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PK/PD model of 6-mercaptopurine treatment in acute leukemia

Abstract In this paper we present an analysis of a mathematical model of 6-MP/6-TGN dynamics during the maintenance therapy of acute lymphoblastic leukemia which was proposed in Le et al. (2018). We first discuss the model with constant treatment, comparing its properties to the case without treatment. Next, we describe the model which switches between models with constant treatment and without treatment depending on frequency of drug administration and the drug's absorption time. We show that the model with the switch has asymptotic periodic dynamics.

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1. Introduction Acute lymphoblastic leukemia (ALL) is the most common cancer in children [1]. It comprises 21% of all childhood cancers, including about 75% of leukemias. ALL is characterized by the overproduction of immature, abnormal white blood cells. These cells are called lymphoblasts.

Chemotherapy treatment of ALL is a three-step process. The first step is to induce remission by high-dose treatment. The next part is consolidation therapy, used to prolong an effect of the first part of the treatment. The last step is called maintenance therapy. At this stage, low-dose treatment is introduced. The maintenance therapy is the longest part of the chemotherapy and could last more than two years. This therapy includes oral administration of 6-mercaptopurine (6-MP, daily) and methotrexate (MTX, weekly) [3]. Both 6-MP [8] and MTX [9] are cytostatic drugs which cause antileukemic effect through their metabolized active forms (6-TGN and MTXPG respectively) [10]. According to the treatment protocol AIEOP-BFM 2009, the number of white blood cells should oscillate in a specific range [7]. An appropriate level provides patients with protection against the relapse of leukemia and other infections.

In [7] Le et al. presented a detailed mathematical description of the maintenance therapy. The model proposed in [7] consists of three modules. Two of these modules reflect the dynamics of the drugs. They are described in the framework of ordinary differential equations with the specific initial conditions. The purpose of this article is to present and analyze the first module related to the 6-MP treatment.

The PK/PD model of 6-MP/6-TGN is a compartment model reflecting the dynamics of 6MP during the therapy. Several 6-MP models have been published, but in [7] authors mentioned [2, 4], both of which have a comparable representation of the absorption and metabolic pathway of 6MP but the model of Hawwa et al. presented in [2] describes the metabolic transformations by first order kinetics instead of Michaelis–Menten kinetics used in [4]. In [7] authors based on an approach used by Jayachadran et al. in [4], but during the maintenace therapy model further development (results presented by Jost et al. in [5]) authors have replaced the 6MP model of [4] with the model described by Hawwa et al. in [2] to obtain a better response to 6MP dosage.

2. Mathematical model In this section, following [7] we will present a model of 6-MP/6-TGN dynamics, where 6-TGN is 6-thioguanine nucleotide – metabolite of 6-MP. The model describing the treatment using 6-MP can be split into two parts. The first one includes drug absorption, the second does not. In [7] it is assumed that the absorption time equals one hour. There is a slight change we would like to make in comparison with the prototype. We assume that the patient takes the drug at regular time intervals.

The time unit in the model is one day. We assume that till $t = 0$ there have been no 6-MP and its metabolites in the patient's organism. The first dose of D miligrams is given at time $t_0 = 0$. For $t \in [t_0, t_1]$, where $t_1 = t_0 + \frac{1}{24}$, the model including drug absorption is used. Similarly for $t \in [t_1, t_2]$, where $t_2 = t_1 + \frac{23}{24}$, the model without drug absorption is appropriate; cf. Fig. 1.

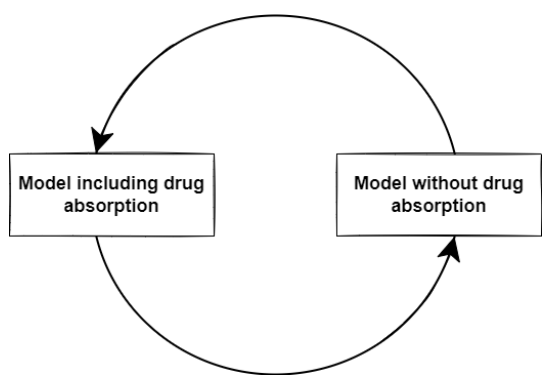


Figure 1: *When $t \in [t_{2k}, t_{2k+1}]$, for $k = 0, 1, 2 \ldots$, where $t_{2k+1} = t_{2k} + \frac{1}{24}$, the model including drug absorption is applied, when $t \in [t_{2k+1}, t_{2k+2}]$, for $k = 0, 1, 2 \ldots$, where $t_{2k+2} = t_{2k+1} + \frac{23}{24}$, the model without drug absorption is applied.*

In the model there are three state variables:

- $x_1(t)$ — amount of 6-MP in gastrointestinal (GI) tract (pmol),
- $x_2(t)$ — amount of 6-MP in plasma (pmol),
- $x_3(t)$ — concentration of 6-TGN in red blood cells (pmol/8×10^8 RBCs).

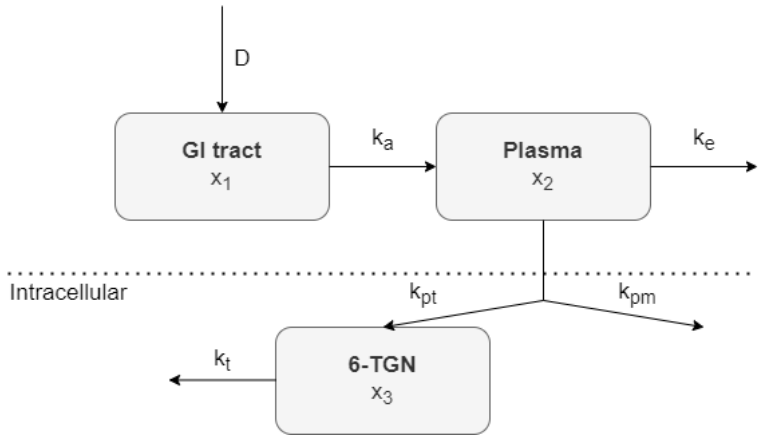


Figure 2: *Scheme of 6-MP/6-TGN model. For the model without drug absorption* $D = 0$*, for the model including drug absorption* $D > 0$.

