Using adaptive model predictive control to customize maintenance therapy chemotherapeutic dosing for childhood acute lymphoblastic leukemia

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Abstract
Acute lymphoblastic leukemia (ALL) is a common childhood cancer in which nearly one-quarter of patients experience a disease relapse. However, it has been shown that individualizing therapy for childhood ALL patients by adjusting doses based on the blood concentration of active drug metabolite could significantly improve treatment outcome. An adaptive model predictive control (MPC) strategy is presented in which maintenance therapy for childhood ALL is personalized using routine patient measurements of red blood cell mean corpuscular volume as a surrogate for the active drug metabolite concentration. A clinically relevant mathematical model is developed and used to describe the patient response to the chemotherapeutic drug 6-mercaptopurine, with some model parameters being patient-specific. During the course of treatment, the patient-specific parameters are adaptively identified using recurrent complete blood count measurements, which sufficiently constrain the patient parameter uncertainty to support customized adjustments of the drug dose. While this work represents only a first step toward a quantitative tool for clinical use, the simulated treatment results indicate that the proposed mathematical model and adaptive MPC approach could serve as valuable resources to the oncologist toward creating a personalized treatment strategy that is both safe and effective.

1. Introduction
Acute lymphoblastic leukemia (ALL), characterized by an uncontrolled proliferation of lymphoblasts in the bone marrow, is the most common childhood cancer. Childhood ALL accounts for more than 60% of ALL cases, with peak incidence occurring between 2 and 5 years of age (Stanulla and Schrappe, 2009). With modern treatment strategies, approximately 95% of children attain remission; however, only 75–85% survive free of cancer for 5 or more years after the original diagnosis (National Cancer Institute, 2009). Of present concern is improving the relapse-free survival rate for children with ALL. Herein, we propose a strategy in which adaptive model predictive control (MPC) is used to personalize chemotherapeutic dosing during the maintenance phase for treating childhood ALL patients using recurrent patient measurements. This work provides a foundation for future advances in the personalized treatment of childhood ALL with implications for the treatment of other chronic and acute diseases.

1.1. Childhood ALL background
Childhood ALL treatment consists of three stages. First is an induction period, in which complete remission is generally achieved within 4 to 6 weeks using intensive chemotherapy. A short consolidation stage follows and targets residual malignant lymphoblasts. Additional directed therapy is often administered during this stage to prevent relapse originating from the central nervous system. Maintenance therapy is the final stage and is critical to sustaining remission by continually reducing any residual leukemic cell population (Stanulla and Schrappe, 2009).

Maintenance therapy lasts approximately 2 years as this treatment length has been shown to correlate most strongly with long-term survival (Richards et al., 1996) and utilizes the chemotherapeutic agents 6-mercaptopurine (6MP) and methotrexate.
6MP must be metabolized into 6-thioguanine nucleotides (6TGN) to achieve cytotoxicity (Bostrom and Erdmann, 1993). Numerous studies have linked elevated levels of metabolized 6MP (6TGN) with a higher probability of relapse-free survival (Bostrom and Erdmann, 1993; Chrzanowska et al., 1999; Lilleymann and Lennard, 1994). A study by Relling et al. (1999) reported a median average 6TGN level of 401 pMol/8 x 10^8 RBCs for 188 childhood ALL patients over 709 total measurements. In this study, 96.8% of children achieved complete remission. Several studies have recommended monitoring 6TGN levels as a way to optimize therapeutic response (Chrzanowska et al., 1999; Lilleymann and Lennard, 1994; Thomsen et al., 1999). However, 6TGN levels are not measured as part of a routine complete blood count, and not all insurance companies will pay for extra metabolite testing (Morales et al., 2007), which costs about three times more than a complete blood count (Dubinsky et al., 2005). As a result, monitoring metabolite levels is not common practice.

Large interpatient variability has been observed in 6TGN levels of children taking a standard 6MP dose (Chrzanowska et al., 1999; Lennard et al., 1983; Schmiegelow and Bruunshuus, 1990). For example, Lennard et al. (1983) showed that children taking a nearly identical 6MP dose exhibited effective 6TGN levels that varied from less than 60 to over 800 pMol/8 x 10^8 RBCs. This variation may be due to a variety of factors. A genetic polymorphism in the enzyme responsible for metabolizing 6MP may lead to significant differences in 6TGN production (Bostrom and Erdmann, 1993). Additional interpatient differences result from factors related to childhood development. Dynamic changes occur in organ function and enzymatic capability throughout childhood and can substantially affect drug clearance (Panetta et al., 2006). The need for personalized medicine is especially great in pediatrics given the large degree of developmental variation among patients (Panetta et al., 2003).

Several studies have investigated the impact of personalized treatment specifically on childhood ALL patients. Evans et al. (1998) studied treatment outcomes for children given conventional therapy (doses based on body surface area) versus individualized therapy (doses based on drug plasma concentrations). The study concluded that individualizing therapy for childhood ALL patients could significantly improve treatment outcome. Additionally, it has been shown that treatment personalization through the estimation of patient-specific pharmacokinetic parameters could lead to improved childhood ALL therapy by using model-based predictions of future drug plasma concentrations to aid in dosing decisions (Piard et al., 2007). Using model-based techniques to achieve individualized dosing capitalizes on the existence of personalized state feedback (patient measurements) and its ability to inform quantitative model predictions.

The idea of integrating model-based decision making and medicine to guide personalized dosing has become more prevalent in recent years (Barrett et al., 2008). The problem of large inter- and intrapatient variability in drug response is not unique to 6MP or childhood ALL. In general (for all major classes of drugs), two individuals of the same weight on the same drug dose can have drug concentrations in the plasma that vary by more than 600-fold. The adverse drug reactions that result may be responsible for more than 100,000 deaths yearly in the United States (Eichelbaum et al., 2006). The need for personalized medicine is especially great in pediatrics given the large degree of developmental variation among patients (Panetta et al., 2003).

