OBSERVATION WITH BOUNDS OF BIOLOGICAL SYSTEMS
A Linear Programming Approach

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Abstract: This paper presents a technique to estimate the states of biological systems that cannot be directly measured, by using available measurements of other states that affect them. More precisely, the proposed technique makes it possible to derive, at each moment, the possible range of variation of these unmeasured states. It is based on having a compartmental model of the system (which might include uncertain parameters), and then solving a Linear Programming problem. A practical example, based on the kinetic model of drug distribution through the human body, is provided to show its applicability.

1 INTRODUCTION

It is well known that most biological systems can be represented mathematically in quite a precise way by compartmental models (Jacquez, 1985). The main characteristic of these compartmental systems is that that the internal states are nonnegative by nature, as they represent concentrations, temperatures, cell birth or losses, etc: See (Hynne et al., 2001; Luzyanina et al., 2007; Linninger et al, 2009) and references therein for many practical examples.

Thus, this paper considers the *compartmental observation problem*, which consists of constructing compartmental observers (Van den Hof, 1998), that is, observers that ensure the compartmental properties of the states (i.e., positivity and conservation). These observers are very important in biological systems: standard observers and filters provided by systems theory (Luenberger, 1966; Gover and Brown, 1992), if they are not designed taking into account the characteristics of compartmental systems, might give some negative values, which are completely illogical (those observers might, for example, estimate that certain concentrations are negative). The method presented here, which circumvents this problem, is based on some recent results on the theory of positive observers (Ait Rami et al, 2007a; Ait Rami et al., 2007b), which can be applied to compartmental models. These results are used here to provide conditions for the observation of biological systems described by compartmental models, providing a simple approach to numerically address the determination of compartmental observers (as linear programs can be solved easily using off-the-shelf software).

Moreover, the proposed compartmental observers can be used to obtain tight upper and lower bounds on the estimated variables, even in the presence of uncertain parameters in the model. That is, if bounds on the initial states of the observed system are known, and uncertainty in the system matrices can be evaluated, which is common in practice, the evolution of the unmeasured states will always be between the estimated bounds, providing a *bounding observer*. Moreover, these estimated bounds converge to the real value, and, compared to previous approaches for bounding observers (Gouze et al., 2000; Rapaport, 2005; Alamo et al, 2005), the proposed observer is simple to implement, and the design of the observer parameters is based on straightforward conditions (this design is based on solving simple Linear Programming conditions).

The proposed approach is directly applicable to many systems in biology (including medicine), such as those in (Hynne et al., 2001; Luzyanina et al., 2007; Linninger et al, 2009). As an example, the kinetic models of the bone-seeking radiopharmaceutical Tc-99m(Sn)methylene diphosphonate (Tc-MDP) in adult humans, that were derived in (Makler and Charkes, 1980), are used here to present the problem, and show that, by using the proposed approach, it is possible to provide tight estimations of the unmeasured states, giving upper and lower bounds on the real states.

The paper is organized as follows: Section 2 presents the example that will be used as case study,

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Section 3 gives the structure of the proposed bounding observer and a methodology to select the observer parameters. Finally, Section 4 presents a complete application to the case study, and some conclusions are given.

2 MOTIVATING EXAMPLE

An example is now given to show the kind of problems we want to solve: Kinetic models are frequently used to determine doses of drugs in radiotherapy. For instance, the short-lived bone-seeking radiopharmaceutical ^{99m}Tc-methylene diphosphonate (Tc-MDP) is used in bone imaging for investigating the state of the skeleton in diffuse metabolic bone diseases (osteoporosis, hyperparathyroidism) or at local abnormalities in metastatic bone disease (Blake et al., 2002). Based on clinical measurements in adult humans, the portion of the administered dose of Tc-MDP in some compartments of the human body was determined (Makler and Charkes, 1980) to be precisely given by the following compartmental model:

$$\frac{dx}{dt} = \begin{bmatrix} -k_{21}-k_{41}-k_{51} & k_{12} & 0 & k_{14} & k_{15} \\ k_{21} & -k_{12}-k_{32} & k_{23} & 0 & 0 \\ 0 & k_{32} & -k_{23} & 0 & 0 \\ k_{41} & 0 & 0 & -k_{14} & 0 \\ k_{51} & 0 & 0 & 0 & -k_{15} \end{bmatrix} x(t),$$

$$y(t) = \begin{bmatrix} c & 0 & 0 & 0 & 0 \end{bmatrix} x(t). \tag{1}$$

where the vector $x(t)$ contains the states, that correspond to the portion of the dose of the Tc-MDP tracer in the different compartments: $x_1(t)$ is the portion of the dose in the blood, $x_2(t)$ in the bone-ECF, $x_3(t)$ in normal bone, $x_5(t)$ in the tubular urine and $x_4(t)$ in the rest of the human body. Some values for the parameters of the model were obtained from physiological data. Our objective is to provide a technique that uses this mathematical model and the available information on the parameters to design an observer that gives time-dependent upper and lower bounds on the portions in the different compartments. The estimations will be continuously updated based on measurements of the dose in the blood just after an injection (this is the only measurement that is assumed here to be available, but the technique can be directly extended to other measurements).

Model (1) corresponds to the general class of positive (compartmental) systems described by

$$\frac{dx}{dt} = Ax(t),\ y(t) = Cx(t),\ x(0) \geq 0. \tag{2}$$

It is well known (Luenberger, 1966) that the observation of the states of dynamical systems described by (2)) can be based on using a classical Luenberger observer, that consists of integrating the linear differential equations, starting from adequate initial conditions, of the following dynamical system:

$$\frac{d\Theta}{dt} = (A-LC)\theta(t) + Ly(t). \tag{3}$$

The observer design is then based on selecting a matrix L that gives closed-loop stability and some performance. This design is frequently based on placing the eigenvalues of the matrix $A-LC$ in desired positions. Once L is selected, it is only necessary to integrate (3), starting from adequate initial conditions, to get estimations that converge to the real state: this simplicity of concept and implementation has made Luenberger observers useful for those practical applications where the system can be precisely described by a dynamical system.

Unfortunately, the Luenberger observer in (3) does not take into account the fact that the system (2) is compartmental, so unrealistic results might be (temporarily) obtained for some of the states.

Moreover, in many applications, it is important to ensure upper and/or lower bounds on the real states, but standard Luenberger observers do not ensure that the estimated states converge from above (or from below) to the real states.

Another problem of classical observers is that the uncertainty in the system parameters or the initial state cannot be easily incorporated into the observer: For example, clinical trials detected a variation between individuals between 0.502 and 0.578 for k_{12}, whereas k_{32} was found to vary between 1.018 and 1.092. Methodologies to include this information for designing the observer are available but are quite complex (Gouze et al., 2000; Combastel, 2005; Rapaport, 2005). Our objective is to give a general methodology that is simple to apply and does not need involved calculations.

Thus, this paper concentrates on providing a practical methodology to estimate states for biological systems, that can be described by (2), which ensures that the estimated states are logical (i.e., never negative), provide tight bounds on the estimated variables, and takes into account uncertain parameters. This proposed methodology is described in the next section.

3 PROPOSED BOUNDING OBSERVER

We assume that the system whose states are to be estimated on-line can be described as a compartmental system (maybe including uncertain parameters), where there are p measured variables (that form the column vector $y(t)$) and n internal states (that describe each compartment, and form the state vector $x(t)$). More precisely, we consider models that can be described by the following linear dynamical model:

$$\dot{x}(t) = Ax(t),\ y(t) = Cx(t),\ x(0) \geq 0 \qquad (4)$$

Thus, the square constant matrix A is composed of $n \times n$ elements (that will be denoted by a_{ij}), and the constant matrix C has n rows and p columns of elements denoted by c_{ij}. These matrices are assumed to be uncertain, but they can be bounded by known matrices $\underline{A}$, $\overline{A}$, $\underline{C}$ and $\overline{C}$, such that

$$\underline{A} \leq A \leq \overline{A} \text{ and } \underline{C} \leq C \leq \overline{C}. \qquad (5)$$

Mathematically, system (4) is said to be compartmental if the matrix A does not have negative off-diagonal elements (it is called a Metzler matrix) and satisfies the following property:

$$\sum_{i=1}^{n} a_{ij} \leq 0. \qquad (6)$$

It is assumed that bounds on the initial state are known: $\underline{x} \leq x(0) \leq \overline{x}$. In the uncertain case $\underline{A}$ does not have negative off- diagonal elements, but $\underline{A}$ and $\overline{A}$ probably do not fulfill the property (6): they provide a positive system, but probably not a compartmental one. As has been discussed in Section 2, classical observers are not adequate for compartmental systems, specially in the presence of uncertainty in the parameters of the system. Thus, we propose to incorporate to the observer the available information on the system uncertainties, by using an observer that gives upper and lower bounds on the real states. This makes it possible to incorporate uncertainty into the initial states of the system, as they are never perfectly known. The proposed approach is based on using an observer with two independent sets of states: one set (denoted $\overline{\Theta}$) is used to derive an upper bound on the real state, whereas the other set ($\underline{\Theta}$) makes it possible to derive a lower bound.

The proposed observer is then given by the following two independent dynamical equations:

$$\begin{aligned} \frac{d\underline{\Theta}}{dt} &= (\underline{A} - L\overline{C})\underline{\Theta}(t) + Ly(t), \\ \frac{d\overline{\Theta}}{dt} &= (\overline{A} - L\underline{C})\overline{\Theta}(t) + Ly(t). \end{aligned} \qquad (7)$$

The states are then estimated by integrating (7), starting from adequate initial conditions. The design is then based on estimating an *observer gain L* which ensures that

1) both sets of dynamical equations in (7) are stable,
2) the integration of the dynamical equations evolve towards the real state,
3) the states are always between $\underline{\Theta}(t)$ and $\overline{\Theta}(t)$
4) the lower bound $\underline{\Theta}(t)$ is always nonnegative, provided that the initial condition is nonnegative.

To characterize the set of observer gains that fulfill these properties the following condition is proposed (based on the results in (Ait Rami et al., 2007b)): *There exists a bounding observer of system (4) of the form (7) if and only if the following Linear Program has a solution:*

$$\begin{cases} \overline{A}^T\lambda - \underline{C}^T \sum_{i=1}^{n} z_i < 0, \\ \underline{c}_i^T z_j \geq 0 \text{ for } i,j = 1,\ldots,n, \\ \underline{a}_{ji}\lambda_j - \overline{c}_i^T z_j \geq 0 \text{ for } i \neq j, \\ \lambda > 0. \end{cases} \qquad (8)$$

The variables of this Linear Programming problem are $\lambda = [\lambda_1 \ \ldots \ \lambda_n]^T \in \mathbf{R}^n$ *and* $z_1,\ldots,z_n \in \mathbf{R}^r$, *whereas L can be obtained from any feasible solution of this LP problem:*

$$L = \begin{bmatrix} \frac{1}{\lambda_1} z_1 \\ \frac{1}{\lambda_2} z_2 \\ \ldots \\ \frac{1}{\lambda_n} z_n \end{bmatrix}. \qquad (9)$$

To clarify the notation, $\underline{a}_{ij}$ are the elements of the matrix $\underline{A}$, $\underline{c}_i$ are the columns of $\underline{C}$, etc. It must be pointed out that the proposed approach can be extended to related problems, such as compartmental systems with delays (Ait Rami et al., 2007b), discrete-time systems (Ait Rami et al, 2007a), disturbances, etc.

4 APPLICATION TO THE EXAMPLE

Based on clinical measurements (Makler and Charkes, 1980) obtained the following parameters for the compartmental model (1), including variability in the parameters: $k_{12} = 0.540 \pm 0.038$, $k_{21} = 0.095 \pm 0.003$, $k_{14} = 0.277 \pm 0.007$, $k_{41} = 0.431 \pm 0.011$, $k_{15} = 0.233$, $k_{51} = 0.024$, $k_{23} = 0.049 \pm 0.001$, and $k_{32} = 1.055 \pm 0.037$. To take into account the unavoidable measurement errors we fix $c = 1 \pm 0.05$.

Based on the result presented in the previous section, the Linear Programming problem (3) can be easily solved to obtain a compartmental observer with the following observer gain:

$$L = \begin{bmatrix} 12 & 0.0365 & 0.005 & 0.335 & 0.024 \end{bmatrix}. \quad (10)$$

It is now shown how the compartmental observer (7), with this gain, can be used to provide upper and lower bounds on the estimated states, taking also into account the unavoidable uncertainty in the system parameters and initial conditions.

For simulation, assume that the concentration in the blood is continuously measured, shortly after injection, so the conditions of the system when the observation starts are bounded within the following range:

$$\begin{bmatrix} y(0)-0.05 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \leq x(0) \leq \begin{bmatrix} y(0)+0.05 \\ 0.2 \\ 0.3 \\ 0.6 \\ 0.04 \end{bmatrix}. \quad (11)$$

with $y(0)$ the first measurement of the dose in blood.

Thus, to get a bounding observer, the initial condition of the lower observer states is $\underline{\Theta}(0) = \begin{bmatrix} y(0)-0.05 & 0 & 0 & 0 & 0 \end{bmatrix}^T$, whereas the initial condition of the upper observer states is $\overline{\Theta}(0) = \begin{bmatrix} y(0)+0.05 & 0.2 & 0.3 & 0.6 & 0.04 \end{bmatrix}^T$. By the result in Section 3, the evolution of the state $x(t)$ will always be between the estimated states $\underline{\Theta}(t) \geq 0$ and $\overline{\Theta}(t)$. Moreover, these estimations converge to the real value, and are always nonnegative.

These claims can be confirmed in Figures 1 to 5, which plot the state evolutions for the parameters obtained for one of the patients in the original study, starting from the initial conditions ($x(0) = \begin{bmatrix} 0.5 & 0.05 & 0.15 & 0.4 & 0.01 \end{bmatrix}^T$), when the dosing has finished (i.e., with null input), together with the bounds estimated using the approach proposed in Section 3 and the gain (11). For simplicity, it is assumed that the system parameters remain constant throughout the experiment (the plant parameters correspond to mean values) and there is no measurement noise. It is possible to see that the estimated states are nonnegative and converge to the real values, giving lower and upper bounds on the real states that converge to the real values.

Thus, for example, using the proposed approach, it is possible to give tight estimations of the concentration of in the bone-ECF (see Figure 2), despite the uncertain initial conditions, and the person-to-person variations in the nominal parameters: for example, in Figure 2, it is possible to see that just two minutes after the start of measurements of the concentration of Tc-MDP in the blood it is possible to predict precisely that the portion of dose in the bone-ECF will be greater than 0.022 and smaller than 0.037, whereas for the non-bone-ECF ten minutes are enough to estimate the portion of dose with a 10% accuracy.

These estimations can be easily used to derive the figures of merits usually used to derive imaging times. In this case, the objective is to distinguish, in the images, the bone from the surrounding tissue, so, following common practice, we define the *target* to be $Q_T = 0.1x_1 + x_2 + x_3$, (assuming a 10% of blood volume in the skeleton), whereas the *background* is provided to be $Q_B = 0.9x_1 + x_4$. This makes it possible to easily derive bounds on figures of merits frequently used, such as the *contrast*, shown in Figure 6:

$$Contrast = \frac{C_T}{C_B}, \quad (12)$$

or the relative contribution of target and background, depicted in Figure 7, which statistically corresponds to the Beck-Harper figure of merit:

$$Q = \frac{(C_T - C_B)^2}{C_T + C_B}. \quad (13)$$

The obtained results agree with those obtained in practice (Subramanian et al., 1975; Rosenthall et al., 1997; Fogelman et al, 1979).

We must point out that parallel results can be obtained when dosing is measured in the urine, maybe simultaneously with measurement in the blood, following the same procedure, and it is directly applicable to other tracers used in medical imaging, such as ^{18}F-Fluoride (Cook et al., 2000). Moreover, the proposed methodology is general, as the only property used is the fact that the system can be described as a compartmental model with uncertainty (which is the case of most biological systems (Jacquez, 1985)).

5 CONCLUSIONS

This paper has proposed a new approach to solve the observation problem for compartmental models in biology, by providing upper and lower bounds on the unmeasured states, which incorporates uncertainty in the parameters and initial conditions of the system. This problem has been studied, and a simple necessary and sufficient condition for its solvability has been proposed, based on solving a Linear Programming Problem. An illustrative case study, based on a radiopharmaceutical problem, shows the feasibility of the proposed approach, and how it can be used to derive upper and lower bounds on the estimated states.

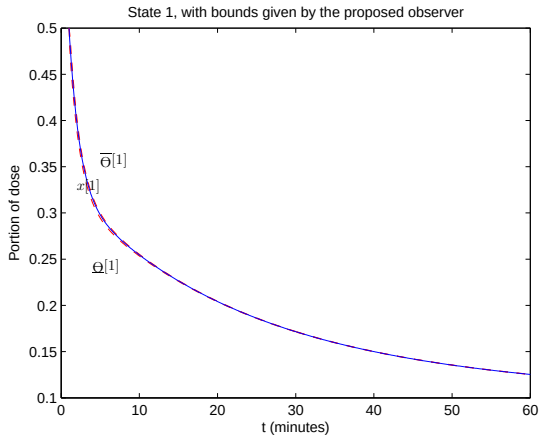

Figure 1: Evolution of the concentration in the blood, and estimated bounds.

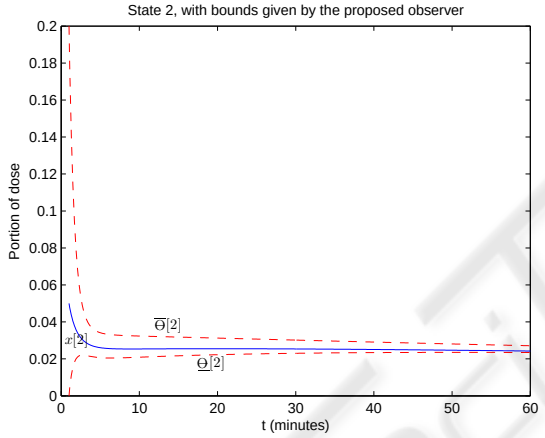

Figure 2: Evolution of the concentration in the bone-ECF, and estimated bounds.

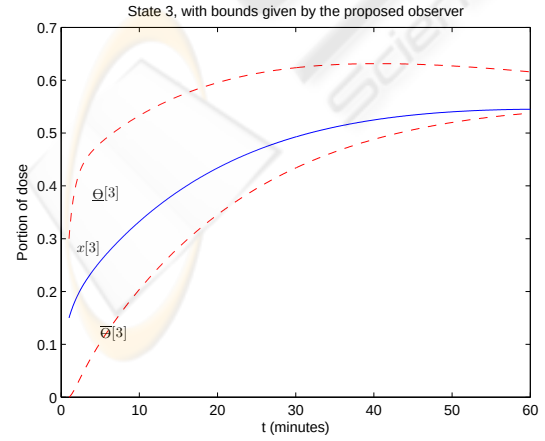

Figure 3: Evolution of the concentration in the bone, and estimated bounds.

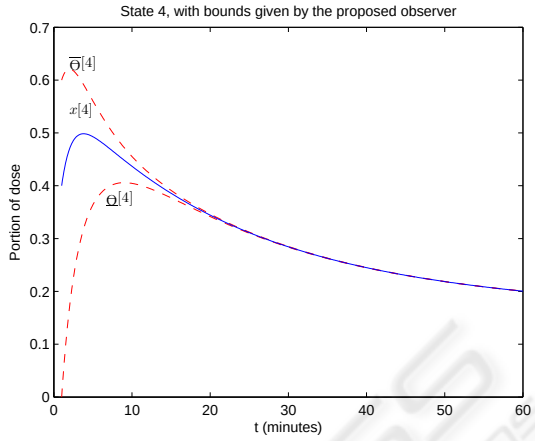

Figure 4: Evolution of the concentration in the non-bone-ECF, and estimated bounds.

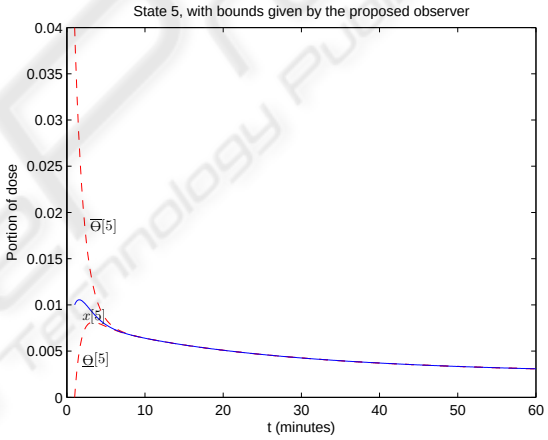

Figure 5: Evolution of the concentration in the urine, and estimated bounds.

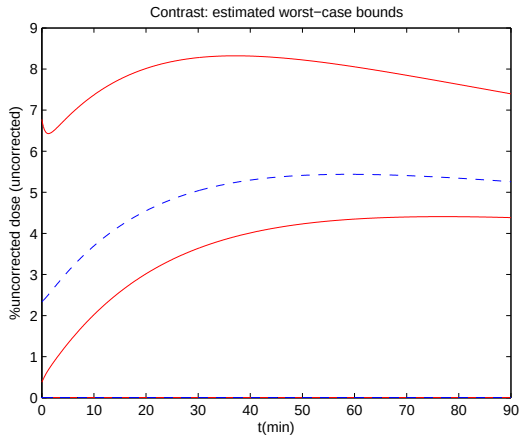

Figure 6: Contrast, with estimated bounds.

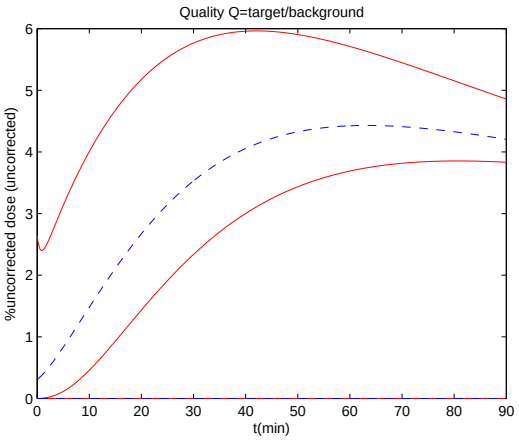

Figure 7: Figure of merit Q with estimated bounds.

Further work is being carried out to include the effect of measurement noise, and applying the proposed technique to complicated problems in biology (including the presence of time-varying delays).

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