The system of ordinary differential equations reflecting the scheme presented in Fig. 2 reads

$$\begin{cases} \dot{x}_1 &= -k_a x_1 + c, \\ \dot{x}_2 &= k_a x_1 - k_e x_2 - \frac{k_{pt}(1-e_{rel})x_2}{K_t+x_2} - \frac{k_{pm}e_{rel}x_2}{K_m+x_2}, \\ \dot{x}_3 &= \frac{v_{pt}k_{pt}(1-e_{rel})x_2}{K_t+x_2} - k_{te}x_3, \end{cases} \tag{1}$$

with initial values

$$x_1(0) = \tilde{x}_1,\ x_2(0) = \tilde{x}_2,\ x_3(0) = \tilde{x}_3, \tag{2}$$

where $\tilde{x}_1 \geq 0$, $\tilde{x}_2 \geq 0$ i $\tilde{x}_3 \geq 0$. All parameters are taken from [7]. Parameter $c = 0$ for the model without drug absorption, while for the model including drug absorption $c = 24FD\alpha$. All other parameters in System (1) are positive and $e_{rel} < 1$ (implying positivity of $1 - e_{rel}$). It should be noted that System (1) with the arbitrary positive parameter c can be interpreted as a continuous treatment using 6-MP. All parameters of System (1) are described and summarized in Table 1.

3. The analysis of the model In this section, we will discuss the proposed model assuming constant drug absorpion. Note that the presented analysis is also valid when there is no treatment, i.e. $c = 0$. Let

$$f(x) = \begin{bmatrix} -k_a x_1 + c \\ k_a x_1 - k_e x_2 - \frac{k_{pt}(1-e_{rel})x_2}{K_t+x_2} - \frac{k_{pm}e_{rel}x_2}{K_m+x_2} \\ \frac{v_{pt}k_{pt}(1-e_{rel})x_2}{K_t+x_2} - k_{te}x_3 \end{bmatrix} \tag{3}$$

denote the right-hand side of System (1). It is obvious that the function f is of class C^1 in $[0,\infty)^3$ and therefore Problem (1)-(2) has a unique solution.

3.1. Boundedness and global existence of solutions Due to the meaning of the variables, for all nonnegative initial data solutions should be nonnegative as well.

Solving the first equation of System (1) we get

$$x_1(t) = \frac{c}{k_a} + \left(\tilde{x}_1 - \frac{c}{k_a}\right) \mathrm{e}^{-k_a t}, \tag{4}$$

and it is obvious that x_1 is nonnegative for $\tilde{x}_1 \geq 0$.

From nonnegativity of x_1 we obtain

$$\dot{x}_2 \geq -k_e x_2 - \frac{k_{pt}(1-e_{rel})x_2}{K_t + x_2} - \frac{k_{pm} e_{rel} x_2}{K_m + x_2},$$

implying

$$x_2(t) \geq \tilde{x}_2 \, \mathrm{e}^{-\left(k_e t + \int_0^t \left(\frac{k_{pt}(1-e_{rel})}{K_t + x_2(\zeta)} + \frac{k_{pm} e_{rel}}{K_m + x_2(\zeta)}\right) d\zeta\right)} \geq 0.$$

Similarly, from nonnegativity of x_2 we obtain

$$\dot{x}_3 \geq -k_{te} x_3,$$

implying

$$x_3(t) \geq \tilde{x}_3 \, \mathrm{e}^{-k_{te} t} \geq 0.$$

Next, we will show that solutions are bounded from above which implies that the maximal interval of existence includes $[0, +\infty)$.
Due to nonnegativity of solutions we get

$$\begin{cases} \dot{x}_1 &= -k_a x_1 + c, \\ \dot{x}_2 &= k_a x_1 - k_e x_2 - \frac{k_{pt}(1-e_{rel})x_2}{K_t + x_2} - \frac{k_{pm} e_{rel} x_2}{K_m + x_2} \leq k_a x_1 - k_e x_2, \\ \dot{x}_3 &= \frac{v_{pt} k_{pt}(1-e_{rel})x_2}{K_t + x_2} - k_{te} x_3 < v_{pt} k_{pt}(1-e_{rel}) - k_{te} x_3. \end{cases}$$

From Equation (4) we get $x_1 \leq x_1^M = \max\left\{\tilde{x}_1, \frac{c}{k_a}\right\}$. Next, using the inequality for $\dot{x}_2$ in the second equation we obtain

$$\dot{x}_2 \leq k_a x_1^M - k_e x_2 \quad \Rightarrow \quad x_2 \leq x_2^M = \max\left\{\tilde{x}_2, \frac{k_a x_1^M}{k_e}\right\}.$$

Similarly

$$\dot{x}_3 < v_{pt} k_{pt}(1-e_{rel}) - k_{te} x_3 \quad \Rightarrow \quad x_3 < x_3^M = \max\left\{\tilde{x}_3, \frac{v_{pt} k_{pt}(1-e_{rel})}{k_{te}}\right\}.$$

Hence, the state variables are bounded. Therefore, solutions of Problem (1)-(2) exist for all $t \geq 0$. Moreover, there is the invariant subspace

$$M = \left\{(x_1, x_2, x_3) \in \mathbb{R}^3 : 0 \leq x_1 \leq \frac{c}{k_a},\ 0 \leq x_2 \leq \frac{c}{k_e},\ 0 \leq x_3 < \frac{v_{pt} k_{pt}(1-e_{rel})}{k_{te}}\right\}$$

which will be crucial for the further analysis.