The above models are directly applicable for investigating the effect of 6TGN on MCV as they either did not include the hematopoietic stem cell maturation process or were not easily modified to include the red blood cell compartment. Herein, we provide a new approach for developing personalized dosing regimens based on the generation of red blood cells. The study concluded that individualizing therapy for childhood ALL patients could significantly improve treatment outcome. Additionally, it has been shown that treatment personalization through the estimation of patient-specific pharmacokinetic parameters could lead to improved childhood ALL therapy by using model-based predictions of future drug plasma concentrations to aid in dosing decisions (Piard et al., 2007). Using model-based techniques to achieve individualized dosing capitalizes on the existence of personalized state feedback (patient measurements) and its ability to inform quantitative model predictions.

This work represents a new approach for mathematical modeling of the treatment of ALL: the inclusion of a clinically relevant output for evaluating treatment efficacy. Previous modeling efforts include a mathematical description of ALL cell kinetics using discrete modeling techniques (Mau et al., 1973). By incorporating the effects of the chemotherapeutic agent vincristine, the model produced results consistent with observed biological data; however, no insights into treatment were provided. A more recent work by Wheldon et al. (1997) presented a two-stage mutation model describing the production of malignant ALL cells. The model was capable of fitting incidence data for childhood ALL, but drug effects and treatment implications were not considered. Panetta et al. (2006, 2002) has developed several models relating to ALL chemotherapeutic drugs, including the kinetics of intracellular methotrexate (2002) and the effect of 6MP on the cell cycle (2006). In general, the above models are directly applicable for investigating the effect of 6TGN on MCV as they either did not include the hematopoietic stem cell maturation process or were not easily modified to include the red blood cell compartment. Herein, we extend and adapt an ordinary differential equation model of hematopoietic stem cell differentiation by Mackey (1978) to reflect the action of 6TGN on the generation of red blood cells.
For personalized medicine, it is always necessary to adjust the level of abstraction in the mathematical model to match the clinically available information and the application. For the childhood ALL application, it would have been unrealistic to use a detailed mechanistic model of the stem cell differentiation process as too many model parameters and cellular mechanisms are uncertain; thus we compacted the process so it was still biologically meaningful while retaining the key processes that give rise to the observable red blood cell count and volume dynamics. Without explicitly incorporating quantitative predictions of these dynamics, it would not be possible to personalize treatment or account for the inertia in the hematopoietic differentiation process.

Control techniques have been widely applied to drug delivery, most commonly for insulin and anesthetics (see Parker and Doyle, 2001; Bailey and Haddad, 2005 for detailed reviews). Nonlinear MPC is especially well suited for drug scheduling as it is robust to model uncertainties and measurement noise, and it accommodates the discrete-time feedback resulting from routine clinical measurements. Nonlinear MPC has been used for dose scheduling applications in the case of HIV (Zurawski and Teel, 2006) and breast cancer (Florian Jr. et al., 2008), although not in the case of leukemia. Adaptive nonlinear MPC enables a further degree of treatment personalization by tuning the model parameters to reflect the observed patient response to therapy. Adaptive linear MPC has been used to tune insulin therapy for type 1 diabetes (Dua et al., 2006; Wang et al., 2009); similar research with adaptive nonlinear MPC has been completed by Hovorka et al. (2004). This is among the first studies to employ adaptive nonlinear MPC to personalize drug dosing for the treatment of leukemia.

Herein, we propose a strategy in which adaptive nonlinear MPC tunes 6TGN dosing using routine MCV measurements. An identifiability analysis of the developed model explicitly considering only patient-specific data that is available via routine measurement of MCV and red blood cell count reveals the patient-specific parameter subset to be identified adaptively for effectively personalizing treatment. The uncertainty in the patient parameters is sufficiently constrained by the recurrent routine complete blood count measurements to support customized adjustments of the 6TGN dose that effectively achieve the target $\Delta$MCV associated with improved relapse-free survival.

2. Methods

2.1. Red blood cell production model

The red blood cell production model shown in Fig. 1 originated from the concept proposed by Mackey (1978) with a glossary of variable and parameter definitions in Table 1. We extended the model interpretation to compact the differentiation process significantly by considering the simultaneous differentiation and proliferation of the hematopoietic stem cells within the bone marrow with explicit recognition that the terminally differentiated cells exit to the bloodstream. It is assumed that stem cells continually differentiate as they proliferate until they enter the bloodstream (i.e. periphery) as differentiated red blood cells. The original Mackey model contained a proliferation phase delay that was neglected for computational efficiency since its duration (0.68 days) is insignificant when compared to the total childhood ALL treatment time (2–3 years). (The insignificance of the delay for this application was confirmed via comparison of simulated outcomes for a number of scenarios.) Additionally, the original Mackey model formulation was extended to include a mature red blood cell compartment and a dynamic description of MCV. The resulting model equations are

\[
\frac{dP}{dt} = -\gamma_{6TGN} P(t) + (1 - e^{-\gamma_{6TGN} t}) \beta(N(t)) N(t) \tag{1}
\]

\[
\frac{dN}{dt} = -\delta N(t) (2e^{-\gamma_{6TGN} t} - 1) \beta(N(t)) N(t) \tag{2}
\]

\[
\frac{dR}{dt} = \delta N(t) - e R(t - 120) \tag{3}
\]

\[
\frac{dMCV}{dt} = \left[ (a C_{6TGN} + MCV_0) \delta N(t) - 0.85 MCV(t - 120) e R(t - 120) - 0.15 MCV(t) e R(t) \right] \frac{1}{R(t)} \tag{4}
\]

