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Identification of Affine Linear Parameter Varying Models for Adaptive Interventions in Fibromyalgia Treatment

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Abstract

There is good evidence that naltrexone, an opioid antagonist, has a strong neuroprotective role and may be a potential drug for the treatment of fibromyalgia. In previous work, some of the authors used experimental clinical data to identify input-output linear time invariant models that were used to extract useful information about the effect of this drug on fibromyalgia symptoms. Additional factors such as anxiety, stress, mood, and headache, were considered as additive disturbances. However, it seems reasonable to think that these factors do not affect the drug actuation, but only the way in which a participant perceives how the drug actuates on herself. Under this hypothesis the linear time invariant models can be replaced by State-Space Affine Linear Parameter Varying models where the disturbances are seen as a scheduling signal signal only acting at the parameters of the output equation. In this paper a new algorithm for identifying such a model is proposed. This algorithm minimizes a quadratic criterion of the output error. Since the output error is a linear function of some parameters, the Affine Linear Parameter Varying system identification is formulated as a separable nonlinear least squares problem. Likewise other identification algorithms using gradient optimization methods several parameter derivatives are dynamical systems that must be simulated. In order to increase time efficiency a canonical parametrization that minimizes the number of systems to be simulated is chosen. The effectiveness of the algorithm is assessed in a case study where an Affine Parameter Varying Model is identified from the experimental data used in the previous study and compared with the time-invariant model.

I. Introduction

Fibromyalgia (FM) is a chronic pain disorder of neuromuscular origin which seems to disproportionately affect women [2], [17]. Other symptoms include sleep disturbances, gastric problems, fatigue among others. There is good evidence that naltrexone, an opioid antagonist, has a strong neuroprotective role and may be a potential drug for the treatment of FM. Towards this, a low dose of naltrexone intervention was conducted by Dr. Jarred

Younger and colleagues [18] at the Systems Neuroscience and Pain Lab in Stanford University of Medicine. The data was gathered from daily diary self-reports completed by the participants. Deshpande *et al.* [4] used that data to identify input-output auto-regressive exogenous (ARX) linear time-invariant (LTI) models that were used to extract useful information about the effect of the drug on pain symptoms. Based on these models the participants of the intervention were classified as responders or non responders to the drug. Deshpande *et al.* also applied these models to design hybrid predictive controllers that can automatically determine the dosage of naltrexone for each patient.

FM is unique among other medical disorders in that its etiology (i.e. causal mechanism) is not well-understood [12]. Hence, there is lack of first-principles models explaining FM symptoms; furthermore, the modeling problem is made difficult given that many of the participants do not experience all of the symptoms. Therefore, there is great interest in understanding the underlying mechanisms of FM and significant insights may be obtained from a dynamical systems perspective. In Deshpande *et al.*, the FM symptoms are considered as the output, drug and placebo as primary inputs and several factors such as anxiety, stress, mood, etc., secondary inputs of the ARX LTI model (see [4] for description of the data). However, it seems reasonable to think the factors considered as secondary inputs are not the cause of FM neither affect the drug actuation. They only influence the way a subject perceives the FM symptoms. For instance, the same individual may report different levels of FM symptoms for different levels of anxiety. Under this hypothesis, the drug actuation could be described by an Affine Linear Parameter Varying (A-LPV) system, i.e, by an affine system where the parameters are functions of scheduling signals that, in this case, could be the secondary inputs identified by Deshpande *et al.*. Thus, A-LPV models could be estimated instead to describe the effect of naltrexone.

LPV system identification has been been an active area of research in the recent years. In fact, many real systems can be approximated by LPV models which increased the interest for this framework in many different areas such as aerospace [10], automotive [11], traffic management [9], robotics [1], bio-engineering [13], gas transportation networks [7], web applications [14], etc.. Fundamental theoretic aspects on LPV modeling and identification can be seen in [15] and recent approaches to the problem are reported in [8].

In this paper the FM symptoms will be modeled by an affine state-space LPV model where only the output equation parameters are dependent of the secondary inputs considered by Deshpande *et al.*. The model dynamics is LTI reflecting the previous referred assertion that secondary inputs do not affect the drug actuation but only the way that a subject perceives the FM symptoms.

The paper is organized as follows: Section II presents the model and Section III formulates the identification algorithm. In Section IV this algorithm is used to estimate an A-LPV model with the clinical data clinical data used by Deshpande *et al.*. The A-LPV and the ARX LTI models are compared. A transfer function (TF) describing the effect of naltrexone on FM is also derived from this model and it is compared with the TFs derived by Deshpande *et al.*. Conclusions and future work are presented in Section V.