3.2. Stationary states: existence and stability

Let $(\bar{x}_1, \bar{x}_2, \bar{x}_3)$ be a stationary state of System (1) with coordinates $\bar{x}_i$ depending on the parameter c. Let us check the number of stationary states of System (1). We equate the right-hand side of System (1) to 0:

$$\begin{cases} -k_a x_1 + c &= 0, \\ k_a x_1 - k_e x_2 - \frac{k_{pt}(1-e_{rel})x_2}{K_t+x_2} - \frac{k_{pm}e_{rel}x_2}{K_m+x_2} &= 0, \\ \frac{v_{pt}k_{pt}(1-e_{rel})x_2}{K_t+x_2} - k_{te}x_3 &= 0. \end{cases}$$

After a few transformations we get

$$\begin{cases} x_1 &= \frac{c}{k_a}, \\ x_2\left(k_e + \frac{k_{pt}(1-e_{rel})}{K_t+x_2} + \frac{k_{pm}e_{rel}}{K_m+x_2}\right) &= c, \\ x_3 &= \frac{v_{pt}k_{pt}(1-e_{rel})x_2}{k_{te}(K_t+x_2)}. \end{cases} \tag{5}$$

Let us draw attention to the second equation of System (5). We would like to prove that for any $c \geq 0$ it has a unique nonnegative solution. Any solution of this equation is a zero of the following function:

$$F(x_2) = x_2\left(k_e + \frac{k_{pt}(1-e_{rel})}{K_t+x_2} + \frac{k_{pm}e_{rel}}{K_m+x_2}\right) - c.$$

It is easy to see that F is continuous on $\mathbb{R}_+$. Moreover, $F(0) = -c$ and $\lim_{x_2\to\infty} F(x_2) = +\infty$. Thus, from Darboux property, F has at least one zero. Next, we need to show that it is unique. We calculate the derivative:

$$\frac{\partial F}{\partial x_2} = k_e + \frac{K_t k_{pt}(1-e_{rel})}{(K_t+x_2)^2} + \frac{K_m k_{pt} e_{rel}}{(K_m+x_2)^2} > 0,$$

and therefore F is strictly increasing on $\mathbb{R}_+$. Hence, there exists exactly one nonnegative zero $\bar{x}_2 \geq 0$ of F. Then

$$\bar{x}_3 = \frac{v_{pt}k_{pt}(1-e_{rel})\bar{x}_2}{k_{te}(K_t+\bar{x}_2)}.$$

Therefore there is the only one stationary state of System (1) for any $c \geq 0$

$$S = (\bar{x}_1, \bar{x}_2, \bar{x}_3) = \left(\frac{c}{k_a}, \bar{x}_2, \frac{v_{pt}k_{pt}(1-e_{rel})\bar{x}_2}{k_{te}(K_t+\bar{x}_2)}\right).$$

For the model without drug absorption, i.e. for $c = 0$, $(\bar{x}_1, \bar{x}_2, \bar{x}_3) = (0, 0, 0)$, and for the model including drug absorption, i.e. for $c > 0$, we obtain positive stationary state.

Let A denote a Jacobian matrix for System (1):

$$A = \begin{pmatrix} -k_a & 0 & 0 \\ k_a & -k_e - \frac{K_t k_{pt}(1-e_{rel})}{(K_t+\bar{x}_2)^2} - \frac{K_m k_{pt} e_{rel}}{(K_m+\bar{x}_2)^2} & 0 \\ 0 & \frac{v_{pt} K_t k_{pt}(1-e_{rel})}{(K_t+\bar{x}_2)^2} & -k_{te} \end{pmatrix}. \tag{6}$$

It is easy to see that at a stationary state all eigenvalues of (6) are real negative, so the stationary state is locally asymptotically stable independently of the parameter c.

Next, let us analyze global dynamics for $c \in \mathbb{R}_+$. We propose the Lyapunov function:

$$V_l(x_1, x_2, x_3) = \frac{(x_1 - \bar{x}_1)^2}{2} + \frac{A(x_2 - \bar{x}_2)^2}{2} + \frac{B(x_3 - \bar{x}_3)^2}{2}$$

for $A = \frac{4k_e}{k_a}$ and $B = \frac{16 K_t k_{te} k_e}{k_a v_{pt}^2 k_{pt}(1-e_{rel})}$. It is obvious that $V_l(x) \geq 0$ and $V_l(x) = 0 \iff x = \bar{x}$. Calculating the derivative of V_l along trajectories of System (1) we obtain

$$\begin{aligned} \frac{d}{dt} V_l(x(t)) &= \dot{x}_1 \cdot (x_1 - \bar{x}_1) + \dot{x}_2 \cdot A(x_2 - \bar{x}_2) + \dot{x}_3 \cdot B(x_3 - \bar{x}_3) \\ &= -k_a (x_1 - \bar{x}_1)^2 + A(x_2 - \bar{x}_2) \left(k_a x_1 - k_e x_2 - \frac{k_{pt}(1-e_{rel}) x_2}{K_t + x_2} - \frac{k_{pm} e_{rel} x_2}{K_m + x_2} \right) \\ &\quad + B(x_3 - \bar{x}_3) \left(\frac{v_{pt} k_{pt}(1-e_{rel}) x_2}{K_t + x_2} - k_{te} x_3 \right) \\ &= -k_a (x_1 - \bar{x}_1)^2 + k_a A (x_1 - \bar{x}_1)(x_2 - \bar{x}_2) - A k_e (x_2 - \bar{x}_2)^2 \\ &\quad - A k_{pt} K_t (1 - e_{rel}) \frac{(x_2 - \bar{x}_2)^2}{(K_t + x_2)(K_t + \bar{x}_2)} - A k_{pm} K_m e_{rel} \frac{(x_2 - \bar{x}_2)^2}{(K_m + x_2)(K_m + \bar{x}_2)} \\ &\quad - k_{te} B (x_3 - \bar{x}_3)^2 + v_{pt} k_{pt} K_t (1 - e_{rel}) \frac{B(x_2 - \bar{x}_2)(x_3 - \bar{x}_3)}{(K_t + x_2)(K_t + \bar{x}_2)}. \end{aligned}$$

Calculating the matrix of this quadratic form we obtain:

$$\begin{pmatrix} -k_a & \frac{k_a A}{2} & 0 \\ \frac{k_a A}{2} & -A \left(k_e + \frac{K_t k_{pt}(1-e_{rel})}{(K_t+x_2)(K_t+\bar{x}_2)} + \frac{K_m k_{pm} e_{rel}}{(K_m+x_2)(K_m+\bar{x}_2)} \right) & \frac{B K_t v_{pt} k_{pt}(1-e_{rel})}{2(K_t+x_2)(K_t+\bar{x}_2)} \\ 0 & \frac{B K_t v_{pt} k_{pt}(1-e_{rel})}{2(K_t+x_2)(K_t+\bar{x}_2)} & -k_{te} B \end{pmatrix}. \tag{7}$$

In this part we restrict our analysis to the invariant subspace M, to which the solutions are attracted. From Sylvester's criterion we obtain that a quadratic form is negative definite $\iff$ $W_1 < 0$, $W_2 > 0$ i $W_3 < 0$, where W_i is a determinant of the i-th leading principal minor. The first condition $W_1 < 0$ is true due to the positivity of the parameters. The second condition is $W_2 > 0$, where

$$W_2 = k_a A \left(k_e + \frac{K_t k_{pt}(1-e_{rel})}{(K_t + x_2)(K_t + \bar{x}_2)} + \frac{K_m k_{pm} e_{rel}}{(K_m + x_2)(K_m + \bar{x}_2)} \right) - \frac{k_a^2 A^2}{4}.$$

Let us estimate from below

$$W_2 > Ak_ak_e - \frac{k_a^2A^2}{4} = 0 \quad \text{for} \quad A = \frac{4k_e}{k_a}.$$

The third condition is $W_3 < 0$, where

$$W_3 = -B\left(k_{te}W_2 - \frac{k_aB}{4}\frac{K_t^2v_{pt}^2k_{pt}^2(1-e_{rel})^2}{(K_t+x_2)^2(K_t+\bar{x}_2)^2}\right).$$

For $A = \frac{4k_e}{k_a}$ we obtain $W_2 = k_aA\left(\frac{K_tk_{pt}(1-e_{rel})}{(K_t+x_2)(K_t+\bar{x}_2)} + \frac{K_mk_{pm}e_{rel}}{(K_m+x_2)(K_m+\bar{x}_2)}\right)$. Let us estimate from the above

$$\begin{aligned} W_3 &< -B\left(k_{te}k_aA\frac{K_tk_{pt}(1-e_{rel})}{(K_t+x_2)(K_t+\bar{x}_2)} - \frac{k_aB}{4}\frac{K_t^2v_{pt}^2k_{pt}^2(1-e_{rel})^2}{(K_t+x_2)^2(K_t+\bar{x}_2)^2}\right) \\ &= -B\frac{K_tk_{pt}(1-e_{rel})}{4(K_t+x_2)(K_t+\bar{x}_2)}\left(4k_ak_{te}A - B\frac{k_aK_tv_{pt}^2k_{pt}(1-e_{rel})}{(K_t+x_2)(K_t+\bar{x}_2)}\right) \\ &\leq -B\frac{K_tk_{pt}(1-e_{rel})}{4(K_t+x_2)(K_t+\bar{x}_2)}\left(16k_{te}k_e - B\frac{k_av_{pt}^2k_{pt}(1-e_{rel})}{K_t}\right) = 0 \end{aligned}$$

for $A = \frac{4k_e}{k_a}$ and $B = \frac{16K_tk_{te}k_e}{k_av_{pt}^2k_{pt}(1-e_{rel})}$.

Hence, we obtain $\frac{d}{dt}V_l(x(t)) < 0$. Thus, from Lyapunov-LaSalle theorem [6] $(\bar{x}_1, \bar{x}_2, \bar{x}_3)$ is globally asymptotically stable.

4. Model with the switch In this section we consider 6-MP/6-TGN model as a model with the switch. This means that we model the treatment using 6-MP basing on switching between models with and without drug absorption.

LEMMA 4.1 The switching equation for x_1 in the 6-MP/6-TGN model with the switch is determined by the following recursive formula:

$$\begin{cases} x_1(t_{2k+1}) &= \frac{c-(-k_ax_1(t_{2k})+c)\,\mathrm{e}^{-k_a(t_{2k+1}-t_{2k})}}{k_a}, \\ x_1(t_{2k+2}) &= x_1(t_{2k+1})\,\mathrm{e}^{-k_a(t_{2k+2}-t_{2k+1})}, \end{cases} \tag{8}$$

where $k = 0, 1, 2...$, $c = 24FD_1\alpha$ and t_{2k+1}, t_{2k+2} described in Section 2.

Proof. By induction. First, we will show that for $k = 0$ Formula (8) is true. Solving

$$\dot{x}_1 = -k_ax_1 + c \tag{9}$$

with the initial value $x_1(0) = 0$ for $t \in [0, t_1)$, we have

$$x_1(t) = \frac{c(1-\mathrm{e}^{-k_at})}{k_a}.$$

Next, we take the limit at t_1 equal to $\frac{c(1-\mathrm{e}^{-k_a t_1})}{k_a}$. Then for $t \in [t_1, t_2)$ we solve

$$\dot{x}_1 = -k_a x_1 \tag{10}$$

with initial value $x_1(t_1) = \frac{c(1-\mathrm{e}^{-k_a t_1})}{k_a}$ and we get

$$x_1(t) = x_1(t_1)\,\mathrm{e}^{-k_a(t-t_1)}\,.$$

Hence, the limit at t_2 equals to

$$x_1(t_2) = x_1(t_1)\,\mathrm{e}^{-k_a(t_2-t_1)}\,.$$

Therefore, Formula (8) is true for $k = 0$.

Now, we assume that for $k = n-1$ Formula (8) is true. Solving (9) with the initial value $x_1(t_{2n}) = x_1(t_{2n-1})\,\mathrm{e}^{-k_a(t_{2n}-t_{2n-1})}$ on $t \in [t_{2n}, t_{2n+1})$, we obtain:

$$x_1(t) = \frac{c - (-k_a x_1(t_{2n}) + c)\,\mathrm{e}^{-k_a(t-t_{2n})}}{k_a}.$$

Next, we take the limit at t_{2n+1} and we get $\frac{c-(-k_a x_1(t_{2n})+c)\,\mathrm{e}^{-k_a(t_{2n+1}-t_{2n})}}{k_a}$. This limit is the initial value for Equation (9) for $t \in [t_{2n+1}, t_{2n+2})$. We obtain:

$$x_1(t) = x_1(t_{2n+1})\,\mathrm{e}^{-k_a(t-t_{2n+1})},$$

with the limit at t_{2n+2} equal to

$$x_1(t_{2n+2}) = x_1(t_{2n+1})\,\mathrm{e}^{-k_a(t_{2n+2}-t_{2n+1})}\,.$$

□

Because we have assumed that the patient takes the drug at regular time intervals Lemma 4.1 implies Lemma 4.2.

LEMMA 4.2 For 6-MP/6-TGN model with the switch and $n = 1, 2, 3...$, where n denotes the number of days of the therapy, the equation for $x_1(n)$ is determined by:

$$x_1(n) = \frac{c\,\mathrm{e}^{-k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)}{k_a\left(1-\mathrm{e}^{-k_a}\right)}\left(1-\mathrm{e}^{-k_a n}\right). \tag{11}$$

Proof. For $t \in [t_{2k}, t_{2k+1}]$, $k = 0, 1, 2\ldots$, where $t_{2k+1} = t_{2k} + \frac{1}{24}$, the model with drug absorption is applied, for $t \in [t_{2k+1}, t_{2k+2}]$, $k = 0, 1, 2\ldots$, where $t_{2k+2} = t_{2k+1} + \frac{23}{24}$, the model without drug absorption is applied. Time for one cycle equals to 1, because $t_{2k+2} - t_{2k} = 1$, where t_{2k} and t_{2k+2} denote the subsequent moments of the drug application. The treatment starts at $t = 0$, hence the next doses are taken by the patient at $t = 1, 2, 3....$ Combining the results for times indexed by even and odd integers from Lemma 4.1 we conclude

$$x_1(t_{2k+2}) = x_1(t_{2k})\,\mathrm{e}^{-k_a} + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right).$$

Substituting $t_{2k} = k$, where $k = 0, 1, 2...$ is the number of subsequent days of the therapy, we get the following recursive formula:

$$x_1(k+1) = x_1(k)\,\mathrm{e}^{-k_a} + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right).$$

Now, we will prove Lemma 4.2 by induction. For $k = 1$ Formula (11) is obvious. Next we assume that Formula (11) is true for $k = n - 1$. Using recursion

$$x_1(n) = x_1(n-1)\,\mathrm{e}^{-k_a} + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right).$$

We substitute equation for $x_1(n-1)$ and we obtain:

$$\begin{aligned} x_1(n) = &\left(x_1(1)\,\mathrm{e}^{-k_a(n-2)} + \frac{c\,\mathrm{e}^{-k_a}}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)\frac{1 - \mathrm{e}^{-k_a(n-2)}}{1 - \mathrm{e}^{-k_a}}\right)\mathrm{e}^{-k_a} \\ &+ \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right). \end{aligned}$$

Next, we simplify the right-hand side of the equation:

$$\begin{aligned} x_1(n) &= x_1(1)\,\mathrm{e}^{-k_a(n-1)} + \mathrm{e}^{-2k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)\frac{1 - \mathrm{e}^{-k_a(n-2)}}{1 - \mathrm{e}^{-k_a}} \\ &\quad + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right) \\ &= x_1(1)\,\mathrm{e}^{-k_a(n-1)} + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)\left(\mathrm{e}^{-k_a} + ... + \mathrm{e}^{-k_a(n-2)}\right) \\ &\quad + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right) \\ &= x_1(1)\,\mathrm{e}^{-k_a(n-1)} + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)\left(1 + \mathrm{e}^{-k_a} + ... + \mathrm{e}^{-k_a(n-2)}\right) \\ &= x_1(1)\,\mathrm{e}^{-k_a(n-1)} + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)\frac{1 - \mathrm{e}^{-k_a(n-1)}}{1 - \mathrm{e}^{-k_a}}. \end{aligned}$$

We substitute $x_1(1)$ and we get the following formula for $x_1(n)$:

$$\begin{aligned} x_1(n) &= \frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)\mathrm{e}^{-k_a n} + \mathrm{e}^{-k_a}\,\frac{c}{k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)\frac{1 - \mathrm{e}^{-k_a(n-1)}}{1 - \mathrm{e}^{-k_a}} \\ &= \frac{c\,\mathrm{e}^{-k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)}{k_a}\left(1 + \mathrm{e}^{-k_a} + ... + \mathrm{e}^{-k_a(n-1)}\right) \\ &= \frac{c\,\mathrm{e}^{-k_a}\left(\mathrm{e}^{\frac{k_a}{24}} - 1\right)}{k_a\left(1 - \mathrm{e}^{-k_a}\right)}\left(1 - \mathrm{e}^{-k_a n}\right). \end{aligned}$$

□

PROPOSITION 4.3 The solution of the switching equation for x_1 converges to a periodic function with period 1.

Proof. From Lemma 4.2 we get the formula for x_1 at $t \in \mathbb{N}$. If $n \to \infty$, then

$$x_1(n) \to \frac{c\,\mathrm{e}^{-k_a}}{k_a} \frac{\mathrm{e}^{\frac{k_a}{24}} - 1}{1 - \mathrm{e}^{-k_a}}.$$

Let $G = \frac{c\,\mathrm{e}^{-k_a}}{k_a} \frac{\mathrm{e}^{\frac{k_a}{24}} - 1}{1 - \mathrm{e}^{-k_a}}$. Next, taking $x_1(n+t)$, where $t \in (0,1)$, we obtain

$$x_1(n+t) = x(n)\,\mathrm{e}^{-k_a t} + \frac{c\,\mathrm{e}^{-k_a t}}{k_a} \left(\mathrm{e}^{k_a \min\{t, \frac{1}{24}\}} - 1\right)$$

implying that the solution of the switching equation for x_1 converges to the periodic function:

$$V(t) = G\,\mathrm{e}^{-k_a(t - \lfloor t \rfloor)} + \frac{c\,\mathrm{e}^{-k_a(t - \lfloor t \rfloor)}}{k_a} \left(\mathrm{e}^{k_a \min\{(t - \lfloor t \rfloor), \frac{1}{24}\}} - 1\right)$$

□

Let us now consider the asymptotic dynamics of the system for x_2 and x_3. This system reads:

$$\begin{cases} \dot{x}_2 &= k_a V(t) - k_e x_2 - \frac{k_{pt}(1 - e_{rel}) x_2}{K_t + x_2} - \frac{k_{pm} e_{rel} x_2}{K_m + x_2}, \\ \dot{x}_3 &= \frac{v_{pt} k_{pt}(1 - e_{rel}) x_2}{K_t + x_2} - k_{te} x_3, \end{cases} \tag{12}$$

Proposition 4.4 Asymptotic dynamics of the System (12) for x_2 and x_3 is periodic with period 1.

Proof. Let $y(t) = x_2(t+1) - x_2(t)$. Therefore, assuming $y \neq 0$,

$$\frac{\dot{y}}{y} \leq -k_e.$$

We need to prove that $y(t)$ converges to 0 for $t \to \infty$. There are two possibilities: $y(t) \geq 0$ or $y(t) < 0$. For $y(t) \geq 0$ estimating the derivative from the above

$$\dot{y} \leq -k_e y$$

We obtain:

$$0 \leq y(t) \leq y_0\,\mathrm{e}^{-k_e t}.$$

For $y(t) < 0$ let $z(t) = -y(t)$. Then

$$\frac{\dot{y}}{y} = \frac{\dot{z}}{z} \leq -k_e,$$

therefore:

$$0 > y(t) > y_0\,\mathrm{e}^{-k_e t}.$$

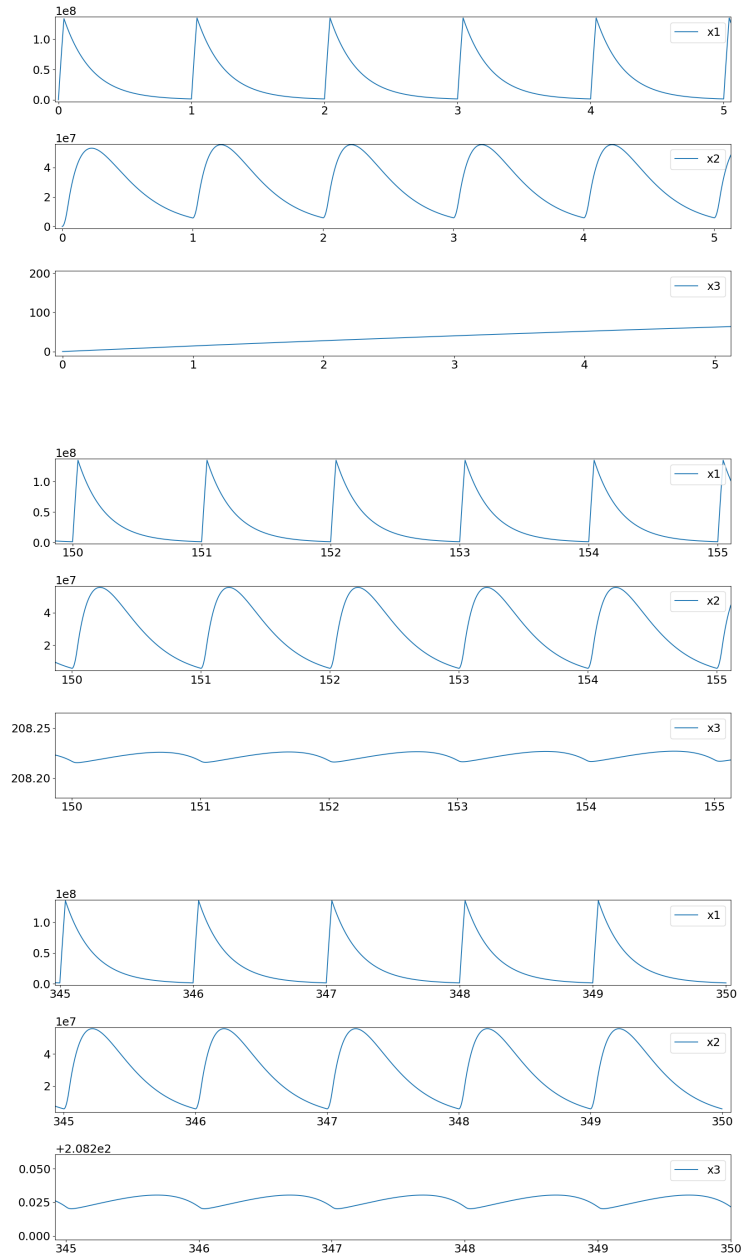
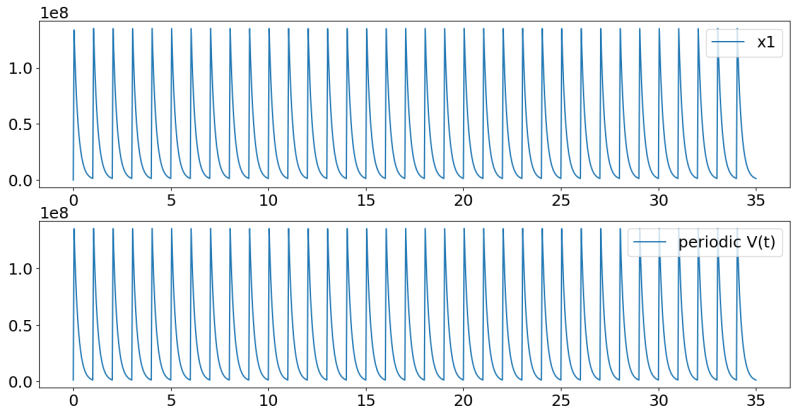
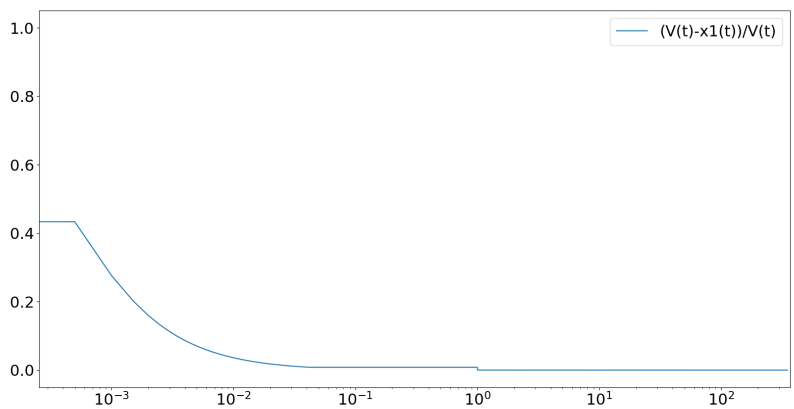


Figure 3: *The comparison of the plots illustrating variables in the 6MP/6TGN model with the switch during different parts of the therapy, where variables are in the following units:* x_1 *— pmol,* x_2 *— pmol,* x_3 *— pmol/8* $\times$ 10^8 *RBCs.*

Hence, the variable x_2 converges to a periodic function. The same proof as for x_2 can be applied to x_3. □



(a) *The comparison of the plots of the solution of the switching equation for x_1 and the periodic function to which this solution converges.*

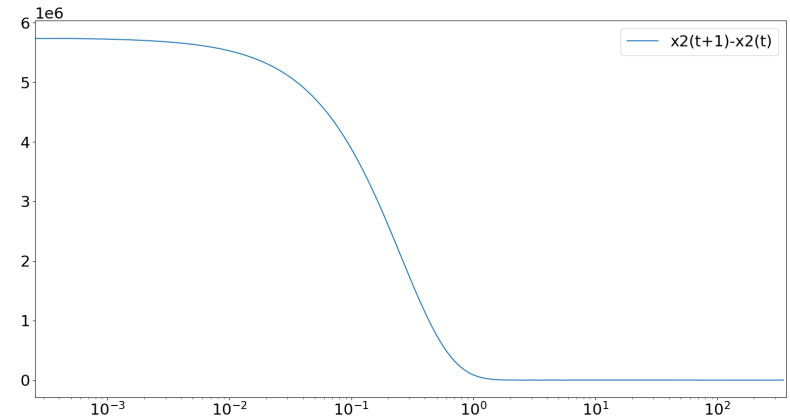


(b) *The plot of the relative error between the solution of the switching equation for x_1 and periodic function. Logarithmic scale is used for X axis representing the time of therapy.*

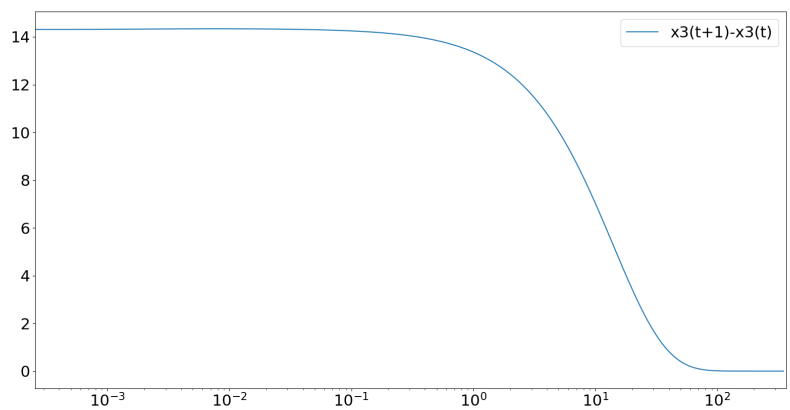
Figure 4: *The plots illustrating asymptotic dynamics of x_1 and its relation to aforementioned periodic function.*

Numerical simulations presented in Fig. 3 support the Assertions of Propositions 4.3 and 4.4. In Fig. 4a we present two separate plots because placing the solution of the switching equation for x_1 and periodic function to which this solution converges in one plot may cause difficulties to distinguish between them. Additionally, in Fig. 4b we present the plot of relative error between the solution of the switching equation for x_1 and periodic function. Fig. 5a and 5b are illustrating asymptotic dynamics of the switching equations for x_2 and x_3. For simulations we used parameters from Table 1 and we

took dose $D = 50$ mg 6-MP.



(a) *The plot illustrating the difference between* $x_2(t+1) - x_2(t)$. *The logarithmic scale is used for X axis representing the time of therapy.*



(b) *The plot illustrating the difference between* $x_3(t+1) - x_3(t)$. *The logarithmic scale is used for X axis representing the time of therapy.*

Figure 5: *For variables* x_2 *and* x_3 *we do not have explicitly defined limit periodic functions, but we can illustrate the difference between the phases shifted by 1.*

5. Conclusions In this work we presented a mathematical model for the maintenance therapy of acute lymphoblastic leukemia described by Le et al. in their paper [7]. Firstly we reported the details of the model in Section 2 and then, in Section 3, proceeded to analyze it. In particular, we have proved boundedness and existence of solutions and discussed its stability and stationary states. For model without drug absorption we obtained

the globally asymptotically stable zero stationary state, whereas for the model with drug absorption we obtained globally asymptotically stable positive stationary state. At the end we described an alternative model which switches between models with and without drug absorption and proved some important properties, including asymptotic periodic dynamics. The obtained results describe chemotherapy with the assumption of the drug administration at regular time intervals. We presented numerical simulations illustrating the solutions of the switching equations and supporting the assertion regarding asymptotic dynamics. Analysis of the model with the switch has potential to be extended and used for other drug models.

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A. Parameters

Parameters	Values	Units	Description
k_a	4,8	$\frac{1}{\text{day}}$	6-MP absorption rate from GI tract
k_e	5,0	$\frac{1}{\text{day}}$	6-MP elimination rate from plasma
k_{pt}	29,8	$\frac{pmol}{\text{day}}$	6-MP to 6-TGN conversion rate
k_{pm}	655,8	$\frac{pmol}{\text{day}}$	6-MP to MeMP conversion rate
K_t	4,04 $\times 10^5$	pmol	Michelis-Menten constant for 6-TGN
K_m	3,28 $\times 10^5$	pmol	Michelis-Menten constant for MeMP
k_{te}	0,0714	$\frac{1}{\text{day}}$	6-TGN elimination rate from RBCs
e_{rel}	0,5		TPMT enzyme activity constant
v_{pt}	1	$\frac{\text{pmol 6-TGN}}{\text{pmol 6-MP}/8\times 10^8 \text{RBCs}}$	6-TGN elimination rate from RBCs
F	0,45		bioavailability factor
D		mg	dose of 6-MP
α	$\frac{10^{12}}{152177}$	$\frac{pmol}{mg}$	unit consistency constant

Table 1: *Parameters of the 6-MP/ 6-TGN model*

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Model PK/PD terapii ostrej białaczki 6-merkaptopuryną

Zofia Gruba

Streszczenie W niniejszej pracy przedstawiono analizę modelu lekowego dynamiki 6-MP/6-TGN podczas terapii podtrzymującej ostrej białaczki limfoblastycznej, który został zaproponowany przez T. T. T. Le al. w 2018 roku. Wykazano kilka podstawowych własności, takich jak istnienie, jednoznaczność, nieujemność i ograniczoność rozwiązań. Znaleziono stany stacjonarne i zbadano ich stabilność. Dodatkowo zaprezentowano alternatywny model z przełączeniem. Wykazano, że asymptotyczne rozwiązania modelu z przełączeniem są okresowe z okresem, z jakim podawany jest lek.

Klasyfikacja tematyczna AMS (2010): Primary: 92C45; Secondary: 92C50.

Słowa kluczowe: równania różniczkowe zwyczajne, punkty stacjonarne, stabilność, model z przełączeniem, ostra białaczka limfoblastyczna.

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