where $P(t)$ is the population of proliferating/differentiating cells, $N(t)$ is the population of resting (quiescent) cells, $R(t)$ is the population of mature red blood cells, and $MCV(t)$ is the mean corpuscular volume of the periphery. Eqs. (1)–(3) follow directly from the model structure shown in Fig. 1. Eq. (4) describes the change in periphery MCV due to entering and exiting red blood cells as well as naturally occurring shrinkage due to red blood cell aging. The first term describes the volume gain resulting from the newly formed red blood cells entering the periphery. The coefficient $\alpha$ comes from the empirically derived linear relationship between 6TGN concentration and $\Delta$MCV observed by Decaux et al. (2000). $C_{6TGN}$ is the 6TGN concentration, and $MCV_0$ is the MCV measured at the initiation of the maintenance therapy. This term represents the incoming MCV as the change in MCV resulting from the current 6TGN concentration plus the initial MCV and is scaled by the rate of entry of red blood cells. The second term in (4) describes the volume loss due to deteriorated red blood cells exiting the periphery. We assume that red blood cells lose ~15% of their volume (Waugh et al., 1992) during their ~120-day lifetime, so exiting cells leave at 85% of the delayed periphery MCV. This term is scaled by the rate of departure of red blood cells. The third term in (4) describes the volume loss due to aging of the current red blood cell population. Volume will decrease 15% over the cell lifetime, and this is scaled by the rate of cell aging. Rather than implementing the discrete 120 day delay shown above for simplicity of notation, the model was simulated using a distributed delay (Foley and Mackey, 2009). As shown in Appendix, the distributed delay implies that the changes in the population of mature red blood cells (3) and MCV (4) are each approximated by a series of 102 ordinary differential equations. (The number of compartments in the delay discretization is constrained by the recurrent routine complete blood count measurements to support customized adjustments of the 6TGN dose that effectively achieve the target $\Delta$MCV associated with improved relapse-free survival.)

The transition rate from the resting state ($G_0$) to the proliferating/differentiating state was assumed to a Hill-type equation similar to that used in Mackey (1978)

\[
\beta(N(t)) N(t) = \frac{\beta_0 N^m(t)}{\beta^m + N(t)^m} \tag{5}
\]

The parameters in the exponential term are assumed to depend on 6TGN concentration: $\gamma_{6TGN}$ and $\gamma_{MCV}$. $\tau_{6TGN}$ is the time required to complete the proliferation cycle. 6MP is known to slow DNA synthesis leading to an increased S-phase duration and an overall increase in proliferation time (Bokkering et al., 1993). This allows the cell more time to accumulate biomass before division, resulting in a volume increase. The proliferation time is represented by

\[
\tau_{6TGN} = (a C_{6TGN} + MCV_0) \frac{\tau_b}{MCV_h} \tag{6}
\]
The death rate of red blood cells is affected by the 6TGN concentration. The relationship is linear and can be described by the equation:

\[
\gamma_{6TGN} = \gamma_0 C_{6TGN}
\]

where \(\gamma_0\) is the linear coefficient and \(C_{6TGN}\) is the 6TGN concentration.

The model output is sampled at times \(t_i\) and consists of \(R(t)\) and \(MCV(t)\) as these are the only measurable states.

\[
y(t_i) = \begin{bmatrix} R(t_i) \\ MCV(t_i) \end{bmatrix}
\]

For simplicity of notation we will denote \(y(i) = y(t_i)\) and \(y(p) = y(t_i)\) for a given parameter set, \(p\).

### 2.2. Parameter identification

#### 2.2.1. Data sources

Two sources of data were used to support model development and validation: published data and actual patient records. The published data included time-course ΔMCV measurements taken over a 7 month period at a constant 6TGN concentration (Decaux et al., 2000) and red blood cell counts given as a function of 6TGN concentration (Innocenti et al., 2000). De-identified data from ten patients with acute lymphoblastic leukemia treated between 2001 and 2007 at Riley Hospital for Children in Indianapolis were obtained. The data included complete blood counts and drug dose (6MP and methotrexate) information for each clinic visit over the course of maintenance therapy. 6TGN levels were not measured during treatment. The patients included 4 females and 6 males with the age at diagnosis ranging from 5 to 22 (median 7.5). The patient data was collected according to approved IRB protocol (0505002519).

#### 2.2.2. Cost function

Model parameters were fit to the data provided in Decaux et al. (2000) and Innocenti et al. (2000) using Matlab’s constrained optimization solver, fmincon. The cost function minimized the square error between the model-simulated measurements and

where the term in parenthesis represents the 6TGN-affected MCV, \(\tau_h\) is an average healthy cell cycle time, and \(MCV_0\) is the child’s normal, healthy MCV (an average value is generally not useful because it can vary significantly among children). The death rate of stem cells from the proliferation/differentiation phase, \(\gamma_{6TGN}\), is also 6TGN concentration dependent. 6TGN is responsible for inducing death in nucleated cells, including leukemia and bone marrow precursor cells, and the relationship was assumed to be linear:

\[
\gamma_{6TGN} = \gamma_0 C_{6TGN}
\]

where \(\gamma_0\) is the linear coefficient and \(C_{6TGN}\) is the 6TGN concentration.
The published data
\[
\text{argmin}_p \left( \sum_{i=1}^{n} \sum_{j=1}^{2} \left( \frac{y_j(i|p) - y_j(i)}{w_j} \right)^2 \right)
\]
for \(w_1 = 10^{12}, w_2 = 10\), where \(y_j(i|p)\) is the model-predicted output for a given parameter set \(p\) and \(y_j(i)\) the published data for the data point \(j\) and model output. The number of data points is represented by \(n\). The weights \(w_j\) normalize the error for each model output such that they are on the same order of magnitude. The estimated parameter values for an average person are listed in Table 2; the source of each parameter value is provided and the confidence in the stated parameter values that were identified via a fit to the Decaux et al. (2000) and Innocenti et al. (2000) data is related to their identifiability (as described in Section 2.3). The fits are shown in Fig. 3 in Section 3.1.

2.2.3. Initial conditions

With the implementation of the distributed delay, there are 206 ordinary differential equations for which initial conditions must be specified. The initial conditions for \(MCV_1(t), \ldots, MCV_{102}(t)\) were set to the patient’s initial MCV measurement. The state variables \(P(t), N(t), \text{and } K_1(t), \ldots, K_{102}(t)\) were initialized to their zero-drug steady-state values for the given model parameter set. \(P(t)\) is not uniquely constrained, so it was calculated from the steady-state value for \(N(t)\) using the same \(P/N\) ratio (0.71 \(\times 10^8/6.43 \times 10^8\) reported in Mackey (1978).

2.3. Sensitivity and identifiability analyses

Treatment will be personalized by considering some model parameters to be patient-specific. These patient-specific parameters will be identified during the course of treatment using patient measurements. Sensitivity and identifiability analyses help pinpoint the identifiable patient-specific parameter subset.

We investigated the output sensitivity of ten factors: all parameters shown in Table 2 except \(n\) (which is an integer-valued parameter assumed to be patient independent). Our numeric local SA quantified the factor sensitivity with respect to the nominal model simulation resulting from small perturbations (1%) about the nominal value for each parameter individually. Our global SA varied factors simultaneously over the entire parameter space to capture the effect of factor interactions on the model output. We used the extended FAST global SA (Saltelli et al., 1999), which quantified the factor sensitivity with respect to the red blood cell count and MCV Riley patient data. For more implementation details, please see Appendix.

An identifiability analysis (IA) quantifies the estimability of the model parameters. It distinguishes an identifiable parameter subset that includes only sensitive parameters whose sensitivity coefficients are not linearly dependent as correlated parameters cannot be uniquely identifiable. Our IA follows the algorithm outlined in Birtwistle et al. (2009) in which a QR factorization is performed on the sensitivity matrix. Two versions of this IA were performed: a “global” IA, which used the global SA sensitivity matrix, and a “local” IA, which used the local SA sensitivity matrix. The findings are described in Table 5 of Section 3.2.

2.4. Adaptive model predictive controller formulation

Adaptive model predictive control is used to calculate a sequence of 6TGN doses to achieve and sustain a desired \(\Delta t\). A schematic of the control process is shown in Fig. 2. MPC uses a mathematical model of the underlying process to predict the future behavior of the system over a finite prediction horizon. At each sampling point, the controller calculates an appropriate input sequence by solving a constrained optimization problem. The first element of this input sequence is applied to the patient for one sampling period, and a new input sequence is calculated at the next sampling point. The controller is adaptive as it uses recurrent state measurements to tune the identifiable patient-specific parameters with each iteration.

2.4.1. Adaptive parameter identification

With each iteration of the MPC design process, the patient-specific parameters are refit as more experimental data becomes available. Matlab’s fmincon was used to find the parameter set resulting in a minimum mean square error between the simulated measurements and the patient measurements

\[
\text{argmin}_p \left( \frac{1}{n_s} \sum_{i=1}^{n_s} \sum_{j=1}^{2} \left( \frac{y_j(i|p) - y_j(i)}{w_j} \right)^2 \right).
\]

for \(w_1 = 10^{12}, w_2 = 10\), where \(y_j(i|p)\) is the model-predicted output for a given parameter set \(p\) and \(y_j(i)\) the patient measurement at the \(i\)th sampled time point for the \(j\)th model output. The current number of sampled time points is \(n_s\), which increases at each iteration with the addition of a new sample. The weights \(w_j\) normalize the error for each model output such that they are on the same order of magnitude.

Each parameter was initialized to its nominal value, \(p_{\text{nom}}\), provided in Table 2, and the optimization was constrained such that

\[ p \in [0.5p_{\text{nom}}, 2p_{\text{nom}}] \]

The resulting best-fit parameter set was then used by the controller to solve the constrained optimization problem for selecting the next control input.

2.4.2. Model predictive controller

The control input optimization minimized the least squares deviation of the controlled output, \(z(k+i|k)\), from the desired output, \(s\), as well as the magnitude of the 6TGN dose (control input, \(u(\cdot)\))

\[
\text{argmin}_u \left( q \sum_{i=1}^{n_u} \|z(k+i) - s\|^2 + r \sum_{i=1}^{n_u} \|u(k+i)\|^2 \right)
\]
where $H_p$ and $H_u$ are the prediction and control horizon lengths and $q$ and $r$ are weighting constants. Here, the controlled output is the predicted $\Delta$MCV from a patient’s healthy MCV ($MCV_h$)

$$z(k+i(k) = y_P(k+i(k) - MCV_h$$

where

$$y(\cdot) = \left[\begin{array}{c} y_1(\cdot) \\ y_2(\cdot) \end{array} \right] = \left[\begin{array}{c} R(\cdot) \\ MCV(\cdot) \end{array} \right].$$

The desired $\Delta$MCV, $\Delta$, was assumed to be 12 fl, but could easily be adjusted by the clinician.

The Matlab function $\text{fmincon}$ was used to minimize the objective function subject to the following control input constraint: $u(k+i(k) \in [0, C_{\text{max}}]$, where $C_{\text{max}}$ is the maximum allowable $6\text{TGN}$ concentration. $C_{\text{max}}$ is fixed for a given patient and can lie between 600 and 1000 pMol/8 $\times 10^8$ RBCs. The value is selected by the controller based on the patient’s effective $6\text{TGN}$, or the $\Delta$MCV required to take the patient from $MCV_V$ to the target MCV. (This effective $6\text{TGN}$ may be larger or smaller than 12 fl depending on the patient’s $MCV_V$ and $MCV_h$.) For more implementation details, please see Appendix.

The treatment duration ($T_f$) and frequency of physician visits (sampling times, $T_s$) were chosen to be consistent with typical maintenance therapy protocol. Treatment was simulated for 2 years. Sampling times occurred every 15 days as patients have complete blood counts weekly to monthly throughout maintenance therapy. The MPC design parameters are summarized in Table 3.

### 2.5 Virtual patient generation and simulated treatment implementation

Virtual patients were created to test the proposed adaptive MPC treatment approach. The generation of virtual patients allows for a large-scale preliminary evaluation of the controller’s ability to personalize $6\text{TGN}$ dosing for a variety of patient responses using sparse and noisy feedback data. It should be noted that because the virtual patients utilize the same model as the controller, any error due to unmodeled dynamics will not be observed.

Table 4 summarizes the controller model initialization and virtual patient generation. Two parameters were assumed to be known precisely: $n$ and $MCV_V$. We previously assumed $n$ to be patient independent and therefore kept it fixed at its nominal value. $MCV_V$ must be known as the target $\Delta$MCV is defined with respect to this value. However, it was observed in the Riley patient data that $MCV_V$ (the steady-state post-treatment value) is generally not equal to $MCV_{\text{max}}$. Additionally, there exists significant interpatient variation in $MCV_V$, so an average value cannot be used. Thus, we must assume this quantity is estimable in some other way. For a given virtual patient, $MCV_V$ was selected from the Gaussian distribution provided in Table 4.

In the controller model, the non-identifiable parameters were fixed at their nominal values. All identifiable parameters except $MCV_{\text{max}}$ were initialized to their nominal values. The six identifiable parameters were then adaptively identified based on the available patient measurements. The virtual patients were generated by randomly perturbing all model parameters (except $MCV_{\text{max}}$) from their nominal values by $\pm$ 30% according to a Gaussian distribution ($\epsilon_p$). These perturbations characterize the interpatient variation in response to treatment. $MCV_{\text{max}}$ is the “true” initial patient MCV and was assumed to be perturbed from the measured value by $\pm$ 2% Gaussian noise ($\epsilon_{MCV}$) (Buttarello and Plebani, 2008).

Mock patient measurements were created by adding realistic levels of Gaussian noise to the simulated feedback data, including $\pm$ 5% noise ($\epsilon_R$) on the red blood cell count and $\pm$ 2% noise ($\epsilon_{MCV}$) on the MCV

$$\tilde{y}(i) = y(i|p) + \begin{bmatrix} \epsilon_R \\ \epsilon_{MCV} \end{bmatrix}$$

for the $i$th sampled time point, where $y(\cdot)$ is the simulated output vector and $\tilde{y}(\cdot)$ the mock measurement vector. The expected noise levels were reported in Buttarello and Plebani (2008) as “total current error,” so the error was assumed to equal $3\sigma$ in the Gaussian distributions.
### 3. Results

#### 3.1. Model parameter identification for the average patient

Simulations showing the model fit to ΔMCV transients from Decaux et al. (2000) and RBC cell counts from Innocenti et al. (2000) are shown in Fig. 3.

#### 3.2. Identifiability analysis results for determining the patient-specific parameter set

The IA results are summarized in Table 5. The parameters have been sorted by decreasing identifiability. The parameters were separated into three groups: identifiable, marginally identifiable, and not identifiable based upon changes in their $R$ coefficients.

### Table 4
Summary of assumptions for controller model and virtual patient model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Source</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_p$, $\gamma_0$, $\delta$, $\epsilon_0$, $\tau_0$, $\text{MCV}_{\text{nom}}$</td>
<td>Parameters for controller model</td>
<td>Fixed at $p_{\text{nom}}$, adaptively identified</td>
<td>Described in Table 1</td>
<td>Non-identifiable parameters</td>
</tr>
<tr>
<td>$\mu_p$, $\gamma_0$, $\delta$, $\epsilon_0$, $\tau_0$, $\text{MCV}_{\text{nom}}$</td>
<td>Parameters for virtual patient model</td>
<td>$p_{\text{nom}} + \epsilon_{\text{p}}$</td>
<td>Estimated from Riley data</td>
<td>Identifiable parameters, (&quot;measured&quot; from virtual patient)</td>
</tr>
<tr>
<td>$\text{MCV}_0$</td>
<td>Known parameters same for both models</td>
<td>Estimated from Riley data</td>
<td>Assumed to be identical for all patients</td>
<td>Assumed to be known</td>
</tr>
</tbody>
</table>

Fig. 3. Model fit to published data for parameter identification. (A) Model fit to time-course ΔMCV data at $C_{\text{6TGN}}=158$ pMol/8×10^8 RBCs. The dashed red lines indicate the expected measurement error (Decaux et al., 2000). The model simulation reaches the target ΔMCV (solid red line) in ~180 days and subsequently sustains it within the limits of measurement error. B. 6TGN concentration-dependent steady-state red blood cell counts for the model (blue crosses) fit to data published in Innocenti et al. (2000) (green circles). The model-predicted values show good agreement with the published values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The first four parameters from the global IA were taken to be identifiable, with the next four considered marginally identifiable given the order of magnitude drop in the identifiability coefficient. The local IA results were used to help refine the marginally identifiable set to include only the necessary parameters. The union of the two marginally identifiable parameter sets includes $\beta_0$, $\tau_h$, and $\delta$, so the identifiability of these parameters was investigated by simulating treatment of three distinctly different Riley patients. All possible permutations of $\beta_0$, $\tau_h$, and $\delta$ were added to the four most identifiable parameters ($MCV_0$, $e$, $\alpha$, $\theta$).

### Table 5

Results for identifiability analysis.

<table>
<thead>
<tr>
<th>Global identifiability analysis (ranked by decreasing identifiability)</th>
<th>Local identifiability analysis (ranked by decreasing identifiability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranked parameters</td>
<td>$R$ coefficient magnitude</td>
</tr>
<tr>
<td>Identifiable</td>
<td>$\beta_0$</td>
</tr>
<tr>
<td>$MCV_0$</td>
<td>13.428</td>
</tr>
<tr>
<td>$e$</td>
<td>5.079</td>
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<tr>
<td>$\alpha$</td>
<td>0.264</td>
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<tr>
<td>$\theta$</td>
<td>0.255</td>
</tr>
<tr>
<td>Marginally identifiable</td>
<td>$b_0$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>0.0145</td>
</tr>
<tr>
<td>$MCV_0$</td>
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</tr>
<tr>
<td>Not identifiable</td>
<td>$\gamma_0$</td>
</tr>
<tr>
<td>$PN_{ratio}$</td>
<td>$1.06 \times 10^{-3}$</td>
</tr>
<tr>
<td>$PN_{ratio}$</td>
<td>$9.05 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

The patient-specific identifiable parameters are indicated in bold.

