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Multiple-Model Adaptive State Estimation of the HIV-1 Infection using a Moving Horizon Approach

Filipe R. Casal, A. Pedro Aguiar and João M. Lemos

***Abstract*— This paper addresses the problem of state estimation under parametric uncertainty of discrete lumped nonlinear systems with application to the HIV-1 infection. We present an estimation algorithm using a multiple-model adaptive estimation approach with a bank of moving horizon estimators with decimated observations. This is motivated by its possible applications to the HIV-1 infection where, in practice, we are unable to observe the patient on a regular basis (non-periodic measurements) and because the HIV-1 dynamics depends on parameters unique to each patient (parameter uncertainty). We show that under reasonable assumptions, the proposed estimation algorithm is robust to parametric uncertainty and the estimation error converges to a small neighborhood of zero. The robustness and performance of the algorithm are illustrated through computer simulations.**

***Index Terms*— Moving Horizon, Estimation, Nonlinear, HIV-1 infection, stability, decimated observations, MMAE.**

I. Introduction

While current clinical practice for the treatment of HIV-1 infection relies mostly on average population models, there is an increasing motivation to consider personalized therapy. Progress in dynamic modeling of HIV-1 infection [17] as well as on associated instrumentation technology based on real-time polymerase chain reaction (PCR) [1] set the ground for the consideration of designing therapy based on control principles for this infectious disease [2], [3], [4], [5], [6]. In this framework, drug dosage is computed depending on the patient, being adjusted along time according on his/her clinical state. A natural way to pursue this objective is to resort to feedback control techniques, which in turn motivates the problem considered here, namely the estimation of the state associated to HIV-1 infection from measurements obtained from blood samples.

When confronted with the problem of state estimation for the HIV-1 dynamics we immediately face two problems: the non-availability of measurements at every sampling instant (referred as decimated observations) and the dependence of the HIV-1 model to parameters that are unique to each patient. Both these problems arise when studying almost all dynamics associated to biomedical applications.

In addition to its intrinsic robustness properties, that makes moving horizon estimation (MHE) adequate to solve estimation problems in the presence of unmodeled dynamics, such as when considering biomedical applications, a major advantage of this approach is the capacity to incorporate constraints [7], [8]. In [14], MHE was extended to operate under decimated observations (DMHE). The strategy proposed in the present paper consists in a Multiple Model Adaptive Estimator (MMAE) with banks of DMHEs so as to tackle the high level of parameter uncertainty typically of HIV-1 infection dynamics.

The main contribution of the paper consists, therefore, on a new estimation algorithm using MMAE with DMHE filters. The convergence properties of the algorithm are presented and a simulation example of its application to HIV-1 infection is described, as well as a comparison with existing estimation methods.

The paper is organized as follows. Section II describes the nonlinear model for the HIV-1 dynamics. In Section III, we recall the Moving Horizon Estimation (MHE) with decimated observations and describe the Multiple Model Adaptive Estimator (MMAE) based on a bank of MHEs with decimated observations for parameter estimation. The convergence properties, both of the parameters and state are presented in Section IV. In Section V we show the performance for the HIV-1 dynamics, as well as a comparison with a MMAE with banks of decimated Extended Kalman filters and finally, in Section VI, we conclude the paper and make final remarks on what could be improved in the proposed algorithm. Due to space limitations the proofs are omitted.

II. HIV-1 Model

This section presents the mathematical model that describes the dynamic interactions between the healthy CD4+ cells, the infected CD4+ cells, and the free viruses. The model adopted in this paper for the estimator design is the following [17]

$$\begin{cases} \dot{T} = s - dT - e^{-u_1}\beta T\nu \\ \dot{T}^* = e^{-u_1}\beta T\nu - \mu_2 T^* \\ \dot{\nu} = e^{-u_2}kT^* - \mu_1\nu \end{cases} \tag{1}$$

where T is the concentration of healthy T-CD4+ cells, T^* is the concentration of infected cells and ν is the concentration of free virus particles, all in units per $[mm^3]$. The quantities u_1 and u_2 are the manipulated variables related to the quantities of drugs administered that model two major categories of antiretroviral drugs: reverse transcriptase inhibitors (RTIs) modeled by u_1 and protease inhibitors (PIs) associated to u_2. The other variables, d, k, s, β, μ_1 and μ_2 collected in

F. R. Casal and A. P. Aguiar are with the Lab. of Robotics and Systems in Engineering and Science, Inst. Superior Tecnico, Lisbon, Portugal; A. P. Aguiar is with the Faculty of Engineering, University of Porto (FEUP), Portugal; and J. M. Lemos is with INESC-ID/IST, Portugal. filipe.casal@ist.utl.pt, pedro.aguiar@fe.up.pt, jlml@inesc-id.pt.

