A Control Engineering Approach for Designing an Optimized Treatment Plan for Fibromyalgia

by

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ABSTRACT

There is increasing interest in the medical and behavioral health communities towards developing effective strategies for the treatment of chronic diseases. Among these lie adaptive interventions, which consider adjusting treatment dosages over time based on participant response. Control engineering offers a broad-based solution framework for optimizing the effectiveness of such interventions. In this thesis, an approach is proposed to develop dynamical models and subsequently, hybrid model predictive control schemes for assigning optimal dosages of naltrexone, an opioid antagonist, as treatment for a chronic pain condition known as fibromyalgia.

System identification techniques are employed to model the dynamics from the daily diary reports completed by participants of a blind naltrexone intervention trial. These self-reports include assessments of outcomes of interest (e.g., general pain symptoms, sleep quality) and additional external variables (disturbances) that affect these outcomes (e.g., stress, anxiety, and mood). Using prediction-error methods, a multi-input model describing the effect of drug, placebo and other disturbances on outcomes of interest is developed. This discrete time model is approximated by a continuous second order model with zero, which was found to be adequate to capture the dynamics of this intervention. Data from 40 participants in two clinical trials were analyzed and participants were classified as responders and non-responders based on the models obtained from system identification.

The dynamical models can be used by a model predictive controller for automated dosage selection of naltrexone using feedback/feedforward control actions in the presence of external disturbances. The clinical requirement for categorical (i.e., discrete-valued) drug dosage levels creates a need for hybrid model predictive control (HMPC). The controller features a multiple degree-of-freedom formulation that enables the user to adjust the speed of setpoint tracking, measured disturbance

rejection and unmeasured disturbance rejection independently in the closed loop system. The nominal and robust performance of the proposed control scheme is examined via simulation using system identification models from a representative participant in the naltrexone intervention trial. The controller evaluation described in this thesis gives credibility to the promise and applicability of control engineering principles for optimizing adaptive interventions.

Dedicated to the memory of my Grandfathers

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INTRODUCTION

1.1 Motivation

Chronic and relapsing diseases such as diabetes, hypertension, mental disorders, substance abuse, HIV/AIDS and cancer are among the leading causes of human suffering and mortality worldwide, with the health care costs running in trillions of dollars [1]. Traditional medical practice is based on treatment plans designed for a typical or an average response where drug dosages are assigned without considering an individual's dynamics and optimal dosage criteria. Many of these dosage strategies are inspired from the acute care model and in spite of effective drugs, are not necessarily efficient for long lasting or chronic disorders. There has been increased interest in efficient strategies to treat chronic diseases, and in particular for more personalized medicine by taking into account the characteristics of the individual and their response to the treatment in presence of external disturbances [2, 3]. A control system paradigm, using models describing the dynamics and predictive control to assign drug dosages, is expected to result in more efficient treatment plans which will minimize waste and maximize effectiveness of the treatment.

The use of adaptive dosage strategies, where adapting dosages is based on participant response over time, is the key motivation for use of control systems. Concepts from control theory can be used as tools for transforming the state of a system to a desired condition; these can be applied, under certain conditions, to any phenomena described as a dynamical system. Traditionally, typical applications have been in areas where the physics of the system is either completely or partially understood (e.g., by using principles such as conservation of energy) and/or the system is inanimate like in industrial and process systems, aerospace, robotics, power sys-

tems and electronics. Considerable interest has been seen in past few decades for application of control in unconventional areas like biology and medicine [2, 4, 3], social and behavioral science [5, 6, 7] and supply chains and economics [8, 9]. In this thesis, we address the application of control engineering principles for optimizing a treatment used for chronic pain disorder known as fibromyalgia [10, 11, 12]. We approach this problem from a systems and controls point-of-view where the *systems* thinking is used to improve disorder diagnosis and its treatment. First, we build models using secondary data analysis on information collected from clinical trials to understand the dynamics of a drug, known as naltrexone, on fibromyalgia symptoms; then, we use predictive control techniques to find the best optimal dosage plan and demonstrate, using simulation on estimated models, that the required performance can be achieved under model error and in the presence of constraints.

1.2 Fibromyalgia - an Introduction

Fibromyalgia Syndrome (also referred to as FM or FMS) is a medical disorder characterized by chronic widespread pain. The characteristic symptoms of FM are diffuse musculoskeletal pain and sensitivity to mechanical stimulation at soft tissue tender points [13, 14]. Other primary symptoms of FM include fatigue, sleep disturbance, joint stiffness, bowel and bladder abnormalities, numbness, tingling, and cognitive or mood dysfunction. It is largely believed that various behavioral and psychological factors such as stress and anxiety are associated with symptoms of FM [15], however they are unlikely the cause. The core symptom of FM is made up of overall daily pain and fatigue although most of the sufferers also complain of poor sleep quality. It is also important to note that not all individuals suffering from FM experience all associated symptoms.

While no specific laboratory test can confirm FM, most patients present with a history of widespread pain and fatigue conditions. Another important issue with FM is that its etiology is largely unknown and without any scientific consensus [16]. FM is a form of chronic disorder that can be more easily grouped with disorders due to break down of the physiology of the body, as a consequence of any number of reasons. Diabetes, epilepsy, hypertension, FM are very distinct from other disorders such as those caused by infections like HIV/AIDS or tuberculosis; these infectious diseases follow a mechanism which can be traced back and represented mathematically with relative ease as compared to complex chronic disorders resulting from physiological problems.

As the cause(s) for FM are unknown, uncertain or disputed and due to its chronic nature, it has been difficult to single out a specific type of treatment for this disease. There is a good evidence to suggest that naltrexone, an opioid antagonist, has a strong neuroprotective role [10, 17] and may be a potentially effective drug for a disease like FM which has a clear neuromuscular origin. A low dose naltrexone (LDN) intervention was conducted by Dr. Jarred Younger and colleagues at the Stanford Systems Neuroscience and Pain Lab (SNAPL), Stanford University School of Medicine. In this thesis, experimental data from these clinical trials conducted on a sample population ($N_{par} = 40$) is evaluated for a control engineering based optimized intervention.

1.3 Adaptive Interventions and Personalized Medicine

With recent understanding and advancements in genetics (like the human genome project), metabolism and pharmacology, there has been increasing interest in the medical community toward developing improved strategies for treating disease by relying on personalized medicine [18]. Similarly in the behavioral sciences, adap-

tive interventions is the umbrella term used to describe the use of individualized optimal strategies used for prevention, treatment and management of chronic and relapsing disorders [19].

Increased information about the individual, such as the dynamical response over time to a particular drug, is key to the success of adaptive interventions. After a good modeling base, an effective treatment strategy has to be implemented which can maintain the desired response in time and space, under disturbances. Individually-tailored strategies can increase intervention potency and greater efficiency can be expected than approaches which apply same strategy to a large cohort [5]. In line with this requirement, the primary characteristic of an adaptive intervention is the focus on individualized treatment, which can vary based on the measured response, and is compatible with the aim of a control system. In this work, we use control engineering as an framework for implementing adaptive interventions.

Within the last ten years, more and more efforts are being placed by communities from control engineering, biology, medicine and psychology, through interdisciplinary collaboration, towards development and use of systems, optimization and control theory for better understanding of biological systems in general, and in particular for diagnosis and treatment of diseases [3, 20, 21, 22]. Among the most successful approach for systems medicine has been in HIV management [21, 23] with significant developments in insulin control [24, 25], anesthesia delivery [26], epilepsy management [27], depression management [28] and in the behavioral sciences [5, 6, 19]. It is interesting to note that in the areas where a better dynamical model is available (e.g., infectious diseases), control strategies have had greater success. Dynamical modeling is either done through first principles [23] or with a combination with various parameter estimation methods on different layers of ab-

straction e.g., In system biology, most of the effort has been on understanding of the dynamics on cellular level [29] where as a systems medicine approach can focus on an overall pharmacodynamic response [30]. Finally, the drug dosage methods have been implemented using various optimal control schemes [21, 23]. Model Predictive Control (MPC) is particularly suited for designing treatment regimens with its finite horizon receding control policy where the typical treatment related constraints can also be well integrated in the design [31, 32].

1.4 Optimized Interventions: A Control Engineering Approach

During a typical treatment phase, clinicians gauge the response of a patient by noting changes in symptoms or expected outcomes and suggest changes in dosages (if required). Even at the disposal of extensive medical history, the approach to assign drug dosages is based more or less on the intuition of the physician; on how they asses changes in symptoms and how they expect these to change with alterations in dosage. Clearly, this approach may not result in an effective intervention. Instead by making use of systematic operationalized techniques as used in control engineering to model and control the dynamics of the disorder, we can achieve better results. This will result in maximizing the possible benefits from the drug from existing resources. It should be noted that the term ‘adaptive’ as is used in this thesis is typically used in behavioral science and psychology literature [33] to imply that the dosage plans are designed with keeping the dynamics of the process in mind and should not be confused with adaptive as used in control literature [34]. Of course, ‘adaptive control’ (where the dynamical model and corresponding control law is updated during control actions) can be also be implemented but that avenue has not been pursued in this thesis.

The engineering approach to designing optimized interventions evaluated in this

thesis can be analyzed in two areas: a) dynamic modeling using system identification and b) control system design using hybrid model predictive control . They are discussed in brief below and, in detail, in the following chapters.

1.4.1 Dynamical Modeling

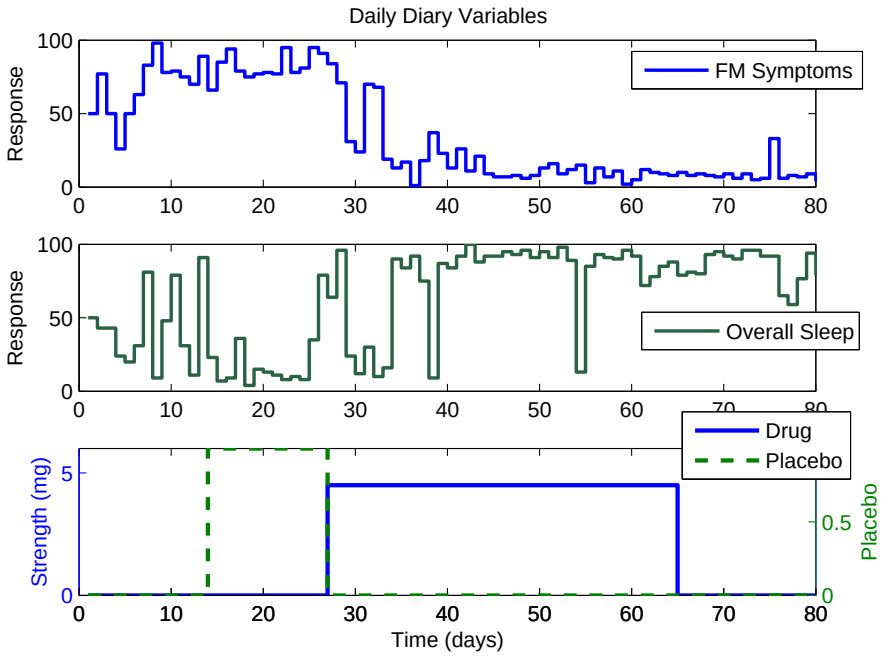
Understanding of the dynamics of a complex system is a fundamental prerequisite for successful control engineering implementation. For a complex phenomena, the approach of describing system behavior as function of its internal components (whose dynamics are then assumed to be known) is difficult as well as may be self defeating in case of chronic disorders, for example, where the dynamics are due to complex interaction between components which may be unexplained at the elemental level. It can be argued that a 'systems level' thinking is best suited to explain these complex dynamics. Systems approach can be understood as a more holistic way of analysis where a system can be analyzed as a single functional unit without breaking down into smaller components, a reductionist approach, or without full understanding of the internal mechanisms. This concept is largely suited for and so has been adopted in systems biology [3, 20, 29].

The classical modeling approach relies on the use of first principles i.e. the dynamics describing the exact mechanisms or physics of the internal components of the system. In light of unknown dynamics of FM, we evaluate a system identification approach for building linear time-invariant models. System identification is a method, with its root in statistics, which uses experimental input-output data to infer a dynamical model [35, 36]. In this thesis, we perform a secondary data analysis on daily reports completed by intervention participants from a previously conducted clinical trial. Inferring model using data is also of particular interest in this work as underlying causes of FM remain largely unknown and hence a largely

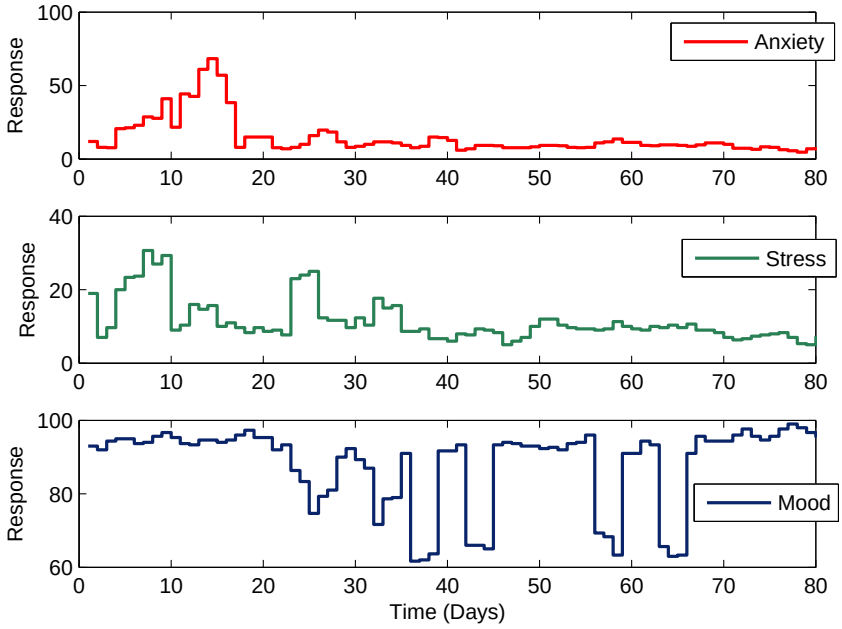
reductionist approach to this problem is rather difficult.

In pharmacological interventions, it is important that the drug dynamics are well understood. It is not enough to just note whether a particular drug produces changes (as is typically noted in the medical literature) but also the speed and magnitude of these effects. Typically for testing new drugs/treatment methods, clinical trials are conducted. For scientific accuracy and to prevent personal bias, clinical trails are conducted as a blind study with some sort of experimental control. In a typical clinical trial, number of endpoints are available which can be potentially grouped together as inputs and outputs to estimate a causal relationship. In the clinical trial conducted by Younger *et al.*, the information is available as 'daily diary reports'. These diary reports include daily *self-assessments* of outcomes of interest (e.g., pain severity, sleep quality) and other external variables that may affect these outcomes (such as stress, gastric symptoms etc) in addition to drug and placebo. Figure 1.1a shows time series of variables FM sym or pain severity and sleep quality (on a scale of 0-100) associated with the clinical trial for one participant. It can be noted that, for this participant, the pain magnitude goes down with introduction of drug suggesting a strong response to medication. The drug (naltrexone) concentration used in this study was 4.5 mg. Placebo is measured as a unit dosage. In Figure 1.1b, time series for three variables (anxiety, stress and mood) are shown which act as disturbances.

The focus of our modeling research has been on identifying parsimonious models that capture inherent dynamics of drug intervention for FM. We use prediction-error methods to estimate a discrete time model from experimental data and then a simplification to a second order continuous model structure with zero. It is important to note that we are *not* modeling the internal mechanisms of FM but rather how the drug and external factors affect a number of FM symptoms so that the



(a)



(b)

Figure 1.1: Selected variables associated with naltrexone intervention of fibromyalgia, as shown for a representative participant.

predictive information can be used by a controller to assign dosages based on measured participant responses. Linear models will be an approximation of what may be a nonlinear phenomena but with well developed techniques for linear modeling and control, it is possible to achieve desired performance in the intervention. It is worth noting that contrary to typical applications of system identification, this work is a secondary analysis of data and does not involve any "input signal" or an experimental design. It is characteristic of clinical trials to follow a fixed protocol for assigning drug dosage and hence in this scenario, we are typically left with no option of an experimental design for influencing system excitation as is possible in typical engineering problems [35]. Likewise, the nature of the protocol creates issues with using the data for meaningful cross validation.

1.4.2 Control System Design

In a control engineering approach to adaptive interventions, the controller assigns dosages to each participant as dictated by model dynamics, problem constraints, and in the presence of measured and unmeasured disturbances. We use control algorithms to decide on the dosage level required for a particular participant based on the dynamics of the disorder as well as the magnitude of relief expected under given constraints. Simple techniques typically used in adaptive interventions, like IF-THEN rules, will not yield good performance for a lagged response [5]. Instead, we can rely on a well designed control system to assign dosages based on model dynamics and performance requirements of the intervention.

We describe a classical feedback/feedforward control system as shown in Figure 1.2. Here, P represents the plant or dynamics expected of the drug intervention on outcomes, P_d represents the disturbance plant modeling the effect of external variables on outcomes, C is the controller which assigns the dosages as per changes

in symptoms in feedback configuration. C' is the feedforward controller which is used to compensate for measured disturbances d_m. The input to the controller is the error function e (generated due to feedback mechanism) which is an indicator of the difference between the measured [y] and desired [r] controlled variable(s).

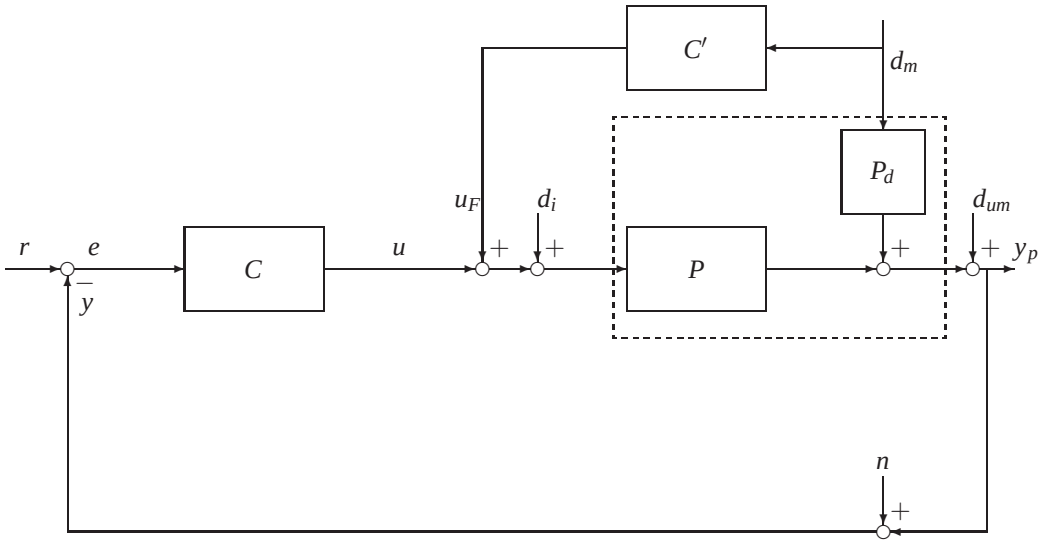


Figure 1.2: A classical feedback/feedforward control system.

The variables d_m and d_{um} represent the measured and unmeasured disturbances acting on the system; d_m is the disturbance acting through known dynamics (P_d) or measured disturbance; and d_{um} is the output disturbance which is more or less beyond the control of the intervention process or unmeasured disturbances. d_i is an unmeasured 'input' disturbance. In an adaptive intervention setting, the input disturbance can be a clinical judgment in which a physician suggest a different dosage than that assigned by the controller; it can also be an error in preparing the compound at the pharmacy, or might be related to adherence of the patient to the treatment. n is the measurement noise to model the imprecise measurement of variables. This control setup can be designed for low frequency reference tracking

and high frequency unmeasured disturbance rejection through the feedback loop and measured disturbance rejection through the feedforward loop.

In this work, we use Model Predictive Control (MPC) as the algorithmic framework for making these systematic dosage assignments. This control technology effectively combines feedback-feedforward control action by on line optimization of a cost function in a receding horizon [37]. It is also naturally suited for multi-input multi-output (MIMO) systems with constraints. The feedforward type control action of MPC is very useful for addressing disturbances which may be known *a priori* and can be measured in the course of the intervention. Furthermore, the controller can respond to unmeasured disturbances; for example, the intervention participant may undergo some unusual or unpredictable event that will affect FM symptoms, consequently requiring an adjustment to their current dosage.

The dynamical systems model serves as the basis for applying model predictive control as a decision algorithm for dosage selection of naltrexone in the face of the external disturbances. The categorical/discrete-event nature of the dosage assignment creates a need for hybrid model predictive control (HMPC) schemes, which we contrast with its continuous counterpart. A multiple degree-of-freedom formulation [31] is evaluated that enables the user to adjust the speed of setpoint tracking, measured disturbance rejection and unmeasured disturbance rejection independently in the closed loop system. In Chapter 4, simulation results for a representative participant in the presence of significant plant-model mismatch demonstrate the performance and broad-based applicability of a predictive control approach to these class of intervention problems.

1.4.3 Example Case

Consider a case for an adaptive intervention. First, since this drug has *not* been established as a standard drug for FM, the participant has to undergo an experiment or a clinical trial. The aim is to judge the effectiveness of drug as well as to collect data to build a model. For an adaptive intervention, as was discussed in section 1.4.1, we rely on estimating models using system identification methods. For cases where the drug/treatment is standard for a given disorder, a clinical trial may still be conducted to collect initial experimental data for modeling. Also, in these cases the system identification methods can be combined with drug pharmacokinetics and pharmacodynamics to build more accurate grey box models.

To take a specific example, let us consider drug dosage assignment to reduce FM symptoms report (FM sym) by 9.5 points. The clinical constraint is that bounds for drug dosages have to be between $0-13.5$ mg. In addition to that, the drug or $u(t)$ can take only discrete values. We use a continuous second order identified model describing the basic dynamics of the intervention as shown:

$$\frac{FMsym(s)}{Drug(s)} = G_1(s) = \frac{-2.47(1.96s+1)}{(1.57)^2 s^2 + 2(1.26)(1.57)s + 1} \tag{1.1}$$

and use the hybrid MPC technique [31] to assign dosages at daily intervals. The output change is shown in Figure 1.3 and is compared with a 'continuous' MPC where $u(t)$ can take any real value in its domain. The pain report is assumed to start from 50 at $t = 0$. The figure also describes the measured disturbance from an anxiety report (11.02 points) acting at $t = 25$ day and unmeasured disturbance (9.63 points) at $t = 45$ day. The tuning parameters related to the multi degree-of-freedom formulation are $(\alpha_r, \alpha_d, f_a) = (0.5, 0.5, 0.5)$. It can be noted that the hybrid MPC assigns dosages under given constraints where the controller performance

is comparable to the case where dosages can be continuous. The details of the controller development are included in Chapter 4.

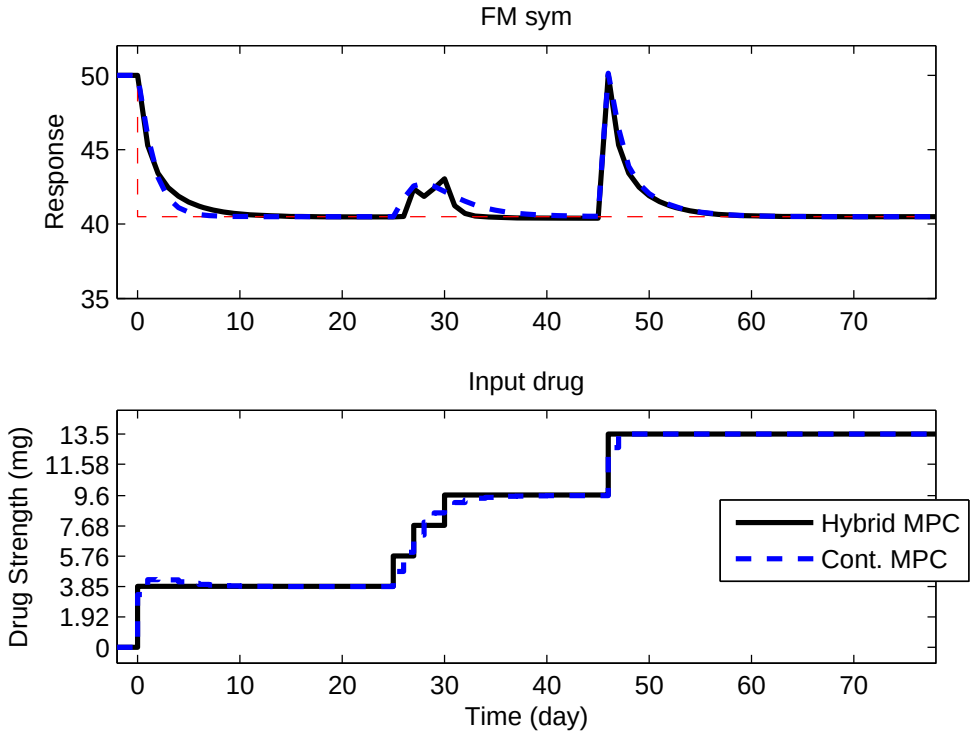


Figure 1.3: Performance of hybrid MPC as compared to continuous MPC for set-point change, measured disturbance (anxiety) and unmeasured disturbance for participant 5. Reference is shown by a dotted (red) line.

The controller evaluation can be expanded to include a plant model mismatch where a real time system can measure the changes in symptoms and then can assign dosage based on those mismatch errors. All this functionality can be incorporated in a model predictive control framework while being tuned for robustness and performance. With exceptional advances in computing technologies in past few years, there is a large scope of using control engineering for implementing an adaptive intervention and personalized medicine strategy.

1.5 Contribution of the Thesis

In this thesis, we have tried to address various aspects of adaptive intervention towards using system identification and model predictive control technique for assigning optimal treatment plans. Some of the aspects of model identification that we touch upon are:

- Use of secondary analysis on clinical data to asses how do the participants respond to drug over time and if so, then how strongly? We discuss how various variables interact within the context of the participant to produce observed effect and its effect on control strategies. Independent variables like drug and placebo can be classified as exogenous manipulated variables in a typical clinical trial. Other variables can be grouped as disturbances. Typical outcomes of interest such as FM symptoms or sleep are chosen as outputs.

- Methods for parameter estimation and model validation. One of the fundamental challenges in working with secondary clinical trial data has been working with finite data set with fixed protocol (no option of user choice in signal designs). The fixed protocol also limits the ability to validate estimated model by cross validation without causing large errors in shortened estimation data set. Prediction-error methods are used to estimate a linear time-invariant (LTI) model.

- Identification of causal and feedback relationships from experimental data. Without *a priori* knowledge, system identification from experimental data generated from feedback loops can be difficult. The direct prediction-error approach is used which can work well with closed loop data [35, 38].

- How does the protocol followed for the trial influence model quality?

The estimated models are then used in a hybrid MPC framework to assign dosages. The control scheme is chosen such that it address the nominal and robust performance requirements. Some of the control aspects covered are:

- How can an adaptive strategy, which can incorporate all the clinical constraints, be implemented? The aim of the control problem is to assign optimal dosages and its effectiveness, in real life setting, will be based on predictive quality of estimated models.

- How is nominal performance evaluated for this control scheme? How do various disturbances effect the control performance?

- How robust is the identification-control paradigm used? This scenario is shown as proof-of-concept by simulating model perturbations and the resulting control action was noted to be satisfying in presence of model errors. The proper trade-off between modeling effort and controller performance will depend on clinical requirements.

Although this work has been developed for the naltrexone intervention for FM, the general framework for system identification can be extrapolated to any similar drug clinical trial and the used control scheme is effectively capable of handling hybrid dynamics, other clinical constraints and plant-model mismatch typically present in such applications.

1.6 Thesis Outline

This thesis has been organized in five chapters. This Chapter was aimed at an introduction to the thesis material. Chapters 2 and 3 carry discussion on modeling using experimental data and in Chapter 4 control results are presented using simulations. Chapter 5 ends with a summary and conclusion.

Chapter 2 deals with methods of developing models using system identification. Some of the issues with the nature of the experimental data and other theoretical questions, typical to the application at hand, are discussed to arrive at a systematic process of estimating dynamical models.

In Chapter 3, serves as an illustration of the developed methods on clinical data for representative cases. We show cases of two participants in detail with discussion on the available variables as inputs and outputs and on the quality of estimated models. We also summarize the dynamical response for all the participants in the clinical trial and on the effectiveness of this clinical trial.

Chapter 4 describes the control problem for an adaptive intervention. It introduces the formulation for a hybrid model predictive controller [31]. It further discusses the nominal and robust performance of the controller, using the estimated model for one representative participant, under different disturbances and plant-model mismatches.

We conclude our study in Chapter 5 with summary of methods and results from system identification and hybrid model predictive control for naltrexone intervention for FM. Finally, we present an outline for planned future work related to design of informative clinical trial protocols, use of data-centric modeling on these informative data sets and the integration of these modeling approaches with a predictive controller formulation as per clinical requirements.

Chapter 2

ESTIMATING PARSIMONIOUS MODELS: THE METHOD

2.1 Overview

Modeling for complex biological systems is a difficult and complicated process. For example, in some areas like behavioral science the exact underlying cause-effect relationship may not be fully understood through first principles, and hence we can significantly benefit from building models using experimental data. We take inspiration from the large number of engineering applications modeled using system identification techniques [39]. We propose a similar framework for identifying a parsimonious dynamical systems model for the effect of naltrexone on FM symptoms.

Our modeling effort in this thesis can be summarized as follows: Since the mechanism of the disorder is not understood, we rely totally on an empirical approach based on experimental data to build models. We apply prediction-error methods to estimate a parametric model which can be best describe the output variance. The aim is to build low order models which can best describe the dynamics of the effect of drug and other external factors on a symptom of interest. We perform a single subject analysis where data for each participant is analyzed individually. These models can then be used by a controller to assign dosages in an optimized intervention.

One of the important issues in data analysis from human subject research and particularly from clinical trials has been on the focus on a single subject vs multiple subject analysis. From a perspective of adaptive interventions, our focus has been on performing a single subject analysis. In a single subject analysis, the participant is considered as a whole experiment in itself and we analyze the changes in symp-

toms (if any) reported due to drug intake, where as in multiple subject analysis, the combined response of all participants are noted. For complex biological systems, finding a common model explaining all observations for a population is possible only when *all* the dynamics are understood. Hence when the modeling techniques are used on multiple participants to estimate a common model, the model uncertainty can be assigned to the unpredictable behavior of participants and such uncertainty bound is generally more than that obtained from single subject analysis [40]. Also, some unusual participant response can be classified as outliers; there can also be a large amount of uncertainty in measured data across the participants (e.g, when participants are asked how they feel which is difficult to quantify) thus reducing the merit of a multi participant model.

Dynamic modeling of the naltrexone intervention for FM is discussed in two chapters. First, in this Chapter 2, we discuss about the nature of data collected from clinical trials and then the methods, issues and challenges in system identification. Some of the key concepts in Chapter 2 are explained using real data from clinical trials. In Chapter 3, we describe a detailed application of the method to some representative cases and provide a summary of results for all participants. The rest of this chapter is organized as follows. In Section 2.2, we talk about the clinical trial of naltrexone for reducing FM sysmptoms with a description of the variables associated with the disorder which are measured in the trial. In Section 2.3, we discuss the classification of variables as inputs and outputs for the dynamical model. In Section 2.4, we summarize the modeling method which has been discussed in detail in following sections: in Section 2.5 we discuss about parametric identification and models structures, in Section 2.6 we discuss the importance of preprocessing of data and in Section 2.7, we discuss the continuous model and its significance to classifying participants as responders and non responders. In Section 2.8, we

present a discussion on issues related to model validity particularly in relation with clinical trials. We conclude the chapter with Section 2.9 where we present various approaches to select inputs for model estimation.