II. A-LPV model

It is well known that the output of a linear system is zero when all inputs are zeros. Consequently, a nonzero output of FM linear model implies that at least a nonzero input. If the model is driven by the naltrexone, placebo and other secondary inputs like anxiety, stress, mood, etc., then, according to this model, the FM symptoms are due to the secondary inputs. Despite the cause of FM is currently unknown it will be admitted that the secondary

effects will not be responsible for this disorder although they may be associated with it. As a result, a constant accounting for the presence of a baseline of FM will be added to the output of the model transforming it into an affine model. On the other hand, reflecting a possible association between FM and the secondary inputs, these will be seen as scheduling signals that modulate model parameters. Assuming the hypothesis that the drug and placebo actuation dynamics is time invariant a state-space model will be adopted with an LTI state equation and an affine LPV output equation, i.e.,

$$\boldsymbol{x}(k+1)=\boldsymbol{A}\boldsymbol{x}(k)+\boldsymbol{B}\boldsymbol{u}(k) \quad (1)$$

$$y(k)=\mathscr{C}[\boldsymbol{p}(k)\boldsymbol{x}(k)+\mathscr{G}[\boldsymbol{p}(k)], \quad (2)$$

where $y(k) \in \mathbb{R}$ is the FM symptoms, $\boldsymbol{u}(k) \in \mathbb{R}^2$ denotes the drug and placebo dosages, $\boldsymbol{x}(k) \in \mathbb{R}^{n_x}$, $\boldsymbol{p}(k) \in \mathbb{R}^{n_p}$ is the scheduling signal consisting in a set of selected secondary inputs, and, for the sake of simplicity, $\boldsymbol{C}[\boldsymbol{p}(k)]$, and $\mathscr{G}[\boldsymbol{p}(k)]$, are linear combinations of basis functions f_i, $i = 0, \ldots, n_f$, i.e.,

$$\mathscr{C}[p(k)]=\sum_{i=0}^{n_f} C_i f_i[p(k)] \quad (3)$$

$$\mathscr{G}[\boldsymbol{p}(k)]=\sum_{i=0}^{n_f} g_i f_i[p(k)], \quad (4)$$

where $\boldsymbol{C}_i=\begin{bmatrix} c_{i,1} & \cdots & c_{i,n_x} \end{bmatrix} \in \mathbb{R}^{1\times n_x}$, $i = 0, \ldots, n_f$, $g_i \in \mathbb{R}$, $i = 0, \ldots, n_f$ and $f_i(p)$ are functions p: $\mathbb{R}^{n_p} \to \mathbb{R}$.

III. A-LPV system identification algorithm

Several algorithms for state-space LPV system identification algorithms can be found in the existing literature. However, as far as the authors know, all assume a full dependence on the scheduling signal and they have to be modified to handle A-LPV models. On the other hand, most of them were designed for large sets of stationary data. Unfortunately such large data sets are impracticable for the FM problem and stationarity cannot be ensured as well. As a result a new algorithm had to be developed. A subspace identification algorithm was first considered. However, likewise most subspace LPV identification algorithms, it requires large data sets. Since the objective is to estimate models for applying control techniques an output algorithm was developed. This algorithm minimizes the cost function

$$V=\frac{1}{2}\sum_{k=1}^{N} e^2(k,\theta), \quad (5)$$

where $e(k, \boldsymbol{\theta})$ is the error between the measured and model outputs and

$$\boldsymbol{\theta}=\begin{bmatrix} \mathrm{vec}\{\boldsymbol{A}\}^T & \mathrm{vec}\{\boldsymbol{B}\}^T & \boldsymbol{C}_0 & \cdots & \boldsymbol{C}_{n_f} & \boldsymbol{G} \end{bmatrix}^T.$$

with $\boldsymbol{G}=\begin{bmatrix} g_0 & \cdots & g_{n_f} \end{bmatrix} \in \mathbb{R}^{n_f+1}$. Here, vec{·} is the operator which forms a vector from a matrix by stacking its columns on top of one another. Since state-space models are not unique, a decision had to be made concerning its parametrization. The alternatives were between fully or minimally parameterized structures. Fully parameterized structures lead to better numerically conditioned models but, as they are over parameterized, the optimization algorithm needs some mechanisms to deal with this over parametrization [16]. On the other hand, the derivatives in order to the elements of $\boldsymbol{A}$ and $\boldsymbol{B}$ are calculated via the simulation of LTI dynamical systems. As there are n_x^2 elements in $\boldsymbol{A}$ and $2n_x$ in B, it would be necessary to simulate at least $(n_x+1)^2 - 1$ systems.

The choice was thus the minimal parameterized structure

$$\boldsymbol{A}=\begin{bmatrix} -a_1 & 1 & 0 & \cdots & 0 & 0 \\ -a_2 & 0 & 1 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ -a_{n_x-2} & 0 & 0 & \cdots & 1 & 0 \\ -a_{n_x-1} & 0 & 0 & \cdots & 0 & 1 \\ -a_{n_x} & 0 & 0 & \cdots & 0 & 0 \end{bmatrix} \quad (6)$$

$$\boldsymbol{B}=\begin{bmatrix} \boldsymbol{b}_1^T & \boldsymbol{b}_2^T & \cdots & \boldsymbol{b}_{n_x-2}^T & \boldsymbol{b}_{n_x-1}^T & \boldsymbol{b}_{n_x}^T \end{bmatrix}^T, \quad (7)$$

with

$$\boldsymbol{b_i}=\begin{cases} \begin{bmatrix} 0 & b_i \\ 1 & b_i \end{bmatrix}, & i=1,\ldots,n_x-1 \\ \begin{bmatrix} 1 & b_i \end{bmatrix}, & i=n_x. \end{cases} \quad (8)$$

In this parametrization $\boldsymbol{\theta}$ becomes

$$\boldsymbol{\theta}=\begin{bmatrix} a_1 & \ldots & a_{n_x} & b_1 & \ldots & b_{n_x} & \boldsymbol{C}_0 & \ldots & \boldsymbol{C}_{n_f} & \boldsymbol{G} \end{bmatrix}. \quad (9)$$

Also equation (2) may be rewritten as

$$y(k)=\boldsymbol{\varphi}(k,\boldsymbol{\theta}_{n\ell})\boldsymbol{\theta}_\ell, \quad (10)$$

with

$$\theta_\ell=\begin{bmatrix} \boldsymbol{C}_0 & \cdots & \boldsymbol{C}_{n_f} & \boldsymbol{G} \end{bmatrix}^T, \quad (11)$$

$$\boldsymbol{\theta}_{n\ell}=\begin{bmatrix} a_1 & \cdots & a_{n_x} & b_1 & \cdots & b_{n_x} \end{bmatrix}^T, \quad (12)$$

$$\boldsymbol{\varphi}(k,\boldsymbol{\theta}_{n\ell})=\boldsymbol{F}^T[\boldsymbol{p}(k)] \otimes [\boldsymbol{x}^T(k)|1], \quad (13)$$

where

$$\boldsymbol{F}[\boldsymbol{p}(k)]=\begin{bmatrix} f_0[\boldsymbol{p}(k)] & \cdots & f_{n_f}[\boldsymbol{p}(k)] \end{bmatrix}, \quad (14)$$

and $\otimes$ stands for the Kronecker product operator [3]. From (10) it is clear that $y(k)$ is a linear function of θ_ℓ. As a result, the minimization of V defined in (5) is a separable nonlinear least squares problem (SNLS). From Theorem 2.1 of [5] and Theorem 1 of [6], V can be minimized by alternatively fixing $\boldsymbol{\theta}_{n\ell}=\begin{bmatrix} a_1 & \cdots & a_{n_x} & b_1 & \cdots & b_{n_x} \end{bmatrix}^T$ and finding $\boldsymbol{\theta}_{n\ell}$ by simple linear least squares estimator. Then $\boldsymbol{\theta}_\ell$ is found by any nonlinear minimization method such as the Gauss-Newton gradient method with $\boldsymbol{\theta}_\ell$ fixed. This algorithm isn't very efficient but it converges to a minimum of V.

Given that the linear least squares estimator has an analytic expression, a more efficient approach is to take $\boldsymbol{\theta}_\ell$ as a function of $\boldsymbol{\theta}_{n\ell}$. Thus, the minimization of V becomes a nonlinear least squares problem in a reduced space only involving $\boldsymbol{\theta}_{n\ell}$ This is the so called Variable Projection Method and it was first proposed by Golub and Pereyra [5]. Defining

$$\boldsymbol{Y}=\begin{bmatrix} y(1) & \cdots & y(N) \end{bmatrix}, \quad (15)$$

$$\boldsymbol{\Phi}(\boldsymbol{\theta}_{n\ell})=\begin{bmatrix} \boldsymbol{\varphi}^T(1,\boldsymbol{\theta}_{n\ell}) & \cdots & \boldsymbol{\varphi}^T(N,\boldsymbol{\theta}_{n\ell}) \end{bmatrix}^T, \quad (16)$$

then $\boldsymbol{Y} = \boldsymbol{\Phi}(\boldsymbol{\theta}_{n\ell})\,\boldsymbol{\theta}_\ell$ and the linear least squares estimator of $\boldsymbol{\theta}_\ell$ is

$$\hat{\boldsymbol{\theta}}_\ell=\boldsymbol{\Phi}^\dagger(\boldsymbol{\theta}_{n\ell})\,\boldsymbol{Y}, \quad (17)$$

where $\boldsymbol{\Phi}^\dagger$ is the pseudoinverse of $\boldsymbol{\Phi}$. Replacing $\boldsymbol{\theta}_\ell$ by (17), the cost function V becomes

$$V=\frac{1}{2}\left[\boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}(\boldsymbol{\theta}_{n\ell})\,\boldsymbol{Y}\right]^T\left[\boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}(\boldsymbol{\theta}_{n\ell})\,\boldsymbol{Y}\right], \quad (18)$$

where $\boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}(\boldsymbol{\theta}_{n\ell})$ is the operator of the orthogonal projection into the orthogonal complement of the column-space of $\boldsymbol{\Phi}(\boldsymbol{\theta})$, given by

$$\boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}(\boldsymbol{\theta}_{n\ell})=\boldsymbol{I}_N-\boldsymbol{\Phi}(\boldsymbol{\theta}_{n\ell})\boldsymbol{\Phi}^\dagger(\boldsymbol{\theta}_{n\ell}). \quad (19)$$

In [5], Golub and Pereyra derived the gradient and the Hessian approximation of (18) to be used in a Gauss-Newton minimization algorithm. In [6], Linda Kaufmann simplified Golub and Pereyra derivative formulas. Using Linda Kaufmann formulas $\boldsymbol{\theta}_{n\ell}$ is updated by

$$\boldsymbol{\theta}_{n\ell}^{(i+1)}=\boldsymbol{\theta}_{n\ell}^{(i)}-\left[\boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}\left(\boldsymbol{\theta}_{n\ell}^{(i)}\right)\mathscr{H}\left(\boldsymbol{\theta}_{n\ell}^{(i)},\boldsymbol{\Phi}^\dagger\left(\boldsymbol{\theta}_{n\ell}^{(i)}\right)\,\boldsymbol{Y}\right)\right]^\dagger\boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}\left(\boldsymbol{\theta}_{n\ell}^{(i)}\right)\,\boldsymbol{Y} \quad (20)$$

with

$$\mathscr{H}(\boldsymbol{\theta}_{n\ell}, \boldsymbol{\beta}, \boldsymbol{\theta}_{\ell}) = [\mathscr{H}_{\alpha}(\boldsymbol{\theta}_{n\ell}, \boldsymbol{\theta}_{c}) | \mathscr{H}_{\beta}(\boldsymbol{\theta}_{n\ell}, \boldsymbol{\theta}_{c})], \quad (21)$$

where $\boldsymbol{\theta}_c = \begin{bmatrix} \boldsymbol{C}_0 & \cdots & \boldsymbol{C}_{n_f} \end{bmatrix}$, and $\mathscr{H}_{\alpha}(\boldsymbol{\theta}_{n\ell}, \boldsymbol{\theta}_c)$ and $\mathscr{H}_{\beta}(\boldsymbol{\theta}_{n\ell}, \boldsymbol{\theta}_c)$ are N × n_x matrices whose columns are

$$(\mathscr{H}_{\alpha})_i = -\begin{bmatrix} \left\{\boldsymbol{F}^T[\boldsymbol{p}(1)] \otimes \frac{\partial \boldsymbol{x}^T(1)}{\partial a_i}\right\} \boldsymbol{\theta}_c \\ \vdots \\ \left\{\boldsymbol{F}^T[\boldsymbol{p}(N)] \otimes \frac{\partial \boldsymbol{x}^T(N)}{\partial a_i}\right\} \boldsymbol{\theta}_c \end{bmatrix} \quad (22)$$

and

$$(\mathscr{H}_{\beta})_i = -\begin{bmatrix} \left\{\boldsymbol{F}^T[\boldsymbol{p}(1)] \otimes \frac{\partial \boldsymbol{x}^T(1)}{\partial b_i}\right\} \boldsymbol{\theta}_c \\ \vdots \\ \left\{\boldsymbol{F}^T[\boldsymbol{p}(N)] \otimes \frac{\partial \boldsymbol{x}^T(N)}{\partial b_i}\right\} \boldsymbol{\theta}_c \end{bmatrix}. \quad (23)$$

Defining $w(k)$ as the first component of $x(k)$, i.e., $w(k) = x_1(k)$, then, from (1) and (6)–(8),

$$w(k) = -\sum_{i=1}^{n_x} a_i w(k-j) + \sum_{j=1}^{n_x} \boldsymbol{b_i} \boldsymbol{u}(k-i), \quad (24)$$

and

$$\frac{\partial x(k)}{\partial a_i} = \begin{bmatrix} \mathbf{1} & 0 & \cdots & 0 \\ 0 & -a_2 & \ddots & -a_n \\ \vdots & \ddots & \ddots & \vdots \\ 0 & -a_n & \cdots & 0 \end{bmatrix} \begin{bmatrix} \frac{\partial w(k)}{\partial a_i} \\ \frac{\partial w(k-\mathbf{1})}{\partial a_i} \\ \cdots \\ \frac{\partial w(k-n_x+1)}{\partial a_i} \end{bmatrix} + \begin{bmatrix} 0 & \cdots & 0 \\ 1(i-2) & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & 1(i-n_x) \end{bmatrix} \begin{bmatrix} w(k+1-i) \\ w(k+2-i) \\ \vdots \\ w(k+n_x-1-i) \end{bmatrix}, \quad (25)$$

where $\mathbf{1}(\tau)$ is the step function defined as

$$1(\tau) = \begin{cases} 0, & \tau < 0 \\ 1, & \tau \geq 0. \end{cases} \quad (26)$$

The derivatives $\partial \boldsymbol{x}(k)/\partial b_i$ have a similar expression but with $\partial w(\cdot)/\partial a_i$ and $w(\cdot)$ replaced by $\partial w(\cdot)/\partial b_i$ and $u_2(\cdot)$, respectively. From (24),

$$\frac{\partial w(k-\ell)}{\partial a_i} = w_a(k-i+1-\ell), \quad (27)$$

were

$$w_a(k) = -\sum_{j=1}^{n_x} a_j w_a(k-j) - w(k-1). \quad (28)$$

Similarly,

$$\frac{\partial w(k-\ell)}{\partial b_i} = w_b(k-i+1-\ell), \quad (29)$$

with

$$w_b(k) = -\sum_{j=1}^{n_x} a_j w_b(k-j) + u(k-1). \quad (30)$$

Consequently, each iteration of a gradient algorithm only requires the simulation of three systems.

The identification algorithm can now be outlined as follows:

Algorithm 1

SNLS A-LPV System Identification

- Initialize $\boldsymbol{\theta}_{n\ell}^{(0)}$
- $\boldsymbol{\theta}_{\ell}^{(0)} \leftarrow \boldsymbol{\Phi}^{\dagger}\left(\boldsymbol{\theta}_{n\ell}^{(0)}\right) \boldsymbol{Y}$
- Set $i = 0$
- Repeat
  - $K \leftarrow 1$
  - Set

    $$\Delta_{\theta_{n\ell}} = \left[\boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}\left(\theta_{n\ell}^{(i)}\right) \mathrm{H}\left(\theta_{n\ell}^{(i)}, \boldsymbol{\Phi}^{\dagger}\left(\theta_{n\ell}^{(i)}\right) Y\right)\right]^{\dagger} \boldsymbol{\Pi}_{\boldsymbol{\Phi}}^{\perp}\left(\theta_{n\ell}^{(i)}\right) Y$$

  - Repeat
    - Set $\boldsymbol{\theta}_{n\ell} = \boldsymbol{\theta}_{n\ell}^{(i)} - \Delta_{\boldsymbol{\theta}_{n\ell}} / K$
    - $K \leftarrow 2K$
  - Until $V(\boldsymbol{\theta}_{n\ell}) < V(\boldsymbol{\theta}_{n\ell}^{(i)})$

Until convergence.

IV. Case Study

In this section the A-LPV identification algorithm is applied to the data used by Deshpande *et al.* in [4]. This data was gathered from a representative participant of the pilot study conducted by Dr Jarred Young and colleagues [18]. The time series is split into baseline, placebo, drug and washout phases with the number of data points equal to 80 sampled daily (see Fig. 1). After a preliminary study, Deshpande *et al* concluded that Anxiety, Stress and Mood were the disturbances that, together with the primary inputs, drug and placebo, help to

better explain the FM symptoms. Based on this, ARX LTI models using the drug and placebo dosages together with combinations of these disturbances as inputs were identified and compared.

In this work, A-LPV models were identified using the SNLS A-LPV system identification algorithm described in the previous section. These were second order models driven by the naltrexone and placebo dosages with the combinations of disturbances considered by Deshpande *et al* as scheduling signals. The scheduling signal was mean-subtracted because it is assumed that the normal state of a patient corresponds to the mean value of these signals. The basis function were $f_0[p(k)] = 1$, and $F_i[p(k)] = p_i(k)$, $i = 1, \ldots, n_p$ which correspond to an A-LPV model with affine dependence on the scheduling signal. The following models were estimated:

1. Model 1 (input signals: Drug and Placebo, scheduling signal: Anxiety)
2. Model 2 (input signals: Drug and Placebo, scheduling signals: Anxiety, Stress)
3. Model 3 (input signals: Drug and Placebo, scheduling signals: Anxiety, Stress, Mood)

Table I compares the percentage of fit (*PF*) of the A-LPV and LTI ARX models estimated by Deshpande *et al.*. Here, *PF* is defined as

$$PF = 100 \times \left(1 - \frac{\| \boldsymbol{Y} - \widehat{\boldsymbol{Y}} \|}{\sigma(\boldsymbol{Y})}\right) \quad (31)$$

where $\boldsymbol{Y}$ is the vector of the measured outputs, $\hat{\boldsymbol{Y}}$ the vector of simulated outputs and $\sigma(\cdot)$ is the standard deviation operator. It can be seen from this table that the indexes of fit of the A-LPV models are significantly superior. This can be confirmed in Fig. 2 and Fig. 3.

Despite having good indexes of fit, the A-LPV model 1 and model 2 are unstable, with the unstable eigenvalue close to 1. Model 3 is stable but also with an eigenvalue close to 1. The existence of this unitary eigenvalue may be explained by the fact observed in Fig. 1 that, after the vanishment of the drug dosage, the FM signal is kept almost constant at a value around 8, denoting an integrating feature. In a stable model the output would converge to the affine constant (63.7 for model M1, 66 for model M2 and 51.4 for model M3). This eigenvalue is visible in Fig. 4 that shows the step responses of the LTI part of the estimated models M1, M2 and M3 for the naltrexone input.

The integrating feature of the A-LPV models means that the symptoms of the chosen participant did not return to the baseline severity during washout. This suggests that there is potentially continued beneficial action following cessation of the drug for this participant. This agrees with the analyses on the outcome variables of Dr Jarred Younger and colleagues study that revealed no difference between drug and washout [18] for the group of drug responders. As a result, it may be argued that if the washout phase is removed from the identification data the integrating feature of the model could disappear and this would lead to a better fitting in the drug phase. The data of the washout phase was thus removed and new A-LPV models (A-LPV2) were identified. In Fig. 5 which displays the step responses of LTI part of these models for the NLD input it can be seen that they are all stable. On the other hand Table II shows that A-LPV2 models have a slightly better accuracy than the former A-LPV models (A-LPV1). However, the accuracy improvement is not significant indicating the existence numerical of problems in the identification algorithm. These problems are the lack of excitability of the input signal. Fig. 6 compares the simulated FM of model M3 with the measured signal. The fit is very good before the washout phase. Due

to the model stability, the simulated signal converges to the baseline in the washout phase. In here the system is better described by the A-LPV1 model which suggests that a piecewise A-LPV model would perform better.

It can also be seen in Table II that the A-LPV2 models have time constants and rising and settling times greater than the ARX LTI models estimated by Desphande *et al*. However this is compensated by a significant increase in the absolute value of the gain which causes that a certain decrease in the FM signal is reached faster with the A-LPV model for the same dose of naltrexone. This is illustrated in Fig. 7.

V. Conclusions and future work

In this paper a state-space A-LPV model structure was proposed to describe the effect of naltrexone on FM symptoms. This model is driven by the drug and placebo dosages. Additional secondary factors such as anxiety, stress and mood are seen as a scheduling signal only acting at the parameters of the output equation. An algorithm for identifying such a model was developed. This algorithm minimizes a quadratic criterion of the output error. Since this error is a linear function of some parameters, the A-LPV system identification is formulated as a SNLS problem. The A-LPV and LTI approach were compared in a case study where A-LPV and ARX LTI models were identified from clinical data. The A-LPV models have better accuracy. However they had an eigenvalue close to 1, denoting an integrating feature indicating potentially continued beneficial action following cessation of the drug. In order to improve the model fit in the actuation phase the washout phase was removed from the identification data. New A-LPV models were identified. They were all stable but the incease of accuaracy was not significant. The step responses of LTI part these models for the naltrexone input was compared with the correspondent step responses of the ARX LTI models. Despite having slower time constants the A-LPV models are more responsive due to their higher gain. A cross validation of the models could not be done because the available data set is small and it had to be entirely used as identification data. In the future, hybrid MPC controllers will be developed based on the identified models and then they will be compared with the controllers proposed by Desphande *et al*. In a first step this can be done in a simulated environment but experiments in real cases supervised by specialized physicians will be also considered. The case study phase suggests that piecewise A-LPV models could be a better description for the naltrexone actuation. On the other hand, there are experimental evidences that pain thresholds increase after the naltrexone administration [18]. These factors will be considered in the model. Finally lack of excitation of the input signals caused numerical problems in the identification algorithm. This problem will be also addressed in the future.

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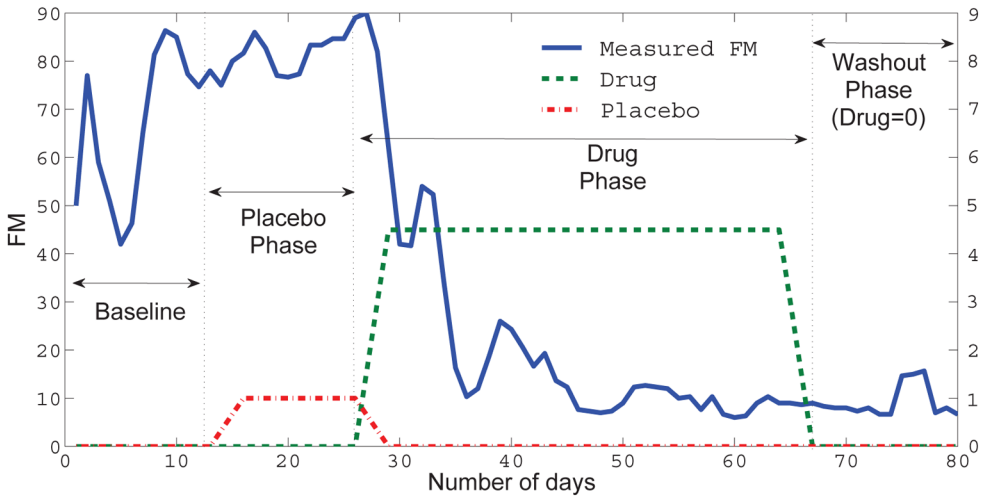

Fig. 1.
Measured FM signal versus Drug and Placebo dosages.

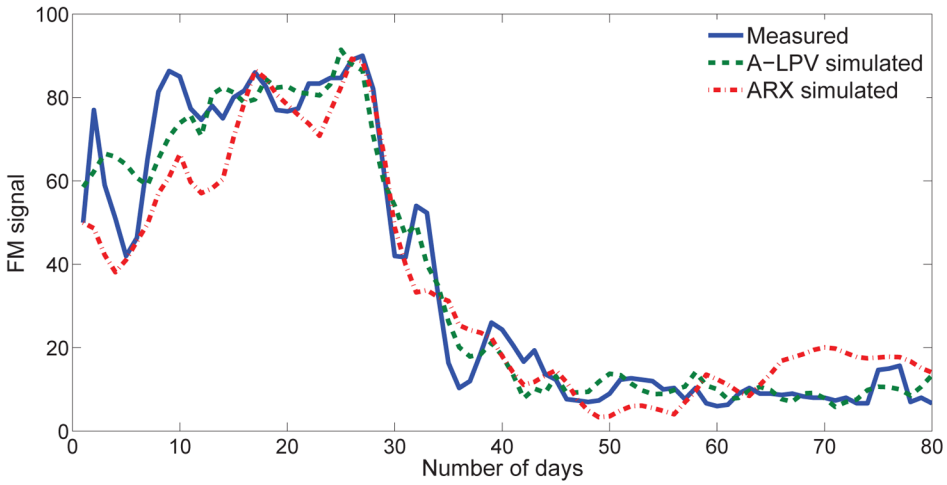

Fig. 2.

Comparison of estimated versus measured FM symptoms output for A-LPV and ARX Models 3 (anxiety, stress, mood as scheduling signal in the A-LPV model and as inputs in the ARX model).

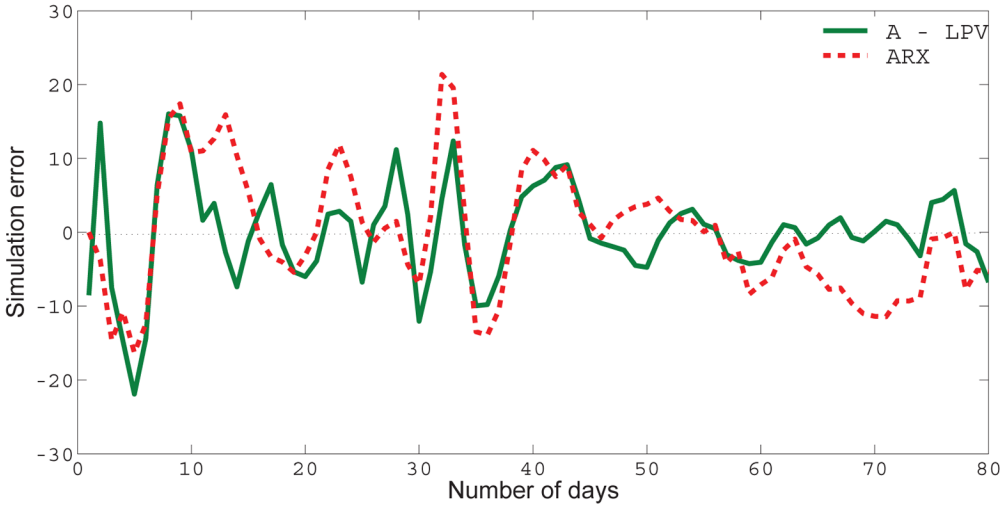

Fig. 3.
Comparison of simulation errors of A-LPV and ARX Models 3 (anxiety, stress, mood as scheduling signal in the A-LPV model and as inputs in the ARX model).

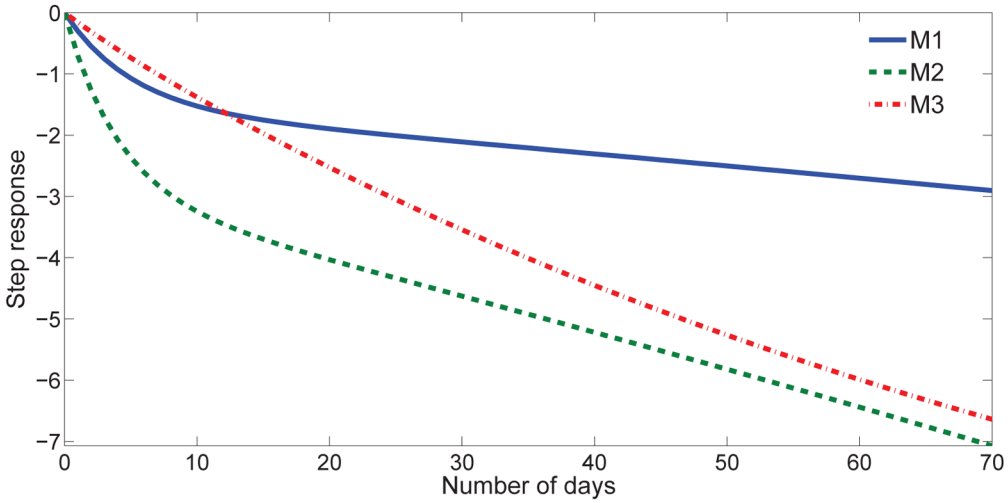

Fig. 4.
LTI part of the estimated A-LPV models step responses for the drug-FM symptoms.

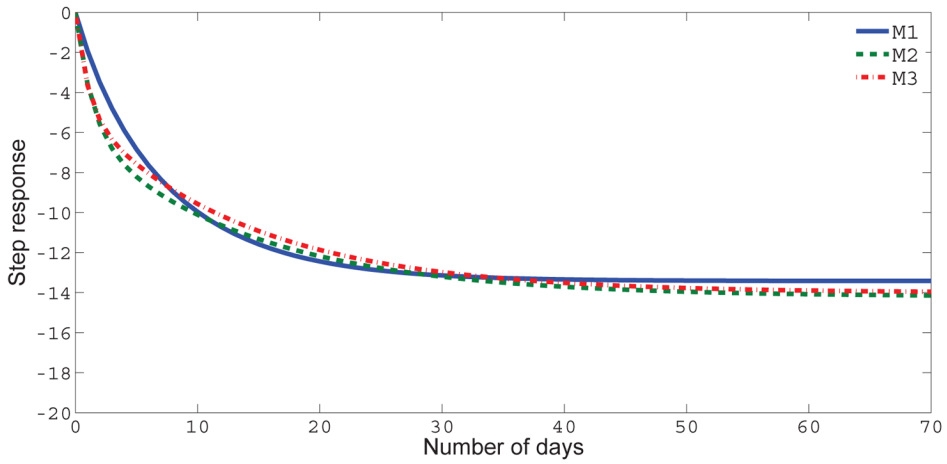

Fig. 5.
LTI part of the second estimated A-LPV models step responses for the drug-FM symptoms.

