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Optimum Experimental Design for Patient Specific Mathematical Leukopenia Models ⋆

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Abstract:
Mathematical models are essential for simulation-driven decision support for clinical doctors. For an estimation of parameters for patient specific models, values such as the number of certain blood cells need to be measured. In this paper we focus on leukopenia, a clinically important side effect arising from the treatment of leukemia with chemotherapy. A mathematical leukopenia model is presented describing the dynamics of leukocytes and we show that the standard deviations of the parameter estimates depend strongly on the timing of the measurements.
We discuss the issue of measurement time points for two patients being in the consolidation phase of acute myeloid leukemia and provide optimal solutions. Optimized measurement time points and the thus enabled accurate simulations have a large impact: drug treatments can be adapted individually and patients may safely leave the hospital for longer and more convenient time intervals.
The dynamics of leukocytes are modeled by a system of ordinary differential equations and the chemotherapy with cytarabine is described by a pharmacokinetics/pharmacodynamics model consisting of two compartments and a log-linear function representing the drug effect. The measurement time points are optimized by optimal experimental design.
With optimal experimental design an average parameter uncertainty reduction of 57% (*Patient 1*) and 80% (*Patient 2*) can be achieved compared to the clinical experimental designs, with the same total number of measurements. These encouraging results motivate further research and an extension of the data basis to more patients.

Keywords: Leukopenia, acute myeloid leukemia, parameter estimation, optimum experimental design, sampling decision.

1. INTRODUCTION

A clinically important side effect arising from the treatment of leukemia with chemotherapy is leukopenia.
In this paper, we focus on acute myeloid leukemia (AML), a cancer of the myeloid stem/progenitor cell compartment of the bone marrow. Immature neoplastic myeloid blasts proliferate rapidly and suppress any normal, matured leukocyte cells (c.f. Arellano et al. (2011)). The overproduction of immatured neoplastic white blood cells harms the function of the immune system and of other organs eventually leading to death, see e.g. Panoskaltsis et al. (2003). The chemotherapy regimen is divided into two phases (induction and consolidation phase), each consisting of several cycles. The main goal of the induction phase is the elimination of cancer cells (immatured blast cells and neoplastic stem/progenitor cells). After the induction phase the number of cancer cells is reduced to a low level, but further chemotherapy cycles in the consolidation phase are needed to prevent a relapse of the disease. However, the chemotherapy applied does not only stop the growth of cancer cells, but also the growth of healthy leukocytes. Hence, there is a critical time for patients in which the number of leukocytes is very low and the risk of bacterial infections is high (c.f. Malka et al. (2012)).

We believe in mathematical modeling, simulation and optimization being the enabling technology for individualized medicine, where risk assessment and timing and dosage of drug treatments are based on decision support. In this particular scenario we use it to predict the dynamics of leukocytes and the influence of chemotherapy towards healthy cells. With an appropriate model in silico simulations and forecasts of the disease and predictions about the leukocytes' nadir can be made for each patient. The onset and duration of nadir, defining the lowest number of leukocytes after chemotherapy, is an indicator for the risk of infections.

1.1 Contribution

Each patient has a different response towards chemotherapy and thus also different dynamics and recovery rates

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of leukocytes. For the identification of patient-specific parameters we compare different measurement time points concerning the associated uncertainty of the parameter estimate. The optimal choice can be determined using optimum experimental design (OED), Körkel (2002). In system and cell biology, the methodology of OED becomes more visible and standard in designing experiments compared to medical applications. As a review see Kreutz and Timmer (2009) and for application examples see Banga and Balsa-Canto (2008) and Bandara et al. (2009). To our knowledge, applying OED to medical applications is only investigated by a few published papers (c. f. Kiran and Samavedham (2013) and Aarons and Ogungbenro (2010)). Due to its large benefits, more studies are required to transfer these method into clinical practice.

2. MATHEMATICAL MODELING OF LEUKOPENIA

Several mathematical models have been published that describe the dynamics of leukocytes during chemotherapy, e.g., in Shochat et al. (2007) the dynamics of neutrophils (part of the leukocytes) in the circulating blood are modeled, and in Rădulescu et al. (2016) a system of delay differential equations is proposed.