2.2 Clinical Trial of Naltrexone Intervention for Fibromyalgia

Clinical trials are designed to test the hypothesis related to health interventions. In accordance with the scientific method to prevent bias, the effect of the intervention component under consideration, e.g. drug, is compared using an experimental control (e.g., placebo). Further, these studies can be developed as a single blind study (where an individual subject does not know whether they are being administered drug or placebo at given instant of time but the experimenter has that knowledge) or as a double blind study (where both an individual subject and the experimenter do not know whether the pill being administered is drug or placebo). It should be noted that the single blind study can result in an experimenter's bias. A crossover design is also generally employed, if possible, where participants receive both treatments and hence act as their own control (they take *both* drug and placebo). This approach primarily reduces the errors caused by extraneous variables and does not rely on large number N_{par} of subjects. Hence such studies are more optimal in terms of statistical efficiency [41].

As the exact nature of FM still remains largely unknown, there have been various efforts to diagnose and treat this disorder. Depending how a researcher sees the cause/mechanisms for the symptoms, there have been experiments with various drugs. At present, there are three FDA (US Food and Drug Administration) approved medications for FM [42] but these treatment(s) cannot be still used as a standard clinical method because either patients just do not respond or they suffer from side effects. Hence, the treatment of FM remains as an open area for ac-

tive research. The aim of clinical trials for FM is two fold : to test the validity of the pharmacological hypothesis and to get an insight into the exact mechanism by which the disorder works by observing the drug response. First, the medications or potential drugs have to tested for effectiveness, purity and other factors on animal models. Naltrexone and its low dose version used in this study are already tested and approved medications by the FDA for treating certain illnesses like alcoholism [43]. Second, the length of the trial has to be established based on the hypothesis/evidence of mechanism of pharmacological dynamics. As stated in [10] and [44], it is expected that naltrexone works slowly on a day-by-day basis and peak effect is expected somewhere around 28-30 days for participants responding to this drug. Hence these studies are designed for as long as 22 weeks to incorporate all the expected dynamics.

Detailed information on this clinical trial can be found in Younger *et.al* [10]. This trial was carried out in two stages: the first study was conducted as initial or *pilot study* using 10 participants and the second study was conducted as a *full study* on 30 participants with a longer protocol. The pilot study was designed as a placebo controlled, single blind, crossover design where as the full study was designed as a randomized placebo controlled, double blind, crossover study.

The schedule and time line used for clinical trial (both pilot and full study) is as follows:

- Baseline : During this phase participants do not receive any kind of medication. The responses noted during this period will represent the “normal” or baseline status of FM symptoms. The duration of the baseline period is of two weeks for both the pilot and full study.

- Drug/Placebo : During this phase, participants receive either drug or placebo

as a part of blind study. In the pilot study, the protocol is designed such that first placebo is administered and then drug. The full study follows the approach where the participants are randomized to be assigned either drug or placebo for a total participant count of 30. Hence, only the 15 individuals who received placebo first have a design that is similar to the pilot study.

- Washout : During this phase, all kinds of medications are stopped and the aim is to observe the symptoms after cessation of either drug or placebo. The washout period consists of two weeks or more.

In order to assess the effectiveness of the intervention, we are interested in noting the changes, if any, in the symptoms closely associated with FM. Since many of the symptoms are behavioral or pathophysiological in nature and there is currently no test per se to *detect* or quantify FM, we rely on the responses entered by participants' judgment based on self-reports. Participants completed daily reports of symptom severity using a hand held computer and visited lab every 2 weeks for tests of mechanical, heat, and cold pain sensitivity. Some of the aspects of data collected from this trial will now be discussed.

2.2.1 General Description of Variables

We begin by grouping the data available from trial in to two broad categories :

- Self reported data : The participants enter their responses daily on a scale of 100 on various symptoms related to FM. These variables are based on self-reports and are rooted in behavioral science rather than being measured in real physical parameters.

- Physically measured data: The participants visited a clinic every 14 days to undergo a quantitative sensory testing to obtain pain thresholds induced by

the application of mechanical pressure, heat and cold. These variables are measured using physical quantities like °C.

The daily diary data acts as the source of primary information on the clinical trial for allowing the experimenter to judge how well the drug affects the symptoms. The sensory testing data is used more in secondary role, like for validating the inferences.

In addition to grouping according to sources of data, we have two sets of data from clinical trials performed. The pilot study follows a Placebo-Drug protocol with total trial length of 98 days and the full study follows both Placebo-Drug as well as Drug-Placebo protocols with a total trial length of 155 days. The data from daily diary (qualitative data) is sampled time $T = 1$ day and physically measured data (quantitative data) is sampled at $T = 14$ days. The questions that form a part of the daily diary reports are shown below. The questions from $1 - 16$ are entered on a scale of $0 - 100$ where 100 is the maximum corresponding to that variable; questions $17 - 20$ are entered in as binary variables (yes or no). These variables (with the common name with which we will address them further) listed below describe more or less the typical symptoms experienced in FM.

1. How would you rate your general satisfaction with life today? [Life]
2. Overall, how severe have your fibromyalgia symptoms been today? [FM sym]
3. How would you rate your general level of pain today? [Pain]
4. What was your highest level of pain today?
5. How fatigued have you been over the day? [Fatigue]

6. How sad, down, or blue have you felt today? [Sadness]
7. How anxious have you felt today? [Anxiety]
8. How stressed have you been today? [Stress]
9. How good has your mood been today? [Mood]
10. How much trouble did you have getting to sleep last night? [Sleep]
11. Overall, how well did you sleep last night? [Overall Sleep]
12. How clearly were you able to think and remember things today? [Think and Rem]
13. Did you experience and bowel or gastrointestinal problems today? [Gastric]
14. Did you suffer any headaches today? [Headaches]
15. How well are you tolerating the medication? [Toleration]
16. Have you experienced any negative side-effects from the medication? [Side effects]
17. Have you taken your capsule for tonight?
18. Did you take your capsule last night?
19. Did you experience any unusually stressful events today?
20. Did you have to take any other pain medication today?

Some of the variables from this data set can be re-organized for clarity and to cut down on some redundant information. For example, we have two reports related to sleep conditions: ‘How much trouble did you have getting to sleep last night?’

and ‘Overall, how well did you sleep last night?’. We primarily use overall sleep as the indicator for sleep quality. Similarly, as pain is the defining symptom of FM, the responses for ‘fibromyalgia symptom severity and ‘average daily pain are more or less similar for all participants and hence *FM sym* is the defining variable for symptom severity.

Based on the questionnaire in the daily dairy data, we can make a couple of important remarks before we move to the topic of dynamical modeling. First, the response entered for questions $1-16$ in range of $0-100$ are based on behavioral status of that participant as reported by them and these response, which are *not* based on actual physical signals, can be misleading. Moreover, the response level of one participant is not expected to match up with other participant. For example, a pain report of $60/100$ for participant A may not be the same for pain report of $60/100$ for participant B because the thresholds for each individual may vary as well as their assessments of the symptoms. It can be argued that all behavioral characteristics have their origin in the complex neurobiology of the human body and one might argue that it will suit best to measure the direct *signals* in the neural pathway to best ascertain the observed condition(s). Again, as mentioned before, such an approach is difficult, if not impossible, for a complex system. Secondly, the discussion on first point reinforces our thinking of single subject analysis or an *idiographic* approach as opposed to a common model applicable to all participants or a *nomothetic* approach [6]. The use of experimental data and the validity of proposed modeling procedure is highly applicable for a single subject analysis.

2.3 Dynamical Modeling

Traditionally in clinical trials, the effectiveness of the intervention is judged using statistical methods [41]. The criteria used by Younger *et al.* to determine a response

to treatment is a thirty point reduction in self-reported symptoms over placebo at the conclusion of the trial [10]. Such an approach may not be very useful to build models that have to be used in decision making scenarios, such as adaptive interventions, as they tend to reflect steady state behavior rather than critical transient dynamics. Hence our approach to this problem is based on dynamical system theory where we try to build models which can be used to best describe the dynamics of the treatment by determining a time-dependent causal relationship between inputs and output. Further, this analysis can be used in a more detailed classification of participants as per response to the drug. We use prediction-error methods [35] to estimate a parametric linear time invariant (LTI) model. Although we lack substantial *a priori* knowledge about the system, we can make some inferences about the nature of the experiment, as discussed further.

Biological systems are characterized by complex interdependent components. Systems such as the human body has evolved a complex internal compensation system; in other words, an internal "controller" which tries to nullify any external factors causing undesired change. This phenomena is known as homeostasis or homeodynamics [45] which is implemented through the natural physiology of the body like in regulation of blood glucose or sometimes through the immune system, in case of infections. The feedback mechanism (both positive and negative), denoted by homeostasis, may result in cross correlation between endpoints and unmeasured noise [38] collected from medical treatments and hence such experiments can be classified, in a classical system identification sense, as *closed loop* experiments. For example, in the case of FM there may be a relationship between variables such that "output" affects "input" e.g., elevated pain condition may effect anxiety levels although the existence of the feedback path is not clear. The feedback path can be through a controller *internal* to the participant or a causal function

which maps variables.

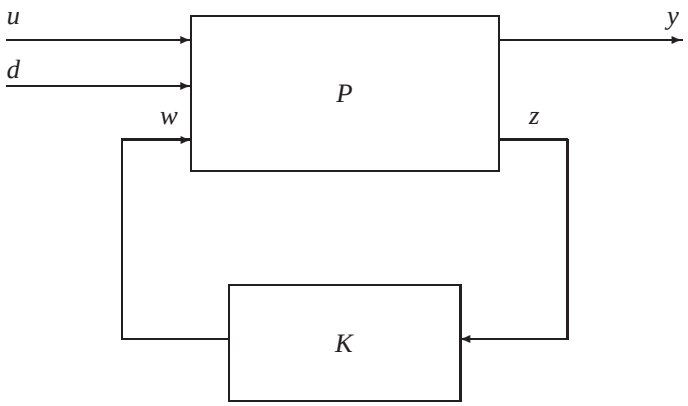


Figure 2.1: Linear Fractional Transform (LFT) model structure for given FM system.

In Figure 2.1, we describe a general structure for this system observed for FM. This representation of the system corresponds to a linear fractional transform (LFT) representation where the two LTI systems are: P the plant and the controller block K. We show how variables might react in such as system where variables can be measured and unmeasured. Variables and blocks represented in the figure are described as:

- P is the plant transfer function through which drug directly affects outcomes under interest such as pain.
- u are the exogenous input signals acting on the system whose values can be influenced by the clinician (e.g., through assigned dosages). These manipulated variables are $u \in \{\text{drug and placebo}\}$.

- d are the *exogenous* disturbance signals acting on the system whose values *cannot* be adjusted by the clinician. e.g., $d \in \{\text{stressful event}\}$

- y are the outcomes of interest which are measured or assessed in the experiment.
  e.g., $y \in \{\text{FM symptoms, overall sleep, fatigue,...}\}$

- w are the measured and unmeasured input signals acting on the system through the feedback path and does not include variables associated with u and d.

- z are the measured and unmeasured output signals acting on the system which may include variables associated with y.

- K is the transfer function for the feedback controller which maps z to w.

The measured variables in u, d, w can be grouped as inputs and measured variables in y, z can be grouped as output to estimate a dynamical model using system identification. The three approaches for closed loop identification can be described as:

- *Direct Method.* It assumes no knowledge of feedback loop and treats the problem as an open loop problem.

- *Indirect Method.* It assumes complete knowledge of the feedback mechanism K and is used in the estimation method to obtain models.

- *Joint Input-Output Method.* The feedback path is assumed to be of certain structure and then use experimental data to infer the feedback transfer function and estimate the plant.

Clearly, the indirect approach is not possible due to lack of information. The third approach also assumes *a priori* information about the structure of feedback which is not known. Hence we approach this problem as in classical system identification by considering it as an open loop system and solve using direct methods. It should be noted that methods like correlation analysis and subspace identification may fail in closed loop whereas *prediction-error methods* work well with enough parameters [35] and hence we use it in further analysis.

Section 2.2 lists out the variables associated with the naltrexone trial. Looking at the Figure 2.1, we note that some of the variables associated with the study may preexist before the administration of either drug or placebo i.e. during the baseline period like anxiety and sadness and hence can be classified as both *w* and *z*. These variables may show changes on application of these external inputs and other external disturbances. The transfer function type mathematical models are used to define the relationship between the input(s) and output(s) from the available measured variables in the clinical trial.

2.3.1 Outputs

We are primarily interested in understanding how drug affects various FM symptoms during the naltrexone intervention and hence the core symptoms of this disorder like pain, fatigue, sleep disturbance, bowel abnormalities and cognitive dysfunction can be classified as outputs or dependent variables. The pilot study [10] classifies FM symptoms (question 2) as primary outcome, which we use as the principal output for our analysis. We also consider overall sleep and fatigue as outcomes of interest in this study. In behavioral sciences, there is increasing effort in understanding the relationship between a primary variable and a *mediator* variable - an output that is an intermediate to another output of interest [46] e.g., the

relationship between pain and sleep or fatigue is clinically very relevant.

2.3.2 Drug and Placebo as an Input Signal

Drug and placebo are classified as the primary inputs in the analysis. They are added externally to the system and can be manipulated by, and are of interest to, the user. In system identification, the quality of models estimated is highly dependent on the richness of the information content in the data which is a function of the persistence of excitation in the input signals [35]. Extensive amount of work has been done in past (Rivera *et al.* [47, 48]) on issues of input signal design to maximize the information content in experimental data under test conditions. In typical system identification scenario, the unknown system under analysis is excited by an input signal specifically designed to excite the frequencies required for further analysis. The input signal can have significant influence on identification results. Specifically for control purposes, we are interested in frequency information content useful to the controller [49]. Typical inputs seen in the literature are white noise, step and impulse inputs, random and pseudo random binary sequence (PRBS) and multisines. It is to be noted that the term input signal used here is with respect to an *external* signal which can be designed by an user and does not apply to all the inputs to a system.

In case of clinical trials in general, the input signal (i.e, which can be manipulated by the user) available is in the form of a step function (or a rectangular pulse function). This can be realized when we look at how the protocols are designed; the aim is to test the effectiveness/usefulness of the intervention (using, say, a drug in this example) and so a clinical dosage is fixed for the period of trial. In other words, the participants receive a fixed dosage for a stipulated time period which translates into a rectangular input - with a low to high pulse input and a high to low pulse

input as shown in Figure 2.2.

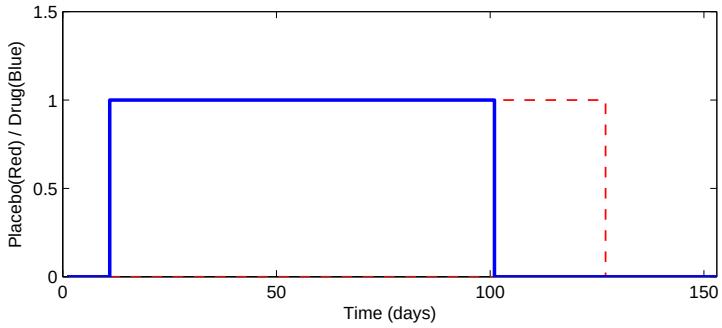


Figure 2.2: Typical external input(s) in a clinical trial; In this figure two independent inputs are shown as Drug (solid,blue) and Placebo (dashed,red).

The possibility of different protocol design on lines of more typical input signals like PRBS is not common in clinical trials and has not been carried out in this work. This issue of input signal design, however, presents itself with problems like clinical constraints and restrictions for example, it may take time for some drug to show effect and hence the dosage level has to be maintained for a time period as per the pharmacodynamics. Also in typical system identification experiments, the excitation is applied periodically to get a large sample size where as in typical clinical trials only one cycle of experimentation is followed. Also, the step input emphasizes low frequencies or steady state behavior. Since in this work we conduct a secondary analysis of data, the main identification problem that needs to be considered is that of estimation.

2.3.3 Other Inputs

As shown in Figure 2.1, we note that in addition to drug there are other variables affecting an output of interest (e.g., pain). Hence we add the variables excluding those we classified as outputs as additional inputs like anxiety, stress and mood are added to these primary inputs to improve the variance of estimated models hence

improving the overall % fit. These inputs are measures which were noted as secondary outcomes in the pilot study [10].

2.3.4 Is There Feedback in Data?

It may be important to detect feedback between variables to truly classify a variable as an exogenous variable specially when we have access only to the experimental data. Asides from gaining system knowledge, the presence of feedback is important from a statistical point-of-view for system identification. Classical analysis approaches the idea of feedback from the notion of causality e.g., if

$$y(t) = f(u(t_{i-1,i-2,\ldots 1})) + v(t) \tag{2.1}$$

then presence of feedback would imply that

$$u = g(f(y(t_{i-1,i-2,\ldots 1}))) + \omega(t) \tag{2.2}$$

where v, ω are random noise and f, g are forward and feedback transfer function respectively. Hence if the finite impulse response (FIR) causal and non causal model describing the process *y* in terms of *u* are *same*, then there is no feedback. Consequently this means that if a non causal FIR model is chosen to represent the impulse response, then significant parameter value for negative lags would imply presence of feedback. Although this is an useful operational technique, it works under the assumption that impulse response can always be estimated [50, 51]. Another approach is a statistical method where using innovation representation for joint process, a hypothesis test (χ^2 test) is conducted to determine there is no feedback from a particular set of input and output [52].

2.4 General Method for System Identification

The daily diary data is used to estimate a dynamical systems model. The modeling process undertaken in this study can be summarized in three subparts as follows:

1. ***Data preprocessing.*** Initially the data is pre-processed for missing entries using a simple mean of immediate neighbors imputation method. To reduce the high frequency content in the time series data, a three day moving average is applied.

2. ***Discrete-time parametric modeling using prediction-error method.*** The filtered data is then fitted to a parametric model using ARX model structure. The procedure here is to begin with drug and placebo as inputs, then add additional input variables (like anxiety, stress and mood) to improve the goodness of fit. While increasing the number of inputs improves the overall fit of the model, an exceptionally high fit does not necessarily correspond to a predictive model; consequently, the set of input variables that we feel appropriately describes the data across all participants must be determined. Having estimated models for these inputs, unit step responses (corresponding to the output change for a magnitude one step change in the input) can be obtained and interpreted.

3. ***Simplification to a continuous time model.*** The step responses from the discrete-time parametric model are fit to a low-order continuous models that conform to 1st and 2nd order differential equations. Gain, time constants, and settling times for each input and participant are noted. Based on these methods, we classify the participants on basis of their response to drug in Section 2.7.

The parametric identification forms the essence of our modeling discussion and hence has been discussed in the following section. Items 1 and 3 are discussed in the sections following parametric identification.

2.5 Parametric System Identification

The procedure for system identification can functionally classified as:

1. Experimental or input design
2. Data collection
3. Model structure (parametric (e.g., ARMAX) or non parametric (e.g., Frequency response))
4. Model estimation
5. Model validation

Since the experimental design and data collection were fixed during the clinical trial phase, the system identification exercise in this work has been limited to items 3 through 5 only. Also as this model has to be used in a control setting, our focus has been on identifying parametric models with information relevant for control. In the process of modeling the dynamics of naltrexone intervention, we are faced with three important questions:

- Which model structure works best for the intervention?
- How can we reduce the bias and variance of estimated models?
- Since we have so many inputs at hand, how can we avoid the problem of over parametrization?

2.5.1 Prediction Error Methods

Prediction error methods are among the most popular methods developed in system identification literature. This approach is based on minimization of certain cost

function of observed data and parameter θ using regression methods. The variable nomenclature as adopted in this section is taken from system identification literature (e.g. [35]). Consider a set of discrete time parametric model structure as a function of θ:

$$y(t) = \tilde{p}(q,\theta)u(t) + \tilde{p}_e(q,\theta)e(t) \tag{2.3}$$

where $\tilde{p}(q,\theta)$ is the plant model, $\tilde{p}_e(q,\theta)$ is the noise model, q is the forward shift operator and t is a discrete time index [35]. Based on the experimental data set $\mathscr{Z}$ containing the set of data $\{y,u\}$ of length N, we can form a cost function of the prediction errors, V_N, which on minimization will converge under asymptotic conditions. For mean square error type prediction error estimate, we can write

$$\hat{\theta}_N = \arg\min\{V_N(\theta, Z^N)\} \tag{2.4}$$

$$= \frac{1}{N}\sum_{t=1}^{N} e^2(t,\theta) \tag{2.5}$$

where $\hat{\theta}_N$ is the estimated parameter vector and $e(t)$ is known as the residual or the prediction error calculated as:

$$e(t) = \tilde{p}_e(q,\theta)^{-1}(y(t) - \tilde{p}(q,\theta)u(t)) \tag{2.6}$$

$\tilde{p}, \tilde{p}_e$ can be alternatively written in parameterized form using polynomials (and removing the need for use of θ, see Table 2.1) and hence in representing a dynamical system, the first step is to find an appropriate structure of the model. The hypothesis is that the chosen model structure should be able to capture the useful dynamics of the excited system. Keeping track of our aim of modeling to develop a parsimonious model for the system using experimental data, we represent the common parametric methods used in system identification literature as following: ARX (Auto-Regressive with eXogeneous inputs), ARMAX (Auto-Regressive Moving-Average

with eXogeneous inputs), FIR (Finite Impulse Response), BJ (Box-Jenkins) and OE (Output Error). The general structure describing these models can be written as in lines of equation 2.3 as:

$$A(q)y(t) = \frac{B(q)}{F(q)}u(t-n_k) + \frac{C(q)}{D(q)}e(t) \tag{2.7}$$

where A, B, C, D and F are causal polynomials in q defined as

$$A(q) = 1 + \sum_{1}^{n_a} a_i q^{-i} \tag{2.8}$$

$$B(q) = \sum_{1}^{n_b} b_i q^{-i+1} \tag{2.9}$$

$$C(q) = 1 + \sum_{1}^{n_c} c_i q^{-i} \tag{2.10}$$

$$D(q) = 1 + \sum_{1}^{n_d} d_i q^{-i} \tag{2.11}$$

$$F(q) = 1 + \sum_{1}^{n_f} f_i q^{-i} \tag{2.12}$$

Table 2.1: Tabulation of five PEM structures.

Method	$\tilde{p}(q,\theta)$	$\tilde{p}_e(q,\theta)$
ARX	$\frac{B(q)}{A(q)}q^{-n_k}$	$\frac{1}{A(q)}$
ARMAX	$\frac{B(q)}{A(q)}q^{-n_k}$	$\frac{C(q)}{A(q)}$
FIR	$B(q)q^{-n_k}$	1
BJ	$\frac{B(q)}{F(q)}q^{-n_k}$	$\frac{C(q)}{D(q)}$
OE	$\frac{B(q)}{F(q)}q^{-n_k}$	1

First clear distinction which can be made based on the structure of these models is the set which uses different parameters to define the plant and noise models, like the BJ method, and the other set, such as the ARX method, which uses common parameters to define both the plant and noise dynamics. This means that for bias

free estimation in the case of ARX models, for example, we need accurate estimation of both $\tilde{p}$ and $\tilde{p}_e$. By setting $C(q), D(q), F(q)$ to unity as described in equation 2.7, we get the ARX model structure which contains only polynomials $A(q)$ and $B(q)$. When compared to the ARX method, ARMAX structure uses extra polynomial $C(q)$ to define the noise model. It can be noted that the noise dynamics (or the poles of estimated noise model) are same to that of the plant model. FIR models are used to define the impulse response of the linear time invariant system. A critical condition that is evident in this scenario is that the FIR model order can be significantly large when we need to capture the full dynamics. Although they do not carry much weight in terms of control relevant identification but they do give an unique insight into the system. In case of last two model structures of BJ and OE, they are generally selected only if the previous structures do not give a satisfactory result. For BJ, we have to permutate with four parameters $(n_b, n_f, n_c, n_d, n_k)$ before converging to a useful model.

On topic of computation, ARX models (and FIR models) estimated with the quadratic criteria function reduces the optimization problem to linear least squares. This means that we are guaranteed a unique minimum (global) solution for our estimation problems. For other model structures, viz. ARMAX, BJ and OE, the optimization problem is nonlinear in nature and the solution is calculated using an iterative optimization scheme with no guarantee of global convergence; however, robust and reliable computation methods (e.g., system identification toolbox, MATLAB) are available.

When answering the question on which structure works best for the naltrexone intervention , we also keep in mind that we have a limited number of data samples or limited duration of identification test. This is a particular issue in case of FIR models where finite, noisy data results in bad estimates (using correlation method,

for example) and where only probabilistic bounds can be derived for estimated models [50]. Upon experimentation, we find that ARX and ARMAX models gave sufficiently good fit to output data in simulation and hence we will use these structure further in our analysis while keeping in mind the variance issues with these structure in presence of significant noise.

Following from equation 2.7, the ARX structure is a linear difference equation that relates the single input $u(t)$ to the single output $y(t)$ as follows:

$$y(t)+a_1y(t-1)+...+a_{na}y(t-n_a)=b_1u(t-n_k)+...+b_{nb}u(t-n_k-n_b+1)+e(t) \tag{2.13}$$

where $y(t)$ is the output and is predicted using delayed inputs and output variables. ARX models are represented as ARX [n_a, n_b, n_k] where, from systems point of view, n_a is the number of poles, n_b is the number of zeros plus one and n_k as time sample before inputs affects the output in discrete time systems (equals one when no time delay). ARX models can otherwise be represented for multi-input case in discrete time polynomial form as:

$$A(q)y(t)=\sum_{i=1}^{n_u}B_i(q)u_i(t-nk_i)+e(t) \tag{2.14}$$

where n_u represents the number of inputs, n_a, n_b and n_k are model orders, $e(t)$ is the prediction error, and $A(q)=1+\sum_{j=1}^{n_a}a_jq^{-j}$ and $B_i(q)=\sum_{j=1}^{n_{b_i}}b_jq^{-j+1}$ are polynomials in q.

2.5.2 Issues in System Identification

After deciding upon a model structure (i.e. ARX model), we divert our attention to the process of model estimation. The mean square error of the parameter estimate can be represented as

$$MSE(\hat{\theta}_N)=(Bias(\hat{\theta}_N,\theta_0))^2+Var(\hat{\theta}_N) \tag{2.15}$$

where θ_0 is the true parameter. Hence the principle error in system identification arise from following two sources:

- *Bias errors*: Bias errors are systematic errors due to the use of an incorrect model structure for generating models; in other words a correct model structure is a requirement for bias free estimation.

- *Variance errors*: Variance errors are from noise in the data. These errors show up as variance in the parametric estimate. This error is irrespective of correct/incorrect model structure chosen. We also group error due to measurement noise into this.

We will address these important points and discuss how these error can be systematically handled.

2.5.2.1 Bias Errors

For illustration, consider a system described by one manipulated input $u(t)$ (e.g., drug), one measured disturbance input $d(t)$ (e.g, anxiety) and noise $v(t)$ with plant and estimated models as follows:

$$\begin{aligned} y(t) &= p(q)u(t) + p_d(q)d(t) + H(q)v(t) \\ &= \tilde{p}(q)u(t) + \tilde{p}_d(q)d(t) + \tilde{p}_e(q)e(t) \end{aligned} \tag{2.16}$$

where p and $\tilde{p}$ are transfer functions corresponding to true plant and estimated plant respectively, H is the real noise model and $\tilde{p}_e$ is the estimated noise model. We use a suitable filter to 'prefilter' the real signals and hence we can define $y_F(t)$ as the filtered version of the real signal y and similarly, $u_F(t), d_F(t)$ are the filtered input

and disturbance signals respectively of the real signals $u(t)$ and $d(t)$.

$$y_F(t) = L(q)y(t) \tag{2.17}$$

$$u_F(t) = L(q)u(t) \tag{2.18}$$

$$d_F(t) = L(q)d(t) \tag{2.19}$$

where $L(q)$ is the filter transfer function. To keep the analysis in terms of real measured signals, we explicitly mentioned the filter in further definitions.

The one-step-ahead prediction error for this system can be written as

$$\begin{aligned} e_F(t) &= \tilde{p}_e(q)^{-1}(y_F(t) - (\tilde{p}(q)u_F(t) + \tilde{p}_d(q)d_F(t))) \\ &= L(q)\tilde{p}_e(q)^{-1}(y(t) - (\tilde{p}(q)u(t) + \tilde{p}_d(q)d(t))) \end{aligned} \tag{2.20}$$

The prediction error power spectrum can be directly related to the prediction error using Parseval's theorem (sum or integral of square of a function is equal to sum or integral of square of its Fourier transform) giving frequency domain insights into the sources of bias errors. Using the discrete version of Parseval's theorem:

$$\sum_{n=-\infty}^{\infty} |x[n]|^2 = \frac{1}{2\pi} \int_{-\pi}^{\pi} |x_f|^2 d\omega \tag{2.21}$$

where x is the discrete series and x_f is the discrete time Fourier transform. Using the definition of the power spectral density and extending for the prediction error, we can write

$$\frac{1}{N} \sum_{t=1}^{N} e_F^2(t) = \frac{1}{2\pi} \int_{-\pi}^{\pi} \Phi_{e_F}(\omega) d\omega \tag{2.22}$$

Based on equation 2.16, we can state the following definition.

Definition 1. *The prediction error spectrum (Φ_{e_F}) for a single input, single distur-*

bance and single output system can be written as

$$\Phi_{e_F}(\omega) = \frac{|L(q)|^2}{|\tilde{p}_e(q)|^2}\{|p-\tilde{p}|^2\Phi_u(\omega) + |p_d-\tilde{p}_d|^2\Phi_d(\omega) + 2Re((p-\tilde{p})(p_d-\tilde{p}_d)^*)\Phi_{ud}(\omega) + |H|^2\sigma_v^2\} \tag{2.23}$$

where v is assumed to be uncorrelated with u and d.

Proof. The equation 2.23 can be derived by using the corollary that a cross spectrum between two signal can be defined as the Fourier transform of the cross covariance function:

$$\Phi_{u_1u_2}(\omega) = \sum_{\tau=-\infty}^{\infty} R_{u_1u_2}(\tau)e^{-j\tau\omega} \tag{2.24}$$

and using the expectation operator, we can define the cross covariance as

$$R_{u_1u_2}(k) = E[u_1(t)u_2(t+k)] \tag{2.25}$$

where $u_1(t), u_2(t)$ is the given jointly quasi stationary. Similar result is true for the case of spectral density of a quasi stationary signal using auto covariance as

$$R_u(k) = E[u(t)u(t+k)] \tag{2.26}$$

Also note the following corollaries:

$$\Phi_{sn}(\omega) = G(e^{j\omega})H^*(e^{j\omega})\Phi_{uv}(\omega) \tag{2.27}$$

$$\Phi_{sn}(\omega) = \Phi^*_{ns}(\omega) \tag{2.28}$$

where u, v are the inputs to transfer functions G, H and s, n are the respective outputs.

Now consider a system as described in 2.16. The one step prediction error can be rewritten using the covariance of $e_F(t)$ and on assuming v is uncorrelated with all inputs. Using the above corollaries, we can arrive at the result.

