{max}}^{\text{G5PCR}}$ | Transition time in G5 under maximal stimulation | 4.168 | fitted |
| $T_{b}^{\text{G5PCR}}$ | Sensitivity of transition time in G5 | 0.2246 | fitted |
| $A_{\text{min}}^{\text{G6PCR}}$ | Postmitotic amplification in G6 under minimal stimulation | 0.3213 | fitted |
| $A_{\text{nor}}^{\text{G6PCR}}$ | Postmitotic amplification in G6 under normal stimulation | 0.3213 | fitted |
| $A_{\text{max}}^{\text{G6PCR}}$ | Postmitotic amplification in G6 under maximal stimulation | 1.0000 | fitted |
| $A_{b}^{\text{G6PCR}}$ | Sensitivity of postmitotic amplification in G6 | 0.3213 | fitted |
| $T_{\text{min}}^{\text{G6PCR}}$ | Transition time in G6 under minimal stimulation | 152.8 | fitted |
| $T_{\text{nor}}^{\text{G6PCR}}$ | Transition time in G6 under normal stimulation | 14.19 | fitted |
| $T_{\text{max}}^{\text{G6PCR}}$ | Transition time in G6 under maximal stimulation | 4.168 | fitted |
| $T_{b}^{\text{G6PCR}}$ | Sensitivity of transition time in G6 | 0.2246 | fitted |
Table A.5: Cell kinetic parameters of the erythropoiesis model

| parameter | meaning                                                                 | value                  |
|-----------|--------------------------------------------------------------------------|------------------------|
| $q_{RET}$ | proportion of RET/RBC in steady state                                     | 0.016                  |
| $T_{ERY_{rnd}}$ | transition time in compartment “RANDOM”                               | 1020.4 [14] set        |
| $T_{ERY_{age}}$ | transition time in compartment “AGE”                                    | 3061.2 [14] set        |
| $s_{ERY}$ | influx regulation factor of RANDOM and AGE                              | 0.9 [6], p. 40 set     |
| $N_{ERY}$ | number of subcompartments                                               | 10 [6], p. 41 set      |
| HK$^{nor}$ | normal value of HK                                                       | 0.43 set               |
| ERY$^{nor}$ | normal value of ERY                                                     | 4.5 set                |
| RET$^{nor}$ | normal value of RET                                                     | 100 set                |
| RET$%^{nor}$ | normal value of RET%                                                   | 9.5 set                |
| HB$^{nor}$ | normal value of HB                                                       | 13.5 set               |
| $P_{endo_{max}}$ | maximal endogenous production                                           | 0.000031 set           |
| EPO$V_c$ | volume of distribution                                                  | 0.032 [9] set          |
| EPO$serum$ | serum concentration                                                     | 15 [9] set             |
| VB | blood volume                                                            | 5.5 [15] set           |
| $a_{BE}^{min}$ | proliferative fraction under minimal stimulation                         | 0.3 [1], p. 71 set     |
| $a_{BE}^{nor}$ | proliferative fraction under normal stimulation                          | 0.33 [1], p. 71 set    |
| $a_{BE}^{max}$ | proliferative fraction under maximal stimulation                         | 0.66 [1], p. 71 set    |
| $a_{BE}^{max}$ | proliferative fraction under intensified stimulation                      | 1 [1], p. 71 set       |
| parameter | meaning | Alpha, Beta, Delta, endog. EPO | Darbepoetin Alfa |
|-----------|---------|-------------------------------|-----------------|
| $k_{el}$  | unspecific elimination from central compartment | 0.102 fitted | 0.062 fitted |
| $k_{12}$  | transition central to peripheral | 0.079 fitted | 0.294 fitted |
| $k_{21}$  | transition peripheral to central | 0.084 fitted | 0.291 fitted |
| $k_{on}$  | receptor binding rate | 0.070 fitted | 0.043 fitted |
| $k_{off}$ | receptor dissociation rate | 14.27 fitted | 9.62 fitted |
| $R(0)$   | EPO receptors (normal value) | 64.31 set [9] | 64.31 set |
| $k_{int}$ | internalisation rate | 2 set [9] | 1.14 fitted |
| $k_{deg}$ | receptor degradation rate | 0.101 fitted | 0.116 fitted |
| $w_{RET}$ | weighting factor for receptor density (RET) | 0.05 set | 0.05 set |
| $w_{MEB}$ | weighting factor for receptor density (MEB) | 0.087 fitted | 0.125 fitted |
| $w_{PEB}$ | weighting factor for receptor density (PEB) | 0.293 fitted | 0.509 fitted |
| $w_{CE}$  | weighting factor for receptor density (CE) | 3.84 fitted | 2.69 fitted |

### BE

| parameter | meaning | Alpha, Beta, Delta, endog. EPO | Darbepoetin Alfa |
|-----------|---------|-------------------------------|-----------------|
| $T_{min}$ | transition time in BE under minimal stimulation | 155.7 fitted | 124.6 fitted |
| $T_{nor}$ | transition time in BE under normal stimulation | 40 set [14] | 40 set |
| $T_{max}$ | transition time in BE under maximal stimulation | 28.60 fitted | 34.22 fitted |
| $A_{min}$ | amplification in BE under minimal stimulation | 1.134 fitted | 3.559 fitted |
| $A_{nor}$ | amplification in BE under normal stimulation | 25.04 fitted | 47.10 fitted |
| $A_{max}$ | amplification in BE under maximal stimulation | 64 set [14] | 64 set |
| $A_{b}$  | sensitivity of amplification in BE | 194.7 fitted | 115.5 fitted |
| $A_{BE}$  | amplification in CE under minimal stimulation | 2.321 fitted | 0.1659 fitted |
| $A_{CE}$  | amplification in CE under normal stimulation | 0.9645 fitted | 0.5717 fitted |
| $A_{max}$ | amplification in CE under maximal stimulation | 32 set [14] | 32 set |
| $A_{b}$  | sensitivity of amplification in CE | 104.7 fitted | 127.8 fitted |
| $T_{min}$ | transition time in CE under minimal stimulation | 0.0438 fitted | 0.3956 fitted |
| $T_{nor}$ | transition time in CE under normal stimulation | 186.7 fitted | 387.3 fitted |
| $T_{max}$ | transition time in CE under maximal stimulation | 40 set [14] | 40 set |
| $A_{min}$ | amplification in CE under minimal stimulation | 15.25 fitted | 36.23 fitted |
| $A_{nor}$ | amplification in CE under normal stimulation | 0.3920 fitted | 0.1305 fitted |
| $A_{max}$ | amplification in CE under maximal stimulation | 99.25 fitted | 178.4 fitted |
| $A_{b}$  | sensitivity of transition time in CE | 48 set | 48 set |
| $T_{min}$ | transition time in PEB under minimal stimulation | 8.809 fitted | 15.74 fitted |
| $T_{nor}$ | transition time in PEB under normal stimulation | 1.301 fitted | 1.847 fitted |
| $T_{max}$ | transition time in PEB under maximal stimulation | 0.6862 fitted | 0.8078 fitted |
| $A_{min}$ | amplification in PEB under minimal stimulation | 64 set [14] | 64 set |
| $A_{nor}$ | amplification in PEB under normal stimulation | 75.38 fitted | 139.6 fitted |
| $A_{max}$ | amplification in PEB under maximal stimulation | 0.4135 fitted | 0.1331 fitted |
| $A_{b}$  | sensitivity of amplification in PEB | 144.8 fitted | 186.7 fitted |
| $T_{min}$ | transition time in MEB under minimal stimulation | 100.2 fitted | 100.2 fitted |
| $T_{nor}$ | transition time in MEB under normal stimulation | 90.17 fitted | 26.98 fitted |
| $T_{max}$ | transition time in MEB under maximal stimulation | 0.5395 fitted | 0.1965 fitted |
Finally, we present parameters which depend on the mode of application, i.e. parameters referring to absorption kinetics (table A.7).

Chemotherapy parameters are specific for cell stage, drug, drug doses, and sometimes, risk group of patients such as young or elderly patients. An overview of estimated parameters can be found in tables A.8 (toxicity to stem cells and granulopoiesis) and A.9 (toxicity to erythropoiesis and lymphopoiesis).
Table A.7: Parameters of EPO absorption kinetics in dependence on mode of application

| Parameter | Description                                      | Alfa, abdomen, upper arm | Alfa, forearm | Alfa, shoulder | Alfa, thigh | Beta, abdomen | Beta, thigh | Beta, forearm | Delta | Darbepoetin Alfa |
|-----------|--------------------------------------------------|---------------------------|---------------|---------------|-------------|---------------|-------------|---------------|-------|-----------------|
| $k_{r}^{F}$ | transition from subcut. comp. to central comp.   | 0.5320                    | 0.7786        | 0.7119        | 0.7374      | 0.3747        | 0.4528      | 0.4077        | 0.6657 | 3.0148          |
| $k_{r}^{E}$ | elimination from subcutaneous compartment       | 0.2713                    | 0.1337        | 0.1263        | 0.3295      | 0.1062        | 0.0656      | 0.1873        | 0.1517 | 0.1938          |
| $k_{L}^{Delay}$ | delay in lymphatic system                      | 0.0390                    | 0.0510        | 0.1460        | 0.0298      | 0.0699        | 0.0410      | 0.0476        | 0.2367 | 0.0241          |
| $k_{L}^{T}$ | transition from lymph. comp. to central comp.   | 0.1172                    | 0.0901        | 0.1326        | 0.1588      | 0.2309        | 0.2024      | 0.4687        | 0.1065 | 1.1192          |
| $k_{L}^{E}$ | elimination from lymphatic compartment          | 0.4334                    | 0.4904        | 0.4066        | 0.4343      | 0.0950        | 0.0557      | 0.1587        | 0.3321 | 0.1769          |
| $k_{L}^{Delay}$ | delay in subcutaneous compartment               | 0.3275                    | 0.3259        | 0.6029        | 0.1626      | 0.3705        | 0.2078      | 0.2819        | 0.7508 | 0.1161          |
| $k_{FL}$  | transition from subcut. comp. to lymph. comp.   | 1.0074                    | 3.6252        | 3.9596        | 0.7213      | 1.2138        | 1.0453      | 1.1987        | 3.4461 | 5.5404          |
Table A.8: Chemotherapy parameters 1: We present toxicity parameters regarding stem cells and granulopoiesis lineage. Values in brackets could not be determined with sufficient accuracy due to lack of data and are irrelevant for the scenarios considered. Numbers after drug correspond to dose in $mg/m^2$.

