332:417 Control Systems Design - FINAL PROJECT

(20 points = 20% of the course grade)

Project assigned December 5, 2021. *Project due by noon on the last day of the final exams*. Professor Gajic will hold regular office hours though out of the reading period and the final week. Special, Final Project office hours will be announced.

Optimal Control (Drug Dosing) to Achieve the Desired Actual Neutrophil Counts (ANC) in Chemotherapy Induced Myelosuppression

Use of mathematical modeling, system analysis, and control systems have attracted attention of pharmaceutical researchers and pharmaceutical industry. Two new important areas known as pharmacodynamics (PD) and pharmacokinetics (PK) have been recently developed. These days, pharmacodynamics and pharmacokinetics play important roles in the development of new drugs.

Project Preparation:
As preparation for this projects, students must master linearization of nonlinear systems (presented in Lecture 20), Simulink and its use for nonlinear systems (Lecture 21 and Lecture 25 Part 2), mathematical model of neutrophil dynamics under chemotherapy, its linearization, and its steady state values (presented in detail in Lecture 22 pages 1-3), and a project demo presented in Lecture 26 Part 2, in which a nonlinear model of a robotic manipulator is controlled via linearization. The linear-quadratic optimal controller used in this project is presented in Lecture 23, pages 1-5.

Project Goal:
In this project we consider the well-known myelosuppression mathematical model from the control systems point of view. We study the linearized model at steady state values. In order to avoid numerical computations with large numbers scaling of system state variables by a factor of 10^9 has been utilized. In the central part of the paper, a method for optimal chemotherapy dosing was considered using a result from optimal control theory in order to reduce the amount of administrated chemotherapy drugs and to keep the number of neutrophil cells above a pre-specified desired ANC (actual neutrophil count) level. It can be noticed from the results of this project that in the *case of continuous dosing, the variable optimal amounts of the drug have to be administrated daily based on feedback information regarding the actual count of neutrophils*. *This result mathematically establishes that administrating constant amount of drugs daily cannot provide the optimal dosing schedule*. The obtained results may be useful for personalized and optimized medicine that requires daily monitoring of fundamental variables and daily drug administration in *variable quantities* based on the actual state of the patient's fundamental variables (parameters).

Project tasks:
Part 1 (10 pts). Build the Simulink block diagram for the considered mathematical model (see Figures 1a and 1b). Simulate this nonlinear system and plot the number of neutrophils during 50 days under given constant drug dosage of 250 mg and the steady state drug dosage that gives a pre-specified actual neutrophil count (see Figures 2-3).

Part 2 (10 pts). Use MATLAB to find the optimal gain and built the corresponding Simulink block diagram for control of this system via linearization (see Figure 4). Plot the number neutrophils and the optimal drug dosage during a 15-day interval (see Figures 5 and 6).

INTRODUCTION

The nonlinear mathematical model of the system that represents dynamics of human bone marrow production of neutrophils under the suppressive impact of chemotherapy, derived by Friberg et al. [1]-[2], was used in many journal publications in PK and PD [3]-[13] and references therein. The paper of Craig, [4], states regarding the model of [1]: "… has undoubtedly become the most frequent and gold-standard approach to modeling the myelosuppresive effects of chemotherapy in the pharmaceutical sciences literature." Mathematical modeling of neutrophil dynamics during has gained increased attention of researchers in PD and PK in the recent years with a goal to achieve a better understanding of time- and dose-dependent scheduling of drug therapy and predict cytotoxic effects of chemotherapy, and study their impact on neutrophil counts [4], [8]-[10].

The PK/PD mathematical model [1] is composed of five compartments: the proliferating compartment with hematopoietic stem cells and neutrophil progenitor cells (*proliferative cells*), three transit compartments (maturation compartments) with *maturing cells*, and compartment of *circulating neutrophils*. Dynamics in each compartment are represented by a first-order differential equation that when coupled together represent a system of five nonlinear differential equations. The dynamics of the proliferative cells are nonlinear due to nonlinear feedback from circulating cells, and the remaining four differential equations are linear, which provides a possibility for simplification of the model due to its predominantly linear dynamics.