□

Definition 2. *The general filtered prediction error spectrum for a system with n input plants and m disturbance plants*

$$y(t) = p_1(q)u_1(t) + ...p_n(q)u_n(t) + p_{d_1}(q)d_1(t) + ... + p_{d_m}(q)d_m(t) + H(q)v(t) \tag{2.29}$$

$$= \tilde{p}_1(q)u_1(t) + ...\tilde{p}_n(q)u_n(t) + \tilde{p}_{d_1}(q)d_1(t) + ... + \tilde{p}_{d_m}(q)d_m(t)) + \tilde{p}_e(q)e(t) \tag{2.30}$$

and when the filtered one-step-ahead prediction error is

$$e_F(t) = L(q)\tilde{p}_e(q)^{-1}(y(t) - (\tilde{p}_1(q)u_1(t) + ...\tilde{p}_n(q)u_n(t) + \tilde{p}_{d_1}(q)d_1(t) + ... + \tilde{p}_{d_m}(q)d_m(t))) \tag{2.31}$$

can be written as

$$\begin{aligned}\Phi_{e_F}(\omega) = \frac{|L(q)|^2}{|\tilde{p}_e(q)|^2}\{&|p_1 - \tilde{p}_1|^2\Phi_{u_1}(\omega) + |p_2 - \tilde{p}_2|^2\Phi_{u_2}(\omega) + ... \\ &+ |p_{n-1} - \tilde{p}_{n-1}|^2\Phi_{u_{n-1}}(\omega) + |p_n - \tilde{p}_n|^2\Phi_{u_n}(\omega) \\ &+ |p_{d_1} - \tilde{p}_{d_1}|^2\Phi_{d_1}(\omega) + |p_{d_2} - \tilde{p}_{d_2}|^2\Phi_{d_2}(\omega) + ... \\ &+ |p_{d_{m-1}} - \tilde{p}_{d_{m-1}}|^2\Phi_{d_{m-1}}(\omega) + |p_{d_m} - \tilde{p}_{d_m}|^2\Phi_{d_m}(\omega) \\ &2Re(p_1 - \tilde{p}_1)(p_2 - \tilde{p}_2)^*\Phi_{u_1u_2}(\omega) + ... \\ &+ 2Re(p_{d_m} - \tilde{p}_{d_{m-1}})(p_{d_m} - \tilde{p}_{d_{m-1}})^*\Phi_{d_md_{m-1}}(\omega) + |H|^2\sigma_v^2\}\end{aligned} \tag{2.32}$$

where $p_1...p_n$ are the n input plants, $p_{d_1}...p_{d_m}$ are the m disturbance plants and v is assumed to be uncorrelated with all inputs and disturbances.

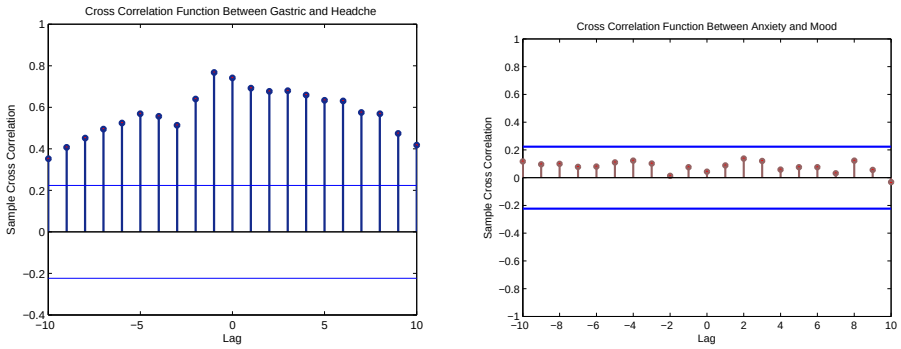
Let us analyze the sources of bias by using 2.23 as our reference. It is possible to obtain insights into how input power, model structure, cross-correlation between signals, and other factors can influence the goodness-of-fit in the identification process as follows:

- *Model structure.* An incorrect plant model structure corresponds to the $|p - \tilde{p}|$ term being non-zero and results in an asymptotic bias. Similarly incorrect structure $\tilde{p}_e$ for the noise model will result in a bias (though this term acts like a scaling factor).

- *Input signals.* In Section 2.3.2, we discussed about external signals like drug and placebo which are administered by the user and other exogenous disturbance signals which are added to improve the variance of estimated models. In all, input signals must show sufficient power (See Figure 2.4) in the frequency range of interest. As in this problem we are not designing input signals, we limit our inference of estimated models to the bandwidth provided by the available signals.

- *Prefiltering.* Prefiltering is used to change the noise characteristics of the data without changing the transfer function relationship in the estimated models. The prefilter can be used as a weight and hence as a means of providing emphasis on frequency intervals of importance to the problem. In this work, a three day moving average filter $L(q)$ is applied as the smoothing filter. It is equivalent to a low pass filter expressed in finite impulse response filter as discussed in Section 2.6.

- *Input cross correlation.* Since various variables are measured in the experiment, the procedure is to choose inputs which have minimum cross spectra ($\Phi_{ud}(\omega)$) to reduce the bias error. Better insight can be gained from the daily reports by studying the cross-correlation between variables. We can use cross correlations to better understand the relationship between variables which are exogenous. For instance in Fig. 2.3, the headache and gastric variables have high degree of cross-correlation, and are also correlated with the FM symp-



(a) Headache and Gastric Symptoms (b) Anxiety and Mood

Figure 2.3: Cross correlation between two variables for 10 lags (shown with 2 standard error bounds) for a representative participant.

toms output. Adding them as inputs did not yield good estimates. In comparison, anxiety and mood variable are essentially uncorrelated and offer good estimates when included as inputs.

Since power spectra of input signal significantly effects the result from system identification, we estimate the possible frequency range of purely exogenous signals like drug which can be specified by the user. The pulse input signal, as shown in Figure 2.2 can be written as following:

$$u(t) = \begin{cases} A & \text{if } t_1 \leq t \leq t_2 \\ 0 & \text{otherwise} \end{cases} \tag{2.33}$$

where t_1 is the first day, t_2 is the last day and $(t_2 - t_1)/2$ is the center of the pulse. The signal can be imagined as two successive step inputs in opposite directions and separated by a time delay. Let the original drug signal shown in Figure 2.2 be a rectangular pulse of width β, height A and is centered at C. This can be represented mathematically as follows: assume that the rectangular pulse starts at origin and

hence is centered at $\beta/2$. We can rewrite $u(t)$ and its Laplace transform as

$$u(t) = \begin{cases} 1 & \text{if } 0 \leq t \leq \beta \\ 0 & \text{otherwise} \end{cases} \tag{2.34}$$

$$U(s) = \frac{A(1-e^{-\beta s})}{s} \tag{2.35}$$

Now, this signal can then be time shifted by $C - \beta/2$ such that the center of the pulse is at C (corresponding to the original signal). Hence, we can write

$$U(s) = \frac{A(1-e^{-\beta s})}{s} e^{-(C-\beta/2)s} \tag{2.36}$$

Similar to a single step, this function will emphasize low frequencies. The informative data sets are related to the persistence of excitation in the input signals. Roughly speaking, the persistence of excitation gives an insight into the order of a model that can be estimated in an unambiguous way (See [53]). As per Ljung [35], Soderstrom [36], a signal $u(t)$ is said to be persistently exciting of order n_{per} if the covariance matrix is positive definite. In relating this concept to the input spectrum, the persistence of excitation means that $\Phi(\omega)$ is non zero for at least n_{per} distinct frequencies in $-\pi \leq \omega \leq \pi$.

Definition 3. *A quasi-stationary input $u(t)$ is persistently exciting of order n_{per} if the matrix*

$$\hat{R} = \begin{pmatrix} R_u(0) & \cdots & R_u(n_{per}-1) \\ R_u(n_{per}-1) & \cdots & R_u(0) \end{pmatrix} \tag{2.37}$$

is positive definite

The Figure 2.4 shows the power spectra for selected inputs from a representative case. It can be noted that most of the exogenous signals are persistently exciting in

range up to 0.6 radians/day. The magnitude difference between drug and placebo and the other inputs is due to the different units of measurement that are used. When used as inputs, these signals were found to of order $n_{per} = 26$. When inferring estimated standard deviations from parameter covariance matrix, we keep in mind the limitations up to excited frequencies only [54].

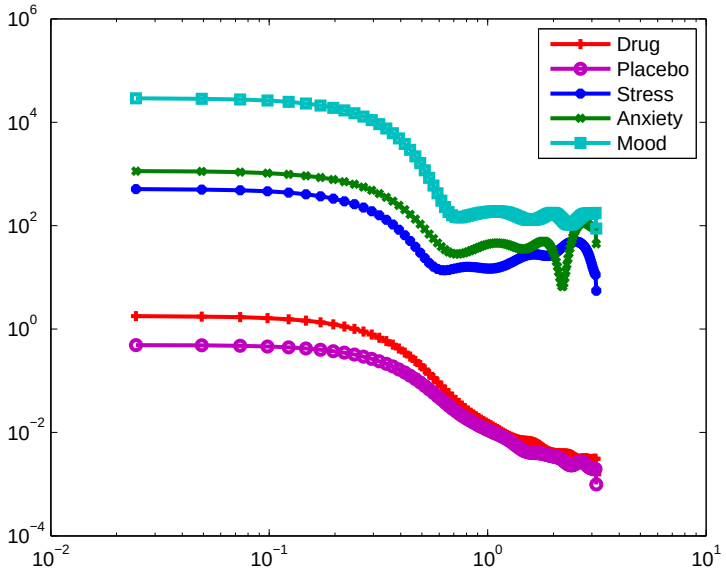


Figure 2.4: Power spectral density of variables associated with naltrexone intervention (as shown in Figure 1.1) using Welch's method with Hamming window.

2.5.2.2 Variance Error

We now come to our second and most important question : How to reduce the variance of estimated models? In a classical sense using the asymptotic results, the variance is affected by the number of model parameters, signal-to-noise ratio and the length of the data set as shown below:

$$Cov(\tilde{p}) \simeq \frac{n}{N}\frac{\Phi_v(\omega)}{\Phi_u(\omega)}$$
$$Cov(\tilde{p}_e) \simeq \frac{n}{N}H(e^{j\omega}) \tag{2.38}$$

where, as before, n is the number of parameters and N is the duration of the identification test. As N is fixed in this experiment, we can vary only the model orders.

It can be noted that the variance of the plant parameter estimates can be affected by input signals where as the variance of estimated noise model is independent of inputs [35]. The equation 2.38 is a valid approximation under under asymptotic conditions in an open loop operation although they may differ for system under consideration or under finite date samples [55, 56]. Although this case under consideration cannot be classified exactly as open loop, the results still hold their validity. As we do not have control over experimental design, the variance of the output can be better described by adding *more inputs* or in other words by estimating a multi-input single-output model. This issue has been discussed using data from a representative case. Our aim is to model the effect of drug on designated output e.g. FM symptoms. After choosing a starting model structure and order (say ARX $[2\,2\,1]$), we notice the variance of estimated model as well as we simulate the model to observe the percent fit. The first model is based on drug as input and FM sym as output. The percentage fits can be seen in Figure 2.5. Adding extra input to improve the quality of our model can be thought of in two ways. First, from the analysis of FM disorder and symptoms associated with it point to the fact that changes in stress or anxiety levels contribute to elevated pain levels and/or worsened sleep patterns. So intuitively speaking, adding extra inputs define our cause-effect relationship in a much better way that what can be just described by drug-FM symptoms model. From a statistical view, it can be shown that adding extra inputs results in improved covariance of the parameter estimate under the assumption that they are independent [57]. Also since ARX and ARMAX model structures use common parameters in plant and noise models, the net benefit of adding these extra inputs is much stronger in ARX/ARMAX than other structure which use independent parameters.

Table 2.2: Tabulation of parameter estimates with standard deviations for participant 5.

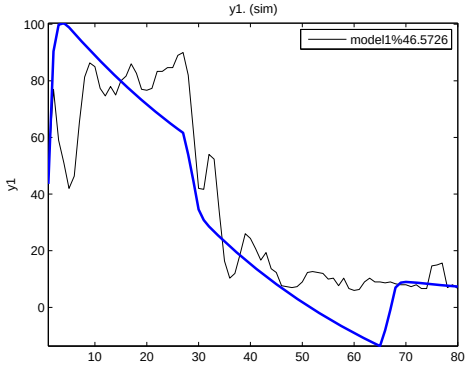
#	A	dA	B	dB
1	1 -1.2163 0.2326	0 0.0975 0.0983	-19.2805 18.3987	7.8729 7.7681
2	1 -1.1755 0.2170	0 0.0949 0.0949	-7.6722 7.5010 23.8433 -20.7684	8.7654 8.6119 8.6107 8.5827
3	1 -1.1183 0.2368	0 0.0971 0.0924	-8.5325 7.9869 15.0847 -7.7456 0.2712 -0.1020	8.7576 8.5380 10.5871 11.5068 0.1131 0.1119
4	1 -1.0265 0.2148	0 0.1001 0.0878	-0.4938 -0.0931 19.7477 -11.4083 0.1451 -0.0195 0.4780 -0.0915	1.9002 1.9076 10.1713 10.8634 0.1130 0.1116 0.1633 0.1739
5	1 -1.0061 0.2001	0 0.1011 0.0885	-1.2124 0.7326 15.5084 -6.6184 0.1469 0.0219 0.4952 -0.0499 -0.0917 0.0739	1.9540 1.9797 10.5228 11.2836 0.1128 0.1151 0.1694 0.1770 0.0670 0.0665

This result reinforces our choice of selecting ARX/ARMAX models over other model structures as we are dealing with a typical multi input single output type scenario. Although input are not completely independent in this work, we see the benefit of using multi input type models in Table 2.2.

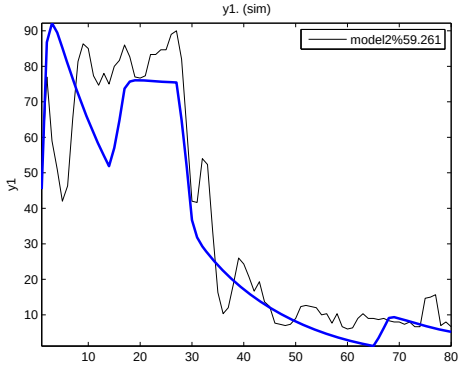
Exact methods of choosing the inputs are discussed in the next section. Although better fit to experimental data is desired, that cannot be the only criteria to be used to judges the usefulness of the estimated models [58]. The 'model fit' terminology used in this thesis points to the amount (percentage) of output variance explained by the model as:

$$\text{model fit (\%)} = 100 \times \left(1 - \frac{||(\hat{y} - y)||}{||(y - \mu(y))||}\right) \tag{2.39}$$

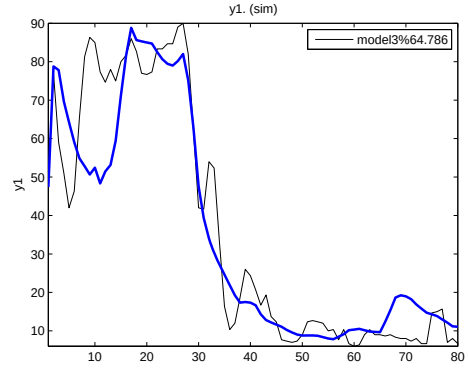
where $\hat{y}$ is the simulated output, μ is the mean operator and y is the measured output. Improvement in estimated models can also be analyzed by observing the step response of each models. The reliability of estimated models is discussed in



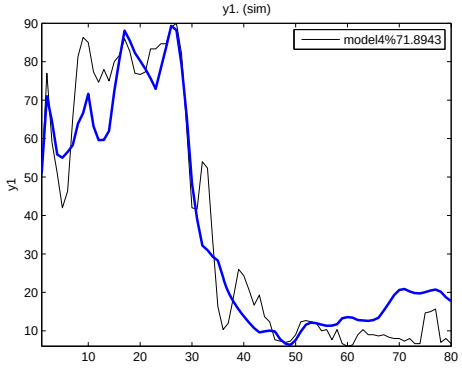
(a) Model 1 - Input = {Drug} Output = {FM sym}



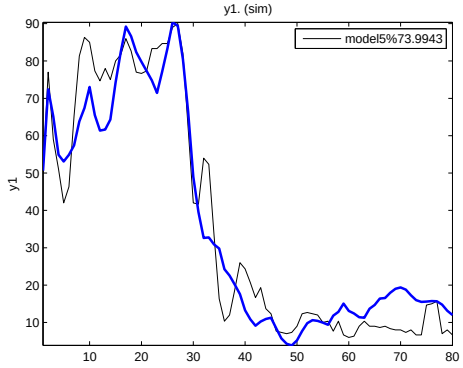
(b) Model 2 - Inputs = {Drug, Placebo} Output = {FM sym}



(c) Model 3 - Inputs = {Drug, Placebo and Anxiety} Output = {FM sym}



(d) Model 4 - Inputs = {Drug, Placebo, Anxiety, Stress} Output = {FM sym}



(e) Model 5 - Inputs = {Drug, Placebo, Anxiety, Stress, Mood} Output = {FM sym}

Figure 2.5: Model fits estimated seven models for Participant 5 from the pilot study.

Section 2.8.

Lastly, since there are inherent noise in the data collected in any experiment, we try to remove the high frequency content of the data using low pass filtering. Besides, the estimated noise model is supposed to capture the noise dynamics and which can be more accurately modeled if noise properties like noise covariance matrix are know *a priori*. In this work, no such information was available. Estimating these properties from input-output data can be pursued although there is no certainty that they will yield good estimates [59]. On a side note regarding noise models, it can be noted that the used models in this work (ARX, and also ARMAX) use the same parametrization for poles as in the plant model. As was noted earlier, using more sophisticated parametrization (ARX to ARMAX) for the noise model did not yield any significant improvements.

2.6 Preprocessing of Data

Before using the experimental data, it has to be preprocessed to be used for system identification techniques for two specific reasons: a) to account for missing data b) prefiltering to emphasize the bandwidth of interest . In general, data from clinical trials presents itself with unique challenges in unusual errors in measurements due to missing data and other anomalies. These two broad deficiencies in this data set are discussed now.

- *Missing Data*. The daily diary data is entered by the participants every night before they go to bed. Sometimes, the entries are not made on time so on a scale of 155 days (e.g., in case of full study), there are anywhere from $5-35$ days missing. On days when the daily dairy was filled, participants tend to miss answering some questions and hence rendering that data point as Not-a-Number (NaN). For handling the missing data, we approach this problem

as a problem of interpolation. Before interpolation, we make sure that all NaNs are taken care by using techniques such as imputation. We average the nearest neighbors and use that value in place to missing data.

$$x[n] = \frac{x[n-1] + x[n+1]}{2} \tag{2.40}$$

After imputation, based on the daily data entries we can note exact dates on which the entries were made and since the start and end dates on the trial are known, dates with missing entries can be noted. It is assumed that although the entries were not available for a particular date, participants did take the drug/placebo as scheduled. Also as the drug works slowly, missing a day or two should not cause dramatic changes. It can also be noted that number of missing days consecutively were 1 in most of the cases and 5 days in the worst case.

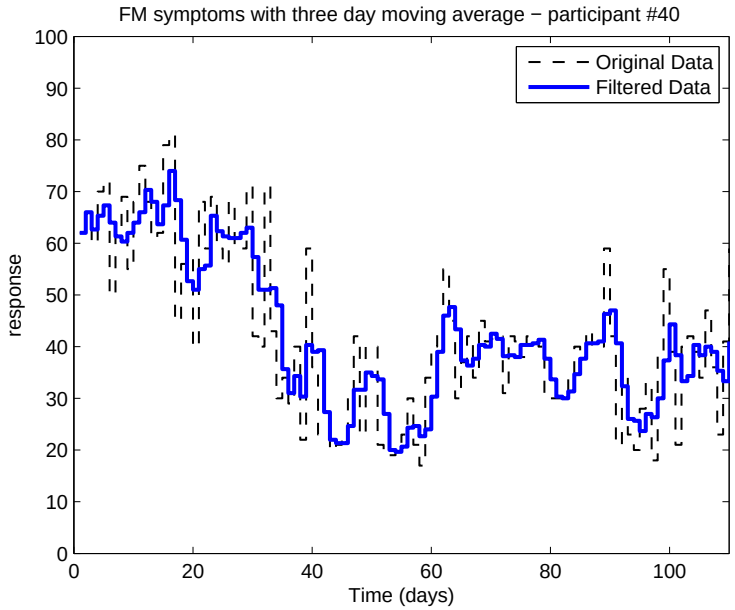


Figure 2.6: Variable FM symptoms (dotted line) along with its filtered through a three day moving average version (solid line) for participant 40.

- *Prefiltering*. Considering the nature of behavioral data that is collected on a daily basis, there is a lot of variability per question, per participant as seen in Figure 2.6. In order to decrease the variance of individual signals and remove high frequency variations that we would like to exclude form our estimated models, we impose a low pass filtering. Our intuition lies in emphasizing the low frequency information content. By working with the data and as suggested in [10], we found that the time domain method of three day moving average worked best in terms of smoothing out the signals.

$$y[n] = \frac{x[n] + x[n-1] + x[n-2]}{3} \tag{2.41}$$

The z transform representation of this prefilter is:

$$L(z) = (1 + z^{-1} + z^{-2})/3 = (z^2 + z + 1)/3z^2 \tag{2.42}$$

It is important to note that the moving average is applied to *all* the input

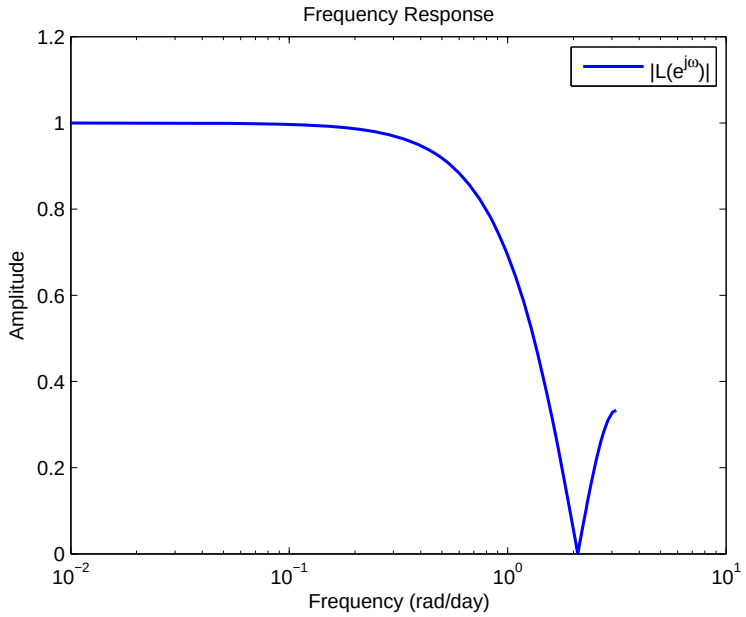


Figure 2.7: Amplitude ratio plot for the three day moving average function.

signals (including drug and placebo) to prevent any bias errors. It can be noted in Figure 2.7 that the moving average filter will emphasis frequencies up to 1 rad/day. This bandwidth limitation will be important later on when performing parameter estimation.

2.7 Continuous Models and Classification of Participants

Clinical trials are conducted to scientifically test the effect of an intervention component and notes outcomes of interest like pain and sleep. Hence after the completion of the trial, the experimenters are interested in the analysis aimed at judging the effectiveness of the intervention. Some of the specific questions of interest are:

- Does a participant respond to the drug?
- If yes, then how fast does the drug cause a measurable effect?
- How does the response compare for different outcomes?
- How does the participant respond to placebo?
- How can the response of two different participants be compared?

The word “response” implies the interest in effect of the prime intervention component, say drug, on primary outcomes as mentioned in the daily dairy report. In a placebo controlled experiment, the drug response has to be stronger than the placebo response for the drug response to be considered significant.

The procedure to generate these low-order process type models is as follows: we use the ‘best’ estimated ARX model as the base model and calculate the step response of these models to generate a *new* set of input-output data. This data is now used to fit a continuous time model. The real input-output data could have been used to generate continuous models directly but we use this two step approach

as the first ARX estimate is a consistent estimate with asymptotic theory [35] and after having obtained such consistent estimate, a reduced parsimonious model is obtained. The estimation of continuous models has been implemented using the 'Process Models' routine in MATLAB. In addition, when the gain of the drug-FM model, for example, is positive, we can say that the FM symptoms have worsened with introduction of drug and hence the participant did not responder to the drug or is a non-responder. Similarly, when the drug-FM gain is negative and lets say another model gain, of placebo-FM, is positive; this will imply that with introduction of drug, FM symptoms were decreased where as with introduction of placebo, they increased. This would be an ideal case and the participant can be called as a responder. In general, we classify a participant as a responder based on the gain of drug-FM model. Similar classification can be made based on gain of drug-sleep model whose gain has to be positive for responders implying improvement in sleep with the intervention.

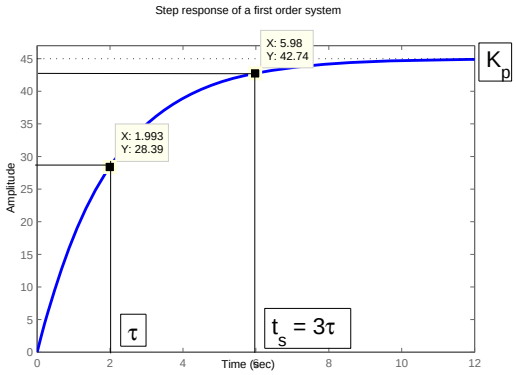
We use the classical Ist order and II order (with zero) models to represent the dynamic characteristics of the system and their step responses are shown in Figure 2.8. The first is a classical first order system shown in differential equation form as

$$\tau\frac{dy(t)}{dt}+y(t)=K_p u(t) \tag{2.43}$$

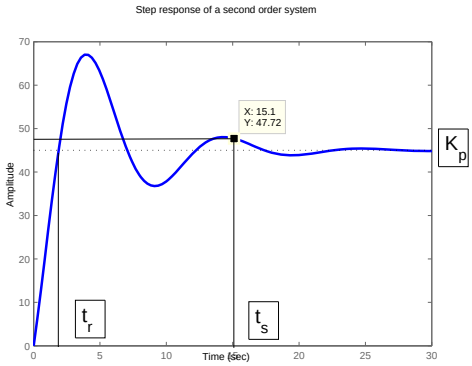
written in transfer function form as:

$$\frac{Y(s)}{U(s)}=G(s)=\frac{K_p}{\tau s+1} \tag{2.44}$$

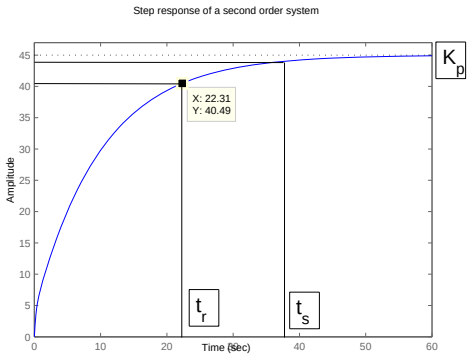
where K_p is the steady-state gain, τ is the time constant and t represents a continuous time variable. The steady-state gain value indicates how much change in the output occurs per unit change in the input at final time; the time constant τ provides a sense for the speed-of-response as shown in Figure 2.8a with $K_p = 40$,



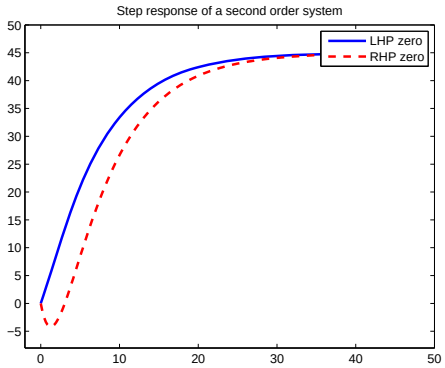
(a) First order system response



(b) Second order underdamped system response $\zeta = 0.3$



(c) Second order overdamped system response $\zeta = 3.3$



(d) Second order system response under LHP and RHP zeros

Figure 2.8: Step response of low order (Ist and IInd) continuous models with labeling of important characteristics.

$\tau = 2$. The first-order model is limited in that it cannot capture oscillatory behavior or overshoots and undershoots in the response.

The second low order model used in this procedure is a second order system with a zero. This simple model can account for a wide array of responses including inverse response and underdamped, critically damped and overdamped system responses. This model can be represented in second order differential equation form as:

$$\tau^2 \frac{d^2y(t)}{dt^2} + 2\zeta\tau\frac{dy(t)}{dt} + y(t) = K_p\left(\tau_a\frac{du(t)}{dt} + u(t)\right) \tag{2.45}$$

or in as a second order transfer function form as:

$$\frac{Y(s)}{U(s)} = G(s) = \frac{K_p(\tau_a s + 1)}{\tau^2 s^2 + 2\zeta\tau s + 1} \tag{2.46}$$

where initial conditions are assumed to be zero. We can quantify the steady-state gain (K_p) which represents magnitude of the effect, rise time (T_r; the time required for the response to first rise from 10% to 90% of its steady state value), peak time (T_p; time requird to reach the maximum of the curve) and settling time (T_s; the time required for the response to reach within 98% of its steady state value) which represents speed of the effect, from a step response of this model. These transients are labelled for both first order and second order responses as shown in Figure 2.8 with paramters values as $K_p = 40$, $\tau = 1.57$ and different ζ as mentioned in the caption. The oscillatory nature of the response is determined by the damping factor ζ (based on which we can classify as underdamped ($0 < \zeta < 1$) as shown in Figure 2.8b, critically damped (ζ = 1) and overdamped ($\zeta > 1$) as shown in Figure 2.8c. In Figure 2.8d, we show the effect of left-half plane (LHP) zeros and right-half plane (RHP) zeros with the inverse response noted in the case of RHP zero. These results are tabulated for all participants in the next Chapter.

2.8 Validation of Estimated Models

Model validation is central in judging the quality of estimation using methods in system identification [35]. We use the following methods for model validation:

- *Classical correlation analysis on residuals or residual analysis*

  We conduct a residual analysis on all estimated models using the auto correlation on the residuals $\hat{r}_e(\tau)$ as

  $$\hat{r}_e(\tau) = \frac{1}{N}\sum_{t=1}^{N} e(t)e(t-\tau) \tag{2.47}$$

  and cross correlation between residuals and input $\hat{r}_{ue}(\tau)$ as

  $$\hat{r}_{ue}(\tau) = \frac{1}{N}\sum_{t=1}^{N} u(t-\tau)e(t) \tag{2.48}$$

  For most of the participants in this study, ARX $[2\,2\,1]$ or $[4\,4\,1]$ met classical prediction error criteria where it was noted that the auto correlation of residuals were white (specially when using ARX structure, they have to be white [35]) and so were the cross correlation between the inputs and residuals. It is also worth noting that correlation between $u(t)$ and $e(t)$ for negative lags can be taken as an indication of output feedback in the input [35].

- *Cross validation*

  Another standard test for model validation is simulating the system for a fresh validation set and noting how much of output was explained by the estimated model; this is called cross validation. When the data was partitioned into estimation and validation, the estimation data was found not to have enough excitation for multi-input estimation and hence we could not cross validate our models. Due to limited data points in this study and due to experiment design followed, it was not possible to maintain enough input power in the

estimation data set. It can probably be said for typical clinical trials, following similar protocol, that there may be a possibility that the data collected will not allow the use of the cross validation procedure. Also, a gap between drug and placebo administrations will reduce cross correlations between these two variables.

