Model of hematopoiesis with structured cell differentiation

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INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Process of hematopoiesis

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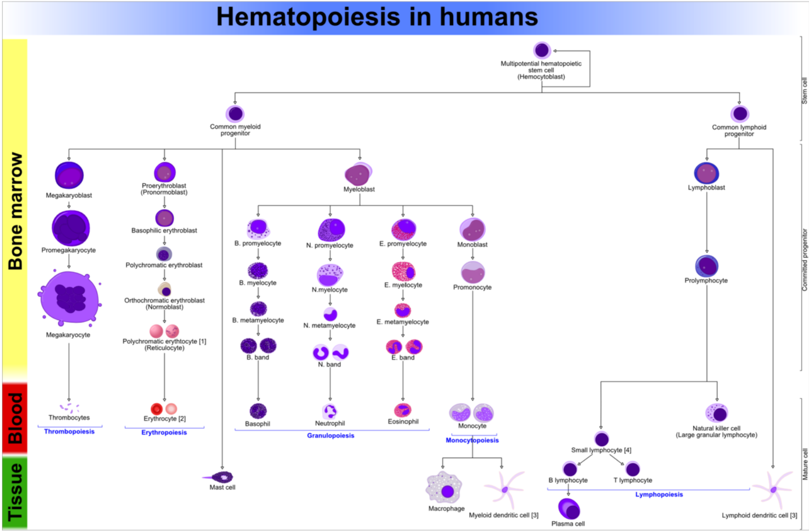
- The count of new cells is controled by negative feedback of actual size of blood cells populations.
- Due to the processes of control delays occur.
- Hematopoietic diseases: Chronic myelogenous leukemia, Cyclical neutropenia, etc.

Scheme of hematopoiesis



Cell characteristics

We observe two characteristics of blood cells: *level and commitment*.

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- 0 ... any commitment
- L, M ... commitment to lymphoid, or myeloid lineage
- M_E, M_{MEG}, M_{GM} ... myeloid cells commitment to erythroid, thrombocytic, or leukocytic lineage
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Then $\mathcal{X}_{i,c}$ stands for the cell of level i and commitment c.

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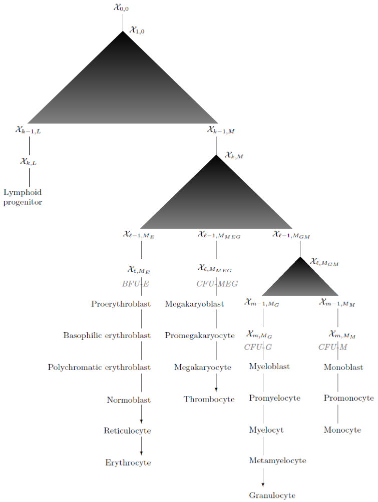

Cell processes

Cell division

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stands for the probability that the cell $\mathcal{X}_{i,c}$ divides to cells $\mathcal{X}_{j_1,c_1}$ and $\mathcal{X}_{j_2,c_2}$

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Processes assumptions

Assume that:

- Probabilities $P_{(j,c_2)}^{(i,c_1)}$ and $Q_{(j_1,c_1),(j_2,c_2)}^{(i,c)}$ which aren't showed are equal to zero.

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$$0 < \sum_{\iota} \sum_{\kappa \in C} P^{(i,c)}_{(\iota,\kappa)} + \sum_{\iota,\lambda} \sum_{\kappa,\delta \in C} Q^{(i,c)}_{(\iota,\kappa),(\lambda,\delta)} < 1,$$

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- With growing level the probability of commitment change decreases, or

$$P_{(j,c_2)}^{(i,c_1)} \geq P_{(j+1,c_2)}^{(i+1,c_1)},$$

$$Q_{(i+1,c_1),(i+1,c_2)}^{(i+1,c_1)} \leq Q_{(i,c_2),(i,c_2)}^{(i,c_1)} \leq Q_{(i,c_1),(i,c_2)}^{(i,c_1)} \leq Q_{(i,c_1),(i,c_1)}^{(i,c_1)}.$$

