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Parameter estimation for leukocyte dynamics after chemotherapy ⋆

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Abstract: Leukopenia is one of the most harmful side effects during chemotherapy treatment, since leukocytes (L) are crucial in protecting patients against bacteria and fungi. A personalized mathematical model of dynamics of L would allow a glimpse into the future and the initiation of tailored countermeasures.
We propose such a mathematical model and calibrate it based on a parameter estimation with real world data. For our study we used data of L during and after consolidation chemotherapy treatment (cytarabine) of six patients contracting acute myeloid leukemia.
We compare two different ways to treat the unknown initial values of the system of ordinary differential equations, discuss patient-specificity of parameter values, and different scalings of the least squares formulation. These three comparisons are necessary considerations for all modeling approaches to biomedicine, and have thus a methodological scope beyond the specific case of leukopenia.
In summary, we show that our approach is able to simulate L dynamics in response to chemotherapy treatment and allows to take patient-specific characteristics into account.

Keywords: Leukopenia, acute myeloid leukemia, parameter estimation, weighted least-squares method, initial value analysis

1. INTRODUCTION

Leukocytes (L) are white blood cells, circulating the blood stream as a part of the immune system, and therefore crucial in protecting humans against bacteria and fungi. Their standard range varies for adults between 4 and 10 thousands cells per microliter. Acute myeloid leukemia (AML) is a common type of leukemia in adults. It is originating in the bone marrow and associated with hematopoiesis, i.e., the process where mature blood cells (MC) differentiate from hematopoietic stem cells (HSC). These HSCs have the capability to proliferate generating either HSCs or precursor cells (PC). There are two lineages of PCs - the myeloid and the lymphoid line - both differentiate through several stages into diverse MCs which are released into the bloodstream as L. AML is characterized by degeneration of cells in early stage within the myeloid line resulting in a rapid increase of so called myeloid blasts, i.e., non-differentiating cells that interfere with the hematopoiesis. Without any therapy, AML is lethal within a few months. Therefore, the initiation of a therapy is usually realized immediately.

The chemotherapy treatment schedule is usually divided into two phases, induction and consolidation, consisting of repeated administrations of chemotherapy infusions. The first usually involves about one or two cycles of induction therapy with complete remission on target. During the last decades, plenty of studies dealt with improving the outcomes of induction, but none of them was able to identify suitable alternatives to the current practice (cf. Eigendorff and Hochhaus (2015)). Therefore, we focus on consolidation therapy, the second period of the treatment schedule.

To maintain complete remission of the induction, it is followed by consolidation with two to four cycles of cytarabine (AraC, $\geq 1000\ mg/m^2$). AraC acts in a two-step process: Firstly it is transformed to AraCTP and, secondly, after being incorporated into DNA leads to cell death (cf. Hamada et al. (2002) for the metabolic pathway). This incorporation into DNA can only take place during the proliferation phase while cells without active DNA replication remain unaffected. AraC operates non-specifically, thus affecting the blasts as well as the HSCs. This can lead to severe hematopoiesis suppression, a real and serious side effect called Leukopenia. As a consequence, the immune system is not capable to adequately react which can result in life threatening infections. Leukopenia is characterized by absolute L counts below one thousand

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cells per microliter blood. The longer this state lasts the higher the mortality. The susceptibility to leukopenia due to chemotherapy shows a large variability among patients.

Mathematical modeling can form a basis for advanced patient-specific analysis and decision support tools. Such a mathematical model must be able to reproduce and in a later stage also predict qualitatively and quantitatively patterns of L during chemotherapy treatment. This retrospective study with the presented mathematical model is a promising start towards advanced patient-specific leukopenia treatment and decision support tools.

2. MATERIALS AND METHODS

2.1 Clinical data

Measurement data of L and therapy plans for six AML patients (denoted by P1, . . . , P6) are provided by the Department of Hematology and Oncology of the University Hospital in Magdeburg (Figure 1 and Table 1).