Our model is based on a semi-mechanistic population pharmacokinetics (PK)/pharmacodynamics (PD) model for myelosuppression published by Friberg et al. (2002). The model consists of one cell line representing leucocytes modeled by several compartments (Fig. 1). The cell maturation in the bone marrow is modeled by one proliferation compartment and several transition compartments. One compartment describes the circulation of cells in the blood. Differing from Friberg et al. (2002), we describe the leukopoiesis with two compartments, one representing the proliferation phase and the other one representing the whole maturation phase. After maturation the leukocytes migrate to the peripheral blood described by a third compartment. A feedback depending on the steady state value of circulating leukocytes denoted by $Base$ and the number of leukocytes at time t is introduced, triggering the proliferation of leukocytes.

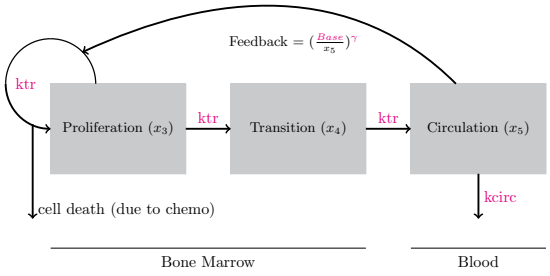

Fig. 1. Schematic model of leukocyte cells' dynamics

In addition to the modeling of proliferation, maturation and circulation of leukocytes we include the chemotherapy and its influence on the cell cycles. Firstly, we therefore modeled the PK of the used agent (here cytarabine) using a two-compartment model (e.g. Pilari and Huisinga (2010); Figure 2). Since we had no information about the cytarabine concentrations, we used published data (Kern et al. (1997)). Secondly, the influence of chemotherapy on the number of leukocytes is modeled by a log-linear function with the slope value from Pefani et al. (2014).

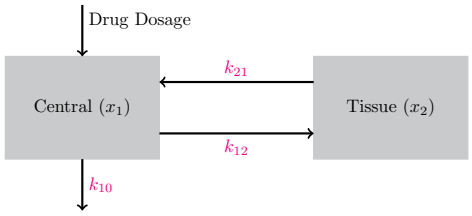

Fig. 2. Two-compartment model describing the pharmacokinetics of the drug cytarabine.

The mathematical model is defined by the following equations, with x_1 and x_2 the amount of cytarabine in the two compartments of Figure 2, and x_3 to x_5 the number of leukocytes in the three compartments of Figure 1.

Pharmacokinetics:

$$\dot{x}_1(t) = -k_{10} \cdot x_1(t) - k_{12} \cdot x_1(t) + k_{21} \cdot x_2(t) + \frac{u(t) \cdot \text{BSA}}{\text{duration}}, \quad (1)$$

$$\dot{x}_2(t) = k_{12} \cdot x_1(t) - k_{21} \cdot x_2(t), \quad (2)$$

Pharmacodynamics:

$$E = slope \cdot ln\left(1.0 + \frac{x_1(t)}{V \cdot MM_{cyt}}\right), \quad (3)$$

Leukopenia Model:

$$\dot{x}_3(t) = ktr \cdot x_3(t) \cdot \left(\left(\frac{Base}{x_5(t)}\right)^\gamma - 1.0\right) - E \cdot x_3(t) \quad (4)$$

$$\dot{x}_4(t) = ktr \cdot (x_3(t) - x_4(t)), \quad (5)$$

$$\dot{x}_5(t) = ktr \cdot x_4(t) - kcirc \cdot x_5(t). \quad (6)$$

The model parameters, constants and controls within the model and their units are listed in Table 1.

Table 1. Model parameters, constants and control with units

Parameters p	Unit	Constants	Unit
ktr	$1/day$	k_{10}	$1/day$
kcirc	$1/day$	k_{12}	$1/day$
γ	-	k_{21}	$1/day$
Base	$\# \cdot 10^9/liter$	Volume	$liter$
slope	$liter/mol$	BodySurfaceArea(BSA)	m^2
Control $u(t)$	Unit	MolecularMass(MM_{cyt})	g/mol
cytarabine dose	mg/m^2	Duration	day

For a more detailed model analysis and discussion see Rinke et al. (2016). For further investigations the system is summarized as $\dot{x}(t) = f(x(t), u(t), p)$.

3. PARAMETER ESTIMATION

Let a set of one-dimensional measurements $\eta_1, \ldots, \eta_m$ and known variances σ_i^2 at time points $t_1, \ldots, t_m$ be given. Assume that the measurements can be described by a nonlinear regression

$$\eta_i = h_i(x^*(t_i), p^*) + \varepsilon_i \quad (7)$$

with the model response h_i containing the true states x^* and true but unknown parameters p^* and the independent and identically distributed measurement errors $\varepsilon_i \sim \mathcal{N}(0, \sigma_i/w_i)$. The additional variables $w_i \in [0, 1]$ are