In this project, a method for optimal chemotherapy dosing using the linear-quadratic optimal control systems theory result is utilized in order to reduce the amount of continuously administrated chemotherapy drugs and to keep the number of neutrophil cells above a pre-specified (desired) ANC (actual neutrophil count) level, using the methodology for control of nonlinear systems via linearization. The solution obtained require feedback from all state variables. The paper [12] indicates that frequent neutrophil (ANC) monitoring can improve the therapy management. The obtained results open a door for personalized and optimized medicine that will require daily *administration of drugs in variable amounts* based on daily monitoring of the actual state of the patient fundamental parameters relevant to the considered decease.

Mathematical model and its steady state quantities

The PK/PD mathematical model [1] is represented by the following system of differential equations

$$\begin{aligned}
\frac{dx_1(t)}{dt} &= -k_{tr}x_1(t) + k_{prol}x_1(t)\left(1-E_{Drug}(t)\right)\left(\frac{Circ_0}{x_5(t)}\right)^{\gamma} = f_1(x_1(t),x_5(t),E_{Drug}(t)), \quad x_1(0)=Circ_0 \\
\frac{dx_2(t)}{dt} &= k_{tr}x_1(t) - k_{tr}x_2(t) = f_2(x_1(t),x_2(t)), \quad x_2(0)=Circ_0 \\
\frac{dx_3(t)}{dt} &= k_{tr}x_2(t) - k_{tr}x_3(t) = f_3(x_2(t),x_3(t)), \quad x_3(0)=Circ_0 \\
\frac{dx_4(t)}{dt} &= k_{tr}x_3(t) - k_{tr}x_4(t) = f_4(x_3(t),x_4(t)), \quad x_4(0)=Circ_0 \\
\frac{dx_5(t)}{dt} &= k_{tr}x_4(t) - k_{circ}x_5(t) = f_5(x_4(t),x_5(t)), \quad x_5(0)=Circ_0
\end{aligned} \tag{1}$$

where $x_1(t)$ are proliferative cells, $x_2(t), x_3(t), x_4(t)$ are maturing cells, and $x_5(t)$ are the circulating blood cells. $E_{Drug}(t)$ stands for the chemotherapy drug effect that is a function of its concentration in the central compartment. $Circ_0$ is the base value of neutrophil count, k_{prol} is the proliferation rate constant, k_{tr} is the transit compartment rate constant, k_{circ} is the rate of neutrophil elimination, and γ is the feedback factor. The input to this nonlinear system is

$E_{Drug}(t)$, and the model output denoted by $y(t)$ is the variable $x_5(t)$, that is $y(t)=x_5(t)$. The model data are taken from [10] with the following values

$$Circ_0 = 5.04\times10^9\,\frac{1}{\mathrm{L}}, \qquad k_{tr} = \frac{4}{120.4}\frac{1}{\mathrm{h}} = 0.0332\frac{1}{\mathrm{h}} = k_{prol} = k_{circ}, \qquad \gamma = 0.16 \tag{2}$$

An important constraint during chemotherapy administration is that the absolute neutrophil count (ANC) should stay above the limit that defines neutropenia ($\mathrm{ANC}=1.5\times10^9/\mathrm{L}$). For that reason, in the long run (steady state) the following relations hold $Circ_0 > x_{5ss} > \mathrm{ANC} = 1.5\times10^9/\mathrm{L}$. Based on the data from [10], the initial count of neutrophils of $5.04\times10^9/\mathrm{L}$, it can be assumed

$$x_5^{ss} = \alpha\times\mathrm{ANC},\ \alpha_{\min}=1<\alpha<\frac{Circ_0}{\mathrm{ANC}}=\frac{5.04}{1.5}=3.36=\alpha_{\max} \Rightarrow Circ_0=\alpha_{\max}\mathrm{ANC}=3.36\times\mathrm{ANC} \tag{3}$$

It will be shown that the presented methodology is flexible in the sense that it allows various choices for the parameter α, which we call the *neutropenia indicator or measure* (when $\alpha\le1$).