**Fig. 4.** Model-simulated treatment for two Riley patients. The actual prescribed drug doses were implemented and the patient’s actual measurements were used for feedback data. Each plot shows the model simulation for the nominal parameter set (dashed line) and the final adaptively-identified parameter set (solid line). The adaptively identified parameters were fit to the patient measurements (green circles). (A) Red blood cell counts for Riley patient 6. (B) MCV measurements for Riley patient 6. (C) Red blood cell counts for Riley patient 7. (D) MCV measurements for Riley patient 7. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
The resulting parameter set was fit to the actual patient measurements at each sampling point using the 6MP doses prescribed (see detailed description in Section 3.4). The patient identification results indicated that of the three candidate parameters ($\beta_0$, $t_h$, $\delta$), only $t_h$ and $\delta$ improved the model fit to the patient data (results not shown). Thus, the final patient-specific parameter set (indicated in bold in Table 5) consists of $MCV_0$, $\varepsilon$, $\alpha$, $\theta$, $t_h$, and $\delta$. These parameters will be adaptively identified throughout maintenance therapy.

3.3. Model corroboration with real patient data

The Riley patient data were used to corroborate the proposed model structure. We simulated the treatment of all 10 Riley patients by implementing the actual prescribed 6MP dose and using the actual red blood cell count and MCV measurements as feedback data. Note that only the adaptive parameter identification (and not the model predictive controller) was used in this case. We refined the patient-specific parameter set at each sampling point as the next measurement was taken, thereby imitating how the parameter identification process would work in practice. The remaining parameters were fixed at their nominal values.

The 6MP data were reported in “percent of maximum dose.” These values were converted to 6TGN levels by assuming 600 pMol/8 $\times$ $10^8$ RBCs to be the 6TGN level equivalent to a 100% 6MP dose. This assumption cannot be made in practice due to variations in inter- and intrapatient bioavailability and was only used to obtain a qualitative picture of the model’s ability to reproduce experimental data. Future work will be needed to personalize this step in treatment design. The red blood cell counts were collected in units of million cells/mm$^3$ and were converted to units of cells/kg (required by the model) assuming a whole blood density of 1060 kg/m$^3$ (Cutnell and Johnson, 1998).

Fig. 4 shows the model-simulated treatment for both the nominal parameter set (dashed line) and the final adaptively identified parameter set (solid line) for two Riley patients. The identified parameters capture the dominant trends in the patient data. Table 6 summarizes the overall mean square error for the model fit to all 10 Riley patient data sets. The mean square error accounts for error in both the red blood cell counts and the MCV measurements, and is calculated according to (10). From Table 6, it can be seen that the adaptively identified parameter set improves the data fit for all 10 patients, cutting the mean square error by more than half on average. While the nominal parameters provided a reasonable qualitative fit, it is necessary to tune the parameters in order to improve the quantitative fit. These results indicate that with adaptive parameter identification, the model is capable of reproducing the fluctuations and changes observed in actual patient data.

3.4. Virtual patient treatment with adaptive model predictive control

A virtual patient treatment example is shown in Fig. 5. The upper plot shows the time-course trajectory of $\Delta MCV$ as directed by the adaptive model predictive controller. Note that $MCV_h$ rather than $MCV_0$ is defined as the origin, and in this case, the virtual patient began treatment with an initial MCV $\sim$2.5 fL higher than $MCV_h$. The lower plot shows the adaptive MPC-derived control strategy. Fig. 6 shows the time-course evolution of parameter identification for $MCV_0$ and $\varepsilon$ (from the same simulated

<table>
<thead>
<tr>
<th>Riley patient Number</th>
<th>Mean square error</th>
<th>Mean square error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nominal parameter set</td>
<td>Identified parameter set</td>
</tr>
<tr>
<td>1</td>
<td>0.5905</td>
<td>0.3570</td>
</tr>
<tr>
<td>2</td>
<td>0.6388</td>
<td>0.2411</td>
</tr>
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<td>3</td>
<td>0.4945</td>
<td>0.3457</td>
</tr>
<tr>
<td>4</td>
<td>1.2388</td>
<td>1.2137</td>
</tr>
<tr>
<td>5</td>
<td>0.8186</td>
<td>0.2799</td>
</tr>
<tr>
<td>6</td>
<td>1.6715</td>
<td>0.4595</td>
</tr>
<tr>
<td>7</td>
<td>0.7582</td>
<td>0.6001</td>
</tr>
<tr>
<td>8</td>
<td>0.9723</td>
<td>0.1491</td>
</tr>
<tr>
<td>9</td>
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<td>0.1292</td>
</tr>
<tr>
<td>10</td>
<td>0.8252</td>
<td>0.4090</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>0.8744</strong></td>
<td><strong>0.4184</strong></td>
</tr>
</tbody>
</table>

Fig. 5. Representative virtual patient treatment example. The upper plot shows the time-course trajectory of $\Delta MCV$ (solid line) as directed by the adaptive model predictive controller. The trajectory reaches the target level of 12 fL (dashed line) by day 90 and subsequently sustains it within $\pm$ 2%. The lower plot shows the MPC-derived control inputs given as 6TGN doses.

Fig. 6. Representative time-course parameter evolution for the virtual patient treatment example shown in Fig. 5. The upper plot shows $MCV_0$ and the lower plot shows $\varepsilon$. In both cases, the evolution of the controller parameter is the solid line, and the actual (and unknown) patient value is the dashed line.
Steady-state performance metrics for evaluating the efficacy of the controller-derived treatment. The results of the 100 treatment simulations were binned based on performance in terms of steady-state ΔMCV, maximal MCV overshoot, and response time. The percent of patients in each bin is indicated along the y-axis. (A) Steady-state ΔMCV. Ninety-eight percent of virtual patients had no detectable offset. (B) Overshoot. Nearly 75% of virtual patients showed no detectable overshoot. (C) Response time. All 100 virtual patients had a response time of 7 months or less.