| Drug Combination | FC  | Delay | S  | CG  | PGB | MGB |
|------------------|-----|-------|----|-----|-----|-----|
| Cyclophosphamide 750, Doxorubicin 50 | 1.038 | 0.061 | 0.023 | 0.915 | 0.334 | 0.040 |
| Etoposide 100 | | | | | | |
| Cyclophosphamide 750, Doxorubicin 50 | 8.425 | 0.116 | 0.000 | 0.008 | 0.500 | 0.002 |
| Etoposide 100 | | | | | | |
| Procarbazine 100 | 1.042 | 0.019 | 0.000 | 0.010 | 0.010 | 0.057 |
| Cyclophosphamide 650, Doxorubicin 25 | 1.038 | 0.061 | 0.087 | 0.591 | 0.013 | 0.000 |
| Bleomycin 10 | | | | | | |
| Cyclophosphamide 1250, Doxorubicin 35 | 8.425 | 0.116 | 0.000 | 0.008 | 0.051 | 0.002 |
| Etoposide 200 | | | | | | |
| Cyclophosphamide 1400, Doxorubicin 32.5 | 1.355 | 0.002 | 0.002 | 0.064 | 0.028 | 0.000 |
| Etoposide 175 | | | | | | |
| Carboplatin, Paclitaxel 225 | 1.000 | 0.077 | 0.001 | 60.00 | 60.00 | 0.000 |
| Doxorubicin 60 | 2.014 | 0.072 | 0.014 | 0.228 | 4.215 | 0.000 |
| Docetaxel 75 | 1.277 | 0.018 | 0.301 | 0.891 | 3.495 | 0.001 |
| Paclitaxel 225 | 1.277 | 0.018 | 0.000 | 0.891 | 3.495 | 0.001 |
| Paclitaxel 175 | 1.121 | 0.064 | 0.136 | 0.733 | 0.093 | 0.000 |
| Cyclophosphamide 600 | 1.308 | 0.050 | 0.000 | 0.054 | 0.189 | 0.001 |
| Etoposide 40 | 3.341 | 0.116 | 0.000 | 0.037 | 0.012 | 0.000 |
Table A.9: Chemotherapy parameters 2: We present toxicity parameters regarding erythropoiesis and lymphopoiesis. Values in brackets could not be determined with sufficient accuracy due to lack of data and are irrelevant for the scenarios considered. Numbers after drug correspond to dose in $mg/m^2$.

| Drug Combination       | Delay | LY     | BE  | CE  | PEB | MEB | RET |
|------------------------|-------|--------|-----|-----|-----|-----|-----|
| Cyclophosphamid 750    | 0.008 | 14.49  | 0.001| 0.011| 0.019| 0.319| 0.000|
| Doxorubicin 50         |       |        |     |     |     |     |     |
| Etoposid 100           | 0.106 | 0.042  | 0.000| 0.000| 0.034| 0.028| 0.000|
| Cyclophosphamid 750    | 0.008 | 17.68  | 0.001| 0.011| 0.016| 0.319| 0.000|
| Doxorubicin 50         |       |        |     |     |     |     |     |
| Etoposid 100           | 0.106 | 0.042  | 0.000| 0.000| 0.034| 0.028| 0.000|
| Procarbazine 100       | 0.000 | 0.000  | 0.000| 0.000| 0.000| 0.000| 0.000|
| Cyclophosphamid 650    | 0.008 | 20.00  | 0.000| 0.001| 0.000| 0.003| 0.000|
| Doxorubicin 25         |       |        |     |     |     |     |     |
| Bleomycin 10           | 0.000 | 0.000  | 0.005| 0.044| 0.000| 0.092| 0.000|
| Cyclophosphamid 1250   | 0.008 | 40.00  | 0.001| 0.012| 0.019| 0.363| 0.000|
| Doxorubicin 35         |       |        |     |     |     |     |     |
| Etoposid 200           | 0.106 | 3.602  | 0.000| 0.000| 0.009| 0.019| 0.000|
| Cyclophosphamid 1400   | 0.008 | 35.85  | 0.003| 0.016| 0.024| 0.407| 0.000|
| Doxorubicin 32.5       |       |        |     |     |     |     |     |
| Etoposid 175           | 0.106 | 50.00  | 0.003| 0.002| 0.034| 0.050| 0.002|
| Carboplatin, Paclitaxel 225 | (0.000) | (0.000) | (1.615) | (1.292) | (4.103) | (0.235) | (0.000) |
| Doxorubicin 60         |       |        |     |     |     |     |     |
| Docetaxel 75           |       |        |     |     |     |     |     |
| Paclitaxel 225         | 0.140 | 0.350  | 0.001| 1.797| 0.984| 0.153| 0.001|
| Paclitaxel 175         | 0.140 | 0.334  | 0.000| 1.423| 0.046| 0.010| 0.000|
| Cyclophosphamid 600    | 0.028 | 4.747  | 0.001| 0.003| 0.035| 0.018| 0.001|
| Cyclophosphamid 2500   | 0.028 | 12.59  | 0.017| 0.010| 0.035| 0.749| 0.007|
| Epirubicin 90          | 0.030 | 2.697  | 0.000| 0.023| 0.170| 0.023| 0.001|
| Epirubicin 150         | 0.030 | 42.26  | 1.549| 9.670| 1.595| 0.249| 0.085|
| Cytarabine 2           | 1.000 | 1.000  | 0.000| 0.000| 0.034| 0.028| 0.000|
| Cisplatin 25           | 0.000 | 0.000  | 0.197| 0.018| 0.457| 1.691| 0.000|
| Etoposide 40           | 0.048 | 1.275  | 0.000| 0.000| 0.034| 0.028| 0.000|
A summary of data used to identify model parameters and to validate our model can be found in table A.10.

Table A.10: **Available data sets.** Studies with access to raw data are indicated with an asterisk.

|   | EPO              | G-CSF | chemotherapy | disease |   |
|---|------------------|-------|--------------|---------|---|
| 1 | Alfa 300 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 2 | Alfa 450 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 3 | Alfa 600 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 4 | Alfa 900 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 5 | Alfa 1200 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 6 | Alfa 1350 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 7 | Alfa 1800 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 8 | Alfa 2400 IU/kg, sc (tigh) | none  | none         | none    | [16] |
| 9 | Alfa 300 IU/kg, sc | none  | none         | none    | [17] |
|10 | Alfa 400 IU/kg, sc | none  | none         | none    | [17] |
|11 | Alfa 600 IU/kg, sc | none  | none         | none    | [17] |
|12 | Alfa 750 IU, sc (upper arm) | none  | none         | none    | [18] |
|13 | Alfa 6000 IU, sc (upper arm) | none  | none         | none    | [18] |
|14 | Alfa 150 IU/kg, sc | none  | none         | none    | [19] |
|15 | Alfa 300 IU/kg, sc | none  | none         | none    | [19] |
|16 | Alfa 100 IU/kg, iv | none  | none         | none    | [20] |
|17 | Alfa 200 IU/kg, iv | none  | none         | none    | [20] |
|18 | Alfa 100 IU/kg, sc (shoulder) | none  | none         | none    | [20] |
|19 | Alfa 200 IU/kg, sc (shoulder) | none  | none         | none    | [20] |
|20 | Alfa 50 IU/kg, sc (upper arm) | none  | none         | none    | [21] |
|21 | Alfa 100 IU/kg, sc (abdomen) | none  | none         | none    | [22] |
|22 | Alfa 40000 IU, sc (forearm) | none  | none         | none    | [15] |
|23 | Alfa 150 IU/kg, sc (forearm) | none  | none         | none    | [15] |
|24 | beta 10 IU/kg, iv | none  | none         | none    | [23] |
|25 | beta 50 IU/kg, iv | none  | none         | none    | [23] |
|26 | beta 150 IU/kg, iv | none  | none         | none    | [23] |
|27 | beta 500 IU/kg, iv | none  | none         | none    | [23] |
|28 | beta 1000 IU/kg, iv | none  | none         | none    | [23, 24] |
|29 | beta 5000 IU | none  | none         | none    | [25] |
|30 | beta 1500 IU, sc | none  | none         | none    | [26] |
|31 | beta 3000 IU, sc (forearm) | none  | none         | none    | [26] |
|32 | beta 100 IU/kg, iv | none  | none         | none    | [27] |
|33 | beta 100 IU/kg, sc (tigh) | none  | none         | none    | [27] |
|34 | beta 100 IU/kg, sc (abdomen) | none  | none         | none    | [27] |
|35 | delta 15 IU/kg, iv | none  | none         | none    | [28] |
|36 | delta 40 IU/kg, iv | none  | none         | none    | [28] |
|37 | delta 75 IU/kg, iv | none  | none         | none    | [28] |
|38 | delta 75 IU/kg, sc | none  | none         | none    | [28] |
|39 | delta 100 IU/kg, iv | none  | none         | none    | [28] |
|40 | Darbepoetin alfa 120 IU/kg, sc | none  | none         | none    | [29] |
|41 | Darbepoetin alfa 140 IU/kg, sc | none  | none         | none    | [29] |
|42 | Darbepoetin alfa 240 IU/kg, sc | none  | none         | none    | [29] |
|43 | Darbepoetin alfa 360 IU/kg, sc | none  | none         | none    | [29] |
|44 | Darbepoetin alfa 780 IU/kg, sc | none  | none         | none    | [29] |
|   | Product | Dose | Schedule | Treatment | Disease |
|---|---------|------|----------|-----------|---------|
| 46 | Darbepoetin alfa 875 IU/kg, sc | none | none | none | none |
| 47 | Alfa Fil. | 480 µg, d 3-10 | E-T-C* | Breast cancer |
| 48 | Darbepoetin alfa 300 µg | none | Platinum, Etoposide-21 | Lung Cancer |
| 49 | none | none | Platinum, Etoposide-21 | Lung Cancer |
| 50 | none | none | CHOEP-21* | NHL |
| 51 | none | none | CHOP-21* | NHL |
| 52 | none | none | BEACOPP-21* | HD |
| 53 | Fil. 480 µg, d 4-13 | CHOEP-21* | NHL |
| 54 | Fil. 480 µg, d 6-12 | CHOP-14* | NHL |
| 55 | Fil. 480 µg, d 4-13 | CHOEPE-14* | NHL |
| 56 | Fil. 480 µg, d 6-13 | CHOEP-21* | NHL |
| 57 | Fil. 480 µg, d 6-13 | CHOEP-14* | NHL |
| 58 | Fil. 480 µg, d 8-15 | BEACOPP-21* | HD |
| 59 | Fil., 480 µg, d 3-10 | E-T-C* | Breast cancer |
| 60 | none | none | EC-T* | Breast cancer |
| 61 | Fil. 5 x 5 µg/kg | none | NSCLC |
| 62 | Fil. 1 x 3 µg/kg | none | none |
| 63 | Fil. 1 x 5 µg/kg | none | none |
| 64 | Fil. 1 x 10 µg/kg | none | none |
| 65 | Fil. 1 x 5 µg/kg | none | none |
| 66 | Fil. 1 x 10 µg/kg | none | none |
| 67 | Fil. 10 x 75 µg | none | none |
| 68 | Fil. 10 x 150 µg | none | none |
| 69 | Fil. 10 x 300 µg | none | none |
| 70 | Fil. 10 x 600 µg | none | none |
| 71 | Fil. 14 x 30 µg | none | none |
| 72 | Fil. 14 x 300 µg | none | none |
| 73 | Fil. 4 µg/kg | none | none |
| 74 | Fil. 8 µg/kg | none | none |
| 75 | Fil. 5 µg/kg, d 1-13 | none | none |
| 76 | Fil. 375 µg | none | none |
| 77 | Fil. 750 µg | none | none |
| 78 | Peg. 30 µg/kg | none | none |
| 79 | Peg. 60 µg/kg | none | none |
| 80 | Peg. 100 µg/kg | none | none |
| 81 | Peg. 300 µg/kg | none | none |
| 82 | Peg. 30 µg/kg | none | NSCLC |
| 83 | Peg. 100 µg/kg | none | NSCLC |
| 84 | Peg. 300 µg/kg | none | NSCLC |
| 85 | Fil. 5 µg/kg, d 2-13 | TA | Breast cancer |
| 86 | Peg. 30 µg/kg, d 2 | TA | Breast cancer |
| 87 | Peg. 60 µg/kg, d 2 | TA | Breast cancer |
| 88 | Peg. 100 µg/kg, d 2 | TA | Breast cancer |
| 89 | Peg. 6000 µg, d 2 | TA | Breast cancer |
| 90 | Peg. 6000 µg, d 2 | TA | Breast cancer |
| 91 | Peg. 30 µg/kg, d 2 | CP | NSCLC |
Stability analysis

Using the above mentioned model parameters results in a stable steady state of the system. However, modifying certain parameters can result in stable oscillations. This especially applies for parameters of the long range stem cell feedback (see figure 3).

Figure 3: Oscillatory behaviour of the model for changed parameter settings of the stem cell feedback: A small perturbation (a single injection of 10 IU EPO at $t = 0$) leads to stable oscillations in compartment sizes. Modified parameter settings: $a^\text{min}_S = 0.01, a^\text{nor}_S = 0.05105, a^\text{int}_S = 0.71047, a^\text{max}_S = 1, p_S = 0.40858$ We present cell dynamics normalised to steady state values.
Sensitivity analysis

We analysed the sensitivity of newly introduced parameters by changing their values by 2.5% and calculating the corresponding deterioration of the fitness function. Results are shown in figure 4. Minimum and normal values of the G-CSF regulations of compartment CE have considerably higher precision than corresponding estimates of maximum values and b-parameters.

Figure 4: Sensitivity of the parameters describing the regulation in compartment CE. Parameters denoted with "*" could not be changed by 2.5% without violating constraints. Parameters were modified by ±2.5%. Relative change of the fitness function is shown as length of corresponding bars.

A.9 Simulation Results

In this section, we present all simulation results of our hybrid model and compare it with available data. We also present extensive comparisons of our hybrid model with the single lineage models of erythropoiesis and granulopoiesis.

Comparison of hybrid model and single lineage models
Figure 5: **Comparison of stem cell dynamics.** Comparison of the behaviour of the combined and the single lineage models after perturbation with EPO, Filgrastim, Pegfilgrastim and CHOP injections. We present stem cell dynamics normalised to steady state values.

Figure 6: **Comparison of CG dynamics.** Comparison of the behaviour of the combined and the single lineage models after perturbation with EPO, Filgrastim, Pegfilgrastim and CHOP injections. We present CG dynamics normalised to steady state values.
Figure 7: **Comparison of PGB dynamics.** Comparison of the behaviour of the combined and the single lineage models after perturbation with EPO, Filgrastim, Pegfilgrastim and CHOP injections. We present PGB dynamics normalised to steady state values.

Figure 8: **Comparison of WBC dynamics.** Comparison of the behaviour of the combined and the single lineage models relative to steady state after perturbation with EPO, Filgrastim, Pegfilgrastim and CHOP injections (WBC).
Figure 9: Comparison of CE dynamics. Comparison of the behaviour of the combined and the single lineage models relative to steady state after perturbation with EPO, Filgrastim, Pegfilgrastim and CHOP injections. We present CE dynamics normalised to steady state values.

Figure 10: Comparison of PEB dynamics. Comparison of the behaviour of the combined and the single lineage models after perturbation with EPO, Filgrastim, Pegfilgrastim and CHOP injections. We present PEB dynamics normalised to steady state values.
Figure 11: Comparison of HB dynamics. Comparison of the behaviour of the combined and the single lineage models relative to steady state after perturbation with EPO, Filgrastim, Pegfilgrastim and CHOP injections (HB).
A.9.1 Simulation Results of EPO applications into healthy volunteers

Flaharty et al. (1990), EPO Beta 10 IU/kg, iv
Flaharty et al. (1990), EPO Beta 50 IU/kg, iv
Flaharty et al. (1990), EPO Beta 150 IU/kg, iv
Flaharty et al. (1990), EPO Beta 500 IU/kg, iv
Flaharty et al. (1990), EPO Beta 1000 IU/kg, iv
Markham, Bryson (1995), EPO Alfa 100 IU/kg, iv
Markham, Bryson (1995), EPO Alfa 200 IU/kg, iv
Markham, Bryson (1995), EPO Alfa 100 IU/kg, sc (shoulder)
Markham, Bryson (1995), EPO Alfa 200 IU/kg, sc (shoulder)