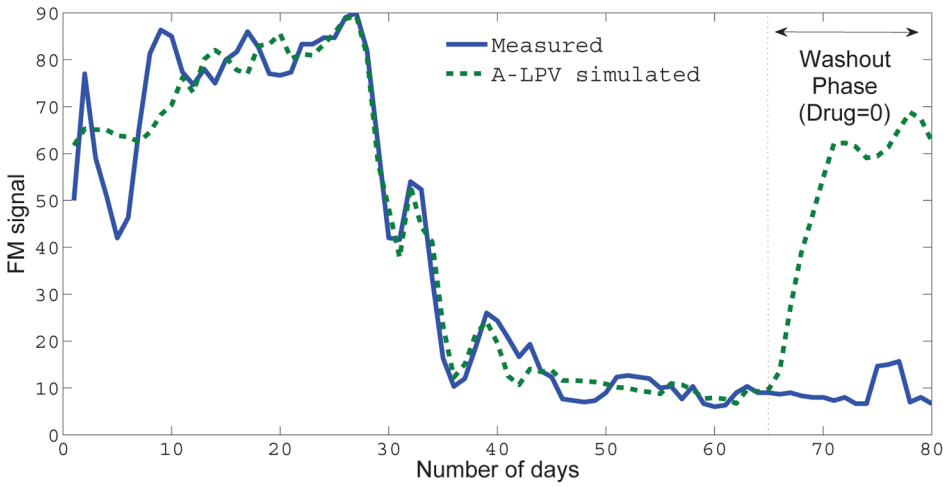

Fig. 6.
Comparison of estimated versus measured FM symptoms output for the second estimated A-LPV Models 2 (anxiety, stress, mood as scheduling).

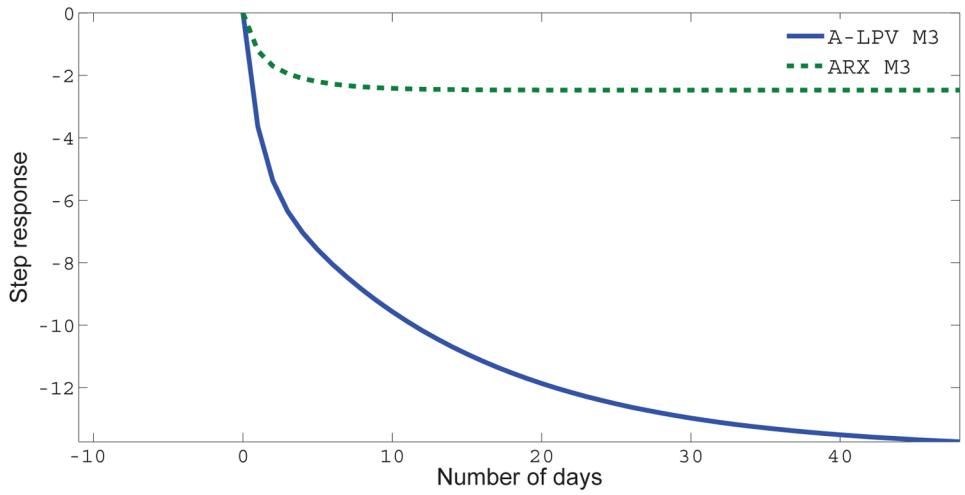

Fig. 7.
Drug-FM step responses of the A-LPV (second estimated) and ARX models.

TABLE I

% fit of A-LPV and LTI ARX models.

Model	1	2	3
A-LPV	76.9	77.9	78.9
ARX	64.7	71.8	73.9

TABLE II

Summary of the second and first estimated A-LPV models (A-LPV2 and A-LPV1, respectively) and ARX models.

Model Structure	Model	% fit	K_p	τ	ζ	τ_a	T_r (days)	T_s (days)
A-LPV2	1	75.8	−13.43	4.06	1.2	2.66	16.8	30.3
	2	78.1	−14.19	4.46	1.74	6.27	24.5	47.8
	3	78.7	−14.02	3.74	1.97	5.38	25.5	48
A-LPV1	1	72.5	—	—	—	—	—	—
	2	77.7	—	—	—	—	—	—
	3	78.7	—	—	—	—	—	—
ARX	1	64.7	−1.02	2.09	1.50	15.30	0.43	25.6
	2	71.8	−3.11	1.82	1.24	0.22	7.53	14.38
	3	73.9	−2.47	1.57	1.26	1.96	5.12	11.49

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