The model (1) can be linearized at steady state values . The steady state values are obtained by setting all derivatives to zero, which leads to the following system of five algebraic equations

$$0=-k_{tr}x_1^{ss}+k_{prol}x_1^{ss}\left(1-E_{Drug}^{ss}\right)\left(\frac{Circ_0}{x_5^{ss}}\right)^{\gamma}=-k_{tr}+k_{prol}\left(1-E_{Drug}^{ss}\right)\left(\frac{Circ_0}{x_5^{ss}}\right)^{\gamma} \Rightarrow E_{Drug}^{ss}=f(x_5^{ss})$$

$$0=k_{tr}x_1^{ss}-k_{tr}x_2^{ss} \Rightarrow x_1^{ss}=x_2^{ss}=\frac{k_{circ}}{k_{tr}}x_5^{ss}$$

$$0=k_{tr}x_2^{ss}-k_{tr}x_3^{ss} \Rightarrow x_2^{ss}=x_3^{ss}=\frac{k_{circ}}{k_{tr}}x_5^{ss} \tag{4}$$

$$0=k_{tr}x_3^{ss}-k_{tr}x_4^{ss} \Rightarrow x_3^{ss}=x_4^{ss}=\frac{k_{circ}}{k_{tr}}x_5^{ss}$$

$$0=k_{tr}x_4^{ss}-k_{tr}x_5^{ss} \Rightarrow x_4^{ss}=\frac{k_{circ}}{k_{tr}}x_5^{ss}$$

The first algebraic equation in (4) produces two important steady state formulas:

$$0=-k_{tr}+k_{prol}\left(1-E_{Drug}^{ss}\right)\left(\frac{Circ_0}{x_{5ss}}\right)^{\gamma} \Rightarrow E_{Drug}^{ss}=1-\frac{k_{tr}}{k_{prol}}\left(\frac{x_5^{ss}}{Circ_0}\right)^{\gamma},\ x_5^{ss}=Circ_0\left(\frac{k_{prol}(1-E_{drug}^{ss})}{k_{tr}}\right)^{\frac{1}{\gamma}} \tag{5}$$

Using the given numerical data from [10] with $x_5^{ss}=\alpha\times\mathrm{ANC}=\alpha\times1.5\times10^9/\mathrm{L}$, the following steady state values are obtained in terms of the neutropenia indicator α

$$x_5^{ss}=\alpha\times\mathrm{ANC},\ 1<\alpha<3.36=\alpha_{\max} \Rightarrow E_{Drug}^{ss}=1-\left(\frac{\alpha\times\mathrm{ANC}}{\alpha_{\max}\times\mathrm{ANC}}\right)^{\gamma}=1-\left(0.2998\alpha\right)^{0.16} \tag{6}$$

$$x_1^{ss}=x_2^{ss}=x_3^{ss}=x_4^{ss}=x_5^{ss}=\alpha\times\mathrm{ANC}$$

NONLINEAR MODEL LINEARIZATION

The linearized systems around its steady state operating points is given by

$$\frac{d\Delta x(t)}{dt}=A\,\Delta x(t)+B\Delta E_{Drug}(t), \qquad \Delta x(t_0)=x(t_0)-x_{ss}, \qquad \Delta y(t)=C\Delta x(t) \tag{7}$$

with the actual nonlinear system variables evolving as

$$x(t) = x_{ss} + \Delta x(t), \qquad E_{Drug}(t) = E_{Drug}^{ss} + \Delta E_{Drug}(t) \tag{8}$$

The linearized system provides information regarding deviations of state space variables around their steady state values. The linearized system matrix is the Jacobian matrix of partial derivatives evaluated at the system operating points, in this case the steady state points. It is given by

$$A = \left[\begin{array}{ccccc} \dfrac{\partial f_1(x_1(t), x_5(t))}{\partial x_1} & 0 & 0 & 0 & \dfrac{\partial f_1(x_1(t), x_5(t))}{\partial x_5} \\ k_{tr} & -k_{tr} & 0 & 0 & 0 \\ 0 & k_{tr} & -k_{tr} & 0 & 0 \\ 0 & 0 & k_{tr} & -k_{tr} & 0 \\ 0 & 0 & 0 & k_{tr} & -k_{tr} \end{array}\right]\Bigg|_{\substack{E_{Drug}=E_{Drug}^{ss} \\ x=x^{ss}}} \tag{9}$$

The (1,1) element in this matrix, a_{11}, is obtained as

$$a_{11} = -k_{tr} + k_{prol}(1 - E_{Drug}^{ss})\left(\frac{Circ_0}{x_5^{ss}}\right)^{\gamma}$$

Using the first steady state equations in (4), it can be shown that this element is equal to zero, that is $a_{11} = 0$. The element a_{15} can be also simplified using the first equation in (4), which leads to

$$a_{15} = -\gamma k_{prol} x_{1ss}(1 - E_{Drug}^{ss})\left(\frac{Circ_0}{x_5^{ss}}\right)^{\gamma}\frac{1}{x_5^{ss}} = -\gamma k_{prol}$$