Figure 12: Serum concentration of erythropoietin, percentage of reticulocytes, simulation (black line) and data (circle), data: [23, 24]

Figure 13: Serum concentration of erythropoietin (simulation and data), data: [20]
Figure 14: Serum concentration of erythropoietin, simulation (black line) and data (circle), data: [27]

Figure 15: Serum concentration of erythropoietin and reticulocytes %, simulation (black line) and data (circle), data: [16]
Figure 16: Serum concentration of erythropoietin (simulation and data), data: [26]

Figure 17: Serum concentration of erythropoietin and reticulocytes %, simulation (black line) and data (circle), data: [16]
Figure 18: Serum concentration of erythropoietin, HB value, RBC, and reticulocytes %, simulation (black line) and data (circle), data: [9]

Figure 19: Intravenous injection (left) and subcutaneous injection (right): serum concentration of erythropoietin, Alfa iv, Alfa sc, data: [20]
Figure 20: Serum concentration of erythropoietin, simulation (black line) and data (circle), data: [19]

Figure 21: Serum concentration of erythropoietin, HB and HK value, simulation (black line) and data (circle), data: [17], [57], from subjects required to have a baseline HK less than 48%. If the HK rose above 55%, phlebotomy was performed.
Figure 22: Serum concentration of erythropoietin, simulation (black line) and data (circle), data: [29]

Figure 23: Serum concentration of erythropoietin, HB, RBC, and percentage of reticulocytes, simulation (black line) and data (circle), data: [22]
Figure 24: Serum concentration of erythropoietin, simulation (black line) and data (circle), data: [18]

Figure 25: Serum concentration of erythropoietin, simulation (black line) and data (circle), data: [21]
Figure 26: reticulocytes, HB, HK and serum concentration of erythropoietin, simulation (black line) and data (circle), data: [28]
A.9.2 Simulation results of scenarios with combined EPO and chemotherapy applications

Figure 27: HB value: simulation (black line) and data (circle), mean ± standard deviation (grey line), Chemotherapy: Platinum plus Etoposide, without EPO support (left), with Darbepoetin alfa, sc (right), data: [31]

A.9.3 Simulation results of G-CSF injections into healthy volunteers

Figure 28: simulation (black line) and data (circle), data: [43, 44]. The blood cell donation in the scenario of Bensinger et al. [44] is not taken into account.
Figure 29: simulation (black line) and data (circle), data: [45]

Figure 30: simulation (black line) and data (circle), data: [41]
Figure 31: simulation (black line) and data (circle), data: [39, 46]
Figure 32: simulation (black line) and data (circle), data: [40, 42, 56]
A.9.4 Simulation results of scenarios with combined G-CSF and chemotherapy application

Figure 33: simulation (black line) and data (circle), data: [47, 49, 50]

Figure 34: simulation (black line) and data (circle), data: [38]
Figure 35: HB value, simulation (black line) and data (circle), percentile 25, 75 (grey line), Chemotherapy: CHOEP 21, CHOEP14, elderly patients, CHOP 21 younger patients, data: [33].

Figure 36: simulation (black line) and data (circle), data: [51–53].
Figure 37: HB value, simulation (black line) and data (circle), percentile 25, 75 (grey line), Chemotherapy: CHOP14, CHOEP 21, CHOEP14, younger patients, data: [33].

Figure 38: HB value, simulation (black line) and data (circle), percentile 25, 75 (grey line), Chemotherapy: CHOEP 21, CHOEP14, elderly patients, data: [32].
Figure 39: simulation (black line) and data (circle), data: [54]

Figure 40: HB value, simulation (black line) and data (circle), percentile 25, 75 (grey line), Chemotherapy: BEACOPP 21 escalated, BEACOPP 21, highCHOEP 21, highCHOEP 14, data: [34, 36, 37, 58]. Caused by Hodgkins lymphoma activity, an increased endogenous G-CSF production is assumed in BEACOPP treated patients, see [2].
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