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the vector $\Theta = (d, k, s, \beta, \mu_1, \mu_2)^T$ are constant parameters unique to each individual. In this paper the following nominal values were adopted [13]: $d = 0.02\,s^{-1}$ - Mortality rate for healthy cells; $\kappa = 100\,s^{-1}$ - Production rate of virus by infected cells; $s = 10\,mm^{-3}s^{-1}$ - Production rate of healthy cells; $\beta = 2.4 \times 10^{-5}\,mm^3 s^{-1}$ - Infection rate coefficient; $\mu_1 = 2.4\,s^{-1}$ - Elimination rate for the virus; $\mu_2 = 0.24\,s^{-1}$ - Elimination rate for infected cells;

It is important to stress that model (1) is highly nonlinear and (with zero inputs) has two equilibrium points [13]. One equilibrium point is unstable and corresponds to the "healthy" individual, and the second equilibrium point, that corresponds to an infected individual, is stable, around which the behavior is oscillatory.

To derive the estimator that will be presented in the next section we will use the discretized system

$$x_{t+1} = \begin{bmatrix} T \\ T^* \\ \nu \end{bmatrix}_{t+1} = \phi(T_t, T_t^*, \nu_t, u_{1_t}, u_{2_t}; \Theta) \qquad (2)$$

with the following update formula given by Euler's method

$$\phi(T, T^*, \nu, u_1, u_2; \Theta) = \begin{bmatrix} T + t_s(s - dT - e^{-u_1}\beta T \nu) \\ T^* + t_s(e^{-u_1}\beta T \nu - \mu_2 T^*) \\ \nu + t_s(e^{-u_2}\kappa T^* - \mu_1 \nu) \end{bmatrix}$$

where t_s is the time interval between two consecutive points in the discretization.

Motivated by the current clinical practice, we consider that we only have measurements of the concentration of the free virus particles ν, and furthermore that these measurements are not available at every sampling instant of time (decimated observations). In this case, the output equation is given by

$$y_{\sigma_k} = h_k(T, T^*, \nu) = \nu,$$

where the function σ_k represents a renumbering of the time index. This renumbering stands for the fact that observations are not available at every time instant, but only in a subset of them (the precise definition is given in the next section). An example is when an observation is only available every n_s samples, in which case $\sigma_k := n_s\,k$.

This model, although one of the simplest HIV-1 dynamics, already accounts for a number of parameters that are unknown and unique to each patient.

III. Multiple-Model Adaptive Estimator

In this section we propose a multiple-model adaptive estimator (MMAE) architecture combined with a moving horizon (MH) strategy. This MMAE architecture is mainly used for two reasons: it is not trivial to estimate both state and parameters of a nonlinear system and the MMAE provides a tool to explore a wide range of the unknown parameters domain (at the expense of computational effort). On the HIV-1 case, since the sampling time might be in the order of days this is not a real issue. The moving horizon strategy is used because of its estimation properties and better performance on the HIV-1 model with respect to other approaches, [14]. In Fig. 1 the structure of the MMAE is outlined – it consists

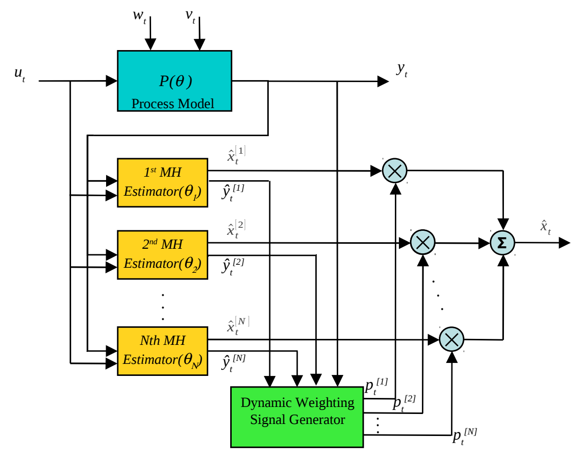

Fig. 1. Schematic Representation of the MMAE model

of *i)* a bank of N state estimators, where each observer is designed based on a given parameterized model of the plant, and *ii)* a dynamic weighting signal generator system that is responsible for the time-evolution of the weights $p_t^{[i]}$. The state estimate $\hat{x}_t$ is given by a weighted sum of the local state estimates produced by the bank of observers. More precisely,

$$\hat{x}_t = \sum_{i=1}^{N} p_t^{[i]} \hat{x}_t^{[i]},$$

where each $\hat{x}_t^{[i]}$, $i = 1, \ldots, N$ corresponds to a local state estimate generated by the i^{th} local observer.