Hence, the linearized system matrix at steady state is given by

$$A = \begin{bmatrix} 0 & 0 & 0 & 0 & -\gamma k_{prol} \\ k_{tr} & -k_{tr} & 0 & 0 & 0 \\ 0 & k_{tr} & -k_{tr} & 0 & 0 \\ 0 & 0 & k_{tr} & -k_{tr} & 0 \\ 0 & 0 & 0 & k_{tr} & -k_{circl} \end{bmatrix} = k_{tr}\begin{bmatrix} 0 & 0 & 0 & 0 & -\gamma\dfrac{k_{prol}}{k_{tr}} \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -\dfrac{k_{circl}}{k_{tr}} \end{bmatrix} = k_{tr} A_f \tag{10}$$

where A_f is the linearized system matrix in the fast time scale. Equation (7) can be written as

$$\frac{d\Delta x(t)}{dt} = k_{tr} A_f \Delta x(t) + B\Delta E_{Drug}(t) \quad \Rightarrow \quad \frac{d\Delta x(t)}{k_{tr} dt} = A_f \Delta x(t) + \frac{1}{k_{tr}} B\Delta E_{Drug}(t) \tag{11}$$

Introducing the fast time scale $\tau = k_{tr} t$, we have

$$\frac{d\Delta x(\tau)}{d\tau} = A_f \Delta x(\tau) + B_f \Delta E_{Drug}(t), \qquad B_f = \frac{1}{k_{tr}} B \tag{12}$$

The linearized model control input matrix B is given by

$$B^T = \left[\frac{\partial f_1(x_1, x_5, E_{Drug})}{\partial E_{Drug}} \quad 0 \quad 0 \quad 0 \quad 0\right]\Bigg|_{\substack{E_{Drug}=E_{Drug}^{ss} \\ x=x^{ss}}} = \left[-k_{prol} x_1^{ss}\left(\frac{Circ_0}{x_5^{ss}}\right)^{\gamma} \quad 0 \quad 0 \quad 0 \quad 0\right] \tag{13}$$

$$= \begin{bmatrix} b_1 & 0 & 0 & 0 & 0 \end{bmatrix}$$

The linearized system output ($\Delta y(t) = \Delta x_5(t)$) matrix is given by

$$C = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 \end{bmatrix} \tag{14}$$

The linearized system output is $\Delta y(t) = C\Delta x(t) = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 \end{bmatrix} \Delta x(t) = \Delta x_5(t)$.

Rescaling system state variables

A way to avoid dealing with huge numbers is to rescale all state variables, including their initial conditions by the factor of 10^9, which also rescales the matrix B by the same factor. This kind of rescaling technique was suggested and used in [13], as well as in our simulation results. The scaled input matrix is given by

$$B_{scaled1}^T = \begin{bmatrix} b_{1scaled} & 0 & 0 & 0 & 0 \end{bmatrix}, \quad b_{1scaled} = b_1 / 10^9$$

OPTIMAL CONTROL (DOSING) VIA LINEARIZATION

An optimal nonlinear control strategy is designed via linearization using the linear-quadratic optimal controller. The strategy minimizes the drug toxicity while keeping the number of neutrophils above the prescribed threshold for neutropenia, a severe immune compromise.

The linearized model has been derived in formulas (7)-(10) and (13)-(14) as

$$\frac{d\Delta x(t)}{dt} = A\Delta x(t) + B\Delta E_{Drug}(t), \quad \Delta x(t_0) = x(t_0) - x^{ss} = Circ_0 \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} - x_5^{ss} \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ \frac{k_{circ}}{k_{tr}} \end{bmatrix} \tag{15}$$

$$\Delta y(t) = C\Delta x(t) = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 \end{bmatrix} \Delta x(t) = \Delta x_5(t)$$

$$x(t) = x^{ss} + \Delta x(t), \quad E_{Drug}(t) = E_{Drug}^{ss} + \Delta E_{Drug}(t)$$