The treatment efficacy (i.e. controller performance) was evaluated based on three metrics: steady-state ΔMCV, maximal MCV overshoot, and response time. The first metric is perhaps the most important as it quantifies the effectiveness of treatment by calculating the difference between the actual and desired ΔMCV (results shown in Fig. 7A). The measurements from the second year of simulated treatment were averaged to estimate the steady state ΔMCV. Patients within ±2 fL of the target ΔMCV are said to have no detectable offset as this is within MCV measurement noise (Buttarello and Plebani, 2008; Decaux et al., 2000). Of the 100 virtual patients, none showed a ΔMCV below the desired level, indicating that none of the patients were undertreated. Avoiding undertreatment is vital to relapse-free survival. Only two patients showed a ΔMCV above the desired level (ΔMCV = 3.4 and 6.1 fL).

The second metric calculates the MCV overshoot (results shown in Fig. 7B). A minimum overshoot is desired as excessively high red blood cell 6TGN levels cause excessive toxicity and may lead to hematological disorders such as neutropenia and leukopenia (Lennard et al., 1983). These disorders require a temporary cessation of treatment, which can worsen the treatment outcome (Relling et al., 1999). Nearly 75% of virtual patients showed no detectable overshoot (within measurement sensitivity), while none showed overshoot greater than 4 fL.

The final metric is the response time, which is defined as the time needed for the ΔMCV to rise to within measurement sensitivity of the desired ΔMCV (results shown in Fig. 7C). It is desired to have as fast a response time as can be tolerated by the patient without causing excessive overshoot. High initial doses are implemented in practice to achieve maximum leukemic cell death, helping to prevent instances of drug resistance that may lead to treatment failure (Henze et al., 1981). One-hundred percent of patients exhibited a response time of 7 months or less, while 99% had a response time of 6 months or less. With the target toxicity level achieved within the first 6–7 months of treatment, the remaining 1.5 years of treatment can focus on continual reduction of the residual leukemic cell population. The fast response time is achieved using several maximum doses initially (see Fig. 5, for example). The controller’s patient-specific quantitative predictions allow the drug dose to be curtailed at the appropriate time so as to prevent overshoot. Making these types of dosing adjustments based solely on intuition may be more difficult than with the support of a quantitative predictive model.

The accuracy of virtual patient parameter identification was measured by the percent error of the identified value with respect to the patient value at the final sampling point. Table 7 summarizes the parameter identification results for all 100 virtual patients by the percent error mean and standard deviation for each identified parameter. The four parameters originally labeled identifiable (MCV₀, α, γ, θ) were the parameters identified most accurately. The two marginally identifiable parameters (τᵣ, δ) were identified to within much poorer accuracy. However, despite the parameter error, the controller successfully directed treatment for nearly all virtual patients. Regardless of the reason for the error, the ultimate objective is the successful treatment of the patient. The model represents a simple abstraction of the very complicated hematopoietic stem cell differentiation process, and the parameters have limited physiological meaning. Precisely identifying these lumped parameters is not nearly as important as effectively directing

<table>
<thead>
<tr>
<th>Identifiable parameter</th>
<th>Parameter identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV₀</td>
<td>0.0076 ± 0.47</td>
</tr>
<tr>
<td>α</td>
<td>0.85 ± 6.78</td>
</tr>
<tr>
<td>γ</td>
<td>1.38 ± 6.80</td>
</tr>
<tr>
<td>θ</td>
<td>0.49 ± 11.98</td>
</tr>
<tr>
<td>τᵣ</td>
<td>12.81 ± 32.98</td>
</tr>
<tr>
<td>δ</td>
<td>−1.79 ± 34.99</td>
</tr>
</tbody>
</table>

Table 7
Success of parameter identification for 100 random virtual patients during adaptive MPC described by percent error mean and standard deviation (ranked by increasing standard deviation).
treatment. As long as the model can be tuned such that the controller more accurately characterizes an individual patient, it can serve as a resource to the physician toward creating a safe and effective treatment strategy.

4. Summary and future work

This work presents a model and an adaptive model predictive control scheme to tune 6TGN dosing for childhood ALL patients using routine MCV measurements. The model structure reflects the dominant processes underlying the generation of red blood cells through the hematopoietic stem cell differentiation and simulates the dynamics of clinically measurable outputs. The MPC-derived treatment strategy is personalized as patient-specific model parameters are adaptively identified throughout maintenance therapy. The recurrent patient measurements serve to constrain the model parameter uncertainty such that the controller predictions more closely reflect the observed patient dynamics. Actual patient data were used to demonstrate the ability of adaptive parameter identification to capture patient-specific dynamics and the appropriateness of the abstracted model structure, while the efficacy of the proposed treatment approach was tested by simulating treatment for 100 virtual patients. The controller-derived treatment achieved the target ΔMCV in 98% of cases, with no virtual patients being undertreated. Nearly 75% of the virtual patients experienced no MCV overshoot, while the remaining in silico patients experienced minimal overshoot. This helps to prevent the excessive toxicity that can cause hematological disorders and treatment interruptions. Additionally, all 100 virtual patients reached the target ΔMCV in 7 months or less, maximizing the period of effective treatment during maintenance therapy. These results indicate that the proposed adaptive MPC could aid in determining appropriate drug dose adjustments. While the experience and intuition of the clinician are indispensable, a quantitative tool such as this could help to inform the clinician’s decisions. The controller is able to quantitatively predict the time-course MCV dynamics of a specific patient, suggesting dose adjustments that are sufficiently strong but not overly aggressive.

This work represents only a first step towards developing a quantitative framework capable of aiding in the personalized treatment of childhood ALL patients. Much work remains to be done before a tool such as this is ready for clinical use. For example, the effect of patient illness and dehydration was not considered here and may alter the value of the MCV as a surrogate for the effective 6TGN level. While we derive a relationship between MCV (a commonly collected measurement) and 6TGN (a reliable predictor of treatment outcome), further research is needed to predict the 6MP dose sequence that will achieve the desired 6TGN dynamics. Quantitatively determining the 6MP dose that will result in the desired 6TGN level is not trivial as the factors determining the bioavailability of 6MP are numerous and complex. Additionally, as an initial effort, we focused only on the treatment implications of 6MP while not considering methotrexate, the other chemotherapeutic drug used during maintenance therapy. These two drugs are known to act synergistically, having a combined effect on MCV by creating a higher intracellular availability of thiopurines (Bostrom and Erdmann, 1993). The success of the proposed treatment scheme also relied on knowledge of the patient’s healthy MCV. One way to approximate MCVₜ is to pause treatment for approximately one week between consolidation and maintenance therapy. Providing this did not affect the risk of relapse. Red blood cells require 7–8 days to mature in the bone marrow before entering the periphery (Hillman and Finch, 1996), so after a week of no treatment, the reticulocytes (the youngest red blood cells in the periphery) would exhibit the child’s healthy MCV. The MCV of the reticulocytes can be measured using density separation techniques (Waugh et al., 1992). The feasibility of this approach could be evaluated in future work. As an additional limitation of this study, the MPC-based treatment strategy was evaluated with virtual patients that were simulated using the same model structure as that used by the MPC so any error due to unmodeled patient dynamics was underestimated. All of these limitations must be addressed, but this work serves to lay the groundwork for these future improvements.

While more research is needed to support the development of a model-based clinical tool for this application, the results indicate that model-based control system designs could play an important role in the movement toward personalized medicine. Radirovoyitch et al. (2006) suggests that drug scheduling could be individualized as a direct consequence of using model-based control system designs and that state feedback-based cancer treatment will become the future standard of care. While applied to the treatment of childhood ALL, the adaptive model predictive control approach to customizing drug treatments presented herein is applicable for systematically adjusting treatments for many types of chronic and acute diseases and represents a preliminary step toward integrating quantitative tools with patient care.

Acknowledgements

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Appendix A

A.1. Distributed delay implementation

For simplicity of notation, R(t−120) and MCV(t−120) have been initially depicted as constant delays. However, a mature red blood cell has a lifetime of 120 ± 20 days (Hillman and Finch, 1996), so a distributed delay was implemented to achieve a probabilistic description of the red blood cell compartment dynamics. A general description of a distributed delay follows as in Foley and Mackey (2009).

A distributed delay is implemented as an integro-differential equation with the form

$$\frac{dx_1}{dt} = f(x_1(t), \int_{t-\tau}^{t} x(\tau) G(-\tau) d\tau)$$

where $G(\cdot)$ is the density function characterizing the distributed delay. Foley and Mackey (2009) provide an example using the gamma density function

$$G(u) = \frac{\alpha^{p+1}}{\Gamma(p+1)} e^{-\alpha u}$$

where $\alpha$ and $p$ are parameters. The delay is implemented using the linear chain trick, which replaces the distributed delay with $p+1$ variables satisfying a sequence of linear, ordinary differential equations

$$\frac{dx_{j+1}}{dt} = f(x_j, x_{p+2})$$

$$\frac{dx_{j+1}}{dt} = a(x_j - x_{j+1}) \quad j = 1, 2, \ldots, p+1$$
where a and p come from the gamma distribution and \( f(t) \) is the function describing the original DDE. For a more detailed derivation, see Foley and Mackey (2009).

We implemented a gamma distribution with parameters \( a=5/6, p=100 \). These parameters were chosen to achieve a distribution mean of 120 days and standard deviation of 12 days. The complete distributed delay model consists of 206 ordinary differential equations

\[
\frac{dP}{dt} = -\gamma_{6TP} P + (1 - e^{-\gamma_{6TP} t}) n(t) N(t)(t)
\]

\[
\frac{dN}{dt} = -\delta N(t) - (2e^{-\gamma_{6TP} t} - 1) \beta N(t) N(t)
\]

\[
\frac{dR_k(t)}{dt} = \delta N(t) - e R_{102}(t)
\]

\[
\frac{dR_{j+1}}{dt} = \frac{5}{6} (R_j(t) - R_{j-1}(t)) \quad j = 1, 2, \ldots, 101
\]

\[
\frac{dM_{CV_j}}{dt} = \frac{5}{6} M_{CV_j}(t) - M_{CV_{j+1}}(t) \quad j = 1, 2, \ldots, 101
\]

where \( R_k(t) \) and \( M_{CV_j}(t) \) represent the non-delayed state variables and \( R_{102}(t) \) and \( M_{CV_{102}}(t) \) represent the delayed state variables. The remaining intermediate variables are used to propagate the delay. To simplify notation, we assume

\[
R(t) = R_1(t)
\]

\[
M_{CV}(t) = M_{CV_1}(t)
\]

A.2. Sensitivity analysis implementation

A sensitivity analysis (SA) quantitatively describes how variation in the red blood cell and MCV model outputs can be attributed to the variation in the input factors, including parameters and initial conditions. The sensitivity coefficients were calculated for each model output at each sample time. Parameter sensitivity was quantified using three distinctly different Riley patient 6MP drug sequences. Since the model is nonlinear, the model output is also dependent on these input factors, including

\[
D = \frac{\partial N}{\partial \gamma_{6TP}} + \frac{\partial N}{\partial \delta} N(t) + \frac{\partial N}{\partial \beta} N(t) N(t)
\]

\[
D = \frac{\partial R_k(t)}{\partial \delta} N(t) - e R_{102}(t)
\]

\[
D = \frac{\partial R_{j+1}}{\partial \delta} (R_j(t) - R_{j-1}(t)) \quad j = 1, 2, \ldots, 101
\]

\[
D = \frac{\partial M_{CV_j}}{\partial \delta} M_{CV_j}(t) - M_{CV_{j+1}}(t) \quad j = 1, 2, \ldots, 101
\]

by the clinician based on preference and past experience

\[
C_{\text{max}} = \begin{cases} 
600 & \text{for } M_{CV_{102}} < 15 \\
700 & \text{for } M_{CV_{102}} < 17 \\
800 & \text{for } M_{CV_{102}} < 19 \\
900 & \text{for } M_{CV_{102}} < 21 \\
1000 & \text{for } M_{CV_{102}} \geq 21
\end{cases}
\]

References