We now provide in more detail the role of each block.

A. Process model

We consider that the process model can be described by a general nonlinear discrete dynamical system of the form

$$\begin{aligned} x_{t+1} &= \phi_t(x_t, u_t, w_t; \Theta) \\ y_{\sigma_k} &= h_k(x_{\sigma_k}; \Theta) + v_k \end{aligned} \qquad (3)$$

where $x_t \in \mathbb{X}_t$ is the state vector of the system, $u_t \in \mathbb{U}_t$ its control, y_{σ_k} denotes the measurements, $\Theta \in \mathbb{R}^{n_\Theta}$ is a constant vector that contains all the unknown model parameters, and $w_t \in \mathbb{W}_t$ and $v_k \in \mathbb{V}_k$ represent input disturbances and measurement noise, respectively. The sets $\mathbb{X}_t$, $\mathbb{W}_t$ and $\mathbb{V}_k$ are subsets (with appropriate dimension) of the Euclidean space that incorporate the constraints associated to (3). The initial condition x_0, the parameter set Θ, and the signals w_t, v_k are assumed to be unknown. In the output equation we address explicitly the case in which the measurements may not be available at every sampling instant t (decimated observations). To this effect, we define M as the set of time instants (indexes) where measurements are available, and $\sigma : \mathbb{N} \rightarrow M$ as the index time given by $\sigma(k) = t$, where t is the time index of the k-th measurement.

B. Local state estimator

For the local estimators we propose a MHE with decimated observations (DMHE) as described in [14]. In this case, each i^{th} estimator is designed according to the process model (3) but assigning a given candidate parameter $\Theta^{[i]}$. To tackle the fact that the measurements do not arrive at every sampling instant of time t, we have first to find a transformation that allows us to apply the MHE strategy in a more convenient representation of (3). For that purpose we introduce two operators. The first operator, denoted by Σ, allows to write in an appropriate way the recursive composition of a function and is defined as

$$\Sigma\left[\{\phi\}_a^{b-1}, z, \{\omega\}_a^{b-1}, a, b\right] := \begin{cases} z, & \text{if } a = b \\ \phi_{b-1}\Big(\Sigma\left[\{\phi\}_a^{b-2}, z, \{\omega\}_a^{b-2}, a, b-1\right], u_{b-1}, \omega_{b-1}\Big), & \text{otherwise} \end{cases}$$

where $\{\phi\}_a^b$ denotes a sequence of functions $\{\phi_a(\cdot), \phi_{a+1}(\cdot), ..., \phi_b(\cdot)\}$, z is the initial state and $\{\omega\}_a^b$ a sequence of input disturbances. Note that the state solution of system (3) at time $t+1$ with initial condition x_0 can be written as $x_{t+1} = \Sigma[\{\phi\}_0^t, x_0, \{\omega\}_0^t, 0, t+1]$.

The second operator, the accumulated noise χ, is defined as the difference between the evolution of state x with input disturbance and the state x with zero input disturbance, that is, $\chi\left[\{\phi\}_a^{b-1}, z, \{w\}_a^{b-1}, a, b\right] := \Sigma\left[\{\phi\}_a^{b-1}, z, \{w\}_a^{b-1}, a, b\right] - \Sigma\left[\{\phi\}_a^{b-1}, z, \{0\}_a^{b-1}, a, b\right]$ For simplicity of notation the following abbreviations are used $\Sigma\left[\phi, z, \omega, a, b\right] := \Sigma\left[\{\phi\}_a^{b-1}, z, \{\omega\}_a^{b-1}, a, b\right]$, $\chi\left[\phi, z, \omega, a, b\right] := \chi\left[\{\phi\}_a^{b-1}, z, \{\omega\}_a^{b-1}, a, b\right]$.

Using the above operators, to design each i^{th} local estimator we use the corresponding process model

$$x_{k+1}^{[i]} = f_k^{[i]}(x_k^{[i]}) + w_k^{[i]} \tag{4a}$$

$$y_k^{[i]} = h_k^{[i]}(x_k^{[i]}) + v_k \tag{4b}$$

where $f_k^{[i]}(x) = \Sigma\left[\phi^{[i]}, x, 0, \sigma_k, \sigma_{k+1}\right]$ and $w_k^{[i]} = \chi\left[\phi^{[i]}, x_{\sigma_k}, \omega, \sigma_k, \sigma_{k+1}\right]$. We have used the abbreviation $\phi^{[i]}$ to denote $\phi(\cdot; \Theta^{[i]})$. Since $f_k^{[i]}(x_k) + w_k^{[i]}$ is equal to $\Sigma\left[\phi^{[i]}, x, \omega, \sigma_k, \sigma_{k+1}\right]$, it is straightforward to conclude that $x_k^{[i]}$ in (4) is equal to x_{σ_k} in (3) with $\Theta = \Theta^{[i]}$. Thus, system (4) describes how the state in (3) is transferred from a point where a measurement is available to the next point where a measurement occurs again for a given parameter $\Theta^{[i]}$. Note however that in (4) $w_k^{[i]}$ might depend on $x_k^{[i]}$.