The feedback controller $\Delta E_{Drug}(\Delta x(t)) = -F\Delta x(t)$ is selected using the linear-quadratic optimal controller [15]-[16], even though other controllers can be used, for example, the eigenvalue assignment controller. The quadratic performance criterion is chosen to minimize the square of deviations of state variables from their nominal (steady state) values, and hence optimally reduce the amount of administrated chemotherapy drugs over a given time interval time $\begin{bmatrix} t_0 & t_f \end{bmatrix}$

$$J = \min_{\Delta E_{drug}(t)} \frac{1}{2} \left\{ \int_{t_0}^{t_f} \left[\Delta x^T(t) R_1 \Delta x(t) + R_2 \Delta E_{Drug}^2(t) \right] \right\}, \quad R_1 \geq 0, \quad R_2 > 0 \tag{16}$$

where the weighting factors R_1 and R_2 are the design parameters that can be arbitrarily chosen (subject to R_1 being a positive semidefinite matrix and R_2 being a positive scalar) to achieve the desired performance. Often R_1 is taken as a diagonal matrix with the non-negative magnitudes of the diagonal elements representing importance of the particular state variables in the optimization process, [16]. The optimal feedback controller is given by

$$\Delta E_{Drug}^{ss}(t) = -F^{opt}(t)\Delta x^{opt}(t), \quad F^{opt}(t) = R_2^{-1} B^T P(t) \tag{17}$$

with matrix $P(t)$ satisfying the differential Riccati equation

$$\frac{dP(t)}{dt} = A^T P(t) + AP(t) + R_1 - P(t)BR_2^{-1}B^T P(t), \qquad P(t_f) = 0 \tag{18}$$

The optimal changes of the state variables are given by

$$\frac{d\Delta x^{opt}(t)}{dt} = A\Delta x^{opt}(t) + B\Delta E_{Drug}^{opt}(t) = (A - BF^{opt}(t))\Delta x^{opt}(t) \tag{19}$$

The optimal performance criterion value is equal to [15]

$$J^{opt} = \frac{1}{2}\Delta x^T(t_0)P(t_0)\Delta x(t_0) \tag{20}$$

The solution of the optimization problem defined by (15)-(16) requires solving the differential algebraic Riccati equation (18) and makes the optimal linearized feedback system (19) time varying. A simpler solution is to use an suboptimal feedback controller, which in the case when the optimization interval $[t_0 \quad t_f]$ is relatively large, tends to the optimal feedback controller [17]. In that case, the differential Riccati equation (18) becomes and algebraic Riccati equation

$$0 = A^T \bar{P} + A\bar{P} + R_1 - \bar{P}BR_2^{-1}B^T\bar{P} \tag{21}$$

with $P(t) \to \bar{P}$, and

$$F^{opt}(t) \to R_2^{-1}B^T\bar{P}, \qquad J^{opt} \to \frac{1}{2}\Delta x^T(t_0)\bar{P}\Delta x(t_0) \tag{22}$$

The original model simplification by changing the time scale

We have already seen that the original system mathematical model, due to its specific structure, can be simplified by changing the time scale. Namely, dividing all differential equations (1) by the positive constant k_{tr}, we will get on the left-hand sides

$$\frac{dx_i(t)}{k_{tr}dt} = \frac{dx_i(\tau)}{d\tau}, \quad \tau = k_{tr}t, \quad i = 1,2,...,5 \tag{23}$$

The original system evolving in the τ time scale is described by the following differential equations

$$\begin{aligned}
\frac{dx_1(\tau)}{d\tau} &= -x_1(\tau) + \frac{k_{prol}}{k_{tr}}x_1(\tau)\left(1 - E_{Drug}(\tau)\right)\left(\frac{Circ_0}{x_5(\tau)}\right)^{\gamma} \\
\frac{dx_2(\tau)}{d\tau} &= x_1(\tau) - x_2(\tau) \\
\frac{dx_3(\tau)}{d\tau} &= x_2(\tau) - x_3(\tau) \\
\frac{dx_4(\tau)}{d\tau} &= x_3(\tau) - x_4(\tau) \\
\frac{dx_5(\tau)}{d\tau} &= x_4(\tau) - \frac{k_{circ}}{k_{tr}}x_5(\tau)
\end{aligned} \tag{24}$$

Since $k_{tr} < 1$, the original time scale $t = \tau / k_{tr}$ is the *stretched time scale* version of the time scale τ by a factor of $1/k_{tr}$, or the other way around, the time scale τ is the *shirked (compressed) time scale* with respect to the original time scale *t*. Note also that the state variables $x_2(\tau), x_3(\tau), x_4(\tau)$ represent linear systems with the time constants equal to 1 (the original system state variables $x_2(t), x_3(t), x_4(t)$ have the time constants equal to $1/k_{tr}$), and the variable $x_5(\tau)$ is also represented by a linear system with the time constant k_{circ}/k_{tr} (the original state variable $x_5(t)$ has the time

constant equal to k_{circ}). Hence, the procedure of changing the time scales has the effect of normalizing the system time constants.

In the case of data used in (2), That is, $k_{prol} = k_{tr} = k_{circ}$, a simple mathematical model that has no parameters is obtained. It only needs information about the input signal equal of the drag dose time evolution (scheduling) $E_{Drug}(t)$, and eventually the model initial conditions for state variables. Of course, at the end of analysis or simulation, the results obtained in the time scale τ should be converted back to the original system time scale *t*.

$$\begin{aligned}
\frac{dx_1(\tau)}{d\tau} &= -x_1(\tau) + x_1(\tau)\left(1 - E_{Drug}(\tau)\right)\left(\frac{Circ_0}{x_5(\tau)}\right)^{\gamma} \\
\frac{dx_2(\tau)}{d\tau} &= x_1(\tau) - x_2(\tau) \\
\frac{dx_3(\tau)}{d\tau} &= x_2(\tau) - x_3(\tau) \\
\frac{dx_4(\tau)}{d\tau} &= x_3(\tau) - x_4(\tau) \\
\frac{dx_5(\tau)}{d\tau} &= x_4(\tau) - x_5(\tau)
\end{aligned} \tag{25}$$

This model will be used in the next section, where we present the simulation results. The results obtained in the τ should be represented and interpreted in the original time scale t.

SIMULATION RESULTS

Part 1: System Analysis of the Friberg's Model (10 points)

The simplified model (25) of the considered model (1) can be implemented in MATLAB/SIMULINK using the block diagram presented in Figure 1a. The SIMULINK block diagram for the transit compartments is presented in Figure 1b. Note that the integrators ($1/s$ blocks) contain information about the initial conditions for all five state variables. According to the model equation (1), all of them are equal, that is $x_i(0) = Circ_0, i = 1,2,...,5$. ***Simulation is performed by rescaling all state variables, including their initial conditions by*** 10^9***, which helps to avoid potential numerical problems of dealing with the very small and very large numbers***. Hence, in simulation the following data should be used $Circ_0 = 5.04$, $ANC = 1.5$.

The model output response under the commonly administrated constant drug concentration, $E_{Drug}(t) = 250\ \text{mg}$ (in simulation use $E_{Drug} = 0.250$), is presented in Figure 2. It can be seen from Figure 2 that continuous application of this drug amount brings the ANC below 1.5×10^9 in day number 10, even down to $ANC \sim 0.65 \times 10^9$ in day 17 and has the steady state value of $ANC \sim 0.8 \times 10^9$. The model output response under the input signal equal to the steady state value that provides the desired ANC using formula (6), is presented in Figure 3.

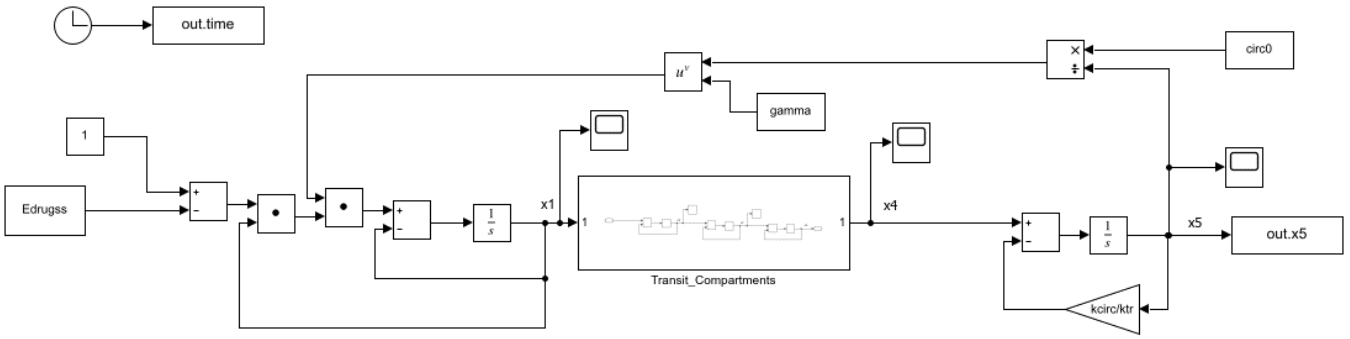

Fig.1a Simulink block diagram of the chemotherapy-induced myelosuppression mathematical model of Friberg and her coworkers