Model scheme

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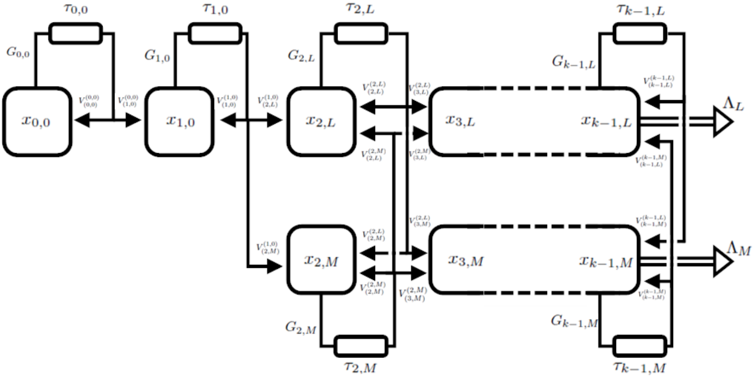

Model equations

$$
\begin{aligned}
x'_{0,0}(t) &= -G_{0,0}x_{0,0}(t) + V^{(0,0)}_{(0,0)}x_{0,0}(t-\tau_{0,0}),\\
x'_{1,0}(t) &= -G_{1,0}x_{1,0}(t) + V^{(1,0)}_{(1,0)}x_{1,0}(t-\tau_{1,0}) + V^{(0,0)}_{(1,0)}x_{0,0}(t-\tau_{0,0}),\\
x'_{2,c_1}(t) &= -G_{2,c_1}x_{2,c_1}(t) + V^{(2,c_1)}_{(2,c_1)}x_{2,c_1}(t-\tau_{2,c_1}) + V^{(2,c_2)}_{(2,c_1)}x_{2,c_2}(t-\tau_{2,c_2})\\
&\quad + V^{(1,0)}_{(2,c_1)}x_{1,0}(t-\tau_{1,0}),\\
x'_{i,c_1}(t) &= -G_{i,c_1}x_{i,c_1}(t) + V^{(i,c_1)}_{(i,c_1)}x_{i,c_1}(t-\tau_{i,c_1}) + V^{(i,c_2)}_{(i,c_1)}x_{i,c_2}(t-\tau_{i,c_2})\\
&\quad + V^{(i-1,c_1)}_{(i,c_1)}x_{i-1,c_1}(t-\tau_{i-1,c_1}) + V^{(i-1,c_2)}_{(i,c_1)}x_{i-1,c_2}(t-\tau_{i-1,c_2}),\\
x'_{k-1,c_1}(t) &= -G_{k-1,c_1}x_{k-1,c_1}(t) + V^{(k-1,c_1)}_{(k-1,c_1)}x_{k-1,c_1}(t-\tau_{k-1,c_1})\\
&\quad + V^{(k-1,c_2)}_{(k-1,c_1)}x_{k-1,c_2}(t-\tau_{k-1,c_2}) + V^{(k-2,c_1)}_{(k-1,c_1)}x_{k-2,c_1}(t-\tau_{k-2,c_1})\\
&\quad + V^{(k-2,c_2)}_{(k-1,c_1)}x_{k-2,c_2}(t-\tau_{k-2,c_2}) - \Lambda_L x_{k-1,c_1}(t),
\end{aligned}
$$

where $i = 3, \ldots, \; k-2$ and $c_1, \; c_2 \in \{L, \; M\}$, $c_1 \neq c_2$.

Coefficients $G_{i,c}$

Assume cell processes coefficinets as functions in the form

$$P^{(i,c)}_{(j,c_t)} = \mu^{(i,c)}_{(j,c_t)} \frac{\left(\theta^{(i,c)}_{(j,c_t)}\right)^n}{\left(\theta^{(i,c)}_{(j,c_t)}\right)^n + x^n_{j,c_t}}, \quad Q^{(i,c)}_{(j_1,c_1)(j_2,c_2)} = \mu^{(i,c)}_{(j_1,c_1)(j_2,c_2)} \frac{\left(\theta^{(i,c)}_{(j_1,c_1)(j_2,c_2)}\right)^n}{\left(\theta^{(i,c)}_{(j_1,c_1)(j_2,c_2)}\right)^n + \left(x_{j_1,c_1} x_{j_2,c_2}\right)^n}.$$

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Next we concider function

$$H_{i,c} = \sum_{\iota} \sum_{\kappa \in C} P^{(i,c)}_{(\iota,\kappa)} + \sum_{\iota,\lambda} \sum_{\kappa,\delta \in C} Q^{(i,c)}_{(\iota,\kappa),(\lambda,\delta)}.$$

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And finally we can define coefficients (functions) used in the system of equations

$$G_{i,c} = M_{i,c} \frac{H^n_{i,c}}{\Theta^n_{i,c} + H^n_{i,c}}.$$

Coefficients V_{j,c_2}^{i,c_1}

During the processes cells can be lost with rate γ_{i,c_1}, i.e. at the end there is overall

$$G_{i,c_1} x_{i,c_1} e^{-\gamma_{i,c_1} \tau_{i,c_1}}.$$

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So we set

$$V_{j,c_2}^{i,c_1} = \left(2Q_{(j,c_2),(j,c_2)}^{(i,c_1)} + \sum_{\iota} \sum_{\kappa \in C} Q_{(j,c_2),(\iota,\kappa)}^{(i,c_1)} + P_{(j,c_2)}^{(i,c_1)} \right) \frac{G_{i,c_1}}{H_{i,c_1}} e^{-\gamma_{i,c_1}\tau_{i,c_1}},$$

where $j \neq \iota$ or $c_2 \neq \kappa$.

Origin of parameters

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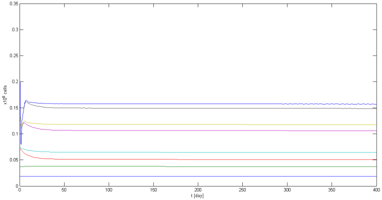
Generally we can say that most important are changes for cell groups $x_{0,0}$ and $x_{1,0}$. For higher levels there is small effect on the whole population. But this presumption has to be investigated on more complex model.

Parameters $\gamma_{i,c}$



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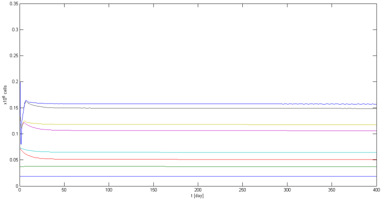

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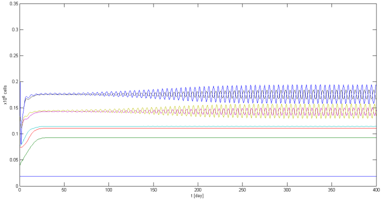

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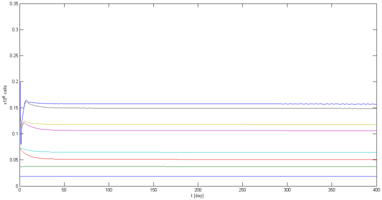

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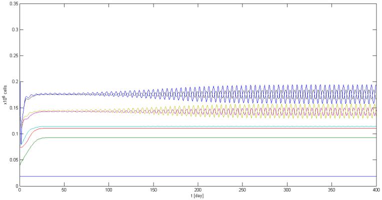

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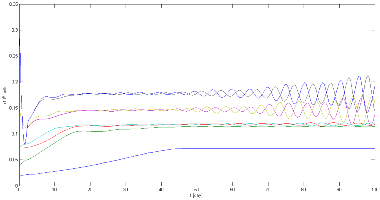

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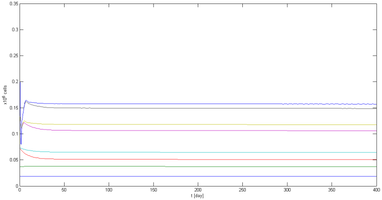

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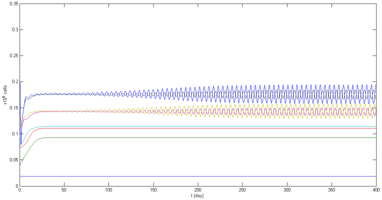

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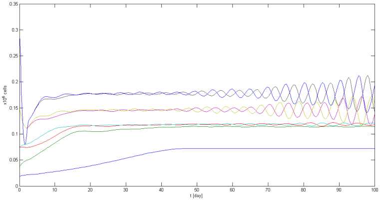

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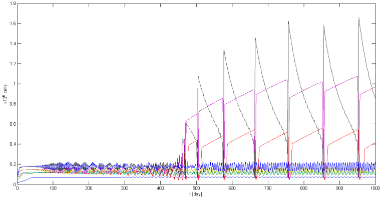

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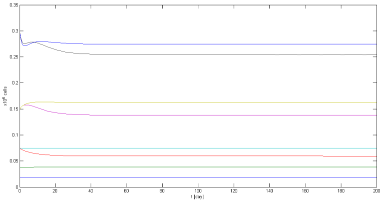
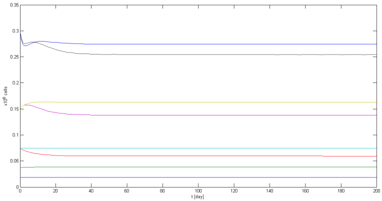
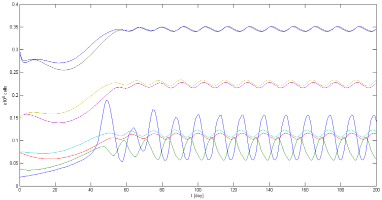


$\Theta_{i,c} = 0.2$ for all i

Parameters $\Theta_{i,c}$

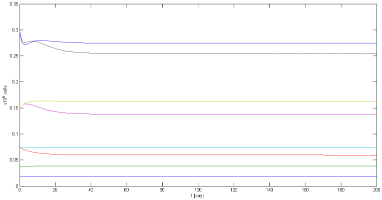


$\Theta_{i,c} = 0.2$ for all i

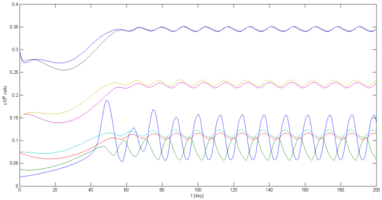


$\Theta_{0,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i > 0$

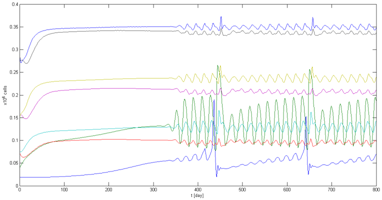
Parameters $\Theta_{i,c}$



$\Theta_{i,c} = 0.2$ for all i

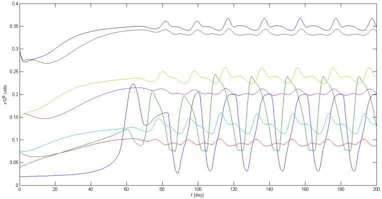


$\Theta_{0,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i > 0$



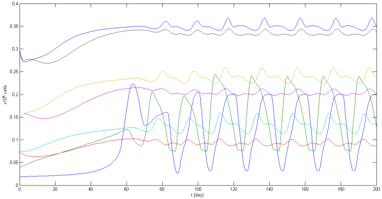
$\Theta_{1,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i = 1$ or $i > 0$

Parameters $\Theta_{i,c}$

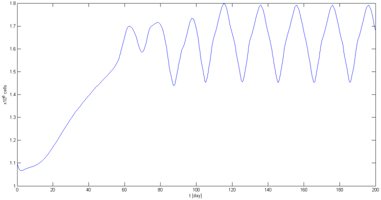


$\Theta_{0,0} = 0.4$, $\Theta_{1,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i > 1$

Parameters $\Theta_{i,c}$

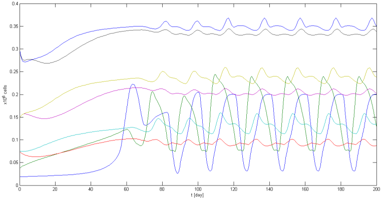


$\Theta_{0,0} = 0.4$, $\Theta_{1,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i > 1$

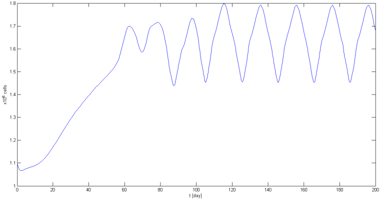


$\Theta_{0,0} = 0.4$, $\Theta_{1,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i > 1$

Parameters $\Theta_{i,c}$

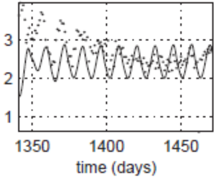


$\Theta_{0,0} = 0.4$, $\Theta_{1,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i > 1$



$\Theta_{0,0} = 0.4$, $\Theta_{1,0} = 0.6$, $\Theta_{i,c} = 0.2$ for $i > 1$

Compare that with simulation in [3]. There is shown model for platelet population in collie with cyclical neutropenia under treatment.



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Thank you for your attention.