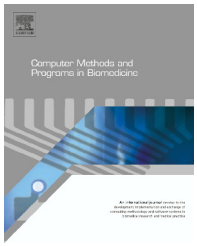
COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 118 (2015) 23–33

journal homepage: www.intl.elsevierhealth.com/journals/cmpb



Individualized model discovery: The case of anemia patients☆

Elom Akabua[a,*], *Tamer Inanc*[a], *Adam Gaweda*[a,b], *Michael E. Brier*[b,d], *Seongho Kim*[c], *Jacek M. Zurada*[a,e]

[a] *Department of Electrical and Computer Engineering, University of Louisville, Louisville, KY 40292, United States*
[b] *Department of Medicine, University of Louisville, Louisville, KY 40292, United States*
[c] *Biostatistics Core, Karmanos Cancer Institute, Wayne State University, Detroit, MI 48201, United States*
[d] *Department of Veteran Affairs, University of Louisville, Louisville, KY 40292, United States*
[e] *Spoleczna Akademia Nauk, 90-011 Lodz, Poland*

ARTICLE INFO

Article history:
Received 3 October 2013
Received in revised form
20 September 2014
Accepted 1 October 2014

Keywords:
Hemoglobin
Robust identification
Erythropoietin
Anemia management
Personalized medicine

ABSTRACT

The universal sequel to chronic kidney condition (CKD) is anemia. Patients of anemia have kidneys that are incapable of performing certain basic functions such as sensing of oxygen levels to secrete erythropoietin when red blood cell counts are low. Under such conditions, external administration of human recombinant erythropoietin (EPO) is administered as alternative to improve conditions of CKD patients by increasing their hemoglobin (Hb) levels to a given therapeutic range.

Presently, EPO dosing strategies extensively depend on packet inserts and on "average" responses to the medication from previous patients. Clearly dosage strategies based on these approaches are, at best, nonoptimal to EPO medication and potentially dangerous to patients that do not adhere to the notion of expected "average" response. In this work, a technique called semi-blind robust identification is provided to uniquely identify models of the individual patients of anemia based on their actual Hb responses and EPO administration. Using the *a priori* information and the measured input-output data of the individual patients, the procedure identifies a unique model consisting of a nominal model and the associated model uncertainty for the patients. By incorporating the effects of unknown system initial conditions, considerably small measurement samples can be used in the modeling process.

1. Introduction

Anemia is a common complication among patients of chronic renal failures. This condition is associated with several complications such as insufficient production of erythropoietin, a glycoprotein promoting the growth of red blood cells in the bone marrow. Until the discovery of recombinant human erythropoietin (EPO) over 30 years ago [1], anemia management primarily involved repeated blood transfusions

☆ The Biostatistics Core is supported, in part, by NIH Center grant P30 CA022453 to the Karmanos Cancer Institute at Wayne State University.

* Corresponding author. Tel.: +1 5028520409.
E-mail address: eakabua@gmail.com (E. Akabua).

http://dx.doi.org/10.1016/j.cmpb.2014.10.001
0169-2607/

– a procedure known to be associated with several health related complications such as infections, allergic reactions [2], and allosensitization that decreases the likelihood of a successful kidney transplant. Exogenous administration of EPO has been shown to slow the progress of anemia of end stage of renal disease (ESRD) [3–5]. However, chronic dosing of EPO is a challenge due to large patient variability in erythropoietic responses. Consequently, decision processes involved in EPO dosage strategies consist mostly of trial-and-error [6]. Therefore, a procedure capable of providing clear and consistent dosage-response method for individual patient based uniquely on Hb and EPO responses could provide better dosing strategy for the individual patients. We propose patient specific modeling technique rooted in feedback control theory to provide models based on individual patient information.

Several attempts to automate EPO delivery have already been reported in the literature [7–20]. Bayesian network drug delivery optimization was performed with patient population data in [8]. This approach was subsequently enhanced by the Fuzzy rule-based control strategies in [15]. In [16,20], Artificial Neural Network modeling techniques were evaluated in anemia patient model developments. Both of these modeling techniques rely on general patient population data. Thus none of the above procedures are able to provide models based on the individual patient measurement information. Few attempts have been made towards the development of individualized patient models [9,19,18,21]. Support vector regression [21] and approximate dynamic programming in [9,19,18] have been proposed previously to personalize EPO dosing. The modeling technique explored in [21] mainly focused on predicting input EPO dosage rather than output Hb measurements. The objective of developing model to inputs, as opposed to outputs, in clinical settings is less desirable since predicting the latter provides a means of determining the former with a properly developed model. In [9,19,18] individualized anemia management was attempted; however, the approach was aimed at optimizing the EPO dosage rather than developing individualized patient models.

Many therapeutic solutions are closely related to system control and feedback measurement problems [22–24]. In the case of drug dosing therapy, physicians wish to achieve and stabilize the responses of certain medications over some desired therapeutic range while minimizing control efforts either to minimize costs or avoid toxic side effects related to large use of the medication. From the views of control engineer, this objective can be translated into a feedback control problem. Basic requirements to translate drug dosing problems to the feedback control problem are the following three components: the model of the plant (patient), control input (EPO dose), and output measurements (hemoglobin concentration). In this context, the model defines the mathematical relationship between the input and measurement output values. Clearly, the only missing piece to successfully translate the problem from dosage therapy domain to the feedback domain is the model of the system. The focus of this work is to provide such missing piece by providing a modeling technique to identify such a mathematical relation linking patients' output hemoglobin to input erythropoietin consequently allowing the implementation of feedback control design techniques.

The technique provided in this work differs from the classical approach to system modeling, namely, *system identification* [33]. A major difference between the two modeling techniques is that in the classical method, it is required that a model structure, with unknown parameters, of the system of interest to be predefined. Here, the aim is to estimate these unknown parameters by using the measurement data while assuming that the predefined structure accurately defines the dynamic profiles of the true system. Furthermore, it is assumed that any discrepancy between the behavior of the model and that of the true system is attributed to noise in the data, which is further assumed to have known statistical properties such as the mean, variance, etc. Clearly, the most challenging and time consuming stage in this approach is the selection of the model structure. Selecting a structure with orders higher than the true system's model order usually result in "over-fitting". On the contrary, selecting model order lower than the true system order results in "under-fitting". Therefore, when the selection of the model structure and/or the statistical assumptions on the system becomes questionable, a modeling technique with no *a priori* model structural requirements on the system is a sound alternative [25]. This modeling technique makes no assumptions on neither the structure of the system nor the noise affecting measurements. It only assumes the system belongs to a certain model *class* (details on this is in the later Section 3) and the noise affecting measurements is assumed unknown but bounded by some value. This bounded noise value is usually available and provided by measuring instrument manufacturers. The result is a model set consisting of models able to explain the *a posteriori* measurement data under given *a priori* assumptions. The center of this model set can now be considered as the nominal model. We previously introduced robust identification procedure to individualized anemia patient model discovery in [26]. This approach did not account for the fact that the system (patient) was already in progress prior to identification and therefore the initial conditions are not zero. Ignoring such information may artificially inflate the model prediction error. Therefore, the aim of this paper is to incorporate such information into the modeling process, consequently providing models with high predictive performance. We refer to this approach as *semi-blind* robust identification [27].

Organization of the paper is as follows. In Section 2, we provide an overview of anemia management problems while pointing out a few of its challenges especially regarding individualized model discovery. Section 3 provides a brief overview on robust identification, especially in ℓ_1 identification framework, subsequently introducing *semi-blind* robust identification procedures in the same section. We combine the robust identification techniques developed in Section 3 with anemia management problems in Section 2 to produce nominal individualized model in Section 4. Section 5 concludes the paper.

2. Anemia management problem

2.1. Introduction

In a healthy human, about 10^{10} red blood cells (RBC) are synthesized per hour in order to maintain sufficient hemoglobin