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MATHEMATICAL MODELING OF ERYTHROPOIETIN THERAPY IN UREMIC ANEMIA. DOES IT IMPROVE COST-EFFECTIVENESS?

Riccardo Bellazzi*, Carlo Siviero*, Roberto Bellazzi°

**Dipartimento di Informatica e Sistemistica, Università di Pavia, 27100 Pavia, Italy; °Unità di Nefrologia e Dialisi, U.S.S.L. 78, Vigevano, Italy*

ABSTRACT

This paper describes the improvements in r-HuEPO therapy of uremic patients that may be obtained by using a mathematical model of patient response together with a delivery control strategy derived from the theory of industrial control. A mathematical model of r-HuEPO action is presented, and its applicability to dialytic patients is shown. Moreover, a new statistical technique for identifying the parameters of the mathematical model analyzing a patient population is summarized, and a control strategy for r-HuEPO delivery in uremic patients based on a Fuzzy Set Controller is introduced. Some results obtained from simulation, are presented.

Key words: mathematical modeling, erythropoietin, erythropoietin therapy, cost-effectiveness, uremic anemia

Although mathematical models occupy a fundamental position in developing strategies for controlling industrial plants, their utility, or necessity, in the control and management of drug delivery and, in general, in the task of therapy assessment, has not yet been properly evaluated.

This seems particularly surprising because models of drug metabolism are studied in the field of pharmacokinetics and pharmacodynamics. Moreover, a variety of mathematical models have been formulated with the aim of giving deeper insight into physiological mechanisms.

The main goal of this paper is to show that problems arising during long-term therapy monitoring are best faced with automation and mathematical modeling. In particular, quantitative methodologies could be very useful in optimizing drug delivery.

A relatively small error in drug dosage may lead to ineffective treatment (if the dosage is too low) or to toxicity (if the dosage is too high). The application of methodologies coming from control theory and mathematics should lead to minimization of side effects, costs and time involved in achieving therapeutic goals. New methodologies, derived from the field of Artificial Intelligence, are now available in the area of both statistics and control theory. They prove able to exploit the powerfulness of mathematical modeling in medicine, where available data are often sparse and not always reliable. As a matter of fact, a well-known problem of mathematical modeling is related to parameter identification: if the data at hand are

Correspondence: Riccardo Bellazzi, Dipartimento di Informatica e Sistemistica, via Abbiategrasso 209, 27100 Pavia Italy, Tel. international +39.382.505367, Fax: international +39.382.505373, E-Mail ricipvaimed3.unipv.it.

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few, and the mathematical model has many parameters, it is not possible to estimate their values. Using a new on-line Bayesian analysis of the population at hand it is now possible to overcome these problems.

The medical problem

Recombinant human erythropoietin (r-HuEPO) belongs to the group of drugs whose cost-effectiveness is currently under discussion,[1] both in the treatment of renal anemia and in the therapy of chronic and chemotherapy-induced anemia related to cancer and HIV infection.

In uremic patients, r-HuEPO is able to correct anemia completely in nearly all patients receiving a standard dose, i.e. 100 U/kg three times a week. Current medical strategy is to treat patients needing transfusions and those showing sustained symptoms of anemia. Comparing r-HuEPO treatment with the traditional use of blood transfusions when a patient is severely anemic shows that present practice does not result in cost effective delivery of r-HuEPO. In Italy a vial of 2000 r-HuEPO U costs public institutions about $20.[2] Thus, for a 60 Kg. patient the weekly cost of using r-HuEPO is $180, and a whole year r-HuEPO treatment would cost about $9,360. A dialysis center that manages 100 patients, all treated with r-HuEPO, would have a total cost of $936,000.

Concern about the possibility of treating all patients with uremic anemia has been voiced, and strategies for reducing the dose or the cost of the drug appear to be warranted. Optimal drug delivery may reduce costs for each patient and allow the number of patients treated to be increased.

The mathematical approach

Treating anemic patients with r-HuEPO aims at making exogenous erythropoietin available so that erythropoiesis can rise to a desired level. Response is usually measured in terms of the increase in *circulating hemoglobin concentration* (Hb) or *hematocrit* (Hct). When r-HuEPO is administered, an initial phase of nearly-linear increase is followed by a maintenance phase at a nearly constant level called a *plateau*. Figure 1 shows the experimental Hb profile under r-HuEPO delivery of a responding uremic patient. The desired level of Hb, the therapeutic goal, is denoted by the shaded area. It is essential to achieve this therapeutic goal, while reducing costs and avoiding side effects, such as hypertension or thrombosis. In order to help the physician achieve this goal, a representation of the system's response characteristics, the patient's individual response prediction and a model of therapy adjustment control must be utilized.

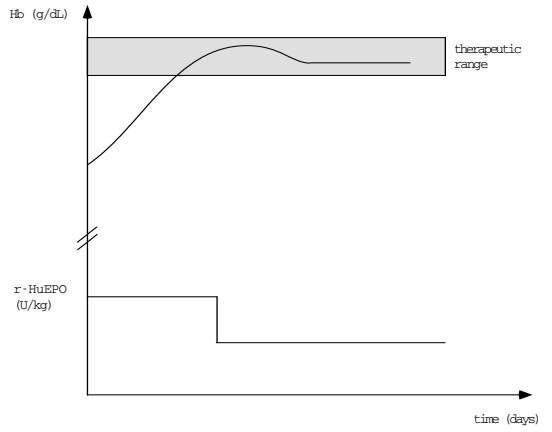

Figure 1. Typical uremic patient response to r-HuEPO delivery. An initial phase of nearly-linear increase is followed by a maintenance phase at a nearly constant level called *plateau*. The desired Hb level, the therapeutic goal, is denoted by the shaded area.

We have defined a computer system for optimizing drug delivery, that is articulated in two modules. The first is aimed at understanding and summarizing what is happening to the patient under the action of the given drug and of the diagnosed disease. This may be viewed as a learning device that utilizes patient response. It is based on a model of the pathophysiological process on which the therapy acts (e.g. the erythropoietic response to erythropoietin) and on a new technique for identifying the parameters of the model during patient monitoring (e.g. modeling the response to r-HuEPO in uremic patients). The second module is aimed at tai-

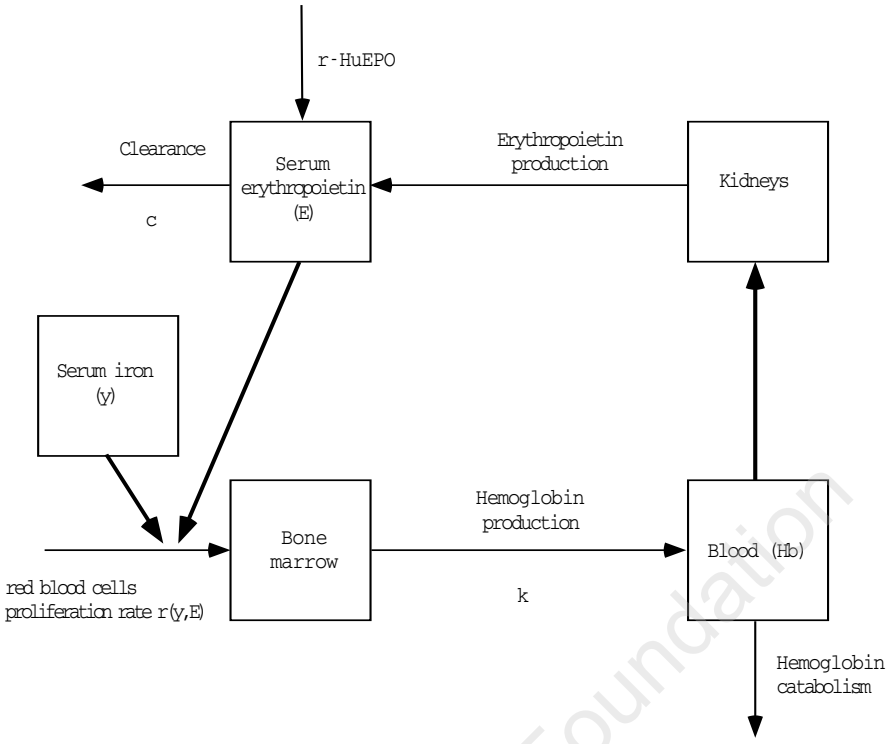

Figure 2. One model for controlling erythropoiesis is via erythropoietin. Rectangles represent body compartments, while the thin arrows represent flows of matter; bold arrows mean signals or controls. Serum iron and serum erythropoietin control red blood cell production.

loring the therapeutic decision by taking into account the results given by the first module. This control strategy is based on the Fuzzy Set Control Theory.

Modeling the erythropoietic response to erythropoietin

Our proposed multicompartmental model for control of erythropoiesis via erythropoietin (Figure 2) is a simplified version of a previous model proposed by Colli Franzone et al.[3,4] and is represented mathematically by a set of integro-differential equations. The rectangles represent body compartments, while the thin arrows represent flows of matter. Bold arrows mean signals or controls.

The serum level of erythropoietin (E) stimulates the production of red blood cell precursors in the bone marrow, and hence Hb production in the blood. When r-HuEPO is delivered intravenously, the serum erythropoietin compartment has two inputs one representing endogenous erythropoietin and the other representing the drug. If the drug is delivered subcutaneously, it is necessary to introduce a second order kinetic model to represent the absorption process.

Particularly interesting here is the model of the serum erythropoietin stimulus on erythropoiesis. We suppose that the action follows a non-linear law, as shown in Figure 3. It expresses the simple physiological assumption that the red cell proliferation rate cannot increase indefinitely with an increasing serum erythropoietin.

The red cell proliferation rate $r(y,E)$ in the bone marrow is a function of serum iron (y) and erythropoietin serum level (E) and may be

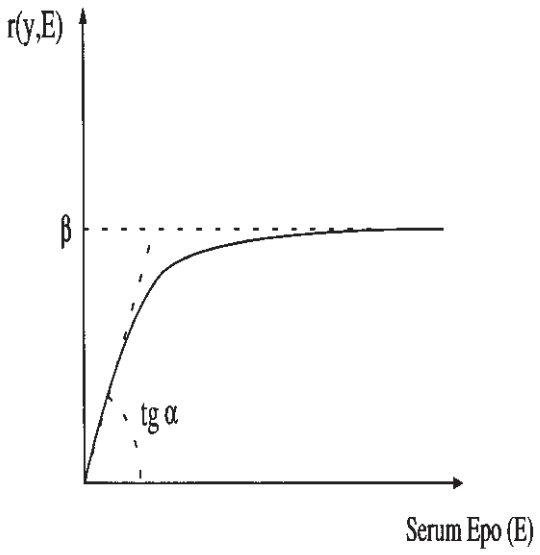

Figure 3. The red cell proliferation rate *r(y,E)* in the bone marrow is assumed to be a non linear function of serum iron (*y*) and the erythropoietin serum level (E), called saturation. This function expresses the physiological statement that *r(y,E)* cannot increase indefinitely with an increasing erythropoietin serum level.

mathematically expressed as follows.

$$r(y,E) = f_1(y) \times f_2(E) \quad (1)$$

$$f_1(y) = \frac{y}{y+y^*} \quad (2)$$

$$f_2(E) = \beta \times (1 - e^{-\alpha E}) \quad (3)$$

where $f_1(y)$ represents a coefficient of iron availability for erythropoiesis while $f_2(E)$ denotes the erythropoietin dependent factor of the red cell proliferation rate. The parameter y^* indicates a plasma iron saturation coefficient and β indicates the maximum erythropoietic effort in response to a large erythropoietic stimulus; α denotes the sensitivity coefficient to a r-HuEPO stimulus.

This assumption of non-linear dependence of erythropoiesis on erythropoietin could be useful for understanding the role of the endogenous erythropoietin level (epo) when delivering r-HuEPO. If epo is in the linear region, as shown in Figure 4a, r-HuEPO could be effective in increasing the rate *r(y,E)* by moving up the working point r^*. Moreover, in this linear region the measured response is dependent only on the r-HuEPO dosage and not on the epo level, because an increase of drug provokes a corresponding linear increase in r^*. This fact could lead to mistakes if only a statistical analysis is used on the cause-effect relationships between epo and patient response. In fact, one can conclude that response is independent of epo levels once the dosage has been assessed.

Otherwise, if epo is in the saturation region, as in Figure 4b, r-HuEPO is completely ineffective because the rate r^* is already at the maximum level. Again, if the problem is examined from a statistical point of view, it would seem

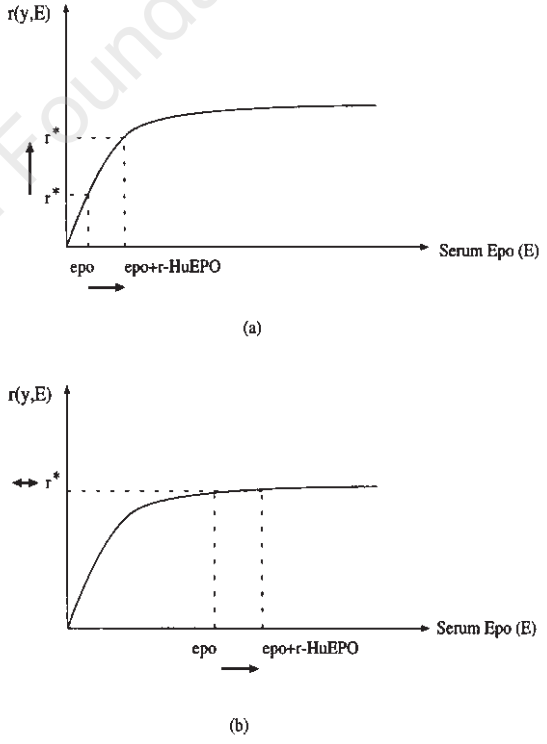

Figure 4. a) A situation in which the endogenous serum level (epo) is in the linear region. In this region r-Hu EPO would be effective in increasing the rate *r(y,E),* by moving up the working point r^*. Moreover, in this linear region, the measured response is dependent only on r-HuEPO dosage and not on the epo level, because an increase of drug provokes a corresponding linear increase in r^*.
b) The endogenous serum level epo is in the saturation region. In this region r-HuEPO is completely ineffective because the rate r^* is already at the maximum level.

that only epo and not the amount of r-HuEPO delivered is related to patient response. If the epo value moves along the saturation profile towards low values, the patient becomes a responder to therapy.

As a matter of fact, the endogenous epo level is always important for understanding the efficacy of r-HuEPO treatment, and it should be determined every time delivery of this drug is to be assessed. This issue is particularly important in patients with anemia of malignancies, where disease could modify parameters β and α, thus changing the maximum value of the rate $r(y,E)$. Response variability should be interpreted as a modification of this curve and not merely registered as a statistical pattern. Great improvement in treating the anemia of malignancies with r-HuEPO could be made by identifying diseases classes on the basis of their saturation curves.

By introducing constraints governing the time invariancy of iron supply to erythropoiesis and the drug delivery schedule, i.e. three times a week, and knowing the half-life of r-HuEPO in hemodialytic patients (6 hours),[5,6] it is possible to calculate the rate of erythropoiesis and solve the overall mathematical model.[4] In this way we have obtained a mathematical formula that gives the relationship between Hb and r-HuEPO dosage. This solution reproduces the shape of the experimental curve shown in Figure 1, and is a characteristic of the patient population with uremic anemia under dialysis. The solution depends on a patient-specific parameter that expresses different individual r-HuEPO response, namely the sensitivity coefficient α to r-HuEPO stimulus. The higher the value of α, the faster Hb increases.

Modeling response to r-HuEPO treatment in uremic patients

Once a disease-specific response model has been implemented, modeling the response in individual patients is a matter of parameter identification. Using the data on Hb response collected from the patient, it is possible to calculate patient-tailored values for the patient-specific parameters of the model, i.e. sensitivity. Moreover, it is necessary to modify the estimates progressively as data collection proceeds.

We used a Bayesian approach for this adaptive estimation process. Bayesian methodologies are widely adopted in many bio-medical applications; moreover, they are now utilized for representing time series, as in pharmacokinetics.[7]

In particular, Bayesian Networks (BNs) have been found to provide a flexible and modular instrument for building probabilistic knowledge bases, and to represent a powerful environment for computing Bayesian inferences.[8,9]

BNs are directed acyclic graphs, in which nodes represent the variables in the problem and arcs define the relationships among nodes in terms of direct causal dependencies; in such a way every node is given a set of parent nodes that are its direct causes. BNs are quantified by specifying the probability distribution of each variable in the network, conditional on any given configuration of values for its parents. For a detailed account of the underlying theory, see Pearl.[10]

Modeling the response to r-HuEPO in the individual patient was performed via a two-step process.

First, BN formalism in order to perform a 'population' analysis of an available data-base of uremic patients undergoing intravenous r-HuEPO treatment. In this analysis it is assumed that every patient (i-th patient) in the data-base shows some common characteristics, i.e. he/she is extracted from the same population. From a Bayesian point of view this means that the prior probability distribution of the r-HuEPO mathematical model parameters (which we indicate with θ) is the same for each patient (hyperdistribution).

The second step of the process is to use this hyperdistribution to obtain a posterior tailored on the basis of data collected on each patient. Estimating the parameters for a new patient will therefore be a compromise between the prior assumption and the available data. The estimating process our system is able to perform is obtained through *Gibbs sampling*, an algorithm based on stochastic simulation.[11-13]

Figure 5 shows the BN layout. The observations are represented by the nodes $Hb_{1,[1,...,M]}$;

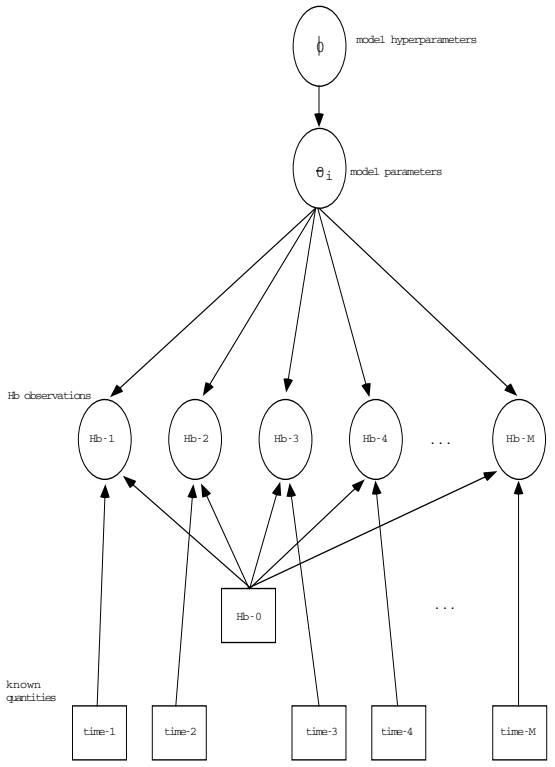

Figure 5. The BN layout: observations are represented by the nodes $Hb_{i,[1,\ldots,M]}$; the parameters to be estimated for each i-th patient are represented by the node θ_i and they define the i-th patient's response (as derived from the compartmental model). The node Φ at the top of the BN represents the hyperprior distribution of each θ_i. The square nodes indicate known quantities, such as the observation times and the pre-treatment hemoglobin concentration.

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Thus it is possible to derive the curve shown in Figure 6, which predicts the increase in Hb values at day=60 if different r-HuEPO delivery strategies are adopted for a population of uremic patients.

In order to estimate reasonable values for the parameters Φ of the model, the BN has been implemented by means of a graphical environment for building and making inferences on Bayesian Networks (GAMEES, GrAphical Modeling Environment for Expert Systems).[14] Population model parameter estimates were derived from data collected by the Nephrology and Dialysis Unit of USSL 78, Vigevano (Italy). The data analysis was reported by Bellazzi.[15]

Modeling the drug delivery control strategy

Evaluating patient response to therapy and modifying therapy on the basis of the response characteristics is part of every-day medical practice. This control action is performed according to experience on past patients, or on the basis of pre-defined protocols. To accomplish this task we adopted a drug delivery decision support system based on a novel class of industrial controllers, the Fuzzy Set controllers.

Fuzzy Control represents an area of growing interest in the context of complex, non-linear processes, where human action is not satisfactory and the classic automatic control theory is not utilizable. For a full explanation of theory

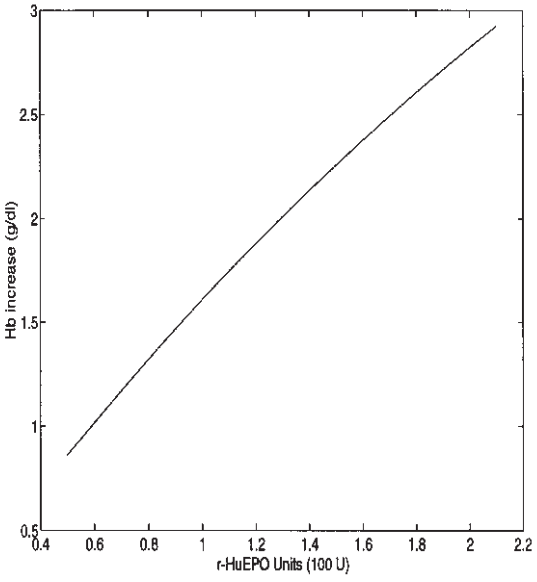


Figure 6. Predictions of Hb increase (g/dL) at day=60 if different r-HuEPO (Units×100) delivery strategies were adopted; after analysis of population of uremic patients.

and applications see References.[16-18]

It is beyond the aim of this paper to describe in detail the theory underlying fuzzy controllers. What follows summarizes the most important features of applying this approach to r-HuEPO therapy.

For a more complete description of the fuzzy controller developed for this problem see Bellazzi et al.[19]

The basic idea underlying a fuzzy control system for drug delivery is to represent each control rule utilized by the physician in a mathematical form, called Fuzzy Relation, and to apply the fuzzy theory to infer new dosages of the drug, which we may call the control variable.[18,20]

As previously mentioned, the physician may choose as the goal of his control strategy improvement of the *blood hemoglobin concentration* (Hb) to a predefined therapeutic range $Hb^* \pm \Delta Hb$, in a given time T^*. Usually Hb^* is chosen as 40% of the basal value: ΔHb=2.5 g/dL and T^*=60 days.

We derived a semi-quantitative control law: the dosage at time i is chosen as $dose(i) = dose(i-1)+K \times |e(i)|$, where $dose(i)$ is the dose of r-HuEPO (Unit/kg), $e(i) = Hb^*-Hb(i)$ and K is calculated by a Fuzzy algorithm.

This control law expresses the assumption that the initial dosage suggested by the physician will be modified according to the distance between the actual and the desired Hb level.

As outlined in the introduction, a control law is usually a very simple statement implementing an action, often based on common sense. In our proposed controller, the 'intelligence' of the procedure stands in the modulation of the K value.

The Fuzzy controller calculates the K value by using three quantities, the error $e(i)=Hb^*-Hb(i)$, the error derivative

$$\Delta e(i) = \frac{e(i)-e(i-1)}{|e(i)|}$$

and the r-HuEPO patient's sensitivity α which is estimated each time i by the BN presented in the previous section.

The Fuzzy controller implements linguistic rules to calculate K, such as

IF e(i) IS POSITIVE LARGE AND $\Delta e(i)$ IS ZERO THEN K IS POSITIVE SMALL

These rules may be expressed in a rule table, like the one shown in Table 1. Each element of the table corresponds to a K value given $e(i)$ and $\Delta e(i)$.

The problem is obviously to translate numbers into linguistic values, and linguistic values into numbers; as a matter of fact $e(i)$, $\Delta e(i)$ and K are numbers.

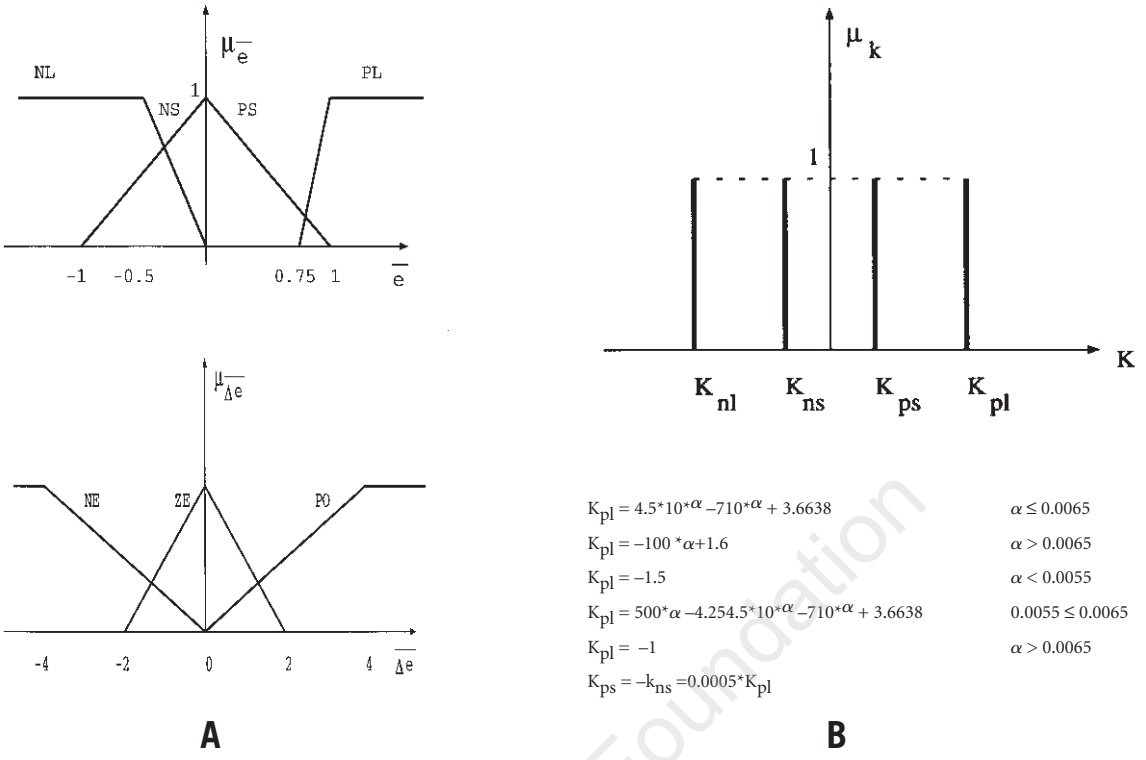
This translation is accomplished by using the concept of fuzzy set. Each variable may be represented with a certain number of linguistic values. For example, the error $e(i)$ is represented with 4 values: *Negative Large* (NL), *Negative Small* (NS), *Positive Small* (PS) and *Positive Large* (PL); each of these values may be viewed as a set of numbers: NL may include $e(i)$ ranges from 4 to 0 g/dL, NS may include numbers from –1 to 0 g/dL, and so on.

The complete definition of the linguistic values for $e(i)$, $\Delta e(i)$ and K is shown in Figure 7 and Table 1.

In Fuzzy logic the numbers belong to a set

Table 1. The rule table of the Fuzzy Controller. Each element of the table represents the linguistic value of K in dependence on the linguistic values of $e(i)$ and $\Delta e(i)$.

		Error derivative $\Delta e(i)$		
		Negative (NE)	Zero (ZE)	Positive (PO)
Error e(i)	Negative Large (NL)	Negative Large (NL)	Negative Small (NS)	Negative Small (NS)
	Negative Small (NS)	Negative Large (NL)	Negative Small (NS)	Positive Small (PS)
	Positive Small (PS)	Negative Small (NS)	Positive Small (PS)	Positive Large (PL)
	Positive Large (PL)	Positive Small (PS)	Positive Small (PS)	Positive Large (PL)



$K_{pl} = 4.5*10^{*\alpha} - 710^{*\alpha} + 3.6638$ $\alpha \le 0.0065$

$K_{pl} = -100 *\alpha + 1.6$ $\alpha > 0.0065$

$K_{pl} = -1.5$ $\alpha < 0.0055$

$K_{pl} = 500*\alpha - 4.254.5*10^{*\alpha} - 710^{*\alpha} + 3.6638$ $0.0055 \le 0.0065$

$K_{pl} = -1$ $\alpha > 0.0065$

$K_{ps} = -k_{ns} = 0.0005*K_{pl}$

Figure 7. **A**) Membership functions of the defined linguistic variable for *e(i)* and Δ*e(i)*. *e(i)* has 4 linguistic values, named NL (Negative Large), NS (Negative Small), PS (Positive Small) and PL (Positive Large) while Δ*e(i)* has 3 linguistic values: NE (NEgative), ZE (ZEro), PO (POsitive). **B**) Membership functions of the defined linguistic variable for K. K has 4 linguistic values, named NL (Negative Large), NS (Negative Small), PS (Positive Small) and PL (Positive Large), and their numeric values depend on the value of r-HuEPO sensitivity α.

with a membership degree. For example, an error *e(i)* of –0.4 may belong to the set of NL with degree 0.4 and to the set of NS with a degree of 0.5. When a number belongs to a set with degree 1, we can say that this number fits the definition of the set completely. This expresses the fact that the linguistic values used by humans include an approximative meaning for the numbers underlying these values.

In order to assign a membership degree to each linguistic set for each number, it is necessary to introduce a membership function for each set, as shown in Figure 7a and 7b.

The values of *e(i)* and Δ*e(i)* are translated into the linguistic representation at each time *i*. Let us suppose for example that the error *e(i)* is a member of PS with degree 0.2 and that Δ*e(i)* is a member of ZE (see Figure 7) with degree 0.3. Now the fuzzy control theory suggests that the rule

IF e(i) IS POSITIVE SMALL AND Δ*e(i)* IS ZERO THEN *K* IS POSITIVE SMALL

is verified with a degree that is the minimum between 0.2 and 0.3.

The membership functions of output K depend on the values assumed by parameter α. In this way the definition of the sets is individualized for each single patient; for example, if the patient is highly r-HuEPO sensitive, the gain of the set POSITIVE LARGE reduces its values. Negative errors will thus produce a mild action on r-HuEPO dosages, thereby taking into account the patient's marked responsiveness to the drug.

The numerical value of K will then be calculated by averaging all the degrees of the rules verified by the current values of $e(i)$ and $\Delta e(i)$.

Referring to our example, we may suppose that $\Delta e(i)$ is also a member of the set PO with a degree 0.4, activating the rule

IF e(i) IS POSITIVE SMALL AND $\Delta e(i)$ IS POSITIVE THEN K IS POSITIVE LARGE

that is verified with a degree that is the minimum between 0.4 and 0.3. K is therefore calculated as

$$K = \frac{0.3 \times k_{pl} + 0.2 \times k_{ps}}{0.3+0.2} \qquad (4)$$

where k_{pl} and k_{ps} are specified in Figure 7b as a function of α.

A case study

In order to evaluate the capabilities of the overall system, we performed a case-simulation study structured as follows: we considered a real clinical case, and characterized this subject in terms of the mathematical model by estimating the model parameter α. Then we considered a fictitious patient with r-HuEPO response characteristics similar to the real patient under analysis. After that we compared the strategy actually used by the physician with that suggested by our controller for the fictitious patient, in order to evaluate both treatments.

Let us consider a patient with a basal hemoglobin value Hb_0 of 5.3 g/dL. The patient's body weight is 44 kg. The goal set by the physician is to increase Hb by about 40% in 60 days of therapy (Hb = 7.51).

The clinician started treating with 100 U/kg. After 3 weeks he decided that the patient's response was not satisfactory and changed the dose to 180 U/kg. After 7 weeks the r-HuEPO dosage was reduced to 67 U/kg in order to avoid hypertension problems. With this policy, the patient's response reached the desired level in 40 days.

The fuzzy algorithm proposed here, suggested starting with 80 U/Kg and increasing the dosage gradually to 90 U/Kg. The therapeutic goal was reached after 60 days. The estimate for the parameter α was $0.0053 \pm 3.1 \times 10^{-4}$.

After 100 days the amount of r-HuEPO utilized by the physician was 64.65×100 U/Kg, while the quantity suggested by the fuzzy controller was 43.24×100 U/Kg, with a savings of 33.12% of the hormone. In terms of costs, this means saving 21.41×100 U/Kg during the first three months of treatment. Since the patient weighed 44 kg., the units saved would be 94,204 (47.1 2000 Unit vials) and the net savings in cost would be $942.

Figures 8a and 8b illustrate the two different drug delivery strategies. The dashed line represents the drug dosage actually delivered, while the continuous line represents the suggested dosage.

The difference in the two strategies is not surprising. As a matter of fact, the physician decided that a time of 60 days was optimal for reaching the therapeutic Hb goal, but his dosages were such that the goal was reached after 40 days. The fuzzy controller used a more rational strategy, following the physician's initial request.

Perspectives and comments

Although the results presented here are only theoretical because the control framework has not been applied *in the field* yet, the potentiality of this approach is clear.

A mathematical model of patient response gives deeper insight into relationships among variables than does a statistical one. Moreover, once the model has been defined, a population analysis of the drug response is essential for characterizing the population of patients under study in terms of model parameters. Finally, an adaptive control strategy is important to rationalize drug delivery and save costs by individualizing therapy.

As a matter of fact, the increasing interest in cost-effectiveness analysis indicates that this kind of approach could be useful in medical practice. Each medical department is usually assigned a budget, and the necessity of not exceeding this budget requires optimizing treatment cost-effectiveness. This issue is crucial for drug delivery: a savings of costs, and hence of

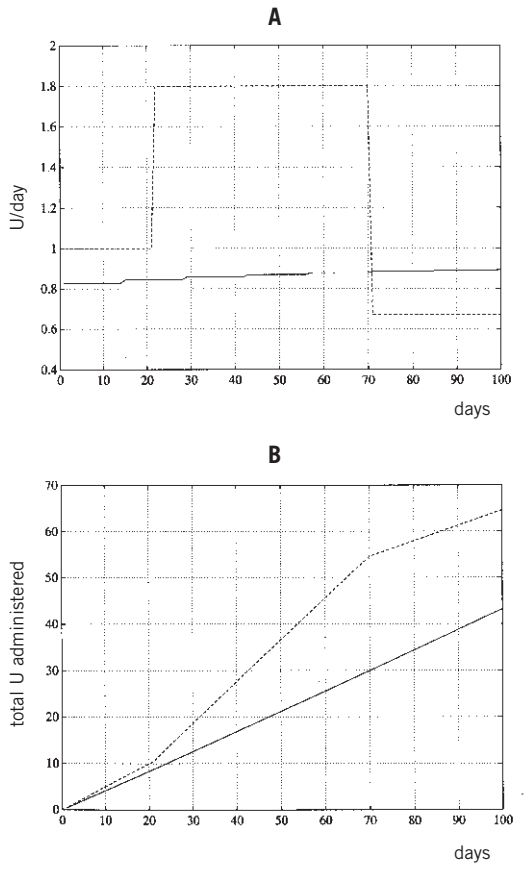


Figure 8. A) The different dose plans: the dashed line represents the drug dosage actually delivered, while the continuous line represents the dosage suggested by the Fuzzy Controller; B) the cumulative amount of drug delivered by the physician (dashed line), and that suggested by the Fuzzy Controller (continuous line): the drug quantity that could be saved after three months of treatment is represented by the difference between the two curves when the time is equal to 90 days.

drug amounts, may allow the number of treated patients to be increased.[21-24]

r-HuEPO is one of these effective, but expensive drugs for which this kind of analysis is worthwhile.[25]

Since PCs and a great variety of mathematical and statistical packages are available nowadays, it is possible to implement mathematical models and control strategies easily. We believe that mathematical models may be important as statistical tests, and that they must become widely employed not only within physiologists, but also in every-day treatment. Moreover, integration of mathematical models and Artificial Intelligence may enlarge the perspectives of decision support systems, allowing explanation of results and more useful man-machine interaction.

The main 'message' of our work is that new mathematical methodologies can introduce new perspectives for optimizing drug delivery, thus allowing more rational utilization of available resources.

Our feeling is that the efficacy of such methodologies in clinical practice is a well-founded expectation; clinical trials and case-control studies must now be carried-on in order to confirm the results of these simulations.

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