Hereafter we use the index k for solutions of system (4) and t for solutions of system (3). We denote by $x(k; z, l, \{w_j\})$ the solution of system (4) at time k when the initial state is z at time l and the disturbance sequence is $\{w_j\}_{j=l}^k$. When $w_j = 0$ we will write $x(k; z, l)$. Also $y(k; z, l, \{w_j\}) := h_k(x(k; z, l, \{w_j\}))$ and $y(k; z, l) := h_k(x(k; z, l))$.

The objective of each local MHE is to find the state sequence $\{\hat{x}_t^{[i]}\}$ that is most likely to be in some sense close to the real state $\{x_t\}$, given the sequence of observations $\{y_{\sigma_k}\}$, the inputs $\{u_t\}$ and the model with constraints described in (3) and assuming a given candidate parameter $\Theta^{[i]}$.

To this effect, we consider the following objective function defined in the equivalent system (4),

$$\Phi_T(x_0, \{w_k\}) := \sum_{k=0}^{T-1} L_k(w_k, v_k) + \Gamma(x_0),$$

where $T > 0$ is the estimation horizon, $v_k = y_k - y(k, x_0, 0, \{w_j\})$, $L_k : \mathbb{W}_k \times \mathbb{V}_k \to \mathbb{R}_{\geq 0}\ \forall_{k\geq 0}$ is the running cost and $\Gamma : \mathbb{X}_0 \to \mathbb{R}_{\geq 0}$ represents a penalty on the initial condition. It is assumed that some prior information of the initial state is known, and this one is captured by $\Gamma(\cdot)$, that satisfies the following property $\Gamma(\hat{x}_0) = 0,\ \Gamma(x) > 0 \quad \forall_{x \in \mathbb{X}_0 \setminus \{\hat{x}_0\}}$, where $\hat{x}_0 \in \mathbb{X}_0$ is the (a priori) most likely value of x_0. The optimization problem can now be stated as follows: find the pair $(\hat{x}_0, \{\hat{w}_k\}_{k=0}^{T-1})$ that minimizes $\Phi_T(x_0, \{w_k\})$ subjected to $(x_0, \{w_k\}) \in \Omega_T$. The constraint set Ω_T arises from the restrictions $\mathbb{X}_{\sigma_k}, \mathbb{W}_k$ and $\mathbb{V}_k$.

In general, this optimization cannot be applied online because the computational complexity grows unbounded with increasing horizon T. To account for this problem and enforce a fixed dimension optimal control problem, a possible strategy is to explore the ideas of dynamic programming by breaking the summation in Φ_T and consider rather the following optimization (for $T > N$)

$$\begin{aligned}\hat{\Phi}_T(z, \{w_k\}) = \min_{z, \{w_k\}_{k=T-N}^{T-1}} \{ &\sum_{k=T-N}^{T-1} L_k(w_k, v_k) \\ &+ \hat{\mathcal{Z}}_{T-N}(z) : (z, \{w_k\}) \in \Omega_T^N \}\end{aligned} \tag{5}$$

where the quantity $\hat{\mathcal{Z}}_\tau(z)$ is an approximation of the so called arrival cost $\mathcal{Z}_\tau(z)$.

From this optimization, we obtain the pair $(z^*, \{\hat{w}_{k|T-1}\}_{k=T-N}^{T-1})$ that allows to compute the sequence

$$\{\hat{x}_{T-N|T-1}^{[i]}, \hat{x}_{T-N+1|T-1}^{[i]}, ..., \hat{x}_{T|T-1}^{[i]}\}$$

by using (4a) with initial condition $x_{T-N} = z^*$.

To compute the estimate of $x_t^{[i]}$ at every instant of time t we use

$$k = \max\{k : \sigma_k \leq t\}, \quad \hat{x}_t^{[i]} = \Sigma\left[\phi^{[i]}, \hat{x}_k^{[i]}, 0, \sigma_k, t\right]. \tag{6}$$

C. Dynamic Weighting Signal Generator (DWSG)

The underline role of the DWSG system is to basically update the weights $p_t^{[i]}$ by continuously comparing the output of the local estimators with the observed measurements. The idea is to give more relevance (weight) to the observer that "better" explains the evolution of the observed measurements. Following the approach in [9] but adapted to the problem of decimated observations, to generate the dynamic weights $p^{[i]}$ we use the dynamic recursion

$$p_{t+1}^{[i]} = \begin{cases} \dfrac{\beta_t^{[i]} e^{-\tilde{y}_t^{[i]}}}{\sum_{j=1}^N p_t^{[j]} \beta_t^{[j]} e^{-\tilde{y}_t^{[j]}}} p_t^{[i]}, & \text{if } t \in M \\ p_t^{[i]}, & \text{otherwise} \end{cases} \tag{7}$$

where $\beta_t^{[i]}$ is a positive bounded function and $\tilde{y}_t^{[i]}$ is an error measuring function that maps the measurable signals of the process model and the states of the i^{th} local observer to a nonnegative real value. Examples of an error measuring function and a $\beta_t^{[i]}$ are $\beta_t^{[i]} = \frac{1}{\sqrt{|S_t^{[i]}|}}$ and $\tilde{y}_t^{[i]} = \frac{1}{2}\|y_t - \hat{y}_t^{[i]}\|^2_{(S_t^{[i]})^{-1}}$, where the $S_t^{[i]}$ are weighted positive definite matrices and $|\cdot|$ denotes the determinant. In (7), we have to impose that the initial conditions $p_0^{[i]}$ are such that $p_0^{[i]} \in (0,1)$ and $\sum_{i=1}^N p_0^{[i]} = 1$. In that case, it can be proved (using similar arguments as in [9]) that due to the particular structure of equation (7), the weights $p_t^{[i]}$ are positive, bounded, and the overall sum $\sum_{i=1}^N p_t^{[i]}$ is always one for all $t \geq 0$, independently of the input signals of the DWSG.

IV. Stability and Convergence Results

In this section we provide conditions under which the state estimate $\hat{x}_t$ converges to a small neighborhood of the true values in the presence of bounded disturbances, noise, and model parametric uncertainty. To this end, we first analyze the stability properties of the individual local estimator.

A. Convergence of the local estimator

This section summarizes the results described in [14] for the DMHE. We were able to relax the linear growth condition in the vector field $\phi(\cdot)$ (Assumption A0 of [14], [18]) by instead imposing a much less restrictive Hölder condition. Due to space limitations, we omit the proofs but these ones are very similar to the ones in [14]. In the sequel, the following definitions will be used.

Definition 1: A function $\alpha : \mathbb{R}_0^+ \to \mathbb{R}_0^+$ is a K_∞*-function* if it is continuous, strictly monotone increasing, $\alpha(x) > 0$ for all $x \neq 0$, $\alpha(0) = 0$ and $\lim_{x\to\infty} \alpha(x) = \infty$.

Definition 2: System (3) is *uniformly observable* if there exist a positive integer N_o and a K_∞ function $\varphi(\cdot)$ such that for any two states x_1 and x_2,

$$\varphi(\|x_1 - x_2\|) \leq \sum_{j=0}^{N_o-1} \|y(\sigma_{k+j}; x_1, \sigma_k) - y(\sigma_{k+j}; x_2, \sigma_k)\|,$$

where $y(\sigma_k; z, \sigma_l) = h_k(x(\sigma_k, z, \sigma_l))$ with $x(\sigma_k, z, \sigma_l)$ denoting the solution of (3) without disturbances at time σ_k when the state starts at time σ_l with value z .

We denote by $\bar{B}_\varepsilon$ the closed ball with radius ε centered in 0. The stability results presented in this section make use of the following assumptions:

A0) The vector field $\phi_t(\cdot)$ in (3) satisfies the following Hölder condition: $\|\phi_t(z_1, u_k, \omega_1; \Theta) - \phi_t(z_2, u_k, \omega_2; \Theta)\| \leq c_\phi \|(z_1, \omega_1) - (z_2, \omega_2)\|^\alpha$ for any $z_1, z_2 \in \mathbb{X}_i$, $u_k \in U_k$, $w_1, w_2 \in W_k$ and some positive numbers c_ϕ and α. The observation function h_k is Lipschitz continuous.

A1) $L_k(\cdot)$ and $\Gamma(\cdot)$ are left continuous in their arguments for all $k \geq 0$. Also, there are K_∞-functions $\eta(\cdot)$ and $\gamma(\cdot)$ such that $\eta(\|(w,v)\|) \leq L_k(w,v) \leq \gamma(\|(w,v)\|)$ $\eta(\|x - \hat{x}_0\|) \leq \Gamma(x) \leq \gamma(\|x - \hat{x}_0\|)$, for all $(w,v) \in (\mathbb{W}_k \times \mathbb{V}_k)$, $x, x_0 \in \mathbb{X}_0$, and $k \geq 0$.

A2) There exists an initial condition x_0 and a disturbance sequence $\{w_k\}_{k=0}^\infty$ such that, for all $k \geq 0$, $(x_0, \{w_k\}_{k=0}^\infty) \in \Omega_k$.

A3) The interval of time between two consecutive measurements is finite, i.e. $\sigma_k - \sigma_{k-1} < n_{max}$ for some n_{max}.

A4) There exists a K_∞-function $\bar{\gamma}(\cdot)$ such that $0 \leq \hat{\mathcal{Z}}_k(z) - \hat{\Phi}_k \leq \bar{\gamma}(\|z - \hat{x}_k\|)$ for all $z \in \mathbb{X}_k$.

A5) Let $\mathcal{R}_\tau^N = \{x(\tau; z, \tau - N, \{w_k\}) : (z, \{w_k\}) \in \Omega_\tau^N\}$ where $\mathcal{R}_\tau^N = \mathcal{R}_\tau$ for $\tau \leq N$. For a horizon length N, any time $\tau > N$, and any $p \in \mathcal{R}_\tau^N$, the approximate arrival cost $\hat{\mathcal{Z}}_\tau(\cdot)$ satisfies the inequality

$$\hat{\mathcal{Z}}_\tau(p) \leq \min_{z, \{w_k\}_{k=\tau-N}^{\tau-1}} \{ \sum_{k=\tau-N}^{\tau-1} L_k(w_k, v_k) + \hat{\mathcal{Z}}_{\tau-N}(z) : (z, \{w_k\}) \in \Omega_\tau^N, \, x(\tau; z, \tau - N, \{w_j\} = p\}$$

subject to initial condition $\hat{\mathcal{Z}}_0(\cdot) = \Gamma(\cdot)$. For $\tau \leq N$, the approximate arrival cost $\hat{\mathcal{Z}}_\tau(\cdot)$ satisfies instead the inequality $\hat{\mathcal{Z}}_\tau(\cdot) \leq \mathcal{Z}_\tau(\cdot)$.

A6) There exists positive constants δ_w and δ_v such that $\mathbb{W}_t \subseteq \bar{B}_{\delta_\omega}$ and $\mathbb{V}_k \subseteq \bar{B}_{\delta_v}$ for all k, where $\bar{B}_\varepsilon = \{x : \|x\| \leq \varepsilon\}$.

Assumption **A3)** was added to the ones considered in [18] to cope with decimated observations and **A0)** was weakened to a Hölder condition. Assumption **A5)** loosely speaking means that the approximate arrival cost should not add "information" that is not present in the data.

The following results share the same reasoning as the results in [18] but replacing the Lipschitz continuity of ϕ by the Hölder condition. Using [14], we can now state the following results, which essentially says that if there are no disturbances or noise, then the estimation error converges to zero. If they are nonzero but bounded, then the estimation error converges to a neighborhood of the true value.

Proposition 1: If assumptions **A1-A6** hold, system (3) is uniformly observable, $N \geq N_o$ and $w_k, v_k = 0$, then for all $\hat{x}_0 \in \mathbb{X}_0$, $\|\hat{x}_t - x_t\| \to 0$ as $t \to \infty$.

Proposition 2: Suppose that **A0)**, **A4)** and **A6)** hold, a solution exists to (5) for all $\hat{x}_0 \in \mathbb{X}_0$, $N \geq N_o$, and system (3) is uniformly observable. Then the estimation error $\|\hat{x}_t - x_t\|$ for $t \geq \sigma_{N_o}$ are bounded by $\alpha(\|\delta_\omega + \delta_v\|)$ where $\alpha(\cdot)$ is a K_∞ function.

B. Convergence of the MMAE

We now show that the overall MMAE with a bank of DMHE under reasonable conditions is robust to model parametric uncertainty and that the estimation error converges to a small neighborhood of zero. In what follows, we consider that the process model (3) is bounded-input-bounded-state (BIBS).

Definition 3 (BIBS): System (3) is said to be bounded-input-bounded-state (BIBS) with input (u_t, w_t) if there exist $\gamma_1, \gamma_2 \in \mathcal{K}$ such that, for any $x_0 \in \mathbb{X}_0$, $u_t \in \mathbb{U}_t$, $w_t \in \mathbb{W}_t$

$$\|x_t\| \leq \gamma_1(\|x_0\|) + \gamma_2(\|(u_t, w_t)\|).$$

The next theorem provides conditions for the convergence of the dynamic weights $p_t^{[i]}$. Roughly speaking, it says that the "model" identified is the one that exhibits least output error energy. The proof of this result can be found in [9].

Proposition 3: Let $i^\star \in \{1,\dots,N\}$ be an index of a parameter vector to estimate Θ and let $\mathcal{I} = \{1,\dots,N\} \setminus i^\star$ be an index set. Suppose that there exist positive constants n' and k' such that for all $k \geq k'$ and $n \geq n'$ the following condition holds for all $j \in \mathcal{I}$

$$\frac{1}{n}\sum_{\tau=k}^{k+n-1}(w_t^{i^\star} - \ln \beta_{i^\star}) < \frac{1}{n}\sum_{\tau=k}^{k+n-1}(w_t^{j} - \ln \beta_{j}) \qquad (8)$$

Then $p_t^{[i^\star]} \to 1$ as $t \to +\infty$.

Condition (8) can be viewed as a distinguishability criterion. The following result establishes the convergence of the state estimate $\hat{x}_t$.

Theorem 1: Consider the process model with decimated observations (3) and assume that it is BIBS. Suppose that assumptions **A0-A6** and the distinguishability criterion (8) hold. Then, the state estimation error $\tilde{x}_t := x_t - \hat{x}_t$ converges to a small neighborhood of zero.

V. Simulation Results

In this section we illustrate the robustness and performance of the proposed MMAE algorithm through simulations of artificial patients infected with the HIV-1 infection using model (2).

The first simulation shows the performance of the proposed algorithm for the estimation problem of the state and the unknown parameter κ in 10 sets of data with a fixed MMAE setup with 5 MHE banks. In each simulation, the data is generated from the HIV-1 model with added Gaussian noise and with κ being randomly selected in the interval $[60, 140]$. The κ nominal value for each i-th estimator in the bank is $60 + 20i$, for $i = 0, \dots, 4$. Fig. 2 shows for each simulation, the mean squared error (MSE) of the difference between the estimated state and the state of the process model. From the figure it can be seen that for $\kappa \in [60, 90]$ and $\kappa \in [120, 130]$ the MSE is roughly constant along those intervals. However, for $\kappa \in [90, 120]$ there is a significant different behavior. This might be due to the model's sensitivity to the κ parameter, and also to the MMAE's internal parameters, which might be tuned to perform better with lower κ values. Concerning the parameter κ estimation, in Fig. 3 a grid is presented, in which it is shown for each of the 10 simulations the real κ parameter and the estimated parameter. The black circles are the κ parameters of the internal estimators in the MMAE. The results suggest that the algorithm is able to make reasonable estimations for the parameter value.

In order to make a thorough analysis of this results, one needs to compare them with other estimation methods. A new simulation was run but instead of DMHE's, we used decimated EKF ([14]) for the estimators in the bank. The same initial conditions were applied and both filters in the bank have the following parameters: $\Sigma_{\bar{x}_0} = \text{diag}(1000^2, 3)$ and $\Sigma_\omega^i = \text{diag}(9, 3)$, $R_{\sigma_k} = 150^2$, the initial condition is $x_0 = (1000, 0, 5)$ and the estimated initial condition is $\bar{x}_0 = (500, 0, 0)$, where $\text{diag}(s, n)$ stands for the $n \times n$ matrix with value s in the diagonal. Although very similar in terms of

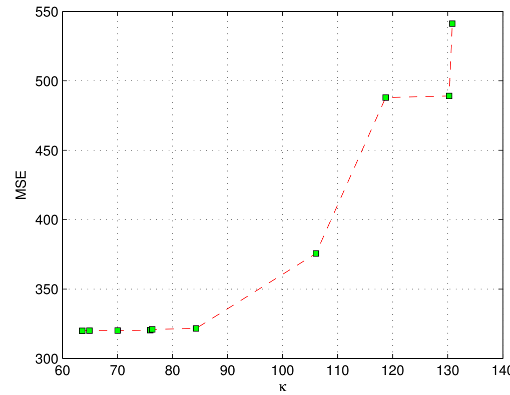

Fig. 2. MSE of the state estimation for each simulation. Each simulation was run with a random κ parameter indicated by the markers in the figure.

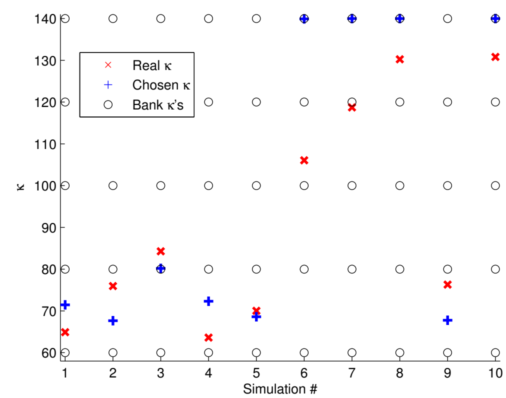

Fig. 3. Real κ parameter and chosen parameter for each simulation. The black circles represent the internal estimators κ parameters.

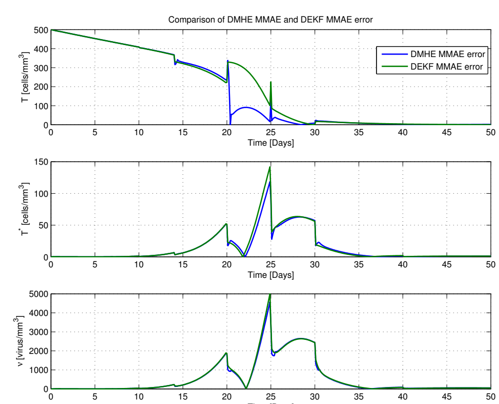

Fig. 4. Comparison between the absolute error of the MMAE using a bank of DMHEs and using a bank of decimated EKFs.

performance for the observable variable, ν, the MMAE with the MHEs performs much better for the variables T and T^* (see Fig. 4).

In the second simulation set (see Figs. 5-6), we consider the case that both β and the production rate of virus by

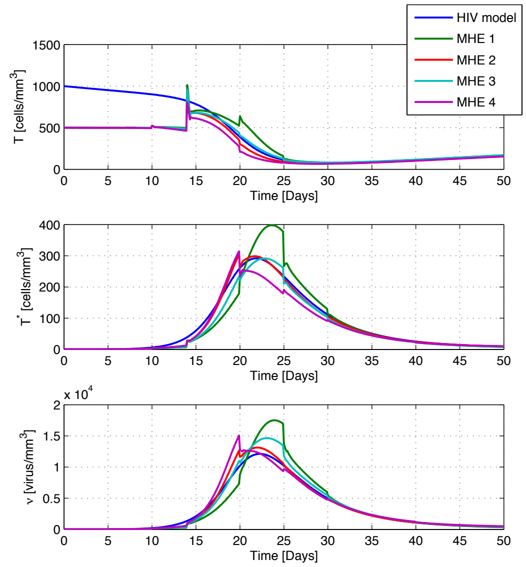

Fig. 5. Evolution of the state of the system and the estimates given by the banks of MHE's.

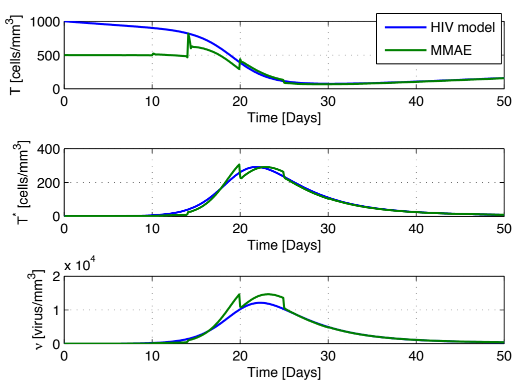

Fig. 6. Evolution of the state of the system and the estimate modeled by the MMAE. We observe that the MMAE is much closer to the model than any of the MHE's in the bank.

infected cells, κ, were not exactly known. In this case, we evaluated the proposed MMAE with a bank of 4 estimators, which parameters are as follows: estimators 1 and 2 have $\kappa = 105$ and estimators 3 and 4 have $\kappa = 120$. Concerning the β value, estimators 1 and 3 have $\beta = 2 \times 10^{-5}$ while estimators 2 and 4 have $\beta = 2.5 \times 10^{-5}$. The real values for β and κ are $\beta = 2.4 \times 10^{-5}$ and $\kappa = 100$. The algorithm is able to converge to the DMHE in the bank with the closest parameters to the real values. In Fig. 6 it can also be observed that the state estimate produced by the MMAE is much smoother than any of the ones from the MHEs in the bank.

VI. Concluding Remarks

This paper addressed the common problem when dealing with dynamics associated with biomedical phenomena: state estimation with non-periodic measurements and parameter uncertainty. We proposed an algorithm to address this problem based on the MMAE algorithm with banks of DMHEs. A comparison with a MMAE algorithm with banks of decimated EKFs was made, where the MMAE with DMHEs performs better. We also observe that the algorithm, if ran with a large number of estimators in the bank, will be very expensive in computational terms. Despite of that, in view of its application to biomedical phenomena, since the interval between two measurements could be days (or even weeks) this problem is not stringent. However, in the general case, some sort of bank design should be considered. Future work would follow this direction, as well as comparing the obtained results in an artificial patient with real data from HIV-1 patients.

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