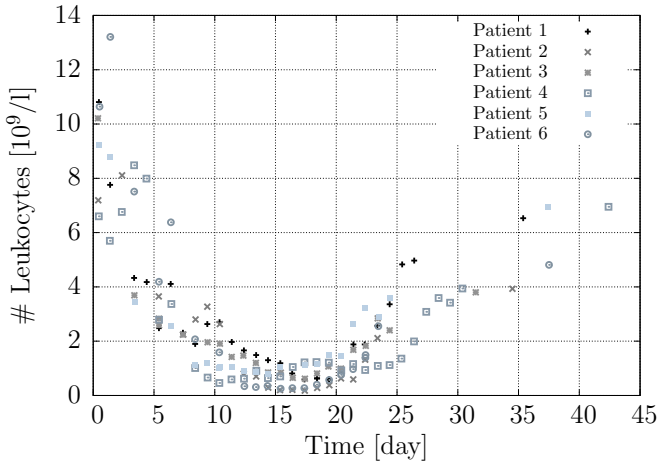

Fig. 1. Measurement data of the six patients, periods ranging from 32 to 43 days.

Here, the first consolidation cycle is considered in which AML was prevented by administer AraC. One consolidation cycle consists of two AraC infusions at day one, three and five. The two infusions last three hours each with a 12 hours in between. The values for the body surface are calculated using DuBois formula (cf. DuBois et al. (2013)).

Table 1. Patient-specific physiological properties, cytarabine application per infusion and numbers of measurements.

	Sex	Age	Height	Weight	BSA∗	Cyt. per inf.	Meas.
	-	(year)	(cm)	(kg)	(m^2)	(mg/m^2)	(#)
P1	F	61	175	92	1.92	3000	29
P2	M	67	176	74	1.89	1000	20
P3	F	74	170	81	1.81	1000	23
P4	F	49	170	71	1.83	3000	31
P5	F	30	166	75	1.72	3000	22
P6	M	64	190	80	2.00	3000	21

∗ BSA = body surface area

2.2 Mathematical model

Since we are focusing on leukopenia during consolidation therapy, we exclusively simulate the dynamics of the

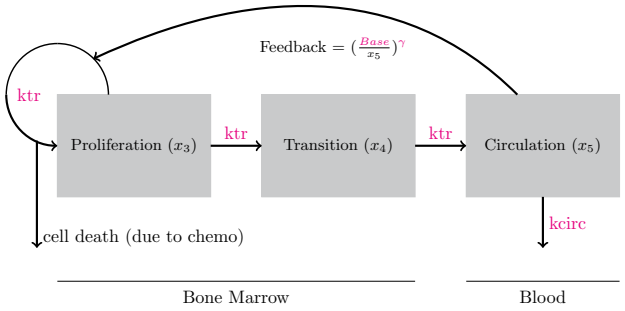

Fig. 2. Schematic model of leukocyte cells' dynamics

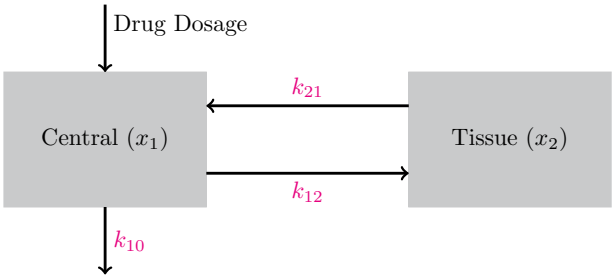

Fig. 3. Two-compartment model describing the pharmacokinetics of the drug cytarabine.

healthy immune cells (L) within the blood stream. The drug impact is accounted for by additional states for pharmacokinetics (PK) and a pharmacodynamic (PD) function.

In order to describe the cell dynamics, we use a compartment model based on Friberg et al. (2002). Referring to the cell differentiation process, the cell-line consists of (i) a proliferating compartment PC sensitive to chemotherapy, (ii) transit compartments TC representing diverse differentiation states and (iii) a compartment with mature, circulating blood cells MC. Savic et al. (2007) showed that the number of transition compartments models the delay between the proliferating cells and circulating cells. As the intermediate maturation steps are of no interest in our setting, and the numerical results indicate that the delay is well captured by using one compartment, we simplified Friberg's model by using one instead of three transition compartments (Figure 2).

Cells mature with a transition rate ktr from the precursor compartment. MCs (x_5) are removed from the blood stream with a death rate of $kcirc$. In order to respond to cell decline, matured cells influence the proliferation rate of proliferating cells by a feedback loop.

A two-compartment model is used for PK (Figure 3). The PD is modeled by a log-linear function E.

The five differential states of our mathematical model are the amounts x_1, x_2 of AraC in two compartments, and the numbers x_3, x_4, x_5 of L in three compartments. The external input is the dose of AraC $u(t)$. The mathematical model is defined by the following equations: