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Simplification of an Erythropoiesis Model for Design of Anemia Management Protocols in End Stage Renal Disease

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Abstract

Many end stage renal disease (ESRD) patients suffer from anemia due to insufficient endogenous production of erythropoietin (EPO). The discovery of recombinant human EPO (rHuEPO) over 30 years ago has shifted the treatment of anemia for patients on dialysis from blood transfusions to rHuEPO therapy. Many anemia management protocols (AMPs) used by clinicians comprise a set of experience-based rules for weekly-to-monthly titration of rHuEPO doses based on hemoglobin (Hgb) measurements. In order to facilitate the design of an AMP based on formal control design methods, we present a physiologically-relevant erythropoiesis model, and show that its nonlinear dynamics can be approximated using a static nonlinearity, a step that greatly simplifies AMP design. We demonstrate applicability of our results using clinical data.

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I. Introduction

In healthy individuals at steady-state erythropoiesis, approximately 10^{10} new red blood cells (RBCs) are produced per hour in the bone marrow to maintain the Hgb level within fairly narrow limits [1]. EPO, a growth factor secreted primarily by the kidneys in response to hypoxia, stimulates the proliferation of RBCs progenitors. As they mature, Hgb is incorporated in the cells. This Hgb binds oxygen for transport throughout the body. The synthesis of Hgb requires iron whose metabolism is coupled with erythropoiesis.

In ESRD, endogenously produced EPO is insufficient to maintain normal Hgb levels, often leading to anemia. In addition, ESRD patients typically exhibit inflammation, a factor affecting iron metabolism. The precise mechanisms coupling EPO, iron, and erythropoiesis are still not completely understood [2]. The discovery of recombinant human EPO has shifted the treatment of anemia for patients on dialysis from blood transfusions to rHuEPO therapy. Although more than 30 years have passed since the discovery of rHuEPO, it is not yet known how to compute the dose and frequency of application of rHuEPO in order to maintain the desired mean level and to minimize variations of Hgb [3].

In the US, clinicians follow the latest KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease [4]. Many clinicians rely on an expert system comprising of a set of rules based on past experience and retrospective studies. From the clinician's viewpoint, this approach is practical; it relies on a few, reimbursable measurements, and is applicable to the entire population. This method is highly imprecise; it accounts neither for inter–patient variability nor intra–patient variability.

A critical aspect of AMPs is that the interaction between an AMP and erythropoiesis renders this biosystem a *closed-loop system*. Thus, it is imperative that AMPs be designed using feedback control techniques. Indeed the possibility that AMPs contribute to oscillations and overshoots in Hgb levels has been recognized by the clinical community (e.g., [3]).

The application of feedback control techniques requires models relating rHuEPO to Hgb. Currently available erythropoiesis models range from detailed, physiologically-driven models [5]–[7]) that are prone to over-parametrization to black-box versions [8]–[10] that cannot be validated for physiologic plausibility. Both classes of models often comprise nonlinear dynamics which significantly complicate the design of AMPs. This paper describes initial results on the theoretical derivation and experimental verification of a simplified dynamical model whose complexity lies between physiologically-detailed and black-box models, allowing the design of AMPs using a number of feedback control techniques.

II. Mathematical Model of Erythropoiesis

The dynamics of Hgb concentration following the administration of intravenous rHuEPO can be described using a combination of pharmacokinetic (PK) and stochastic pharmacodynamic (PD) models (e.g., [5]–[7]). The PK model comprises a single dynamic pool of EPO in plasma, E_P, which is the sum of endogenous EPO, E_{en} and exogenous rHuEPO, E. Anticipating that EPO measurements are rarely available, we assume that E_{en} is

a constant, baseline level of endogenous EPO. The kinetics of EPO are described by a Michaelis-Menten function representing nonlinear clearance. Our PD model aggregates the stimulatory effects of EPO on differentiation, maturation, and proliferation of erythroid-restricted progenitor cells during erythropoiesis resulting in new RBCs (Figure 1). Following [5] and [6], the stimulatory effect of total EPO in plasma E_P, k_{in}, is described by a nonlinear function. We present here the PK and production relations together since they are simplified later:

$$\begin{aligned} \dot{E}(t) &= \frac{V_{max}E(t)}{K_m+E(t)} + \sum_{i=0}^{\lfloor \frac{t}{T} \rfloor} d_i \delta(t-iT), \; E(0)=E_0 \\ E_P &= E+E_{en} \\ k_{in}(t) &= \frac{S_{max}E_P(t)}{SC_{50}+E_P(t)} \end{aligned} \quad (1)$$

where V_{max} denotes maximal clearance rate, K_m is the amount of E which produces half maximal E clearance rate, d_i is the i'th rHuEPO dose modeled as an impulsive input administered at time iT, where T denotes the periodicity of dosing (e.g., weekly or monthly), δ denotes the Dirac delta function, S_{max} is the maximal stimulation rate by E_P, and SC_{50} is the amount of E_P which produces half maximal production rate.

The dynamics of the RBC population is described by

$$\dot{R}(t) = k_{in}(t-D) - \int_0^\infty k_{in}(t-\lambda-D)\ell(t-\lambda,\lambda)d\lambda \quad (2)$$

where $\ell(\lambda, \tau)$ is the probability density function (pdf) of the lifespan τ of an RBC entering the pool at time λ (we assume that $\ell(\lambda, \tau) = 0$ for $\tau < 0$), and D is the total time required for pluripotent hematopoietic stem cells to become RBCs (ie, the progression through burst-forming units, colony-forming units, erythroblasts, and reticulocytes). Following [6] we assume the pdf is a time-invariant gamma density and, for simplicity, 2nd-order:

$$\ell(\tau) = \frac{1}{\tau_0}\tau e^{-\frac{\tau}{\tau_0^2}} \quad (3)$$

where τ_0 is half the mean lifespan of RBCs. Using a state-space representation of (3), (2) becomes

$$\begin{aligned} \dot{R}(t) &= k_{in}(t-D) - \frac{x_1(t)}{\tau_0^2}, \quad R(0)=R_0 \\ \dot{x}_1(t) &= x_2, \quad x_1(0)=x_{10} \\ \dot{x}_2(t) &= k_{in}(t-D) - \frac{x_1(t)}{\tau_0^2} - \frac{2x_2(t)}{\tau_0}, \quad x_2(0)=x_{20}. \end{aligned} \quad (4)$$

Hgb is incorporated into each maturing cell and the total amount of Hgb equals

$$H(t) = K_H R(t) \quad (5)$$

where K_H is the average amount of Hgb per RBC. In this paper we assume complete iron repletion and a constant K_H = 29.5 g/dL[1]. If iron kinetics is included in the model, a time-

varying $K_H(t)$ would represent mean reticulocyte Hgb content. Equations (1)–(5) describe our erythropoiesis model.

Two of the initial conditions, x_{10} and x_{20}, depend explicitly on the conditions at $t = 0$ and $t \to \infty$. Let $H_0 \equiv H(0) = K_H R_0$, $dH_0 \equiv \dot{H}(0) = K_H \dot{R}(0)$, and $H_{en\infty}$ denotes the endogenous level of Hgb due to E_{en}. We assume that at $t = 0$, $E(0) = 0$, which is quite reasonable given that the half-life of the rHuEPO under consideration is 4–13 hours [14].

When RBC production rate is constant, specifically if E_P is zero, since all RBCs must disappear as $t \to \infty$, it is straightforward to show that

$$\lim_{t\to\infty} R(t) \doteq R_\infty = 2\tau_0 \frac{S_{max} E_{en}}{SC_{50} + E_{en}} + R_0 - \frac{2x_{10}}{\tau_0} - x_{20}.$$

If $E_P(t) = 0$ beyond some time, then $k_{in} = 0$ and all RBCs would disappear as $t \to \infty$ resulting in the constraint

$$R_0 = \frac{2x_{10}}{\tau_0} + x_{20}.$$

The initial slope dH_0 provides another constraint

$$dH_0 = \frac{S_{max} E_{en}}{SC_{50} + E_{en}} - \frac{K_H x_{10}}{\tau_0^2}.$$

The three relations above translate into the following constraints

$$\begin{aligned} E_{en} &= \frac{SC_{50} H_{en\infty}}{2\tau_0 K_H S_{max} - H_{en\infty}} \\ x_{10} &= \frac{\tau_0}{K_H}(0.5 H_{en\infty} - \tau_0 dH_0) \\ x_{20} &= \frac{1}{K_H}(H_0 - H_{en\infty} + 2\tau_0 dH_0). \end{aligned} \quad (6)$$

In the context of using linear time-invariant feedback control techniques to design an AMP, we will use an “averaging technique” to render the nonlinear dynamic described in (1) to an approximating nonlinear function. Subsequently, one can then use classical linearization or sector-like techniques to deal with this memoryless nonlinearity in designing AMPs.

The operating point of a closed-loop feedback system, associated with application of a stabilizing AMP to (1)–(5), is characterized by constant EPO doses, $d_i \equiv d_0$. Such doses result in a non-constant, T-periodic production rate $k_{in}(t)$ which varies on a time scale much faster than the response time of the RBC dynamic (5). Specifically, while $k_{in}(t)$ varies on a

[1]Due to lack of measured data beyond Hgb, we have fixed this value within the range of mean cell Hgb (MCH) of [25–35] pg/cell [13].

time-scale of 7 days, the RBC pool operates with a time-constant on the order of 45–85 days [15]. Consequently, the RBC pool responds only to the value of $k_{in}(t)$ averaged over T.

We note that this averaging technique is comparable to the analysis of those engineered systems using pulse-width modulation as a means of converting digital signals to analog. Also, averaging circumvents the direct linearization of (1) about a (non-constant) operating solution.

The mean for a single dosing period, $iT \leq t < (i + 1)T$ is

$$\overline{k}_{in}=\frac{1}{T}\int_0^T k_{in}(t)\,dt.$$

It was shown in [17] that this mean equals (this involves a change of variable in the above integral based on (1)

$$\overline{k}_{in}(d)=\frac{S_{max}}{TV_{max}}\left[\left(K_m-SC_{50}-\frac{K_mE_{en}}{SC_{50}+E_{en}}\right)ln\left(\frac{SC_{50}+E_{en}+d}{SC_{50}+E_{en}}\right)+\left(1-\frac{E_{en}}{SC_{50}+E_{en}}\right)d\right]+\frac{S_{max}E_{en}}{SC_{50}+E_{en}} \quad (7)$$

where $d = d_i$. The design of AMPs using this model simplification and its implementation is currently under a pilot human study.

III. Illustrative Examples

To investigate the suitability of (1)–(5) and its simplified version to model anemia of ERSD, we have used retrospective data from 49 dialysis patients collected over a 15-month period. These data consist of administered rHuEPO doses and Hgb measurements. We estimated model parameters for each individual patient using the Mathworks Simulink Design Optimization software [12] (we used the Levenberg-Marquardt method with the sum of squared errors cost function).

In estimating model parameters, we seek to portray accurately qualitative and quantitative aspects of the clinical data. Qualitatively, the simulation should exhibit salient features such as rate of increase or decay, peaking, and steady-state behavior. Quantitative accuracy aims for reasonable estimation of a smoothed clinical response, given that our model is a simple, second-order type, and cannot be expected to follow the data in detail. We would like to re-iterate that our model does not include iron metabolism, effect of disturbances such as inflammation, and the estimation does not consider sensor uncertainty.

Estimation results for patient #1 confirm that physiologically acceptable parameters (Table I) for (1)–(5) can be successfully estimated. The model Hgb response closely tracks the clinical Hgb data (Figure 2). The variability of clinical Hgb stems from several sources [10], none included in our or any other published model.

The dynamics of patient #17’s Hgb data reveal a key characteristic of most ESRD patients. Inflammation, blood loss, and changes in iron metabolism are among a the factors that result

in changes in erythropoiesis. As a result, the underlying dynamics can vary over period of months. The initial model estimate accurately tracks Hgb data up to $t = 200$ days, but beyond that time it over-estimates the patient's response to rHuEPO. A second set of model parameters (Table II) can be successfully estimated for $t > 200$ days (Figure 3). In both patients, the estimated parameters are within reported ranges: PK parameters V_{max} and K_m result in EPO clearance within reported half-life values of 4–14 hours [16], reduced RBC mean lifespan [15], and time to maturation [1]. Our production parameters S_{max} and SC_{50} which represent an aggregation of several erythropoiesis stages do not have reported values in the ESRD literature. As an extension to this work, we are investigating nonlinear mixed-effect modeling which includes intra- and inter-patient variability, intercurrent event effects (inflammation, etc.), time-varying covariates, and measurement error.

For a thrice-weekly dosing AMP, we evaluated the static relation for $\bar{k}_{in}$ and its linearized version for these two patients. We observe in Figs. 4–5 that for both patients, $\bar{k}_{in}$ is essentially linear in the rHuEPO dose for $d > 1000$. In contrast, $\bar{k}_{in}$ is rather nonlinear for $d < 1000$, a characteristic that complicates the design of robust AMPs. This is consistent with our experience in current human trials with new AMPs where the hyper-responsive patients, those requiring small rHuEPO doses, tend to exhibit decreased closed-loop robustness.

IV. Conclusions

Regular administration of rHuEPO in the treatment of anemia of ESRD is an essential component of the overall therapy. Practitioners employ a wide variety of AMPs to periodically titrate rHuEPO doses based on Hgb measurements. Because the design of such AMPs does not take into account the closed-loop nature of the system, it has been suggested that AMPs contribute to oscillations and overshoots in patients' Hgb levels. In order to facilitate the design of an AMP based on formal feedback control design techniques, we demonstrated that a simplified, physiologically-relevant erythropoiesis model can be derived, a step that should greatly simplify AMP design. We demonstrated the applicability of the model and the accuracy of its approximation using clinical data.

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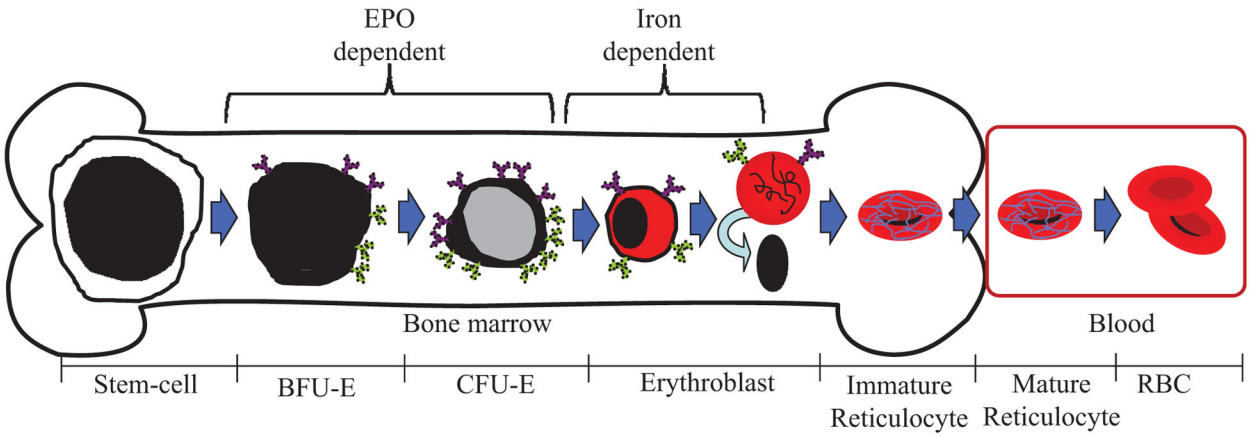

Fig. 1.
Schematic of erythropoiesis stages.

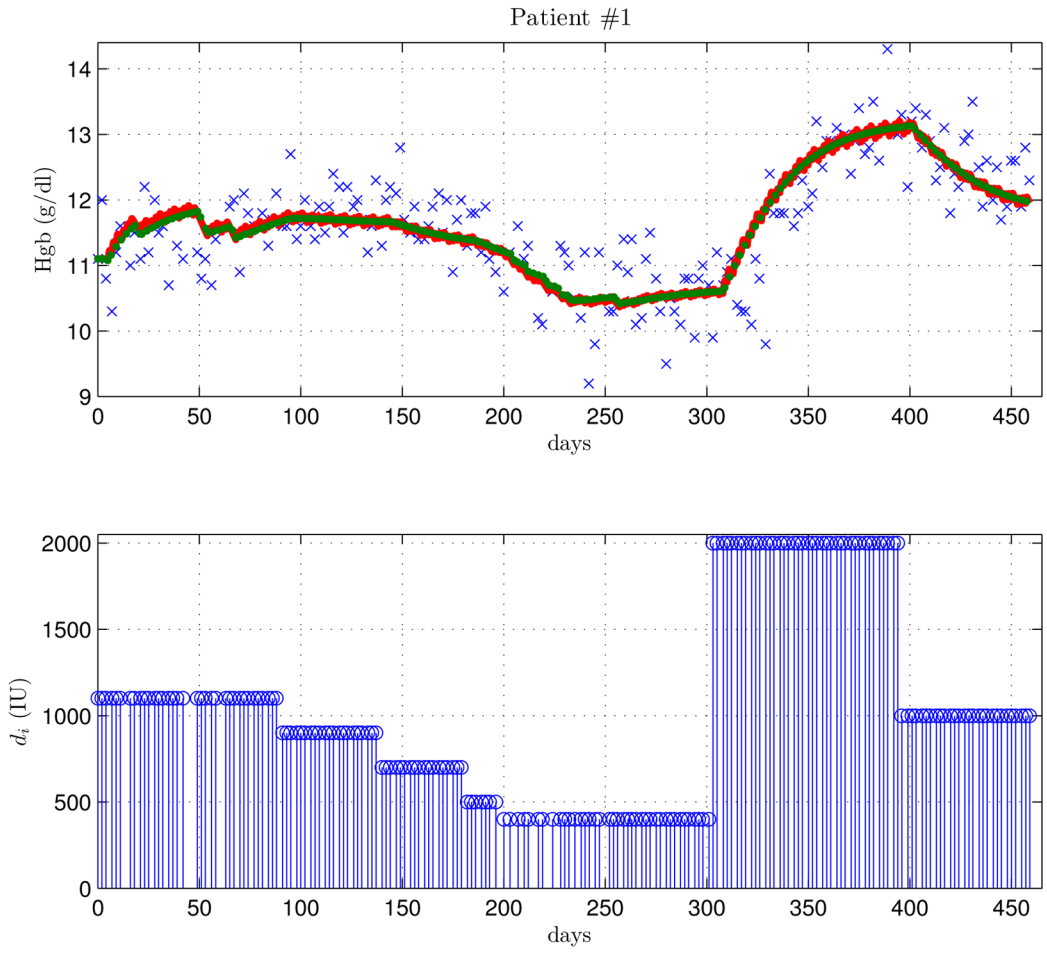

Fig. 2.

Estimation results for Patient #1 using parameters in Table 1; (top) x - clinical data, solid/red - using (1), circle/green - using (7); (bottom) Administered rHuEPO doses.

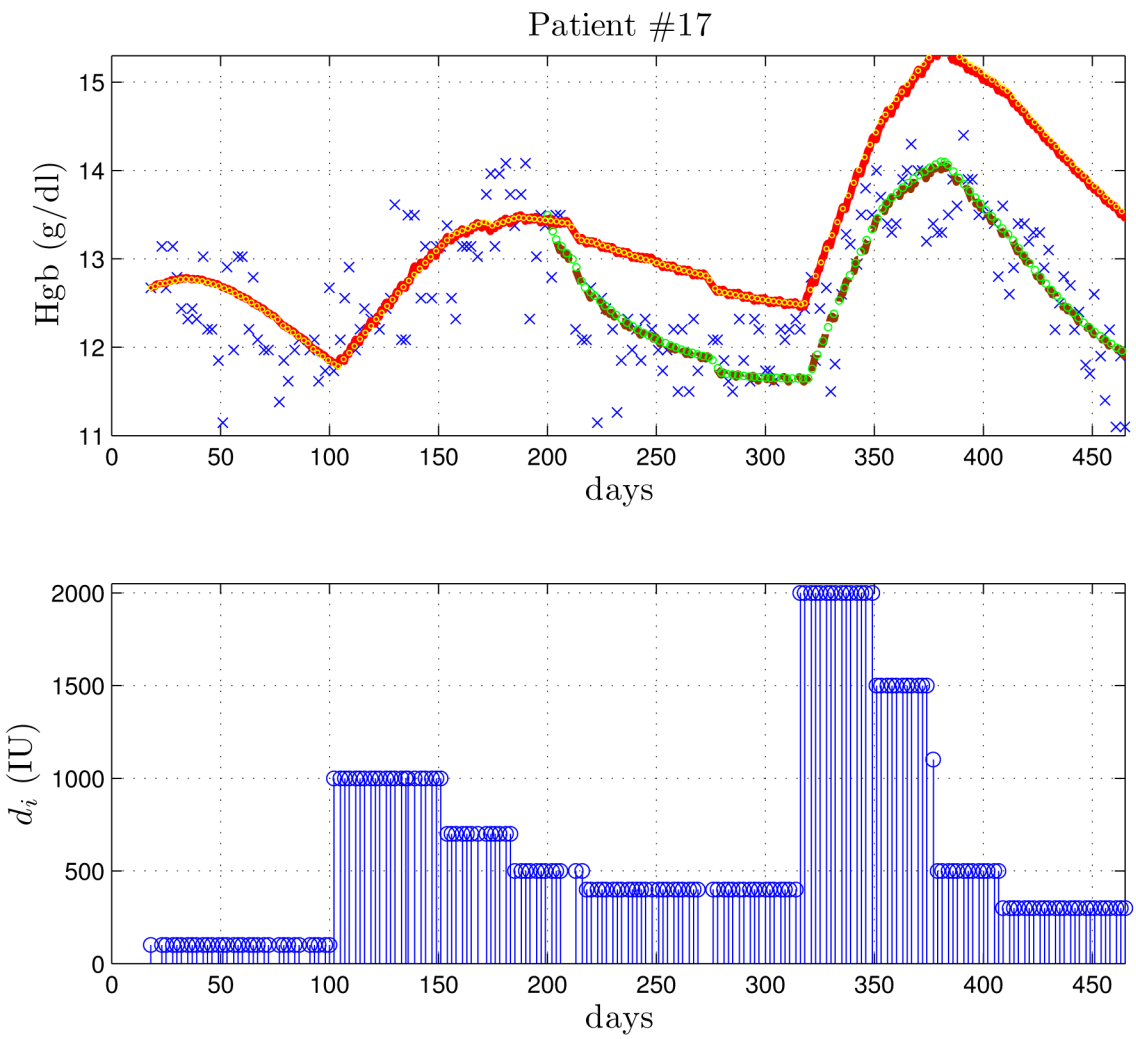

Fig. 3.

Estimation results for Patient #17 using parameters in Table 2; (top) x - clinical data, solid/red - using (1) and model A, circle/yellow - using (7) and model A, solid/brown - using (1) and model B, circle/green - using (7) and model B; (bottom) Administered rHuEPO doses.

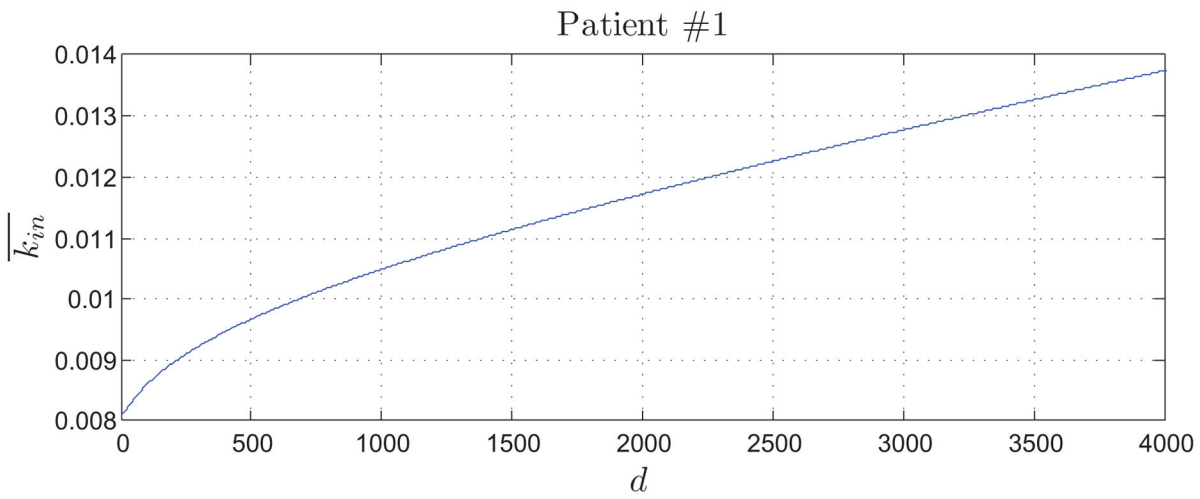

Fig. 4.
Approximation of the PK-production relation (1) by (7) for patient #1.

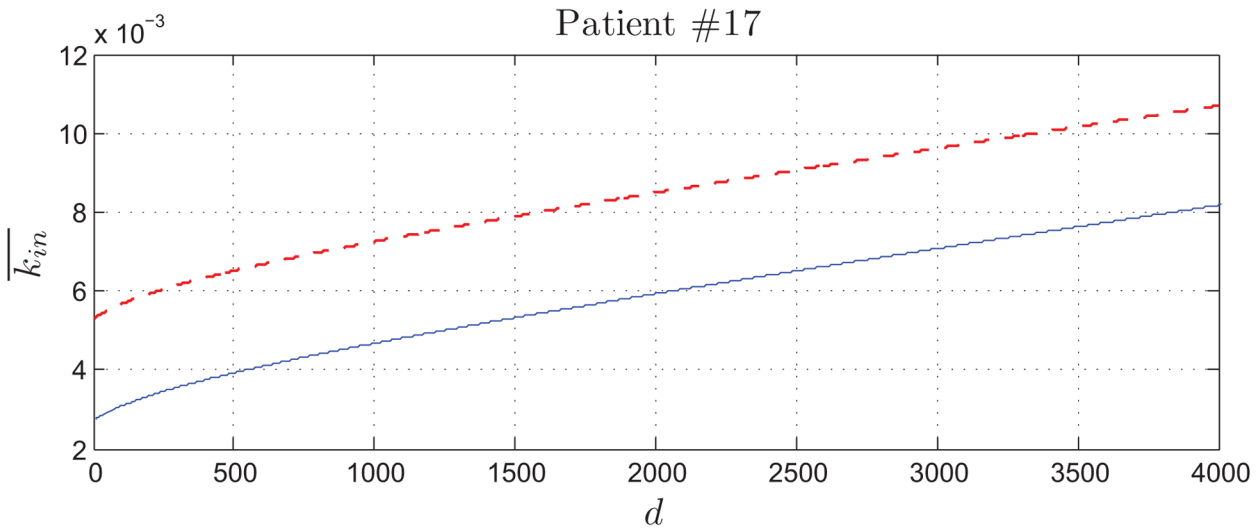

Fig. 5.

Approximation of the PK-production relation (1) by (7) for patient #17 (blue/solid - model A, red/dash - model B.)

TABLE I

Estimated parameters for patient #1.

H_B (g/dL)	V_{max} (IU/day)	K_m (IU)	S_{max} (cell/day)	SC_{50} (IU)	D (day)	$2\tau_0$ (day)
9.06	6979.9	1041.6	2.07e-2	67.14	4.99	19.09

TABLE II

Estimated parameters (a: t ≤ 200, b: t > 200) for patient #17.

	H_8 (g/dL)	V_{max} (IU/day)	K_m (IU)	S_{max} (cell/day)	SC_{50} (IU)	D (day)	$2\tau_0$ (day)
A	8.9	2321.1	567.1	.798e-2	77.32	1.8	55.78
B	9.73	2321.1	567.1	1.04e-2	54.48	3.64	31.26

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