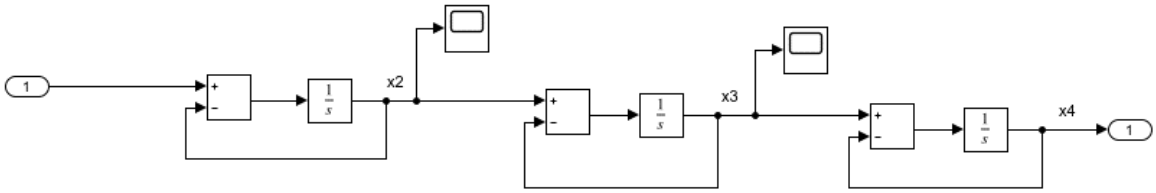

Fig.1b The transit compartments in the Simulink block diagram of the chemotherapy-induced myelosuppression mathematical model of Friberg and her coworkers

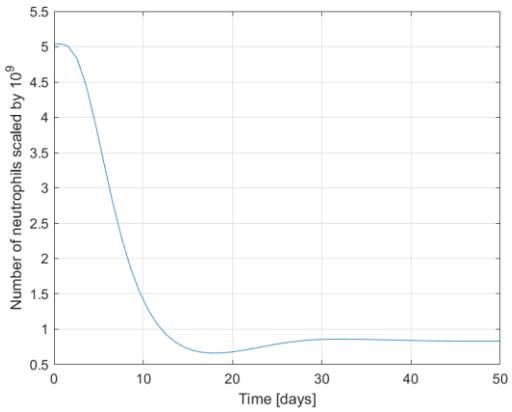

Fig. 2 Number of neutrophils under the constant input drug concentration $E_{Drug}(t) = 250\ \text{mg}$

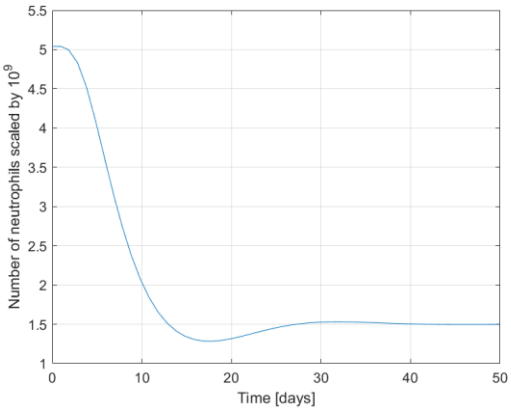

Fig. 3 Number of neutrophils under the drug steady state concentration obtained from (6) for $\alpha = 1 \;\Rightarrow\; x_{5ss} = ANC = 1.5\times 10^9, \;\; E_{Drugss} = 0.1763 \;\; (176.3\,\text{mg})$

Part 2: Optimal Control (Dosing) of Freberg's Model (10 points)

The SIMULINK that incorporates a set-point controller with an optimal feedback controller obtained via the linearization technique is presented in Figure 4.

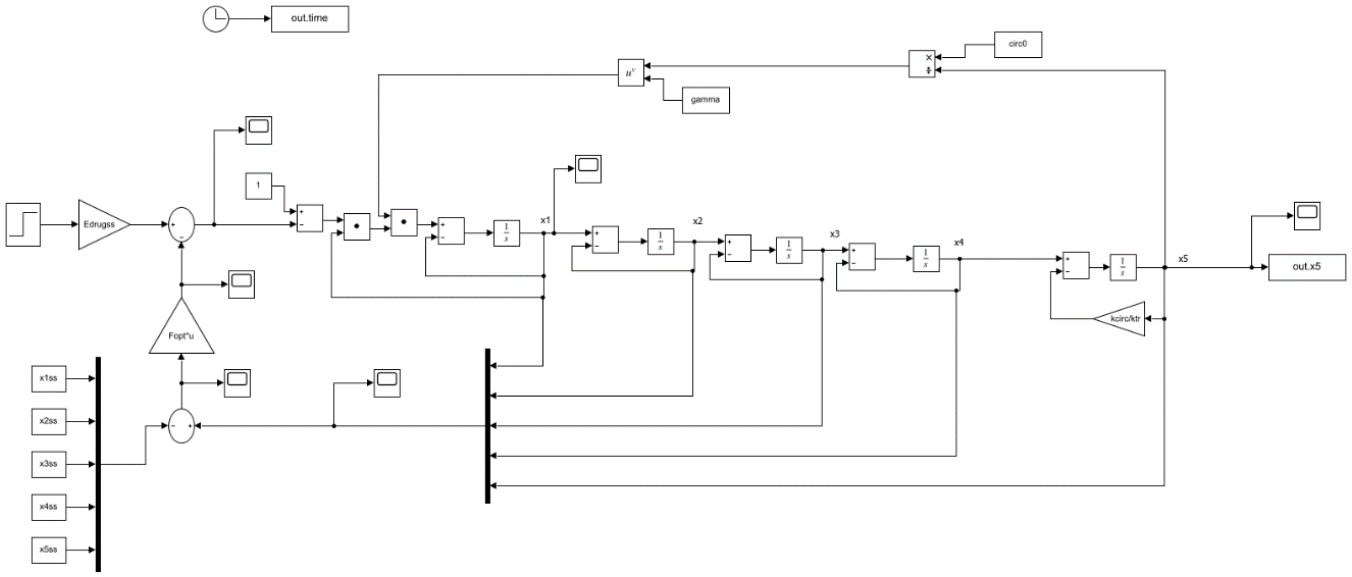

Fig. 4 Simulink block diagram for optimal control via linearization

The obtained optimal variable drug dose and the corresponding counts for the optimal number of neutrophils and optimal numbers of all system state variables are presented in Figures 5-7. The steady state value for the number of neutrophils is taken as $x_{5ss} = 1.5$. The matrices defined in the optimal performance (16) are taken as $R_1 = I_5, R_2 = 25$. You may experiment with different weights that are the design parameters and observe their impact.

It can be seen from Figure 5 the optimal drug administration keeps ANC above 1.5×10^9 . At the same time the amount of administrated drug is minimized.

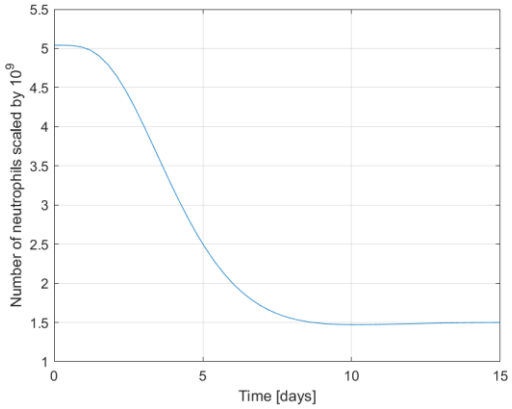

Fig. 5 Number of neutrophils under the optimal variable drug dose schedule

It could be seen from Figure 6 that the optimal drug administration initial dose given as $E_{Drug}(0)=250\ \text{mg}$ should be quickly reduced $E_{Drug}(1)\sim 50\ \text{mg}$ and $E_{Drug}(2)\sim 20\ \text{mg}$, and then stopped in day number three, $E_{Drug}(3)\sim 0\ \text{mg}$, slightly increase in day number four $E_{Drug}(4)\sim 10\ \text{mg}$ and then continuously given at the constant dose of $E_{Drug}(i)\sim 20\ \text{mg}$, $i=5,6,...$ as long as the drug is needed.

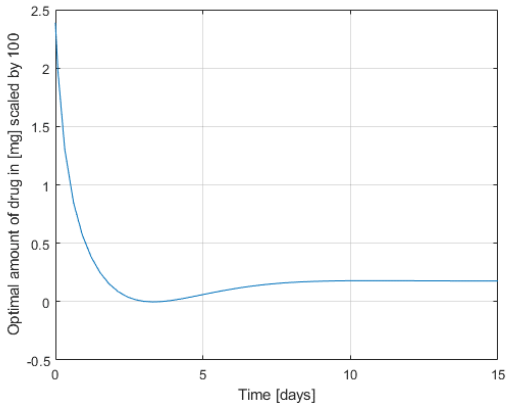

Fig. 6 Optimal continuous drug schedule

References

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