- *Model error model*

  Classical criteria such as residual analysis and cross validation do not give any insight into model error useful for control. Another method, which is called model error analysis [60], can give additional insight with better representation of model error in the frequency domain. In a prediction error framework, asymptotic theory can be used to generate probabilistic or 'soft' uncertainty bounds given that there are no unmodeled dynamics [35]. A model error model can be used as an alternative to test the model quality and any presence of unmodeled dynamics.

  As the name suggests, we fit a model to the input-output data defined as inputs signals in the original model to the model residuals, which can be defined as:

$$e(t) = G_e(q)u(t) + H_e(q)w(t) \tag{2.49}$$

  where G_e is estimated using a *high order* ARX model (which acts as an consistent estimator [35]) or an OE model and H_e will be the noise model for this model error model. Ideally, the estimated model should be zero (or of very small gain) and can be analyzed by Bode plots (with the estimated standard deviations) of the model error model. The norms of these models can be used in robust control techniques.

- *Step responses from estimated ARX models*

After a model has passed residual analysis, we also take a look at the step responses. Models which may not describe great deal of output variance, we can notice a ramp type response to step input as shown in Figure 2.9, model 1. Similarly in the same figure, we show step responses of five models as discussed before in Section 2.5.2.2. We can notice that second input onwards, the responses tend to settle in steady state with some dynamics. In addition, step response bounds can be constructed as shown in Figure 3.18 for example, to give time domain information on the model uncertainty.

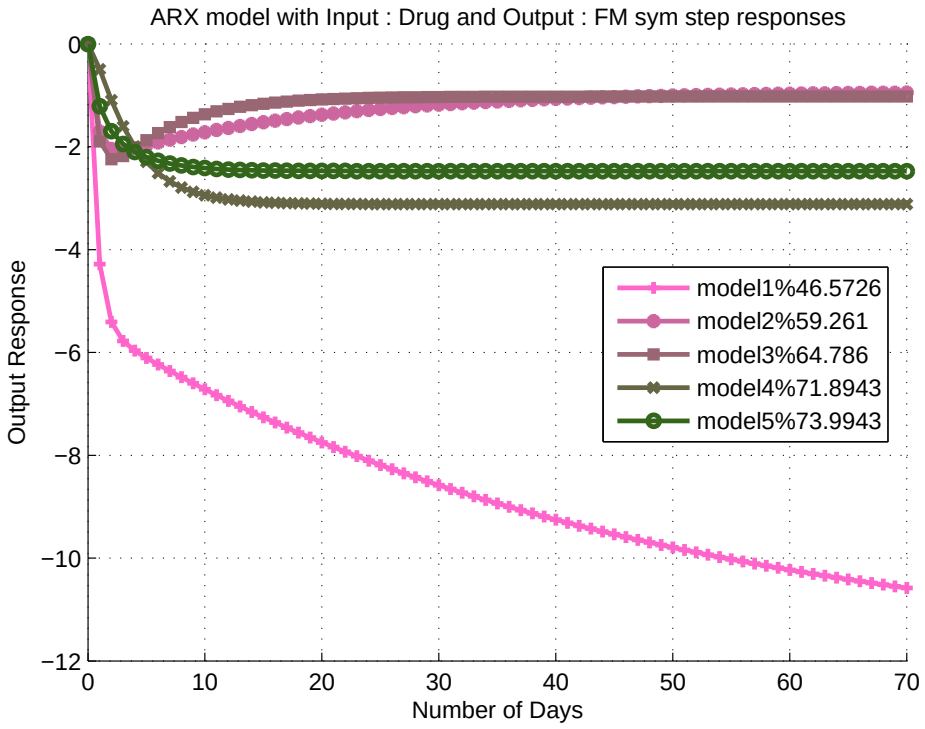


Figure 2.9: ARX model step responses for the drug-FM symptoms as shown for participant 5.

2.9 Algorithms for Input Selection

In previous sections, we discussed on how data is preprocessed, fitted to a parametric model using prediction error methods and then is approximated as a continuous

model. We specifically emphasize how the problem at hand is about estimating multi-input single-output (MISO) models. Hence, in addition to using standard system identification methods we use specific techniques which deal primarily with the choice of inputs for MISO model estimation. These methods are:

- *Manual method*

  In this procedure, we manually add or remove inputs and experiment with different orders and input combinations to arrive at a conclusion. We try to answer the question: Which input combination will best describe the output variance? The best input combination is such that a trade off between bias and variance is achieved. There also could be *a priori* knowledge that enters into choices of inputs in this approach. First, we also look for cross correlation of those variables with output (e.g., FM sym) and if significantly correlated, that variable can be probably classified as an output. This implies that as pain symptoms go down, the variable under choice also changes indicating a possible output. Now, excluding these variables and forming a sub-domain of *m* inputs, we can estimate multi input models. Not all inputs can be chosen from this set; we choose those variables which we feel are good candidates as inputs. This is tested, first, by primarily looking at any significant cross correlation and cross spectra (such variables are not good inputs as they will result in a biased estimate) and secondly by looking the improvement in the model fit (if any). Each input combination will differ for each participant and hence the model is adapted to the dynamics of each participant (and underlines our approach for single subject analysis). In each estimated model, we look at different model fits for different input combinations, their step responses and finally, we validate the model using residual analysis and other

model validation methods.

- *Step-by-Step method*

  In step-by-step method, we first define a criteria based on which model quality can be judged initially. For example, let us consider this criteria to be percent fit. The algorithm then first estimates a SISO model with the input which best described the output variance. This input is selected out of a given *n* inputs by the user. After this, the algorithm estimates a two-input model where the first input was already selected in previous step. Hence, the best second input which describes the output variance is selected and the process is repeated until the best model structure is found. If we use percent fit as the criteria, there is no check for over parametrization and hence we have to rely on user discretions for model interpretation. As an alternative, Akaike's Final Prediction Error (FPE) can also be used as the criteria. The final model obtained is then validated with standard tests such as residual analysis. If the model is not validated, the process is repeated with different input combinations. For many participant cases, the step-by-step procedure converged to the multi-input model estimated manually by the user thus validating each other in process.

- *All-combinations method*

  This is a brute force approach where a particular outcome is selected as output (e.g, pain) and then the algorithm estimates all possible input combinations (i.e., 1-input, 2-input,.., *m*-input) models and uses a criteria to find the best possible model. The total number of models that have to evaluated in this

method can be given as:

$$\binom{m}{1} + \binom{m}{2} + ... + \binom{m}{m} = 2^m - 1 \tag{2.50}$$

This approach is used primarily to see if there are any other input combination which might have been overlooked by previous two approaches. In most of the cases, the models arrived upon by manual choices or by the step-by-step method represent the best possible model description under given model orders. This was confirmed with comparison of model from all-combinations approach where it was noted that adding too many inputs resulted in an over parametrized model which though of a higher fit is not necessarily predictive. The results from this method have not been presented in this thesis for brevity.

Chapter 3

ESTIMATING PARSIMONIOUS MODELS: RESULTS AND SUMMARY

3.1 Overview

In this chapter, we illustrate the system identification modeling procedure discussed in Chapter 2. We provide a summary and tabulation of responses from all participants, presenting one final dynamical model which best describes their response. To further expand the modeling discussion, we rely on two representative cases: 'Participant #5' from the pilot study and 'Participant #38' from the full study. Both of these participants are responders to drug.

To analyze the intervention, we build multi-input single-output models for each participant where the outcomes of interest are used as outputs (e.g., pain and overall sleep) and drug, placebo other external factors are used as potential inputs. For reference, we restate our modeling steps as following: (i) data preprocessing, (ii) discrete-time parametric modeling using ARX model structure and (iii) simplification to a first and second order continuous time model . We begin with "eyeballing" the available data and looking for changes in the time series, particularly once the drug is introduced. We also use statistical relationships tools such as correlation to extract useful information, such as any cross correlation between possible variables of interest which could give biased estimates (as discussed in Section 2.5.2.1). In the ensuing step, we use an ARX model of order $[2\,2\,1]$ and higher as a base model structure for analysis using possible n_u inputs, as chosen by the user. In an approach to select the input combinations, we present the model estimation method using the 'manual method' i.e. the model cases which are chosen manually by looking at the input signal correlations, power spectra and then finally comparing based on model fit and residual analysis of the estimated model. In this method, we

aim at not including ‘too’ many inputs, as overfitting will reduce predictive ability. We also briefly explore the alternative i.e., the ‘step-by-step’ approach, as described in Section 2.9, as an alternative where we use the percent fit as the criteria to choose inputs.

Looking at the available variables as inputs from the daily diary report, we can list them as (1) drug (2) placebo (3) life (4) sadness (5) anxiety (6) stress (7) mood (8) think and remember (9) gastric symptoms (10) headaches (11) toleration (12) side effects . It can be noted the variables included here are assessed on a scale of $0 - 100$. This leaves potentially 12 variables as inputs. Data from the physical tests has not been used for modeling purposes. Also, adding typical ‘outputs’ as inputs did not yield good estimates and hence their inclusion is not seen as beneficial. The initial model is formed with drug as input and FM symptoms as output. In the second model, placebo is added as the second input. For the manual method, similarly more inputs are added to the primary inputs (drug and placebo) as they result in better goodness of fit. In case of step-by-step method, the algorithm chooses the inputs. In all these models, FM symptoms is kept as the only output. A similar procedure can be adopted for other outputs, and is further examined in our analysis for the case of overall sleep variable as output.

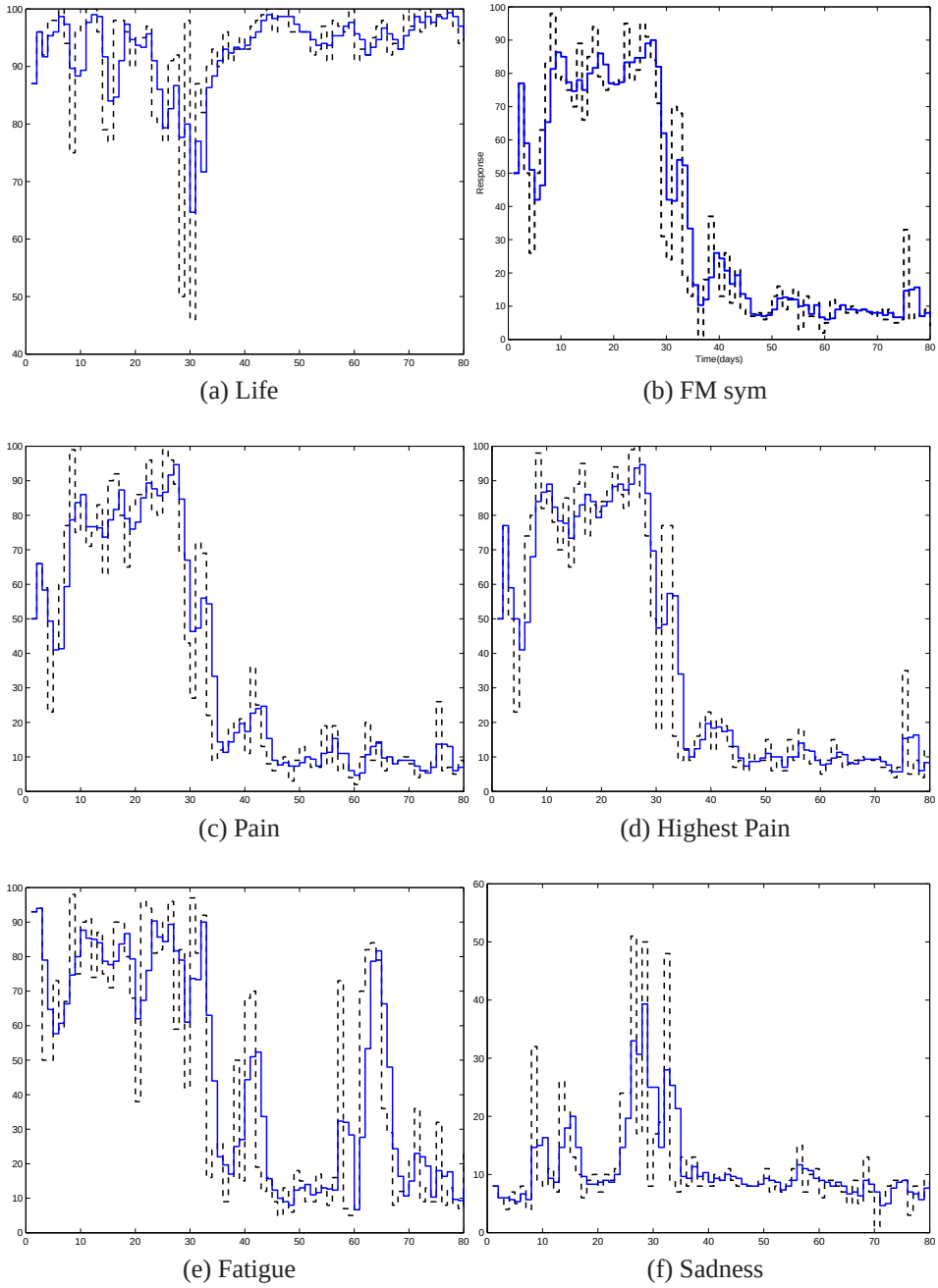
The rest of the chapter is organized as follows. In Section 3.2, we discuss the modeling results for Participant 5. Section 3.3 provides a summary of results for all the participants in the pilot study. In Section 3.4, we apply the procedure, as explained for Participant 5, to illustrate modeling results for Participant 38. In Section 3.5, we summarize the results for all the participants in the full study and we end with comments on the secondary data analysis for naltrexone intervention in Section 3.6.

3.2 Participant 5

The original data was treated for missing entries using simple mean of immediate neighbors and was prefiltered with a three day moving average. There were some missing days but there were no cases where data was missing for many consecutive days (where the method using means will fail). First, let us examine various time series for this participant as shown in Figures 3.1-3.4. This participant is a particular example of a typical 'responder' or a subject that shows a strong reaction to drug in reducing general pain symptoms (see Figure 3.1b). In addition to the primary outcome, we notice that overall sleep quality (Figure 3.2e), fatigue (Figure 3.1e), gastrointestinal symptoms (Figure 3.3a) and headaches (Figure 3.3b) also improve with drug administration.

Next, we look at possible cross correlation between variables which can be added as inputs. As drug and placebo are used as primary inputs, we are interested in their time lagged correlation functions with the 12 potential inputs as well as other outputs. The cross correlation plot for drug is shown in in Figure 3.5 and for placebo in Figure 3.6. In both figures, the horizontal band represent the bound for statistical significance at two standard deviation i.e. $\simeq$ 95% confidence interval. The correlation has been shown for $\pm$20 lags.

First, we note that drug and placebo are significantly correlated at time lags away from zero. This is primarily due to the experimental design where there was no 'gap' between the time drug was stopped and placebo was administered and vice-versa. It can be argued that a washout period between drug and placebo would have helped reduce the cross correlations. Since this is a secondary analysis, we neglect this consideration and proceed with other inputs. In the case of drug, it has almost significant cross correlation at lags for most of the variables although at lag

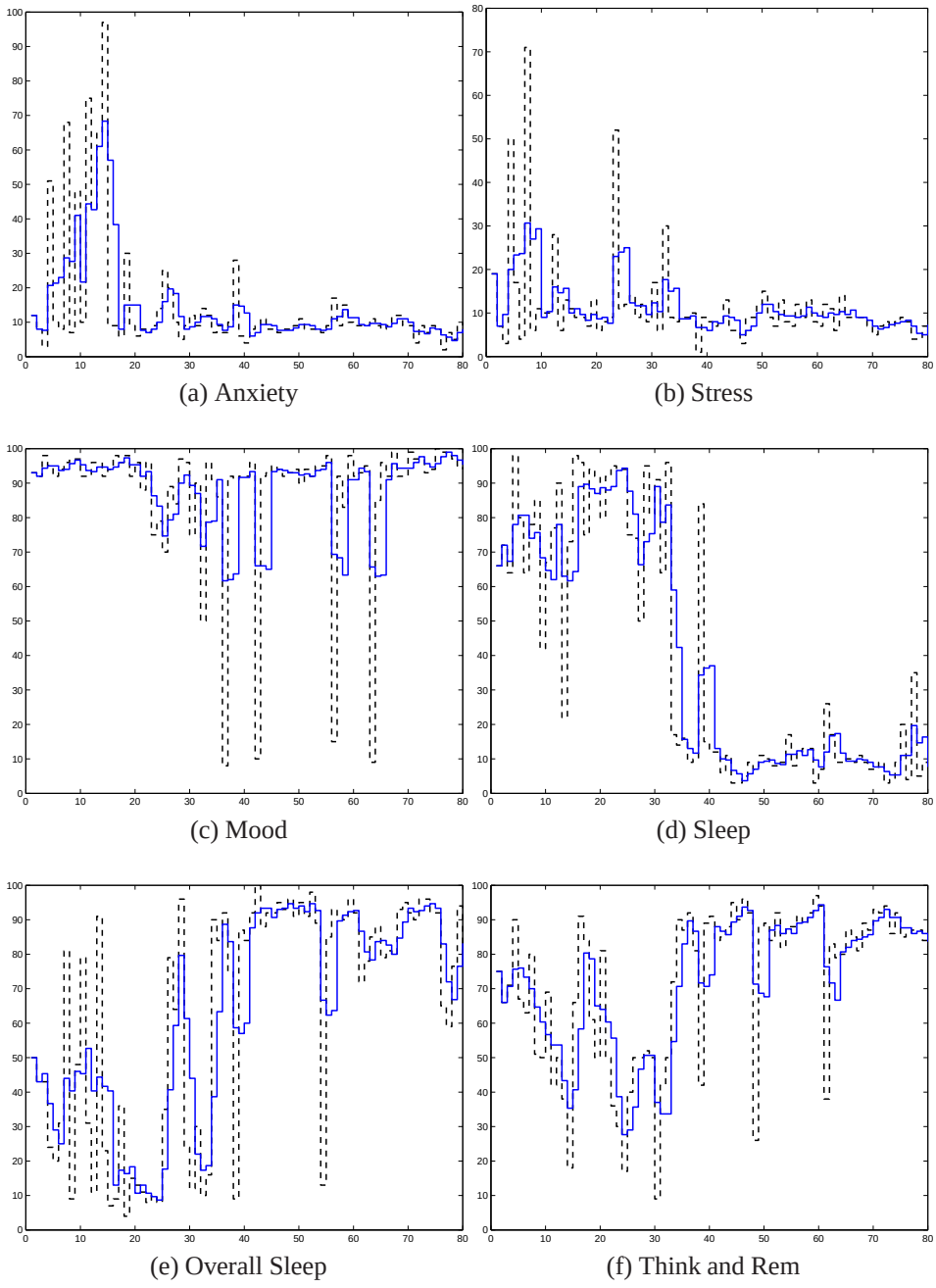


(a) Life (b) FM sym

(c) Pain (d) Highest Pain

(e) Fatigue (f) Sadness

Figure 3.1: Original data time series (dashed) with three day moving averaged data (solid) for variables 1 through 6 for Participant 5. X-axis represents time (days) and Y-axis represents the response.

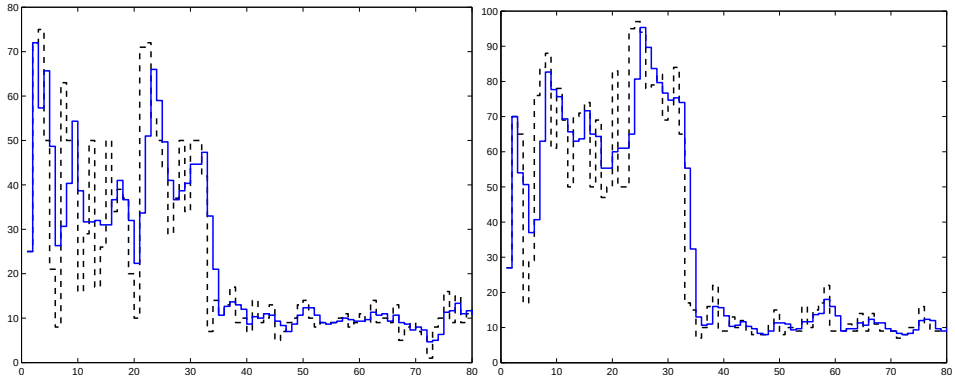


(a) Anxiety (b) Stress

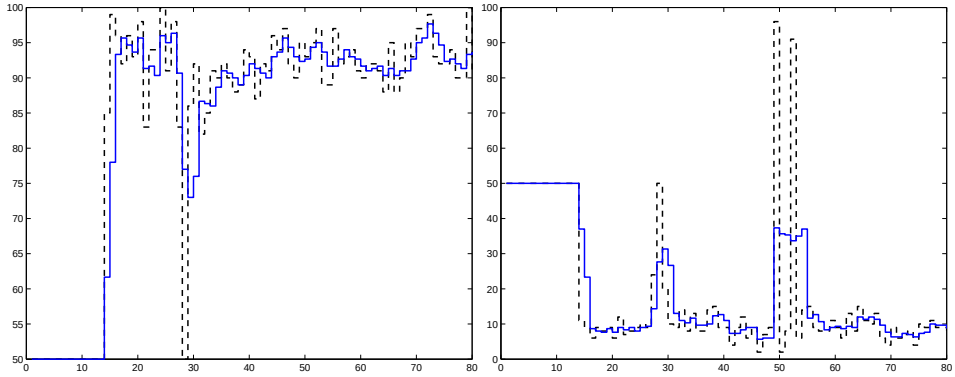
(c) Mood (d) Sleep

(e) Overall Sleep (f) Think and Rem

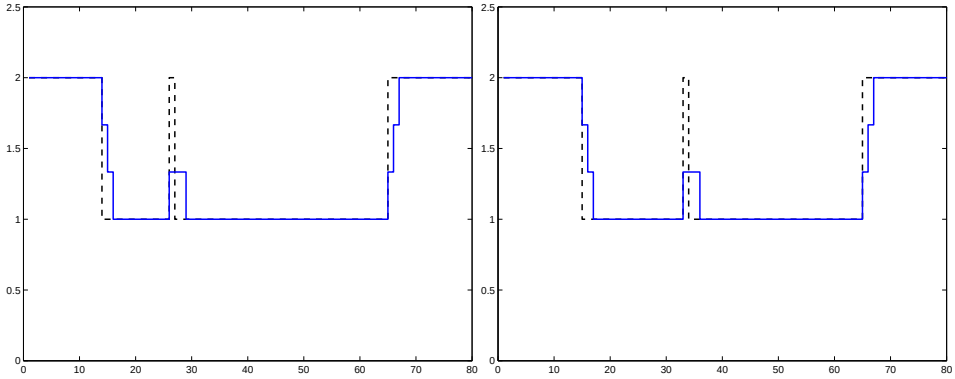
Figure 3.2: Original data time series (dashed) with three day moving averaged data (solid) for variables 7 through 12 for Participant 5. X-axis represents time (days) and Y-axis represents the response.



(a) Gastric (b) Headaches

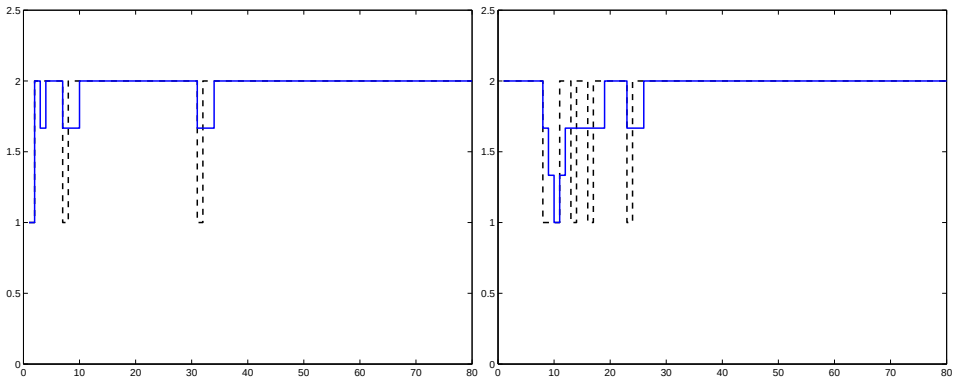


(c) Toleration (d) Side Effects



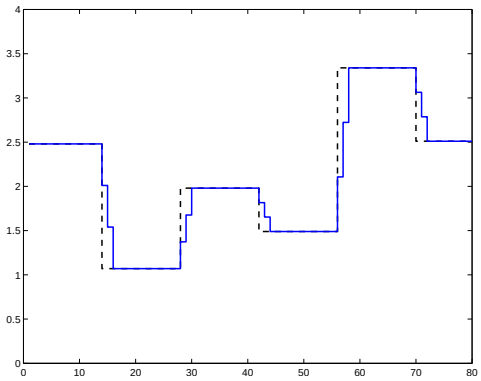
(e) Capsule for tonight (f) Capsule for last night

Figure 3.3: Original data time series (dashed) with three day moving averaged data (solid) for variables 13 through 18 for Participant 5. X-axis represents time (days) and Y-axis represents the response.

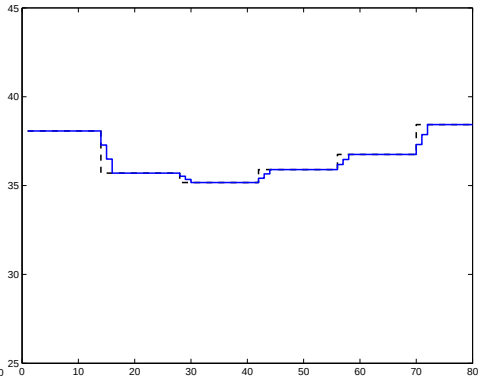


(a) Unusual stressful event

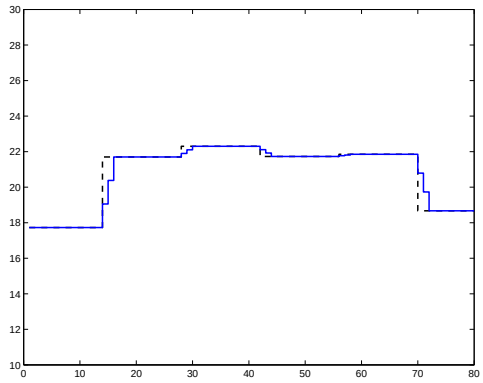
(b) Any other pain medication



(c) Mechanical pain



(d) Thermal pain

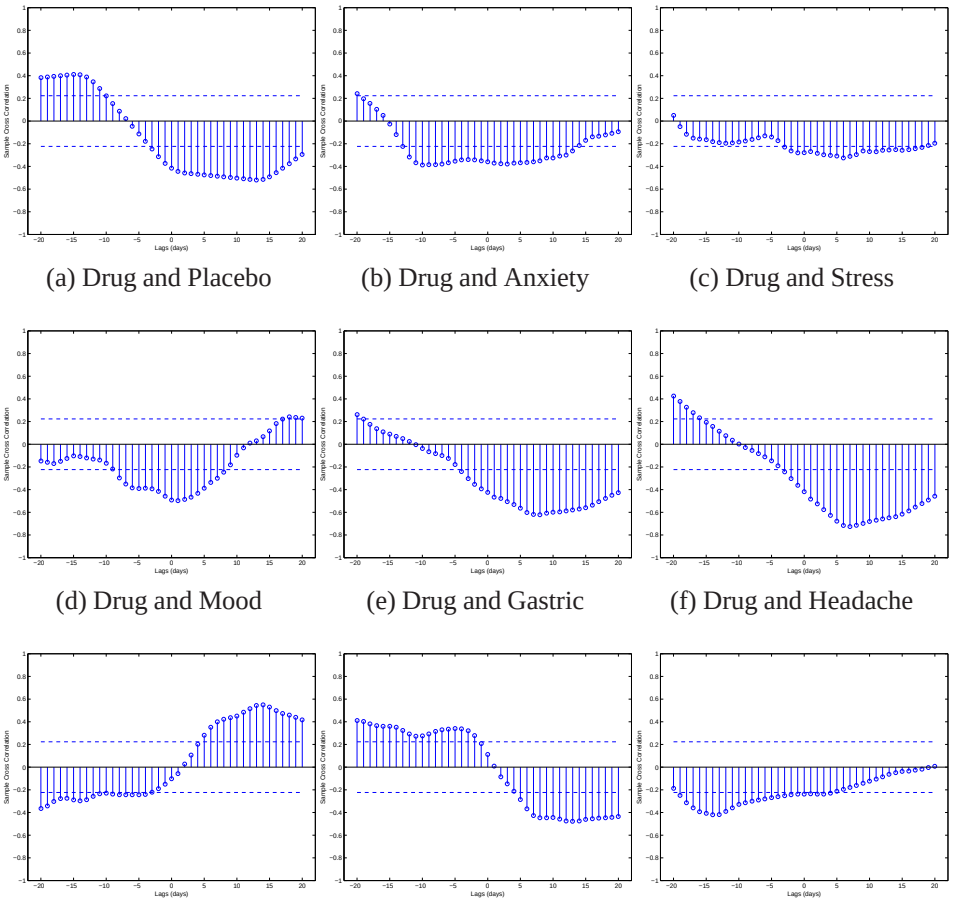


(e) Cold pain

Figure 3.4: Original data time series (dashed) with three day moving averaged data (solid) for variables $19, 20$ and the three measurements from physical tests for Participant 5. X-axis represents time (days) and Y-axis represents the response.

0, we do not see a very strong relation. Similarly for placebo, we see significant correlation with most of the inputs and is more prominent than that in the case of drug. An important inference can be made that in most of the cross correlation scenarios, the correlation of drug with other variables is in positive or in other words it helps in improving the symptoms where as for placebo, we see mostly correlation is negative implying worsening of condition with introduction of placebo. As will be noted in the discussion on model gains, the placebo response is with a positive gain for placebo-FM model.

After evaluating the correlations associated with drug and placebo, we look at other variables. In Figure 3.7 and 3.8, we show cross correlations between anxiety, mood, stress, gastric and headache and note that variables gastric and headache are cross correlated with rest of the them (i.e., anxiety, mood, stress) as well as with the output (FM sym) (as shown in Figure 3.8) and hence excluding them may be necessary. These cross correlations give insights into the potential bias if used as inputs and will be used later on in the chapter.

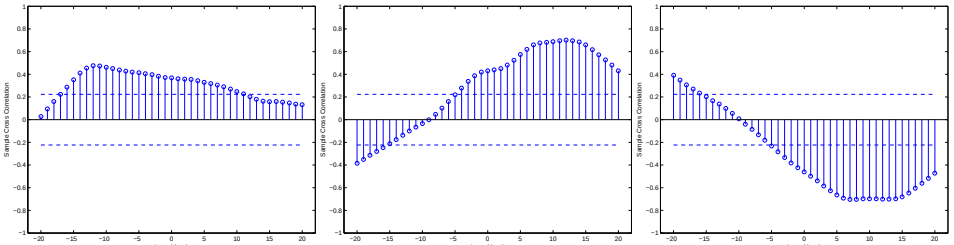


(a) Drug and Placebo (b) Drug and Anxiety (c) Drug and Stress

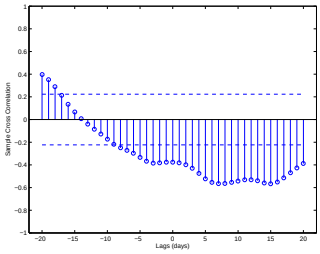
(d) Drug and Mood (e) Drug and Gastric (f) Drug and Headache

(g) Drug and Life (h) Drug and Sadness (i) Drug and Side Effects

Figure 3.5: Correlation plots between drug and other variables with two standard error bounds over $\pm$ 20 lags for Participant 5 (cont.).

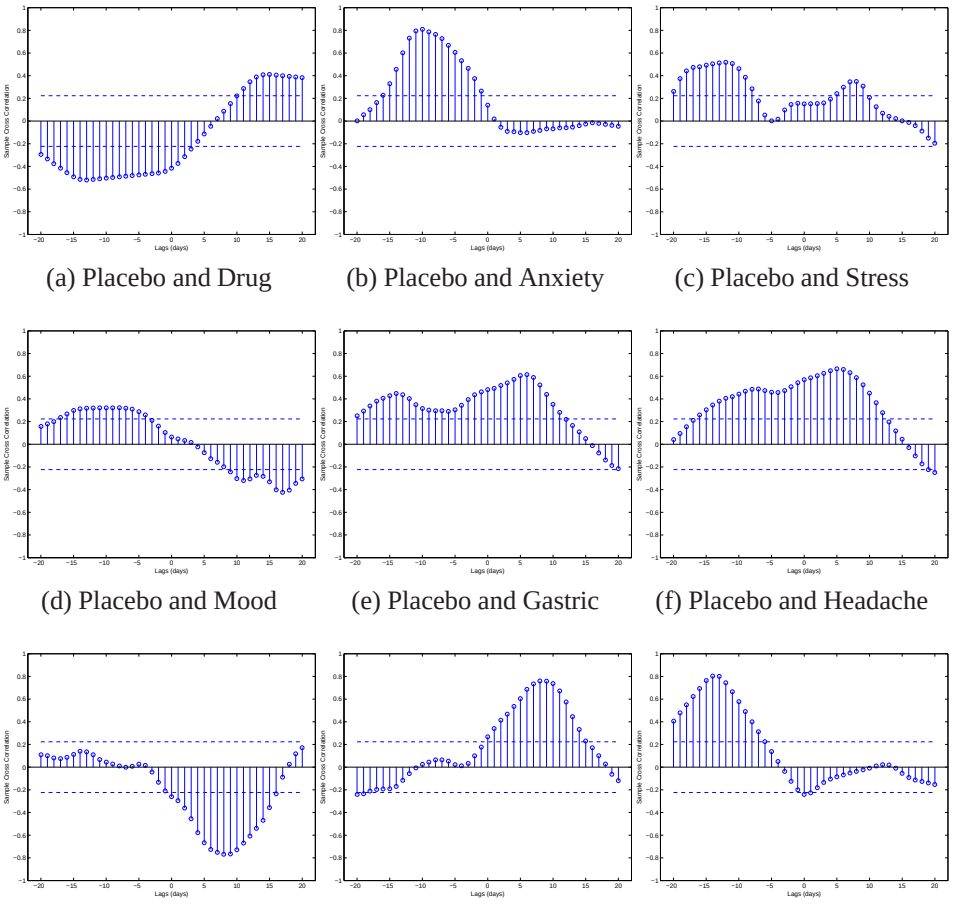


(j) Drug and Toleration (k) Drug and OSleep (l) Drug and Sleep



(m) Drug and Fatigue

Figure 3.5: Correlation plots between drug and other variables with two standard error bounds over $\pm$ 20 lags for Participant 5.

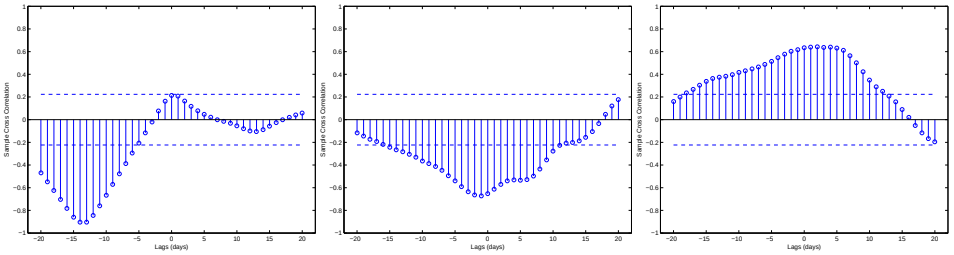


(a) Placebo and Drug (b) Placebo and Anxiety (c) Placebo and Stress

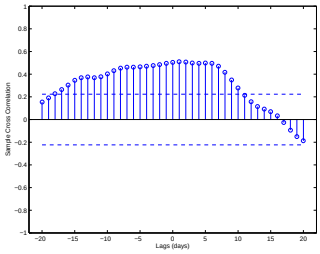
(d) Placebo and Mood (e) Placebo and Gastric (f) Placebo and Headache

(g) Placebo and Life (h) Placebo and Sadness (i) Placebo and Side Effects

Figure 3.6: Correlation plots between placebo and other variables with two standard error bounds over $\pm$ 20 lags for Participant 5 (cont.).

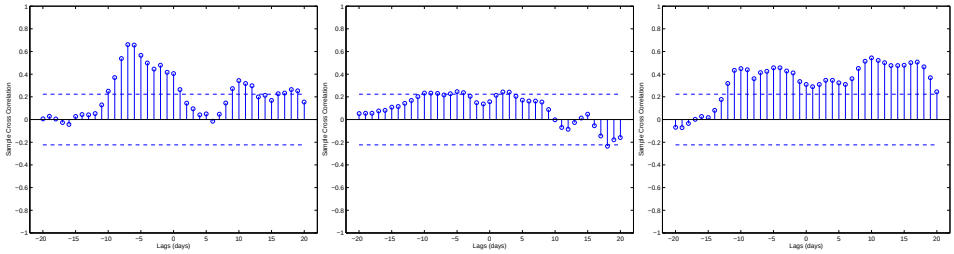


(j) Placebo and Toleration (k) Placebo and OSleep (l) Placebo and Sleep

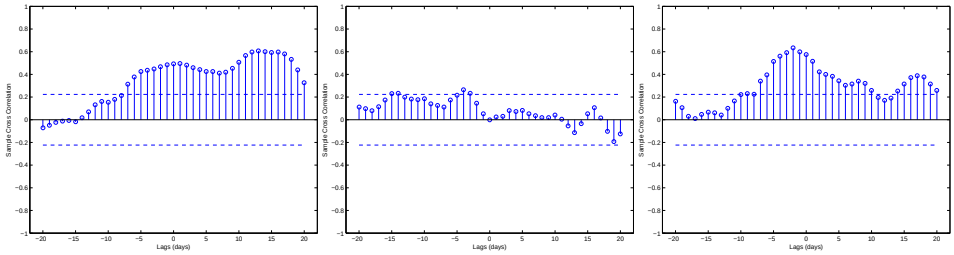


(m) Placebo and Fatigue

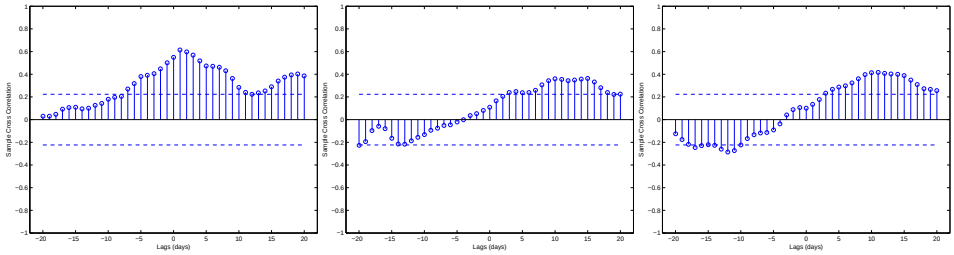
Figure 3.6: Correlation plots between placebo and other variables with two standard error bounds over $\pm$ 20 lags for Participant 5.



(a) Anxiety and Stress (b) Anxiety and Mood (c) Anxiety and Gastric



(d) Anxiety and Headache (e) Stress and Mood (f) Stress and Gastric

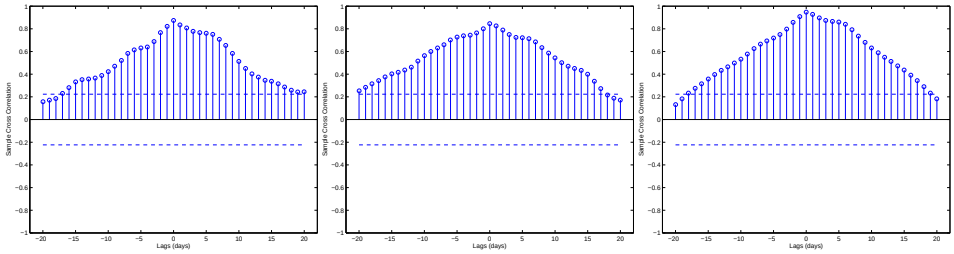


(g) Stress and Headache (h) Mood and Gastric (i) Mood and Headache

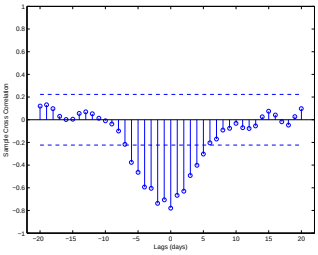
Figure 3.7: Cross correlation plots between some selected variables with two standard error bounds over $\pm$ 20 lags for Participant 5.

Before moving on to estimating models, we look at the power spectra for various variables involved in this study as shown in Figures 3.9, 3.10 and 3.11. We note that different magnitudes for some signals is due to the different units of measurements that are used (e.g. drug (mg), thermal pain ($^{\circ}$C)). From theory, we note that system identification results in frequency band without excitation may be highly uncertain [35]. It can be noted in Figure 3.9-3.11, the bandwidth of the available signals is approximately 0.6 rad/day.

Upon experimenting with several input combinations, we can construct the fol-



(a) Gastric and headache (b) FM sym and gastric (c) FM sym and headache



(d) Life and sadness

Figure 3.8: Cross correlations between selected variables (including the output FM sym) with two standard error bounds over $\pm$ 20 lags for Participant 5.

lowing seven models for our analysis of Participant 5:

1. Model 1 (Drug)

2. Model 2 (Drug, Placebo)

3. Model 3 (Drug, Placebo, Anxiety)

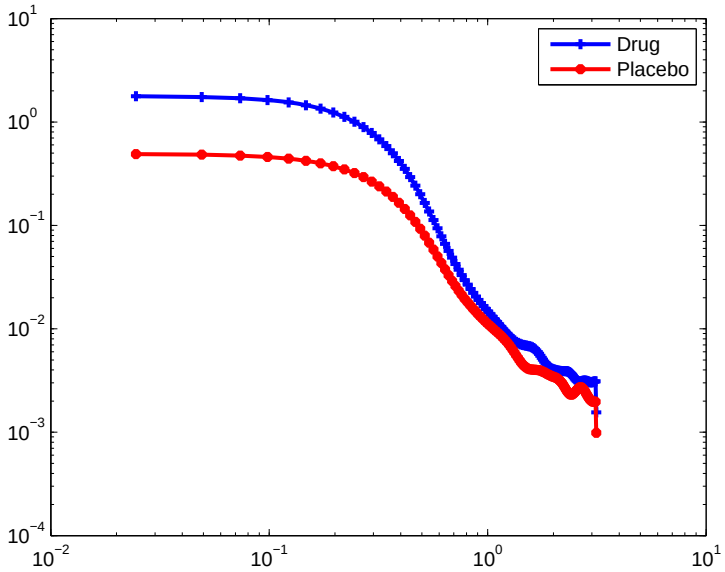
4. Model 4 (Drug, Placebo, Anxiety, Stress)

5. **Model 5 (Drug, Placebo, Anxiety, Stress, Mood)**

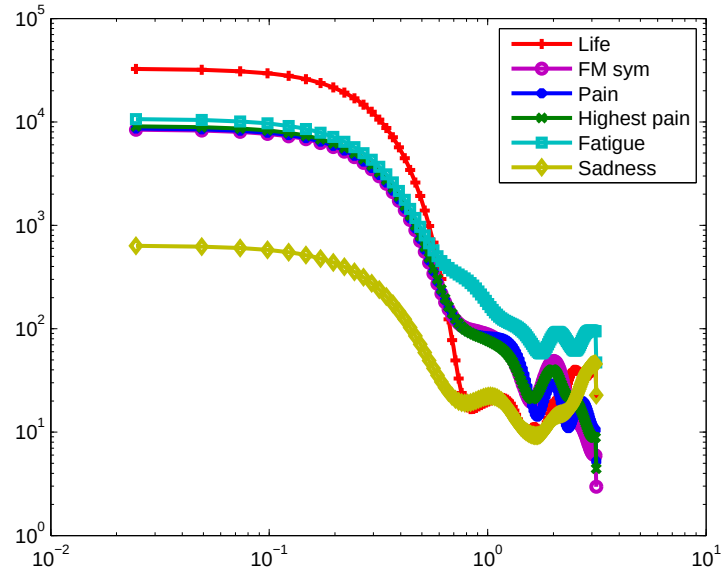
6. Model 6 (Drug, Placebo, Anxiety, Stress, Mood, Gastric)

7. Model 7 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache)

8. Model 8 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life)

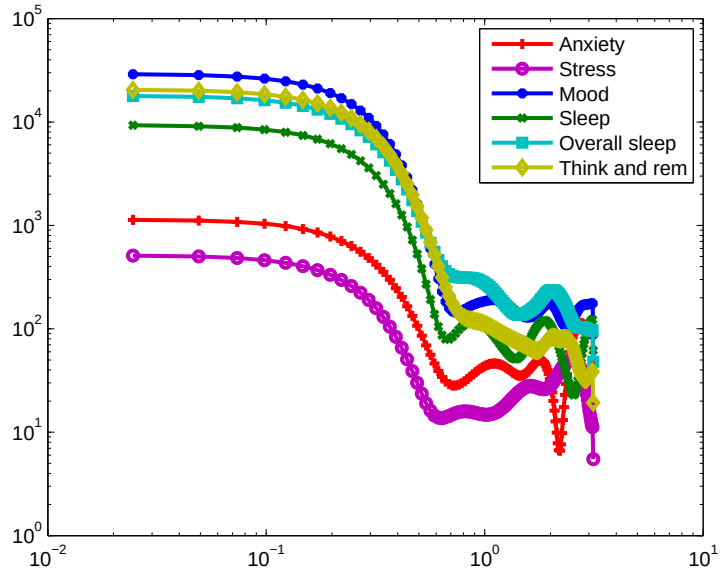


(a) Drug and Placebo

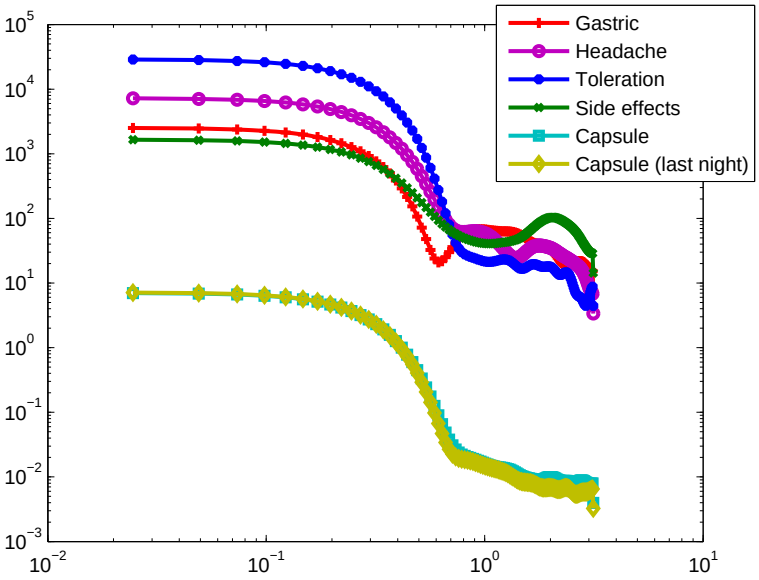


(b) Variable 1 through 6

Figure 3.9: Power spectral density of all variables for Participant 5.

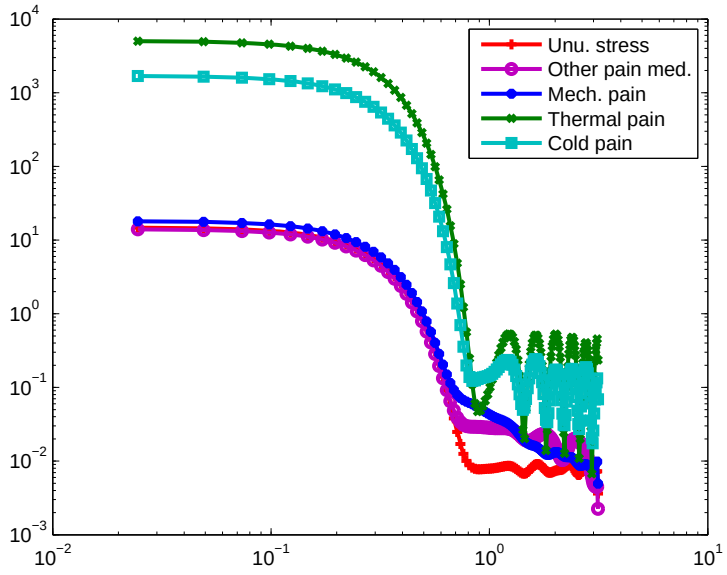


(a) Variable 7 through 12



(b) Variable 13 through 18

Figure 3.10: Power spectral density of all variables for Participant 5.



(a) Variable 19 through 23

Figure 3.11: Power spectral density of all variables for Participant 5.

9. Model 9 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life, Sadness)

Each of these models has FM sym variable as its output. Although we do include life and sadness as potential inputs as they are not very strongly correlated with other variables (although it can be noted they are cross correlated among themselves as in Figure 3.8), these variables did not cause any significant change in model accuracy. The case of Model 5, in our opinion, works best among the choices available as these input combinations did not seem to correspond to overparameterization; this is further discussed in the following paragraphs. It is important to note that this conclusion is only for participant 5 and cannot be generalized.

ARX [2 2 1] models were found to be adequate and hence higher model orders were not used. When higher order models were used, the model step response was observed to be unstable. Further adding headache and gastric (i.e. model 6 and 7)

did not yield any significant improvements. Adding variables 'toleration' and 'side effects' did not yield any good estimates either. Similarly life and sadness also did not add much to the discussion. It should be mentioned here that just using drug and placebo as inputs yields a model fit of upto 59% which suggests that drug and placebo have a strong effect on the output and hence the model can explain a significant amount of output variance as shown in Table 3.1. In conclusion, choosing inputs is first initiated by looking the time series, their cross correlations and then the final usefulness is judged by the quality of models resulting from them.

Table 3.1: Tabulation of model fits of models using FM sym as output, for participant 5.

Model	% fit
1	46.5
2	59.2
3	64.7
4	71.8
5	73.9
6	71.1
7	74.4
8	74.5
9	79.6

The evolution of percent fit is shown in Figures 3.13 and 3.14 as represented by model 1 to model 9. It can be observed that after model 5, the fit does not improve significantly as well as do the steady state gains and hence can be see as an increasing signs of over parametrization. The models are first validated using the standard residual analysis [35]. Figures in 3.12, we show autocorrelation of the residual and cross correlation of the residual with other inputs and hence the estimated model passes the whiteness test. If the model is assumed to be in the model class, it can be assumed ideally that model has no significant unmodeled dynamics as well as the parametric uncertainty is reliable [60].

An uncertainty region can be constructed as per the prediction-error framework. Since we do not have the flexibility of input signal design, we have tried the best combination that gives tighter bounds. The bound are show in frequency domain as the Bode plots of estimated models along with the corresponding model error models (as discussed in Section 2.8) in Figures 3.15-3.16. The bound is shown in the shaded region around the nominal or mean response representing 95% confidence region. The model error model is estimated using the high order ARX $[8\,8\,0]$. Althouh the model error model response is smaller in magnitude as compared to corresponding Bode plot for the nominal model, we do not have tight bounds. The same can be said about the bounds for the nominal model, that these are not tight. Also, in Figure 3.17 we show the frequency magnitude plot for the estimated noise model. It can be noted how the bounds get tighter in the higher frequency region.

Similarly, the bounds (95%) are shown in the *time domain* in Figure 3.18 using the step response although we show only two cases: drug-FM model and placebo-FM model. In all these bounds (both frequency domain and time domain), it is important to state that although the bounds are not very tight for these estimated models, the model has been validated by the residual analysis. Also, as these estimated models do not become unstable due to the uncertainty bounds, they are more or less acceptable for the intended control application. Ultimately, the control design goes hand-in-hand with modeling and hence the control system has to be designed robust enough for plant-model mismatch.

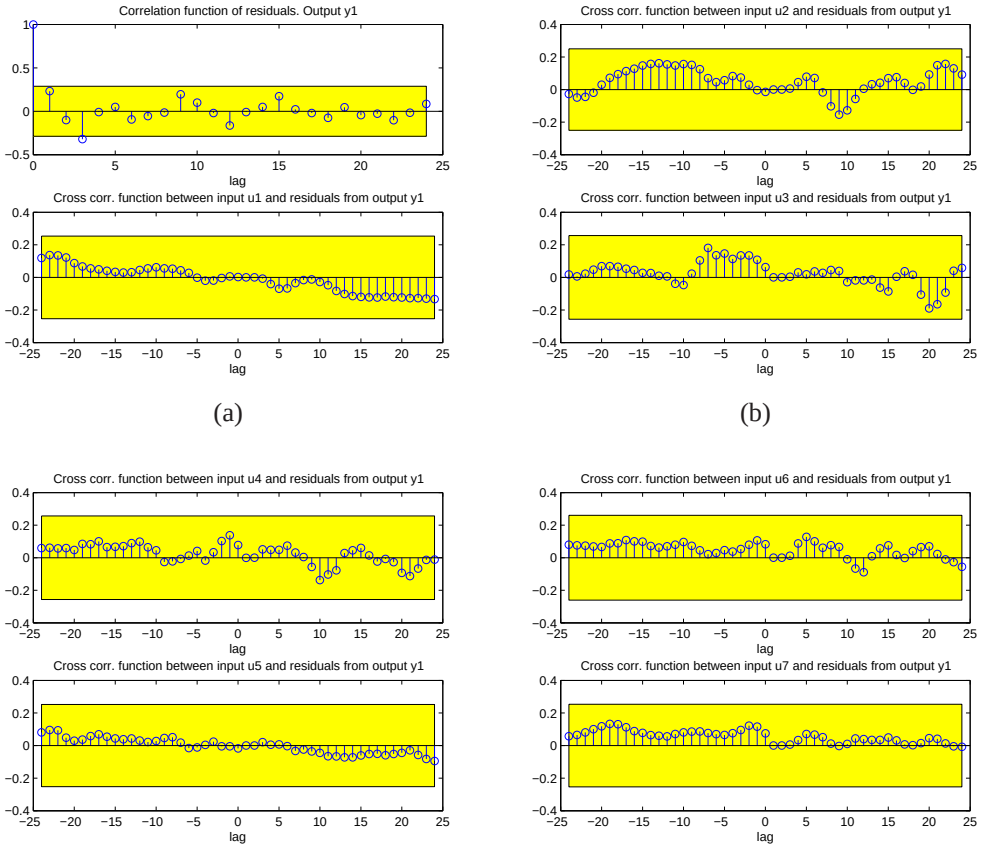
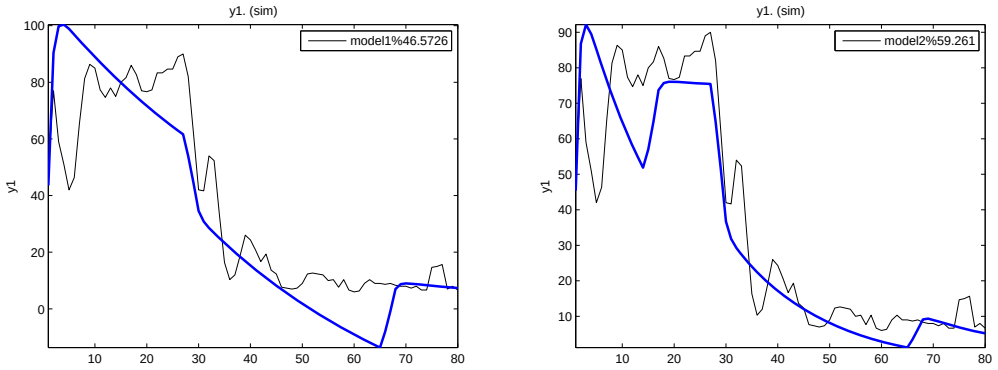
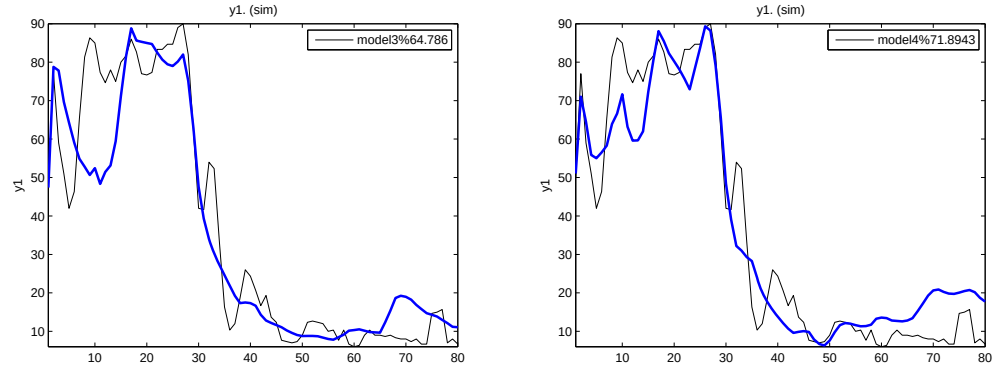


Figure 3.12: Classical correlation analysis test on residuals (with 99% confidence intervals) using 7 inputs (or model 7) for Participant 5. Similarly model 5 meets the requirements for residual analysis.



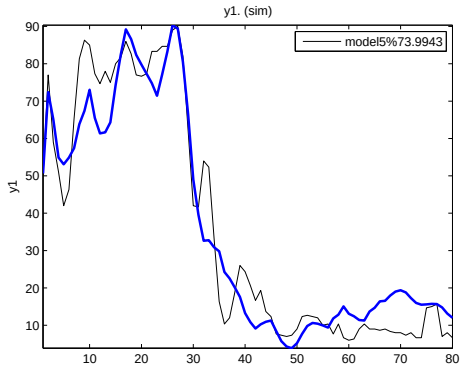
(a) Model 1

(b) Model 2



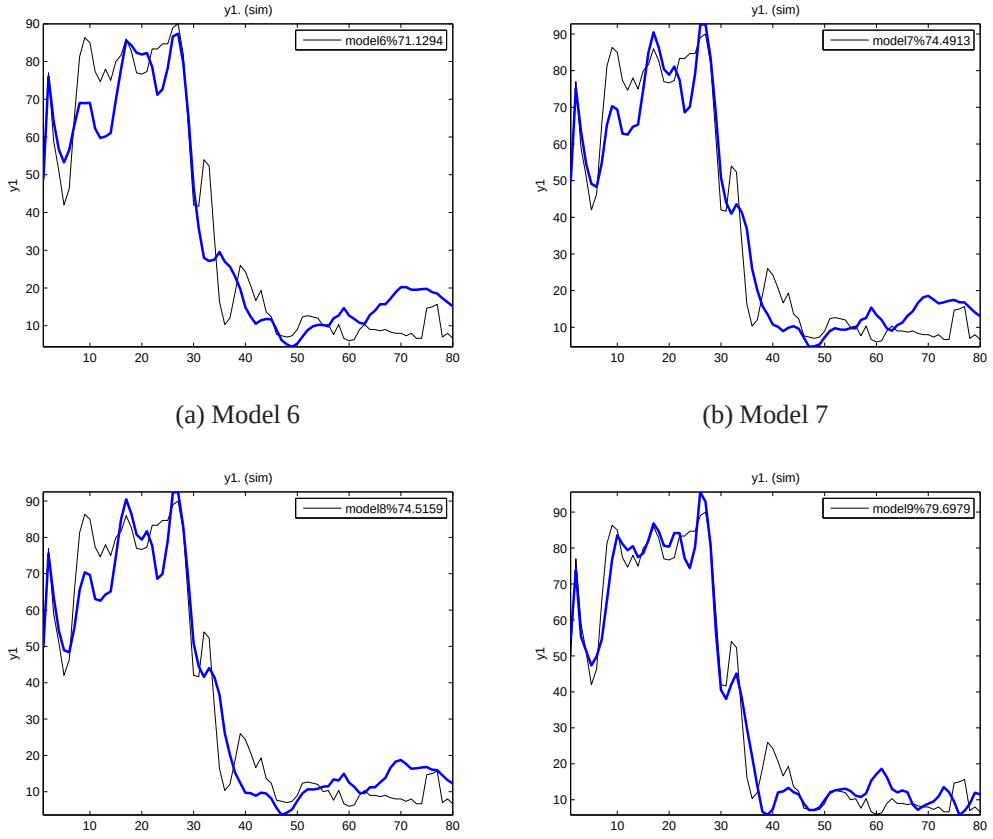
(c) Model 3

(d) Model 4



(e) Model 5

Figure 3.13: Estimated model (1-5) output vs. actual (FM sym) output using ARX [2 2 1] for Participant 5.



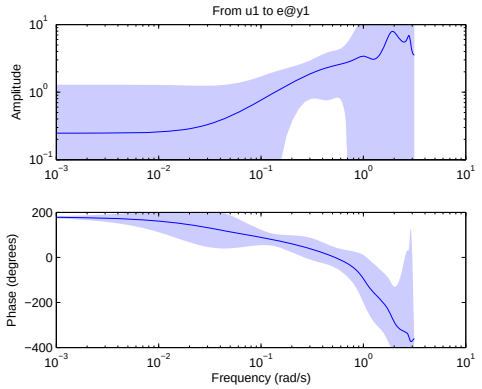
(a) Model 6

(b) Model 7

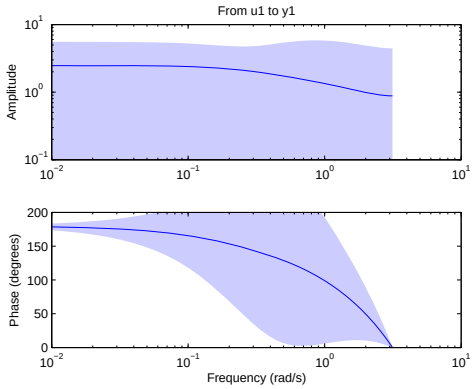
(c) Model 8

(d) Model 9

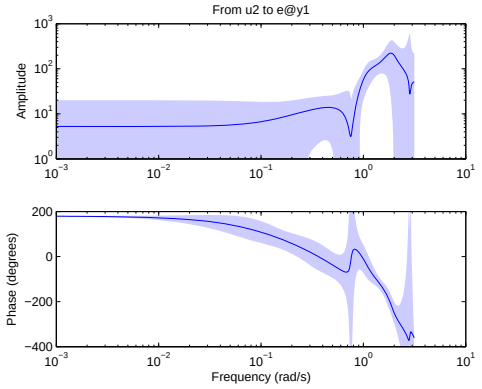
Figure 3.14: Estimated model (6-9) output vs. actual (FM sym) output using ARX [2 2 1] for Participant 5.



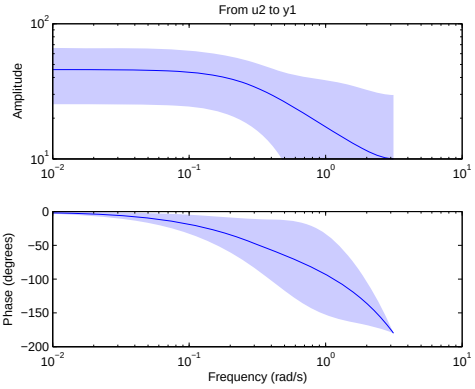
(a) Drug to *e*



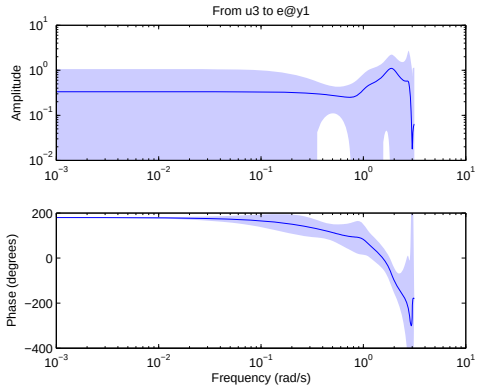
(b) Drug to FM



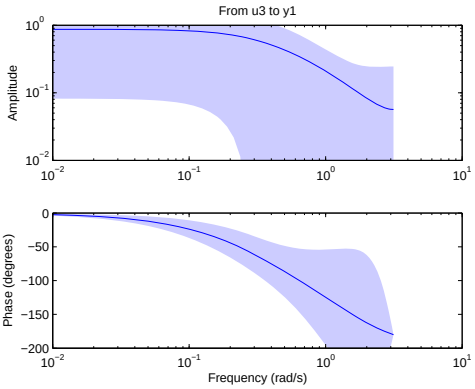
(c) Placebo to *e*



(d) Placebo to FM

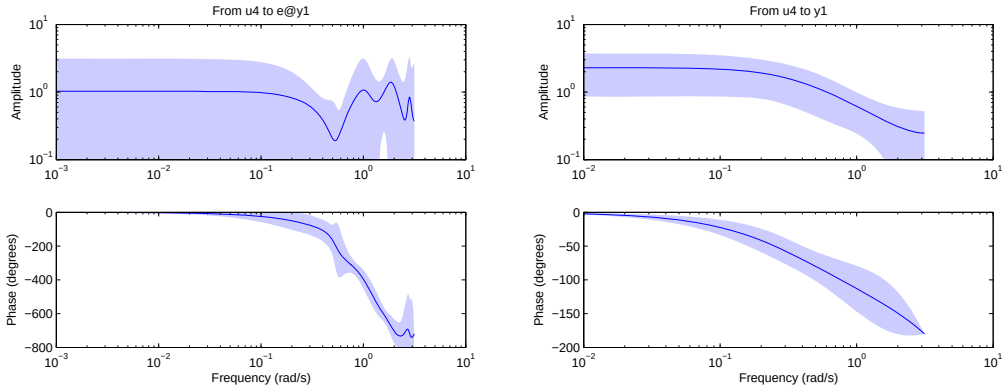


(e) Anxiety to *e*



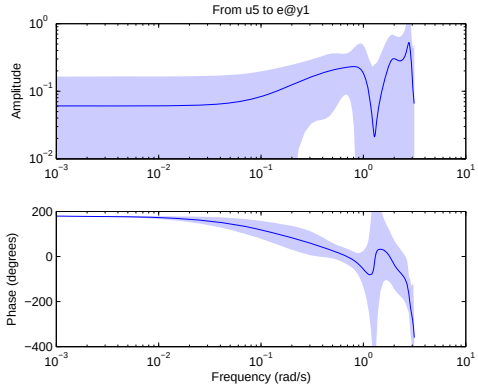
(f) Anxiety to FM

Figure 3.15: Bode plots for the model error model and nominal model (with 95% confidence interval) of estimated ARX model using model 5, for participant 5.

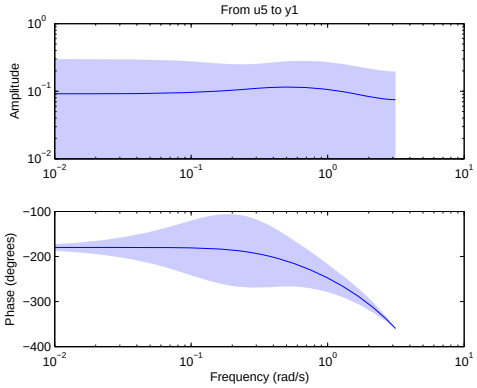


(a) Stress to e

(b) Stress to FM

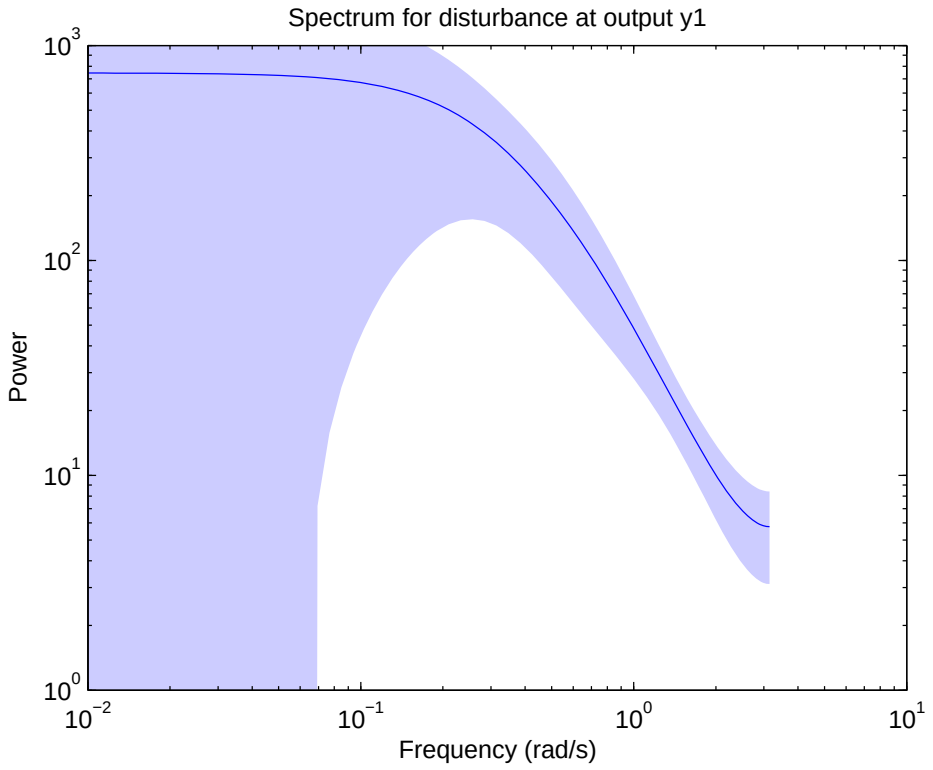


(c) Mood to *e*



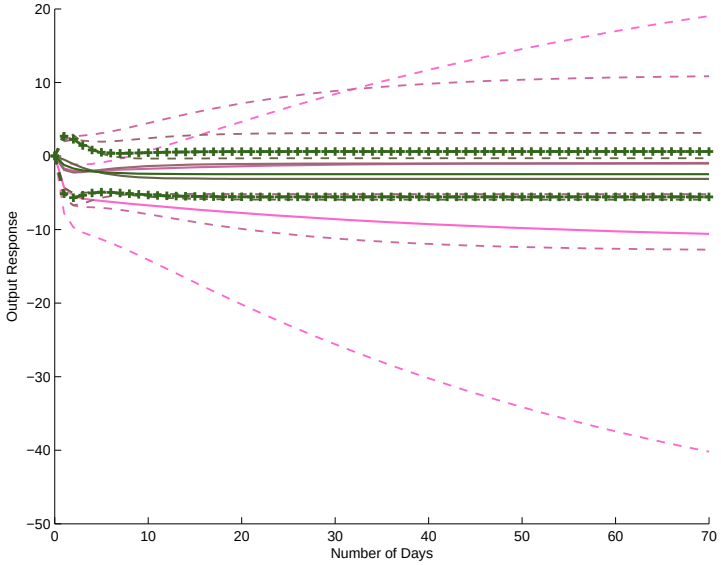
(d) Mood to FM

Figure 3.16: Bode plots for the model error model and nominal model (with 95% confidence interval) of estimated ARX model using model 5, for participant 5.

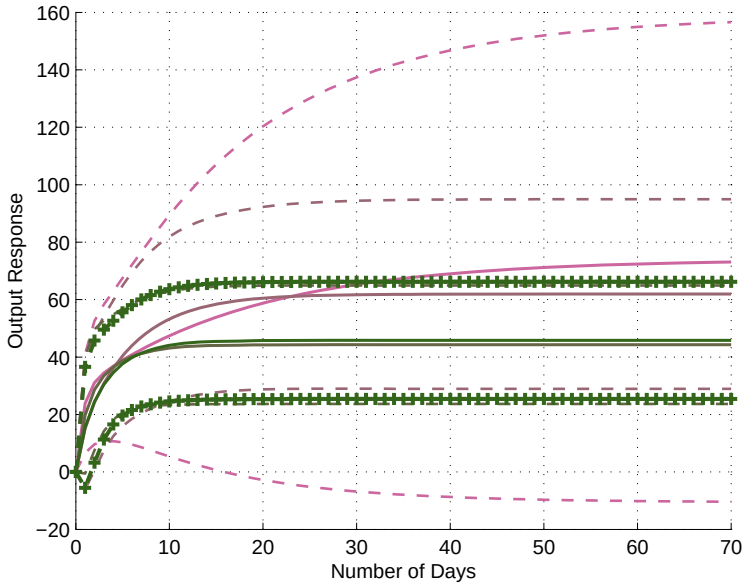


(a) Frequency response of estimated ARX model noise transfer function

Figure 3.17: Frequency magnitude plot (with 95% confidence intervals) of noise model for Participant 5.



(a) Drug to FM



(b) Placebo to FM

Figure 3.18: Step responses with 95% confidence intervals (marked by '+') of model 5 of drug-FM and placebo-FM pairs for Participant 5.

Coming to last step (iii) of system identification procedure, we now present a tabulation of models and step responses. From Figure 3.19 onwards, we show the step responses of estimated ARX model where FM sym is chosen as the output. In each figure, an input is taken from the multiple inputs in the model, and the change in output is seen for a step change in that chosen input. Each figure is also accompanied with tabulation of first and second order continuous time model approximations. It can be restated here that since we estimate five input models, the first input-output pair (namely, drug-FM) is present in five models (i.e. model 1 to model 5), the second input-output pair is present in four models and so on.

The model parameters for each case of step response have been tabulated in Tables 3.2-3.7. Looking at the tabulations for respective step response, we note that the participant responds to the drug with final gain for drug-FM model being negative (implying decrease in pain and this was expected from the time series trends as shown in Figure 3.1b) and the final gain for placebo-FM model is positive (implying worsening of pain). The evolution of the gain and other dynamical system characteristics can also be noted in the tabulations. In Figure 3.24, we show a drug-Overall Sleep model to analyze the effect of drug on sleep. Here we note that the final gain is positive, implying that the administration of drug has resulted in an improvement in sleep.

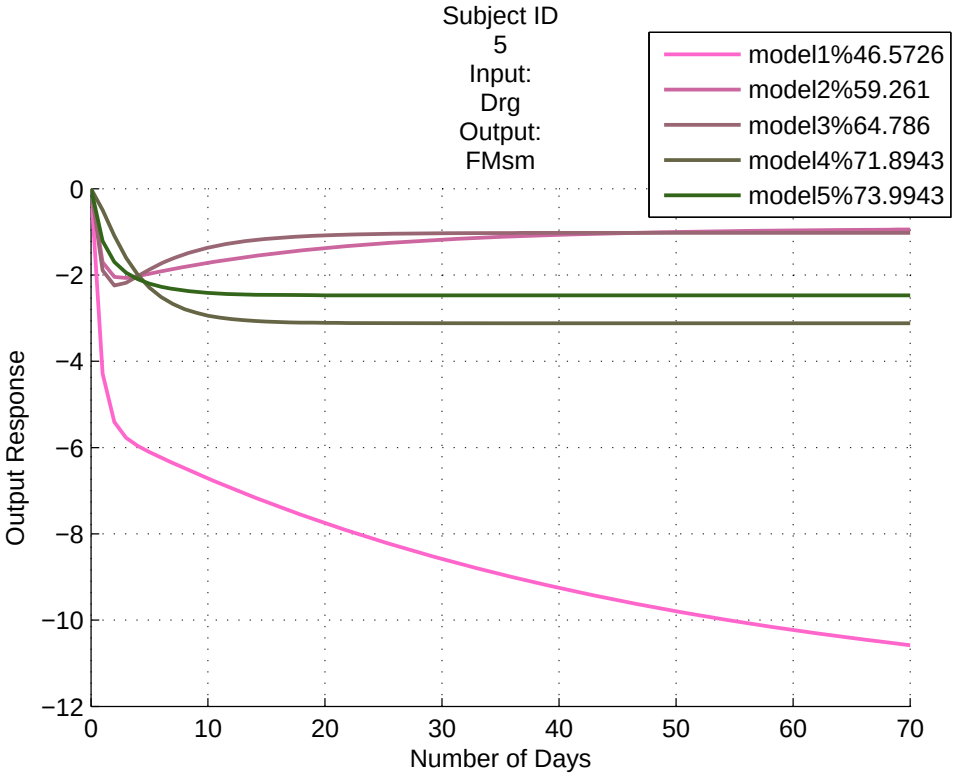


Figure 3.19: Step response of drug-FM model for Participant 5.

Table 3.2: Step response tabulation of drug-FM model for Participant 5.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
1	46.57	-11.82, 4.25	-12.03, 5.67, 4.14, 21.3	75.5	139.69
2	59.26	-1.03, 0.001	-0.91, 3.5, 2.67, 44.4	0.43	75.06
3	64.78	-1.07, 0.001	-1.02, 2.09, 1.5, 15.3	0.43	25.68
4	71.89	-3.11, 3.79	-3.11, 1.62, 1.24, 0.22	7.53	14.38
5	73.99	-2.46, 1.84	-2.47, 1.57, 1.26, 1.96	5.12	11.49

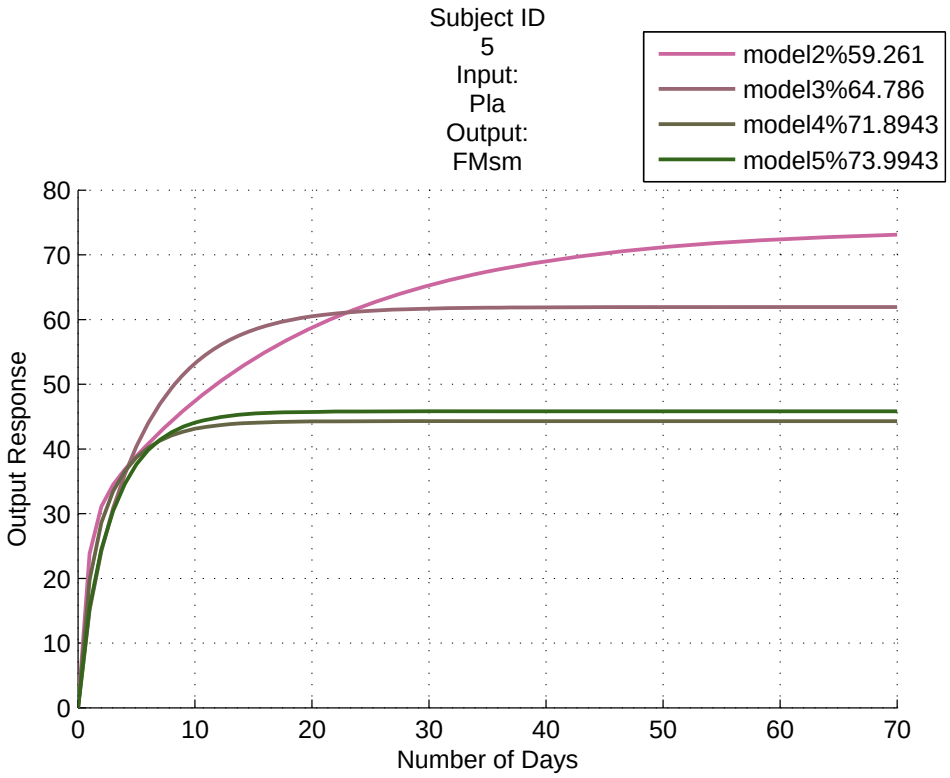


Figure 3.20: Step response of placebo-FM model for Participant 5.

Table 3.3: Step response tabulation of placebo-FM model for Participant 5.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
2	59.26	73.66, 13.71	74.07, 3.5, 2.67, 7.17	32.81	63.18
3	64.78	61.87, 4.89	61.92, 2.09, 1.5, 1.46	11.48	21.79
4	71.89	44.25, 2.09	44.3, 1.62, 1.24, 1.79	5.56	11.96
5	73.99	45.79, 2.78	45.81, 1.57, 1.26, 1.15	6.59	13.06

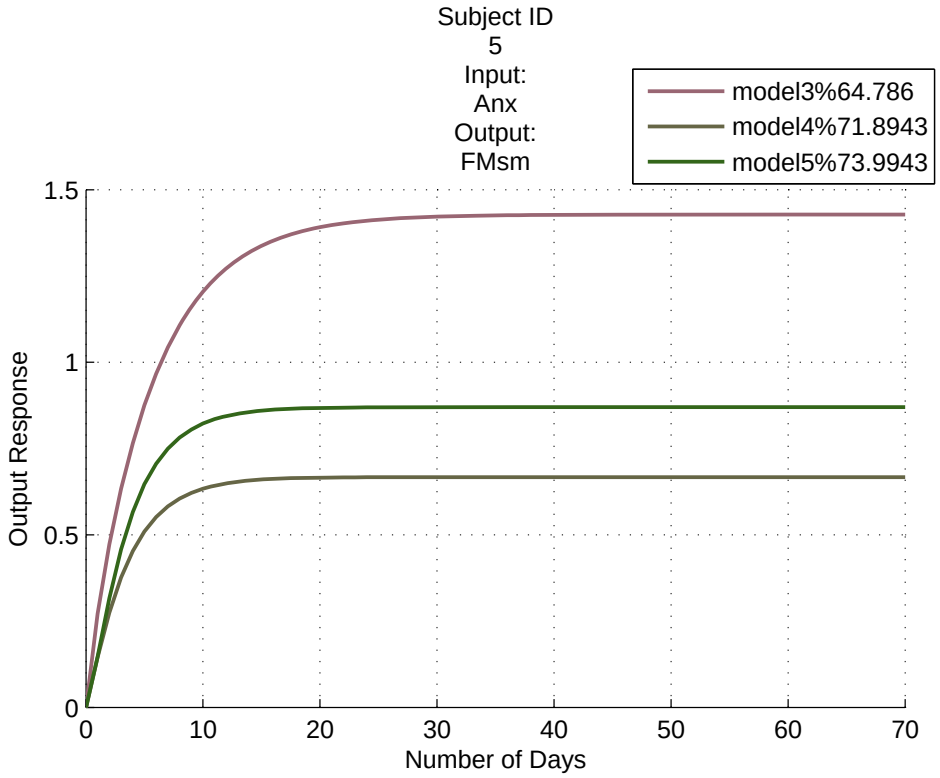


Figure 3.21: Step response of anxiety-FM model for Participant 5.

Table 3.4: Step response tabulation of anxiety-FM model for Participant 5.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
3	64.78	1.42, 5.34	1.42, 2.09, 1.5, 1.04	11.97	21.39
4	71.89	0.66, 3.49	0.66, 1.62, 1.24, 0.54	7.34	13.98
5	73.99	0.87, 3.72	0.86, 1.57, 1.26, 0.24	7.45	14.24

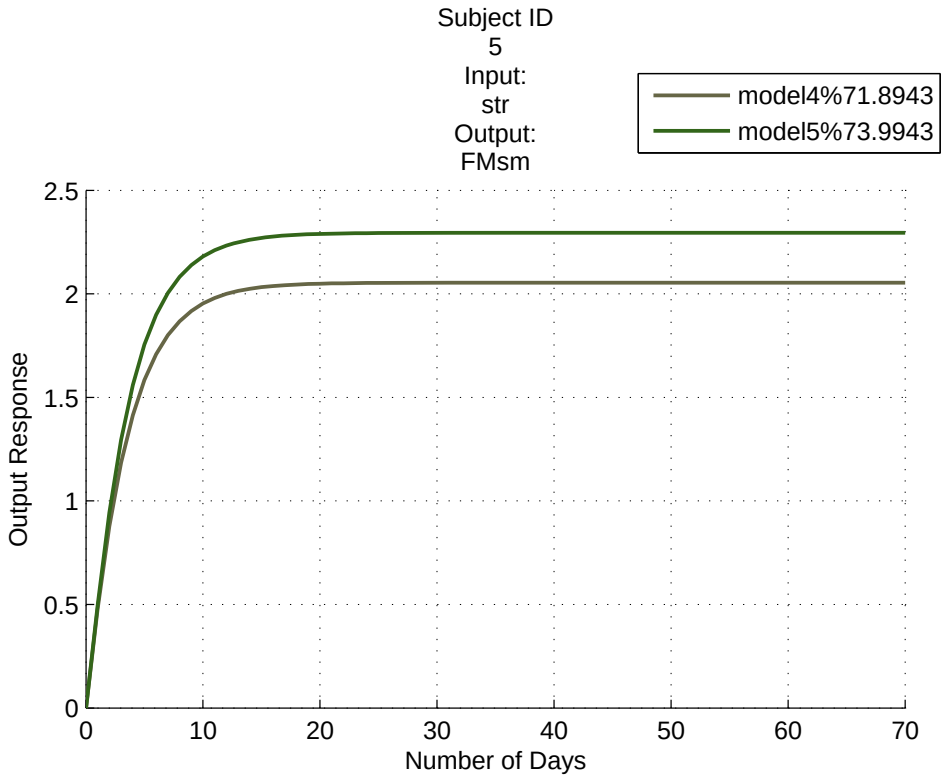


Figure 3.22: Step response of stress-FM model for Participant 5.

Table 3.5: Step response tabulation of stress-FM model for Participant 5.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
4	71.89	2.05, 3.41	2.05, 1.62, 1.24, 0.63	7.28	13.89
5	73.99	2.29, 3.49	2.29, 1.57, 1.26, 0.49	7.31	13.94

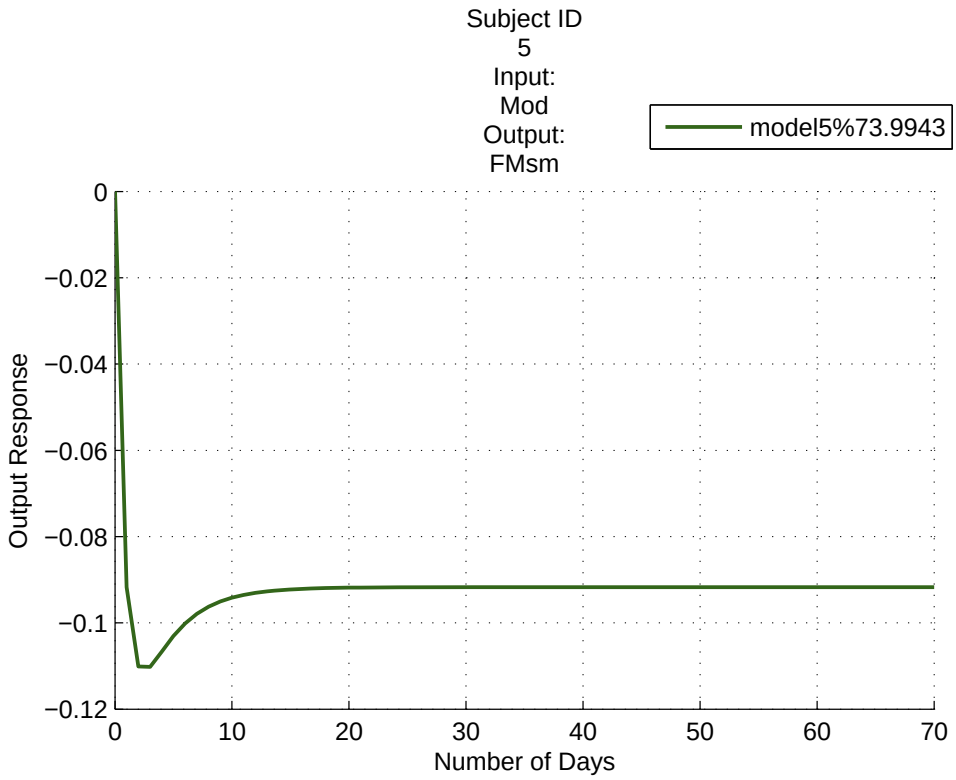


Figure 3.23: Step response of mood-FM model for Participant 5.

Table 3.6: Step response tabulation of mood-FM model for Participant 5.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
5	73.99	-0.092, 0.18	-0.091, 1.57, 1.26, 4.67	0.8	11.93

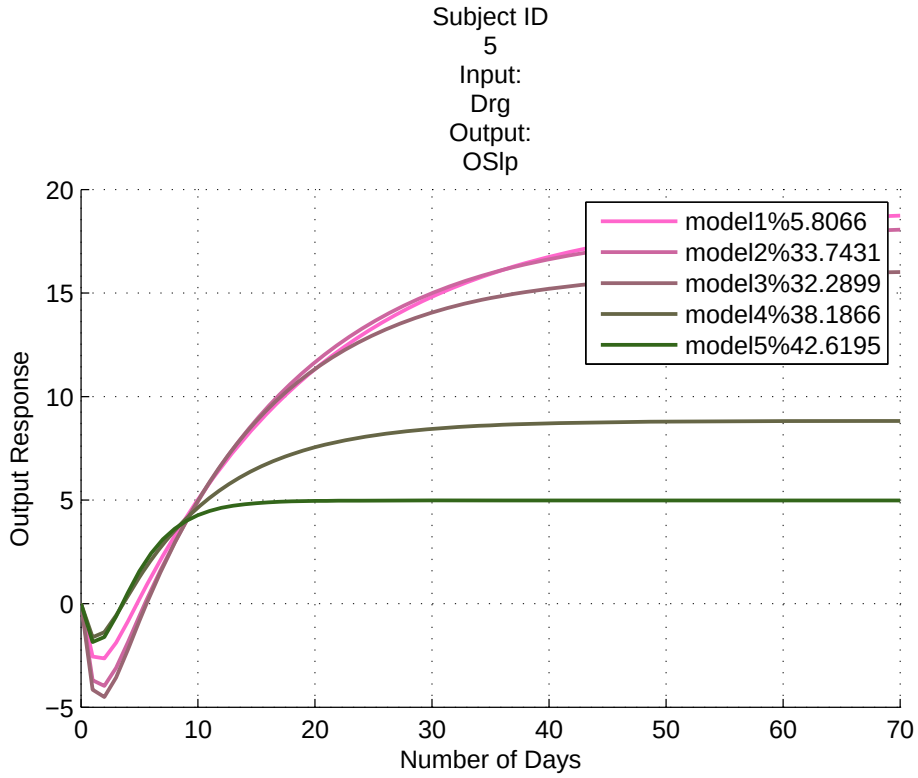


Figure 3.24: Step response of drug-overall sleep model for Participant 5.

Table 3.7: Step response tabulation of drug-overall sleep model for Participant 5.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
1	5.80	19.23, 19.04	19.14, 4.1, 2.18, -4.27	37.21	69.88
2	33.74	18.35, 16.78	18.25, 3.72, 2.04, -5.27	31.3	59.41
3	32.28	16.17, 14.6	16.08, 3.42, 1.86, -5.63	25.86	49.76
4	38.18	8.86, 10.66	8.82, 2.86, 1.64, -3.17	18.52	36.22
5	42.61	5, 6.36	4.98, 2.13, 1.04, -3.35	7.06	15.83

So far we have discussed the procedure which we refer to as the manual method. Similarly, we now briefly mention the results from the step by step procedure. When give nine inputs as drug, placebo, anxiety, stress, mood, gastric, headache, life and sadness, the algorithm chooses the input combination as follows based on the improvement in model fit in the following order of inputs: placebo, headache, anxiety, sadness, stress, drug, mood and gastric.

It is interesting to note that in the step-by-step procedure, drug was chosen as the sixth input. As the algorithm uses the model fit as the criteria to choose inputs, we cannot conclusively comment on this result as to why drug was chosen so later. Overall, we can say that most of the result from both the manual approach and the step-by-step approach converge to more or less similar choice of inputs for participant 5. Hence, detailed modeling results are not shown for step-by-step approach due to similar conclusions.

3.3 Summary for Pilot Study

There were a total of 10 participants in the pilot study which included participant 5. From analysis of the results, we note that participant 5 is one of the stronger responders to the drug. In this work, we try to use a common model structure (ARX) as well as common input combinations (as in model 5) to compare all the results from different participants as it worked more or less for all cases but for some cases e.g. for participant 9, different input combinations are examined. The model order used was ARX [2 2 1] unless otherwise noted. We observed that it was necessary to go beyond the primary inputs (drug and placebo), in order to improve model fits to the diary data. However, simply adding inputs does not necessary result in models with predictive ability. Hence we tried to systematically arrive at the most useful and interesting input-output combinations, which resulted in the five or more input combinations as noted. Figures 3.25, 3.26 shows the percentage fits using model 5 (drug, placebo, anxiety, stress, mood) for all participants. Here we observe that the best fit was obtained for participant #5 and the worst for participant #6. It can be noted that most of the poor fits were observed for cases which did not react to the intervention or in other words, the time series was more or less flat. All tabulations refer to Tables 3.8 and 3.9.

In [10], participants # 5, 7, 9, 10, 11 and 12 are classified as responders and participants # 3, 6, 8 and 14 are classified as non-responders. The basis of classification used is that the responders are subjects who show a 30 point reduction of symptoms over placebo. Based on our analysis on the Drug-FM symptoms response curve, we classify the subjects as 'responders' if the response gain or the nominal gain is negative and 'non-responders' if the gain is not negative. As noted previously, negative gain implies that drug lowers FM symptoms and hence for 'responders', we expect

gain to be negative. Under this classification, Subjects # **5, 7, 9, 10, 11, 8 and 14** classify as responders (seven participants) and # **12, 3, 6** (three participants) as non responders in our analysis. When compared to [10], we notice that participant # 12, who is classified as a responder, is a non-responder in our analysis and participants # 8 and # 14, who are classified as non-responders, are responders. Although it has to be noted there are borderline cases on both responder and non-responder sides, including # 12, as we classify based on the nominal gain of estimated models and hence on incorporating the standard deviation, from the prediction error method, a range can be established in which a participant can be both a responder and a non-responder.

Our *a priori* assumption is that naltrexone lowers FM symptoms and hence we expected that the drug-FM response should reflect a negative gain. Because the magnitude and speed of this change can vary significantly among participants, we show a single-subject analysis. All participants were analyzed in detail, but for the sake of brevity, we have presented, in detail, both step response plots and corresponding dynamical system tabulations only for Participant 5 (as discussed before). For all participants, we tabulate responses using one final model for drug-FM, placebo-FM, drug-overall sleep and placebo-overall sleep cases as shown in Tables 3.8 and 3.9.

Another point to note is the response to placebo as input. All participants (except # 7, #8, #10 and #14) show a positive gain for Placebo-FM symptoms response implying increase in symptoms with Placebo intake. For sleep as an *output*, all participants show positive gain for drug intake except #7, #6 and #11. Researchers working on FM are interested in finding an answer to the question of the relationship between sleep and pain among the various participants. To this end, we conducted our analysis using sleep as the output in lieu of FM symptoms. Here our

hypothesis was that comparing the speed-of-response/settling time from the drug response for these two outputs would give us some insights into this issue. For responders, based on *averaged* response we observe that the drug-sleep response is faster than the drug-FM response (i.e., the drug-sleep response displays a shorter settling time) as noted in Table 3.8 although such a relationship is not conclusive and is not prominent across all participants.

Some of our particular findings from the secondary analysis are as follows:

- The set of inputs which seem to be appropriate for all participants were: drug, placebo, anxiety, stress, mood, gastric and headache i.e. model 7 however model 5 was found to be a better alternative. Specific ARX models formed from this set of inputs are mentioned in Section 3.2. The goodness of fit obtained from the estimated ARX models (using FM as output) ranged from 73.99% (for participant #5) to 16.98% (for participant #6) as shown in Figures 3.25,3.26. Similarly, the goodness of fit obtained from the estimated ARX models (using Overall sleep as output) ranged from 42.61% (for participant #5) to 11.6% (for participant #8) as shown in Figures 3.27,3.28.

- The participants are re-classified [10] as responders and non-responders based on the value of the *nominal* gain of the drug-FM symptoms model. For responders, the drug-FM response has negative gain while for non-responders the drug-FM response shows a positive gain. Based on this criteria, we classify participants # 5, 7, 9, 10, 11, 8 and 14 as responders and # 12, 3, 6 as non-responders. Goodness of fit varied from 18.85% to 73.99% for responders and from 16.98% to 23.92% for non-responders, as noted in Table 3.8.

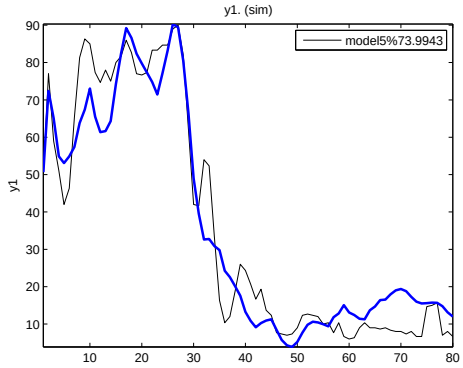
- How strongly participants responded to naltrexone is quantified by the gain of the drug-FM response. It was noted that participant #9 showed the largest

gain and participant # 14 showed the least gain for responders; the gain of drug-FM response ranged from -2.31 (for participant #7) to -11.08 (for participant #9), as summarized in Table 3.8.

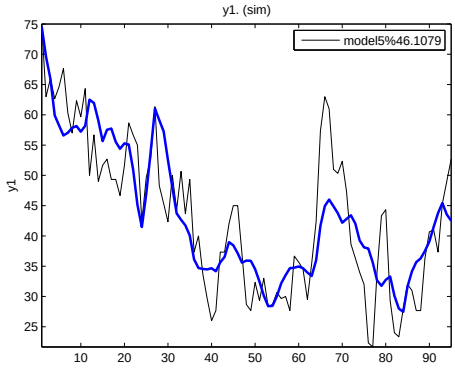
- The settling time for participants classified as responders ranges from 8.3 days to 50.9 days and 9.5 days to 11.9 days for non-responders. The fastest settling time was observed from participant #9 and the slowest from participant #11, as noted in Table 3.8.

- The effect of placebo on fibromyalgia symptoms was also examined. Participants #7, 8, 10 and 14 show a negative gain for placebo-FM response, (implying a decrease in pain with placebo) whereas for the remaining participants all reported increases in pain with placebo (positive gain). The fastest response to placebo was observed for participant #7, while the slowest response was for participant #11, as noted in Table 3.9.

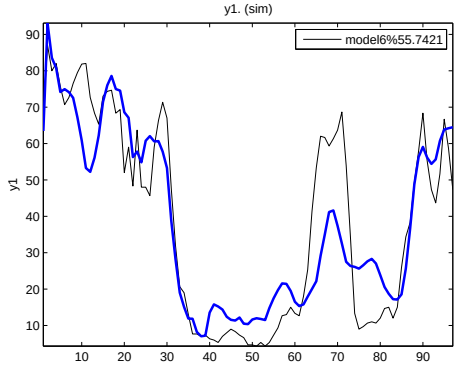
- A comparison of responders and non-responders when the outcome considered is overall sleep rather than fibromyalgia symptoms was considered. We note that only participants #7 and #11 showed a negative gain for drug-sleep response, implying a worsening of sleep quality as drug is introduced. The remaining participants showed a clear positive gain implying improvement in sleep quality with drug intake. All the participants classified as non-responders, except #6, show improvement in sleep quality with drug intake.



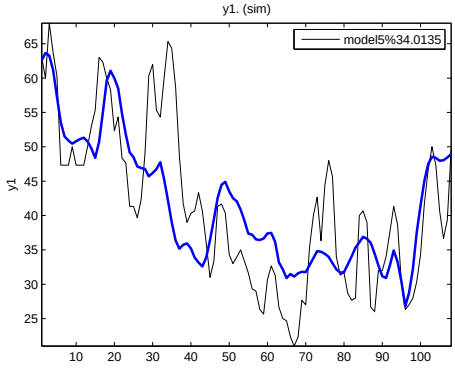
(a) Participant #5 (73.99%)



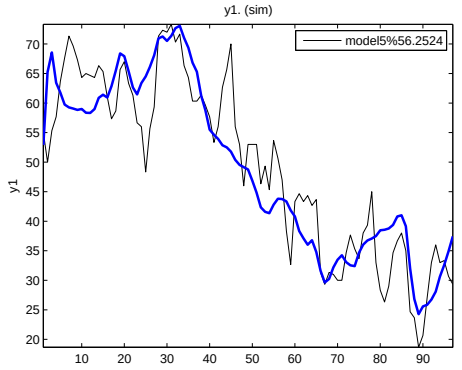
(b) Participant #7 (46.1%)



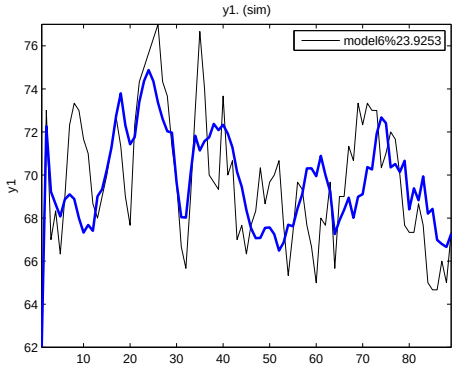
(c) Participant #9 (55.74%)



(d) Participant #10 (34.01%)

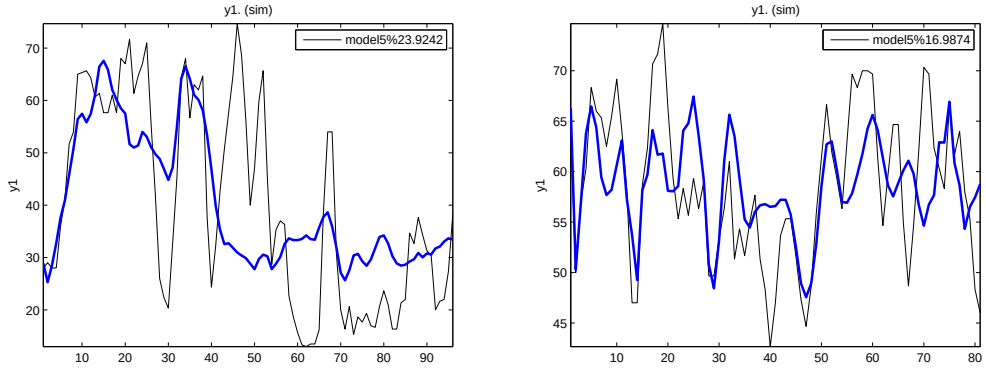


(e) Participant #11 (56.25%)



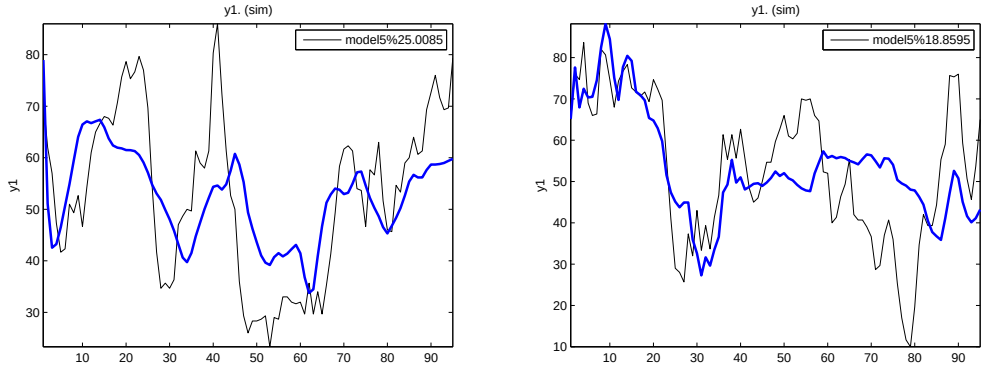
(f) Participant #3(23.92%)

Figure 3.25: Estimated model output vs. actual output (FM sym), using an ARX $[2\,2\,1]$ structure per model 5 (unless otherwise mentioned) for the participants of pilot study. Model fits are mentioned in parenthesis.



(a) Participant #12 (23.92%)

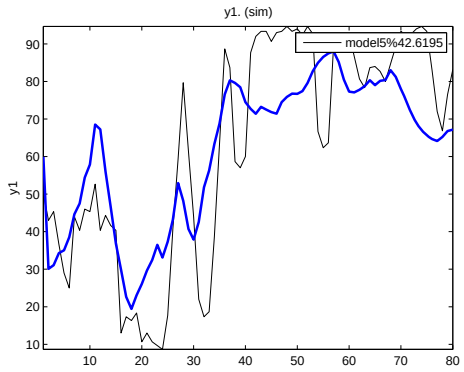
(b) Participant #6 (16.98%)



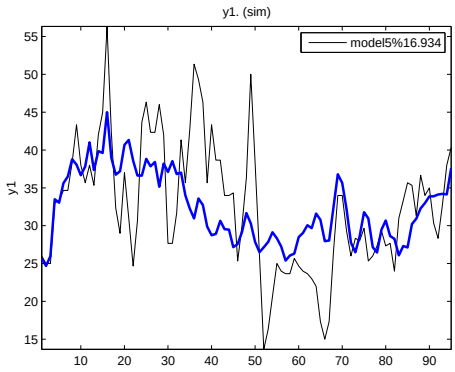
(c) Participant #8 (25%)

(d) Participant#14 (18.85%)

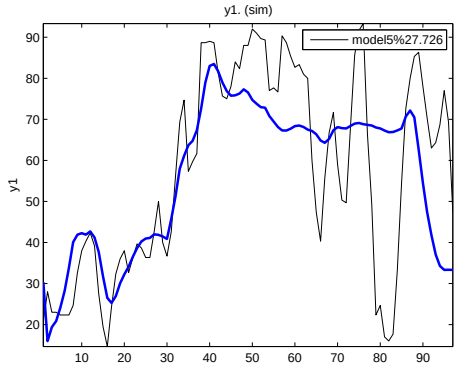
Figure 3.26: Estimated model output vs. actual output (FM sym), using an ARX $[2\,2\,1]$ structure per model 5 (unless otherwise mentioned) for the participants of pilot study. Model fits are mentioned in parenthesis.



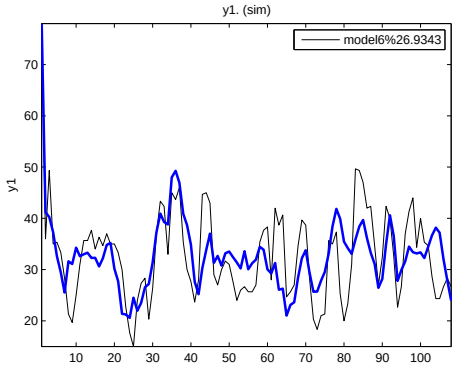
(a) Participant #5 (42.61%)



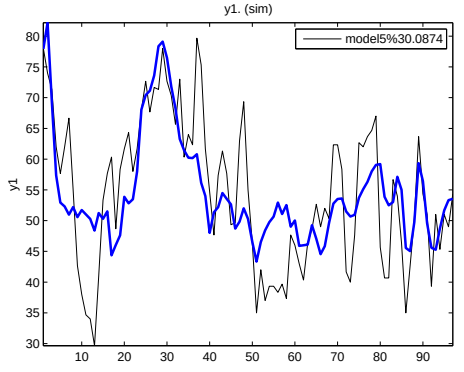
(b) Participant #7 (16.93%)



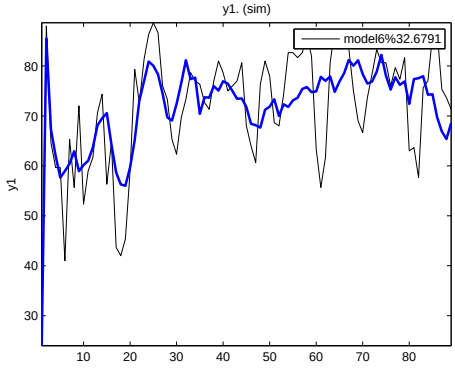
(c) Participant #9 (27.72%)



(d) Participant #10 (26.93%)

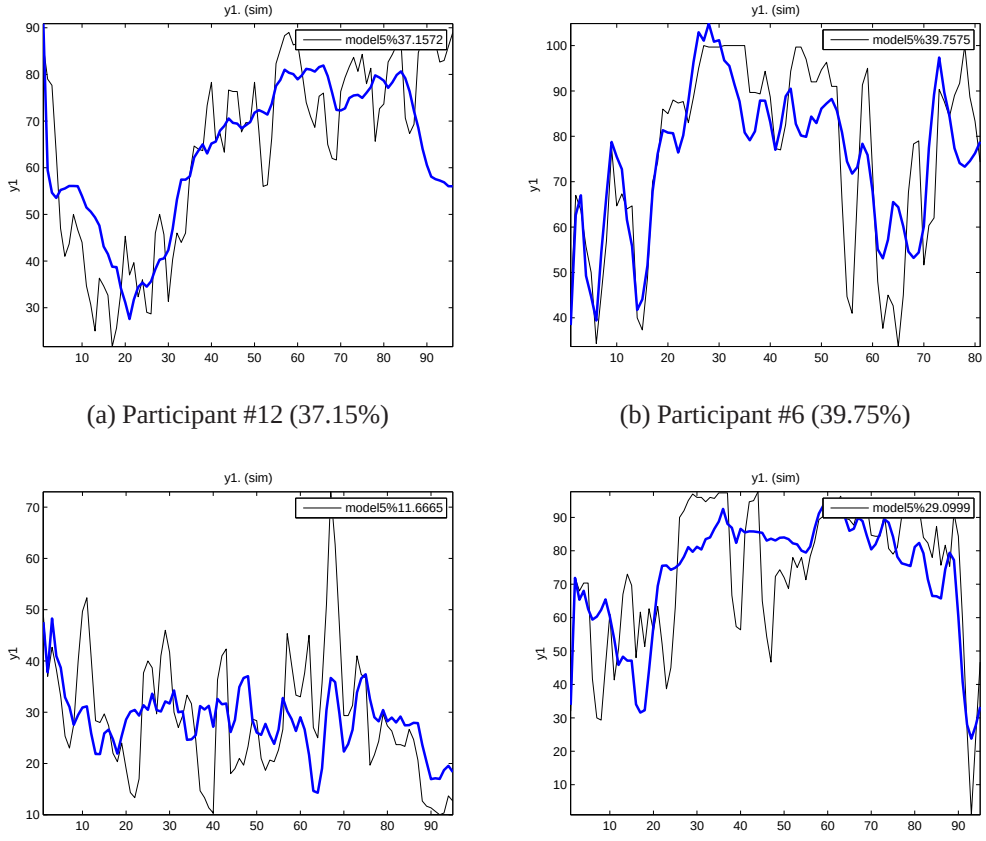


(e) Participant #11 (30.08%)



(f) Participant #3 (32.67%)

Figure 3.27: Estimated model output vs. actual output (overall sleep), using an ARX $[2\,2\,1]$ structure per model 5 (unless otherwise mentioned) for the participants of pilot study. Model fits are mentioned in parenthesis.



(a) Participant #12 (37.15%)

(b) Participant #6 (39.75%)

(c) Participant #8 (11.66%)

(d) Participant#14 (29.09%)

Figure 3.28: Estimated model output vs. actual output (overall sleep), using an ARX $[2\,2\,1]$ structure per model 5 (unless otherwise mentioned) for the participants of pilot study. Model fits are mentioned in parenthesis.

Legend

- The system responses are grouped into four cases: **DFM** or Drug FM response, **DS** or Drug overall sleep response, **PFM** or Placebo FM response and **PS** or Placebo overall sleep response
- K_p**(DFM/DS)** is the gain (units of change in outcome per unit dose of LDN) and T_s**(.)** is the settling time (in days) of system response,
- **ESR** (Erythrocyte Sedimentation Rate) values for each participant
- Goodness of fit of estimated models is shown by **% fit**
- **"Average values"** are the mean of data in respective columns
- ω : Using ARX [441] on model 5 input combinations
- γ : ARX [221] using inputs : Drug, Placebo, Anxiety, Stress, Mood and Life
- κ : ARX [221] using inputs : Drug, Placebo, Gastric, Headache, Life and Sadness
- The standard deviation (σ) on data is shown by $\pm$. Please note that σ values in rows corresponding to each participant is the variability on estimated gains (from system identification) where as σ values in rows corresponding to average values is the deviation of mean of each participant's response

Table 3.8: Tabulation of system responses to drug for Placebo-Drug protocol.

#	Sub.	ESR	Pro.	% fit(DFM)	K_p(DFM)	T_s(DFM)	% fit(DS)	K_p(DS)	T_s(DS)
Responders									
1	5	45	PD	73.9	-2.47±1.54	11.49	42.61	4.98±4.09	15.83
2	7	8	PD	46.1	-2.72±1.36	11.9	16.9^{ω}	-3.37±2.49	26.9
3	8	28	PD	25	-4.38±3.06	17.5	11.6^{ω}	2.16±2.69	13
4	9	50	PD	55.7^{γ}	$-11.08^{\gamma} \pm 2.77$	8.3	27.7	9.43 ± 3.85	10.9
5	10	27	PD	34	-3.69±1.42	12.9	26.93^{κ}	2.3± 0.97	6.29
6	11	20	PD	56.2	-5.46±5.1	50.9	30.08	-1.8±1.83	14
7	14	31	PD	18.85	-2.31±3.29	23.7	29.1	8.28±2.26	7.81
Average Values (std. deviation for nominal gain only)									
—	—	29.85	—	44.25±19.48	-4.58±3.08	19.52±14.71	26.41±9.95	3.14±4.79	13.53±6.78
Non Responders									
10	3	0	PD	23.9^{κ}	0.28 ± 0.4	11.9	32.6^{κ}	2.6 ± 1.05	7
11	6	2	PD	16.98^{ω}	0.61±1.18	20.41	39.75^{ω}	-3.38±6.08	31.4
12	12	28	PD	23.92	-0.33±2.34	9.52	37.15	6.11±4.1	23.19
Average Values (std. deviation for nominal gain only)									
—	—	10	—	21.6±4	0.18±0.47	13.94±5.72	36.5±3.61	1.77±4.79	20.53± 12.41
Total Average Values (std. deviation for nominal gain only)									
—	—	23.9	—	37.45±19.39	-3.15±3.41	17.85±12.6	29.44±9.62	2.73±4.56	15.63±8.74

Table 3.9: Tabulation of system responses to placebo for Placebo-Drug protocol.

#	Sub.	ESR	Pro.	% fit(PFM)	K_p(PFM)	T_s(PFM)	% fit(PS)	K_p(PS)	T_s(PS)
Responders									
1	5	45	PD	73.99	45.81±10.2	13.06	42.61	-14.89±29.47	15.99
2	7	8	PD	46.1	-9.57±8.2	11.42	16.93^{ω}	-11.35±17.07	20.36
3	8	28	PD	25	-23.61±23.49	17.93	11.66^{ω}	8.73±18.98	21.3
4	9	50	PD	55.74^{γ}	4.08±15.46	12.75	27.72	9.04±19.75	11.69
5	10	27	PD	34	-1.14±9.32	13.33	26.93^{κ}	4.59±5.85	9.6
6	11	20	PD	56.25	9.81±27.5	33.37	30.08	14.11±10.71	14.03
7	14	31	PD	18.85	-18.009±19.79	23.94	29.09	33.19±14.01	7.73
Average Values (std. deviation for nominal gain only)									
—	—	29.85	—	44.25±19.48	1.05±23.01	17.97±8.04	26.41±9.95	0.76±11.23	14.38±5.17
Non Responders									
10	3	0	PD	23.9^{κ}	2.99±2.42	4.12	32.67^{κ}	11.75±6.47	7.36
11	6	2	PD	16.98^{ω}	-1.23±7.06	16.23	39.75^{ω}	16.99±35.01	33.34
12	12	28	PD	23.92	10.61±12.55	8.93	37.15	-3.72±23.96	25.4
Average Values (std. deviation for nominal gain only)									
—	—	10	—	21.6±4	4.12±6	9.76±6.09	36.5±3.61	8.34±10.76	22.03±13.31
Total Average Values (std. deviation for nominal gain only)									
—	—	23.9	—	37.45±19.39	1.97±19.06	15.5±8.19	29.44±9.62	3.03±11.1	16.68±8.41

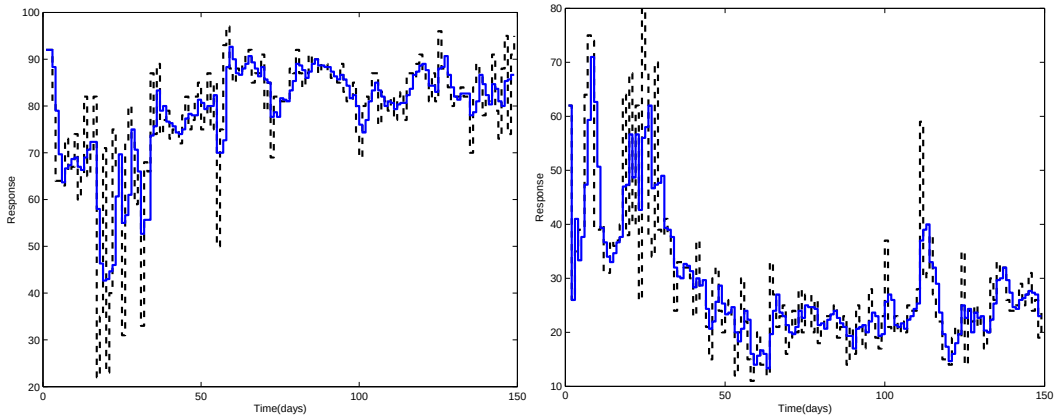
3.4 Participant 38

The data analysis from the pilot study had shown promise for the use of naltrexone for FM treatment and hence a full study was under taken by Younger *et al.* to investigate the drug intervention under stricter experimental conditions and longer duration. The modeling procedure is similar to that shown for the pilot study. First, the data was preprocessed for missing days and the data trends are shown in Figures 3.29-3.32. When compared to participant 5, we do not see a very strong response to drug although this participant had one of the strongest responses in the full study. It should be noted that this participant follows as Placebo-Drug protocol, similar to participant 5. In particular, we do not see any improvement in the sleep quality with drug intervention. The data was also prefiltered with three day moving average. Also, this data has significant variations or high frequency content as compared to Participant 5, whose response were smoother. It can be commented that since the data is obtained from self-reports, the way of reporting and the quality of data can vary significantly between participants.

Next, we look at the cross correlation of drug and placebo with other variables. It is shown in Figures 3.33 and 3.34, respectively. The data is correlated with drug above significant levels for some cases like mood, anxiety and side effects. In contrast with Participant 5, we see almost no correlation between drug and overall sleep which was present in the first case (and hints at no effect of drug on sleep quality). Also drug seems to make causing side effects (Figure 3.33i) and similar inference can be made for placebo where the correlations seems to be stronger. In Figure 3.35, we show cross correlation between other selected variables. It can be noted that variables gastric and headache are not correlated with themselves and with the output and hence may merit their inclusion as inputs. The placebo

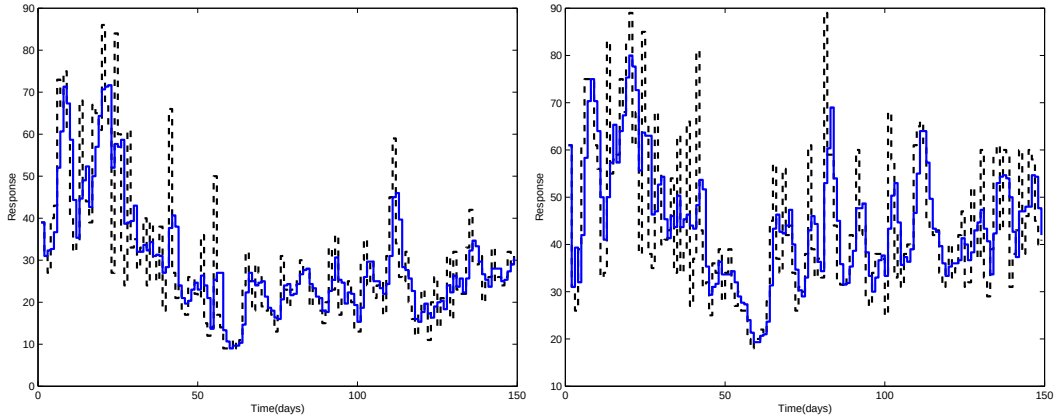
seems to make the response worse and drug makes them better, in line with what was observed with Participant 5, but the relations are not distinct e.g., some of the variables used in previous case study seem to more correlated in this case like anxiety, stress, life and sadness.

The power spectra for inputs has been shown in Figures 3.36, 3.37 and 3.38. Since this is longer protocol, we see an increase in power for some signals (e.g., drug) and the bandwidth is near 0.4 rad/day.



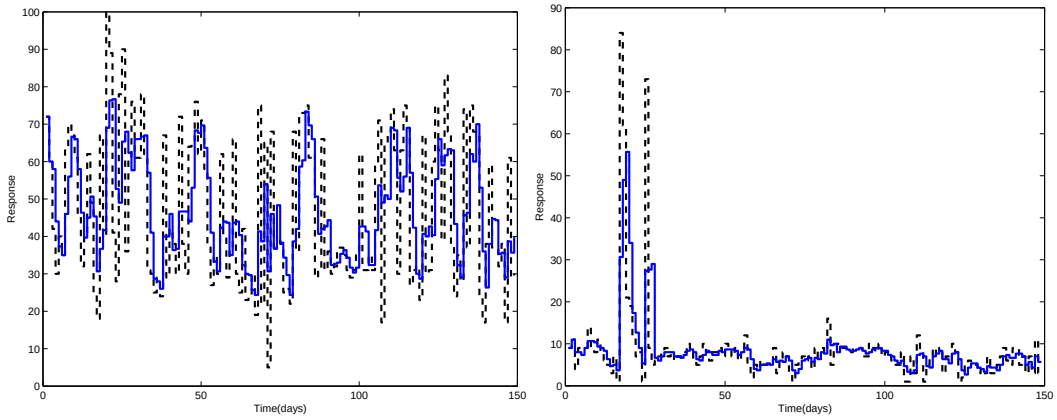
(a) Life

(b) FM sym



(c) Pain

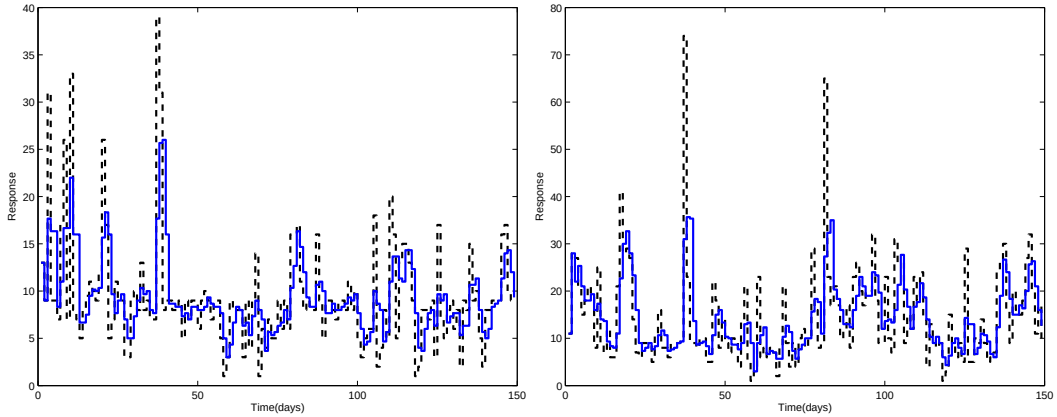
(d) Highest Pain



(e) Fatigue

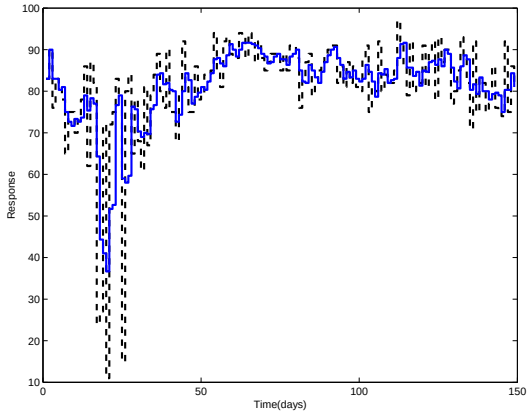
(f) Sadness

Figure 3.29: Original data time series (dashed) with three day moving averaged data (solid) for variables 1 through 6 for Participant 38.

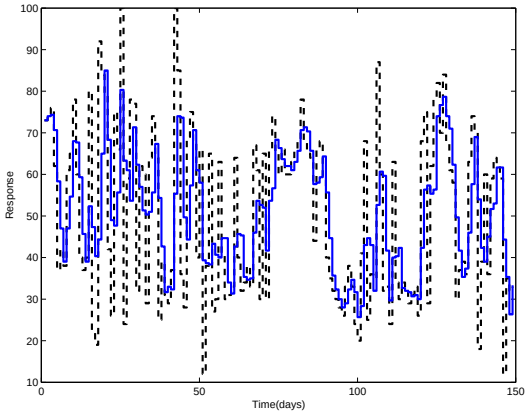


(a) Anxiety

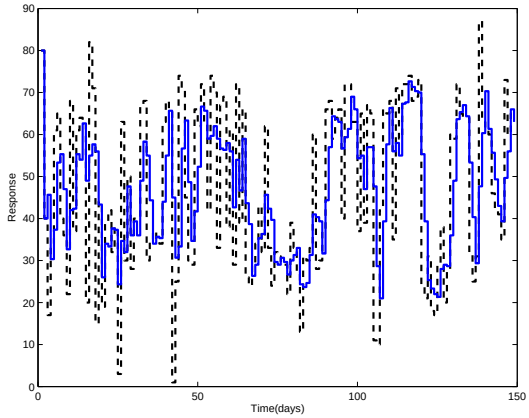
(b) Stress



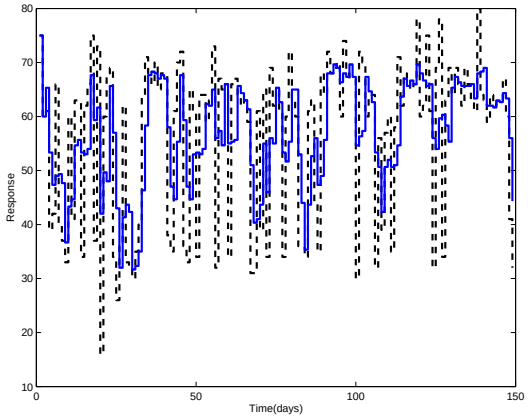
(c) Mood



(d) Sleep

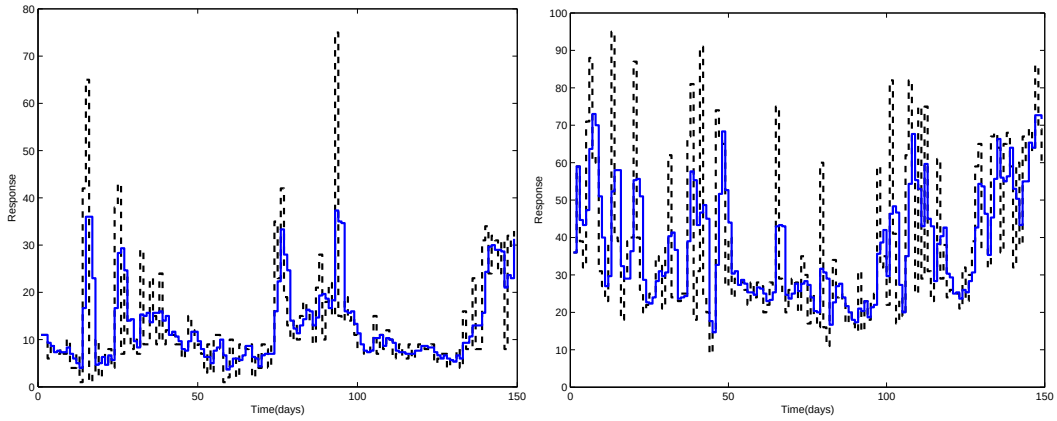


(e) Overall Sleep



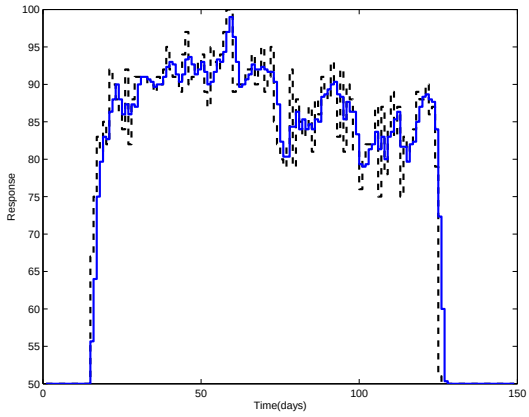
(f) Think and Rem

Figure 3.30: Original data time series (dashed) with three day moving averaged data (solid) for variables 7 through 12 for Participant 38.

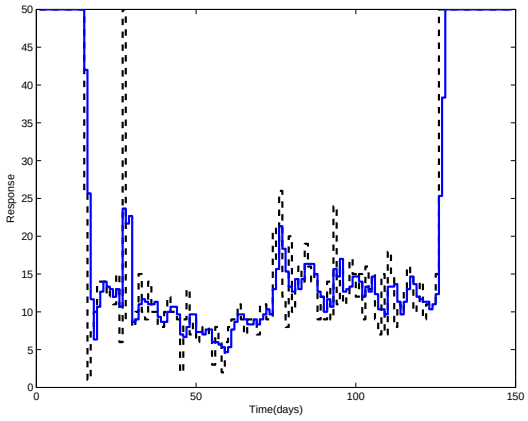


(a) Gastric

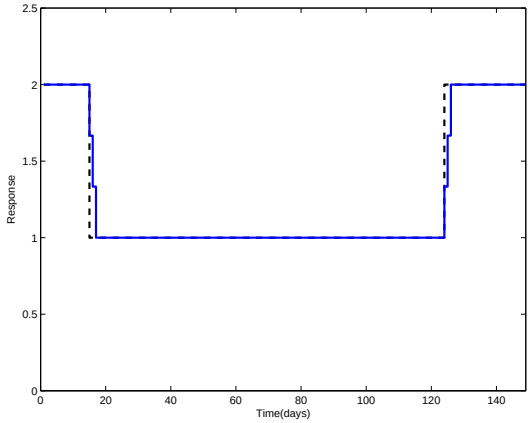
(b) Headaches



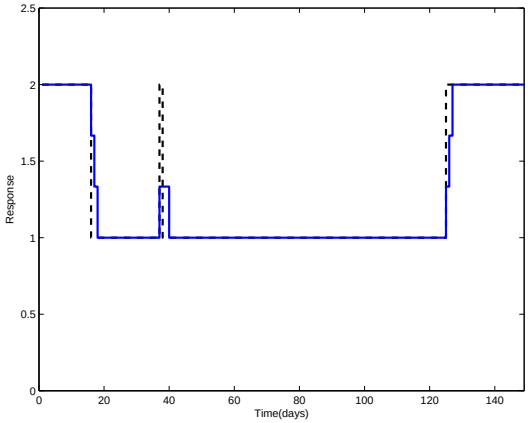
(c) Toleration



(d) Side Effects

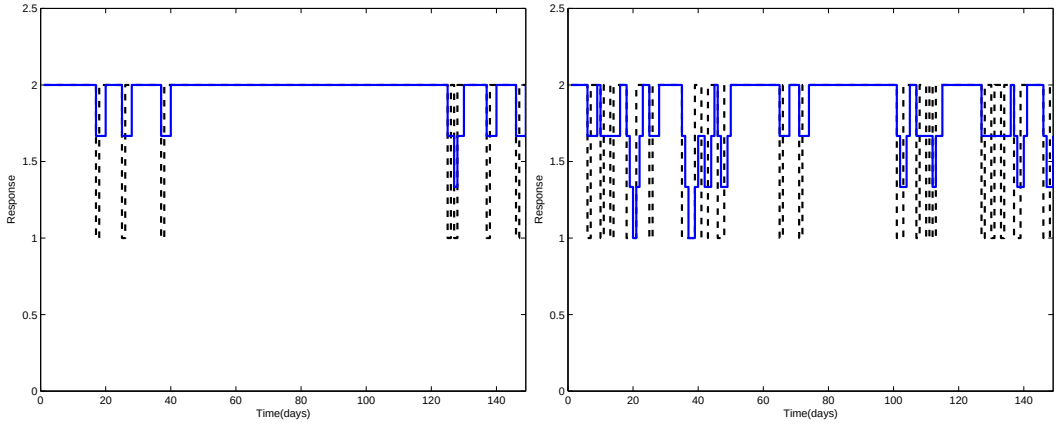


(e) Capsule for tonight



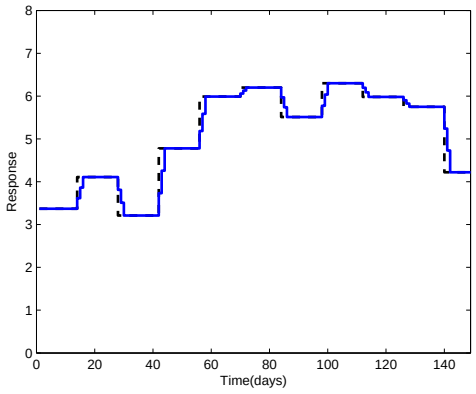
(f) Capsule for last night

Figure 3.31: Original data time series (dashed) with three day moving averaged data (solid) for variables 13 through 18 for Participant 38.

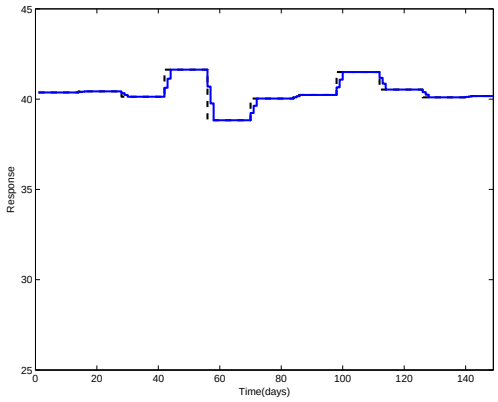


(a) Unusual stressful event

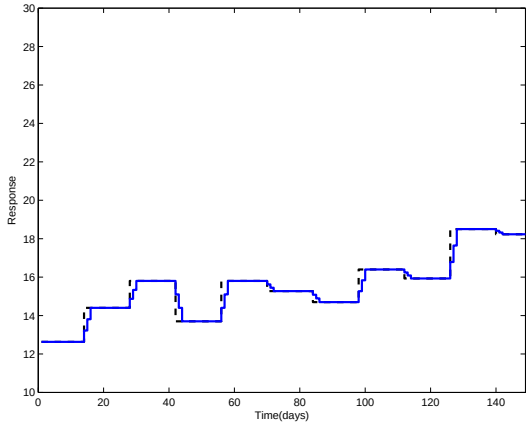
(b) Any other pain medication



(c) Mechanical pain

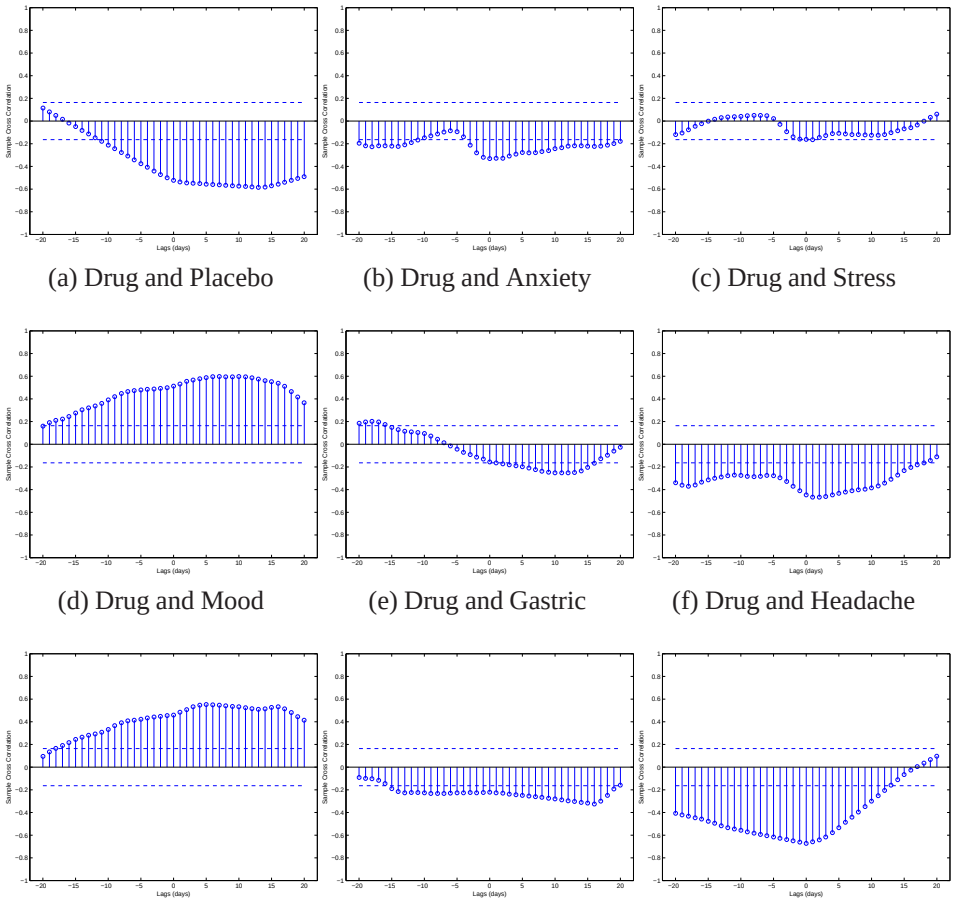


(d) Thermal pain



(e) Cold pain

Figure 3.32: Original data time series (dashed) with three day moving averaged data (solid) for variables 19, 20 and three measuremenst from the physical tests for Participant 38.

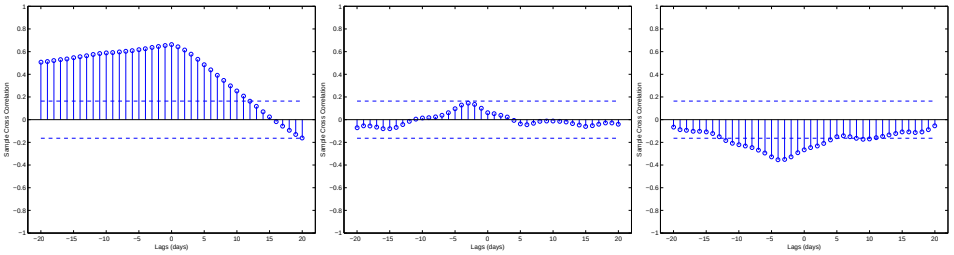


(a) Drug and Placebo (b) Drug and Anxiety (c) Drug and Stress

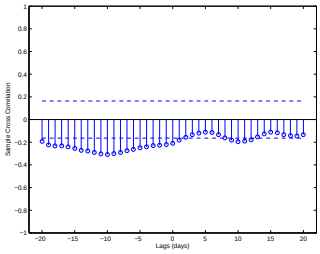
(d) Drug and Mood (e) Drug and Gastric (f) Drug and Headache

(g) Drug and Life (h) Drug and Sadness (i) Drug and Side Effects

Figure 3.33: Correlation Plots between drug and other variables with two standard errors over $\pm$ 20 lags for Participant 38 (cont.).

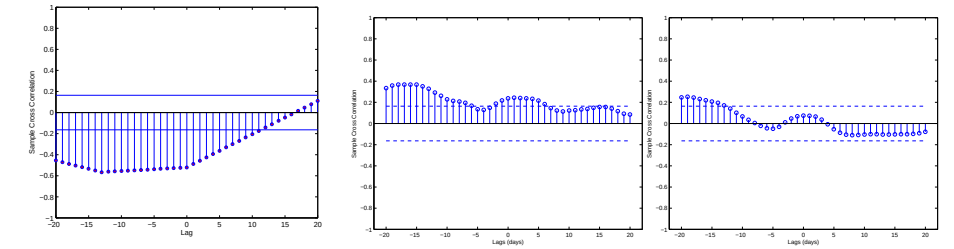


(j) Drug and Toleration (k) Drug and Overall Sleep (l) Drug and Sleep

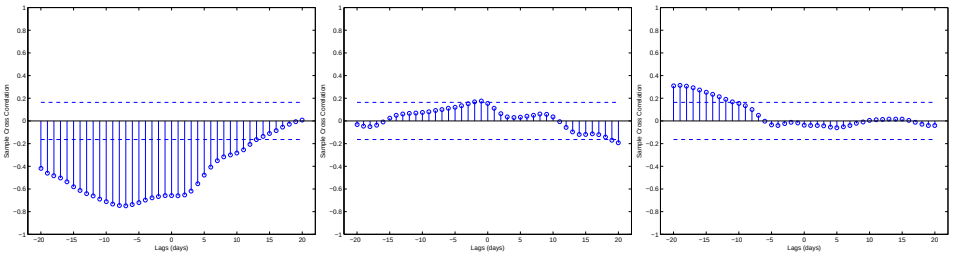


(m) Drug and Fatigue

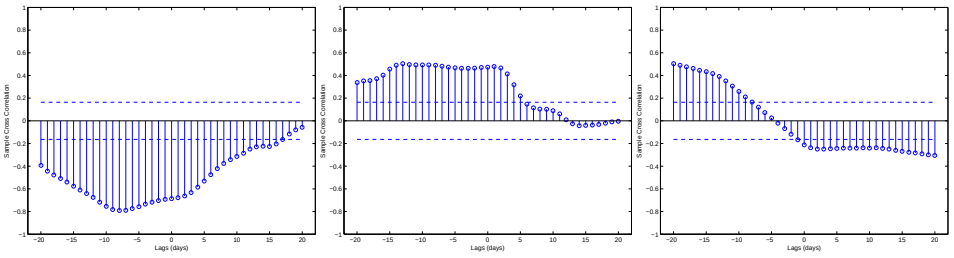
Figure 3.33: Correlation Plots between drug and other variables with two standard errors over $\pm$ 20 lags for Participant 38.



(a) Placebo and Drug (b) Placebo and Anxiety (c) Placebo and Stress

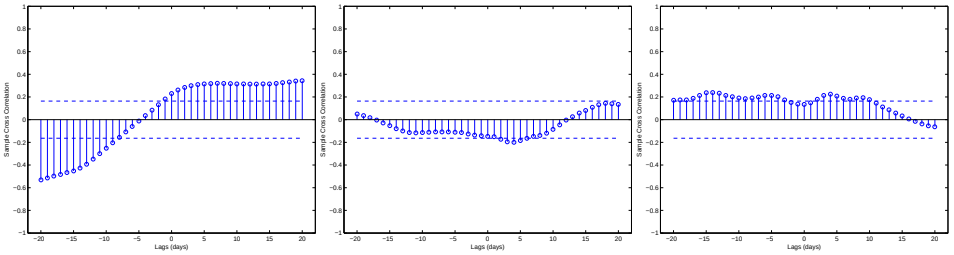


(d) Placebo and Mood (e) Placebo and Gastric (f) Placebo and Headache

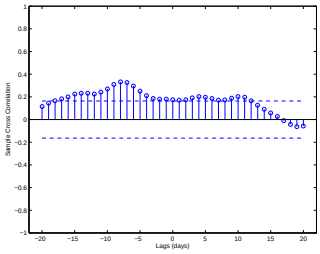


(g) Placebo and Life (h) Placebo and Sadness (i) Placebo and Side Effects

Figure 3.34: Correlation Plots between placebo and other variables with two standard errors over $\pm$ 20 lags for Participant 38 (cont.).

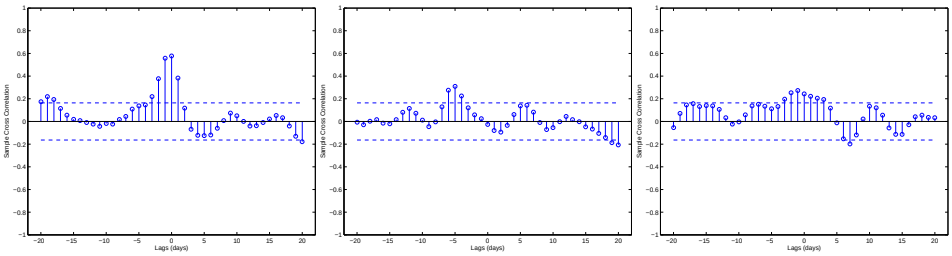


(j) Placebo and Toleration (k) Placebo and Overall Sleep (l) Placebo and Sleep

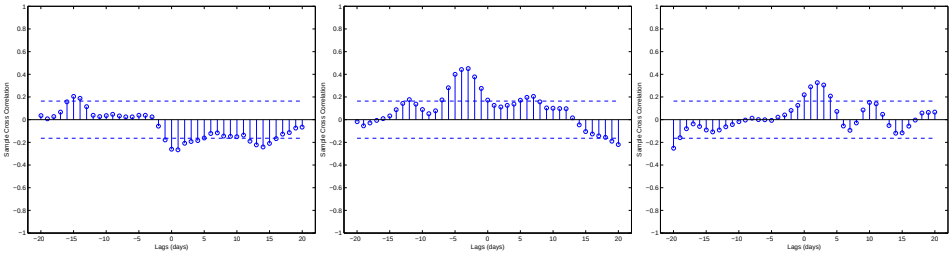


(m) Placebo and Fatigue

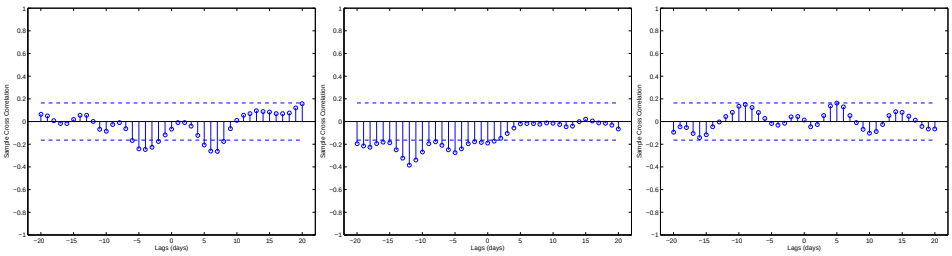
Figure 3.34: Correlation Plots between placebo and other variables with two standard errors over $\pm$ 20 lags for Participant 38.



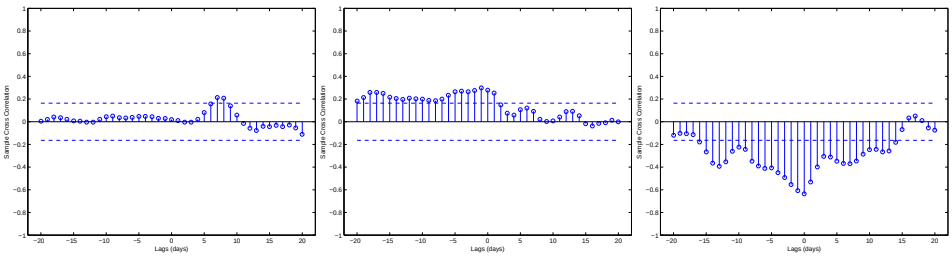
(a) Anxiety and Stress (b) Anxiety and Gastric (c) Anxiety and Headache



(d) Stress and Mood (e) Stress and Gastric (f) Stress and Headache

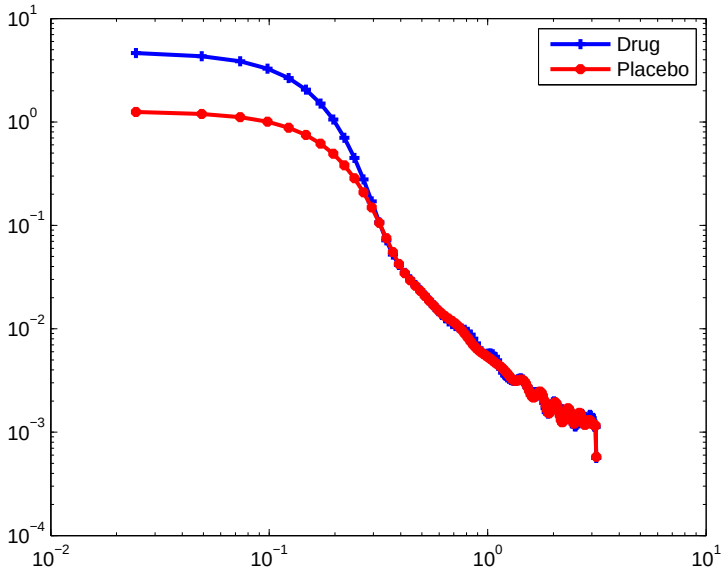


(g) Mood and Gastric (h) Mood and Headache (i) Gastric and Headache

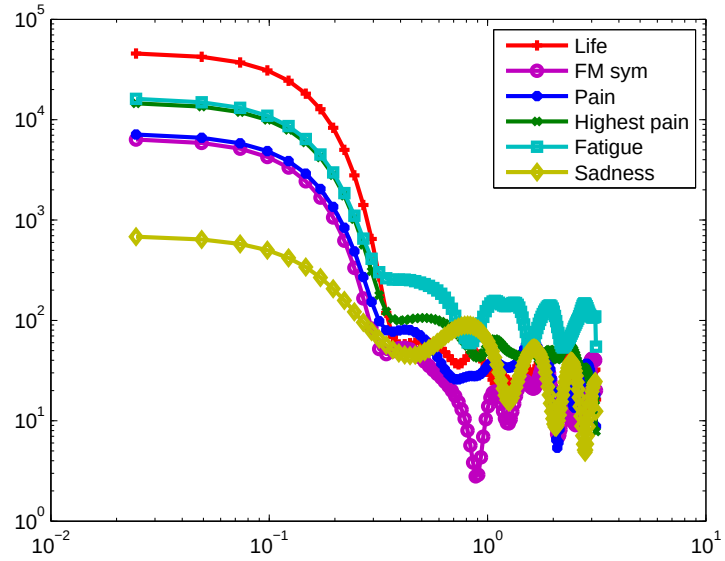


(j) FM sym and gastric (k) FM sym and headache (l) Life and sadness

Figure 3.35: Cross correlations between various variables with two standard errors over $\pm$ 20 lags for Participant 38.

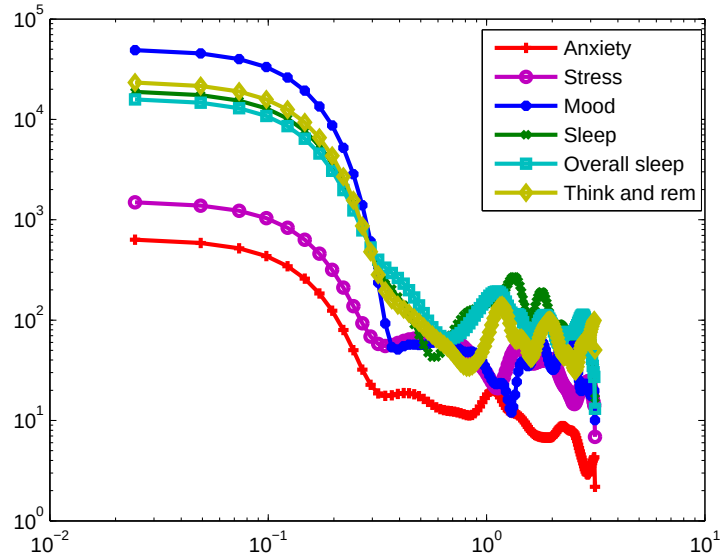


(a) Drug and Placebo

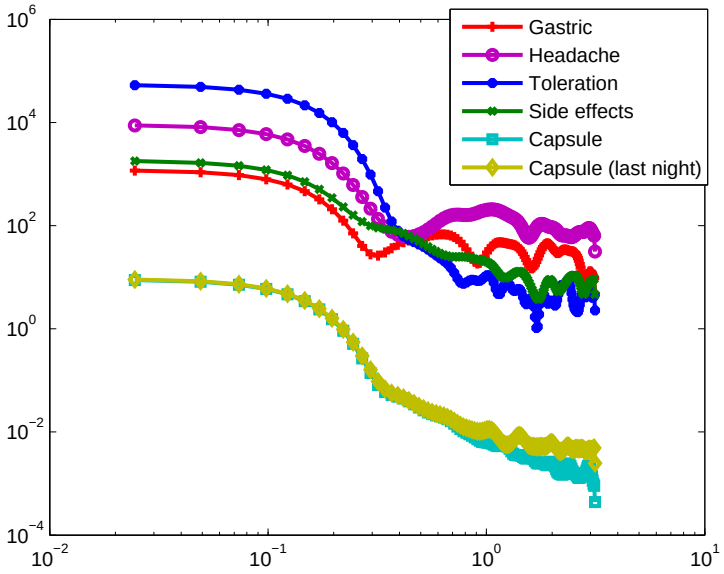


(b) Variable 1 through 6

Figure 3.36: Power spectral density for all variables for Participant 38.

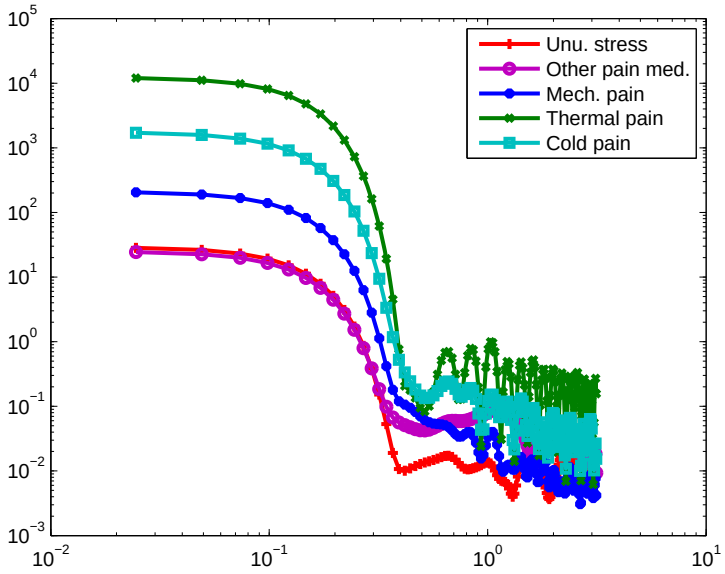


(a) Variable 7 through 12



(b) Variable 13 through 18

Figure 3.37: Power spectral density for all variables for Participant 38.



(a) Variable 19 through 23

Figure 3.38: Power spectral density for all variables for Participant 38.

With manual experiments based on the possible input cross correlation, we can construct the following models:

Model 1 (Drug)

Model 2 (Drug, Placebo)

Model 3 (Drug, Placebo, Anxiety)

Model 4 (Drug, Placebo, Anxiety, Stress)

Model 5 (Drug, Placebo, Anxiety, Stress, Mood)

Model 6 (Drug, Placebo, Anxiety, Stress, Mood, Gastric)

Model 7 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache)

Model 8 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life)

Model 9 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life, Sadness)

Model 10 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life, Sadness, OverallSleep)

Model 11 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life, Sadness, OverallSleep, Sleep)

Model 12 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life, Sadness, OverallSleep, Sleep, Fatigue)

Model 13 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life, Sadness, OverallSleep, Sleep, Fatigue, Toleration)

Model 14 (Drug, Placebo, Anxiety, Stress, Mood, Gastric, Headache, Life, Sadness, OverallSleep, Sleep, Fatigue, , Toleration, Side Effects)

It can be noted that some variables like sleep, which are classified as an output, has been used from model 10 onwards primarily in an attempt to improve the model fit (although that does not always work). Since headache and gastric are not very correlated as shown in Figure 3.35i, we included them in our analysis (model 6 and 7). Similarly we also include life and sadness as inputs which give good estimates (model 8 and model 9) for many participants. We do not pursue anything above model 9 as it was not fruitful.

The model were estimated using ARX $[4\,4\,1]$ structure. When comparing with participant 5, we note that more inputs (and higher model orders) are required to get improvements in model fits. The correlation analysis on the residuals is shown in Figure 3.39. Also, on using drug and placebo as the only inputs yielded a model fit up to 39%, as noted in Table 3.10, which is not as good as the first case (participant 5) suggesting a not very strong respnse to drug. A higher model order provided a better description of output variance. The step responses are, of course, not smooth as compared with ARX [2 2 1] modeling.

The evolution of model fits is shown in Figures 3.40 and 3.41. The improvement in model fit is not gradual as well. Similar to previous analysis of participant 5, we show the Bode plots of the model error model and nominal model as shown in Figures 3.42-3.44. The model error was constructed using an ARX $[8\,8\,0]$ model. Since the data did not seem to suggest a strong response to drug, we do not observe tight bounds for the estimated models. To get a sense of bounds in the time domain, we generate step responses with 95% confidence intervals, for model drug-FM and placebo-FM, as shown in Figure 3.46. In line with inference drawn in the case with

Table 3.10: Tabulation of model fits of models using FM sym as output for participant 38.

Model	% fit
1	38.8
2	39.6
3	41.2
4	40.4
5	43.3
6	47.9
7	48.0
8	52.8
9	54.7

models for participant 5, the wide uncertanity bounds do not cause system instability and usefulness of such models depends on the intended control application.

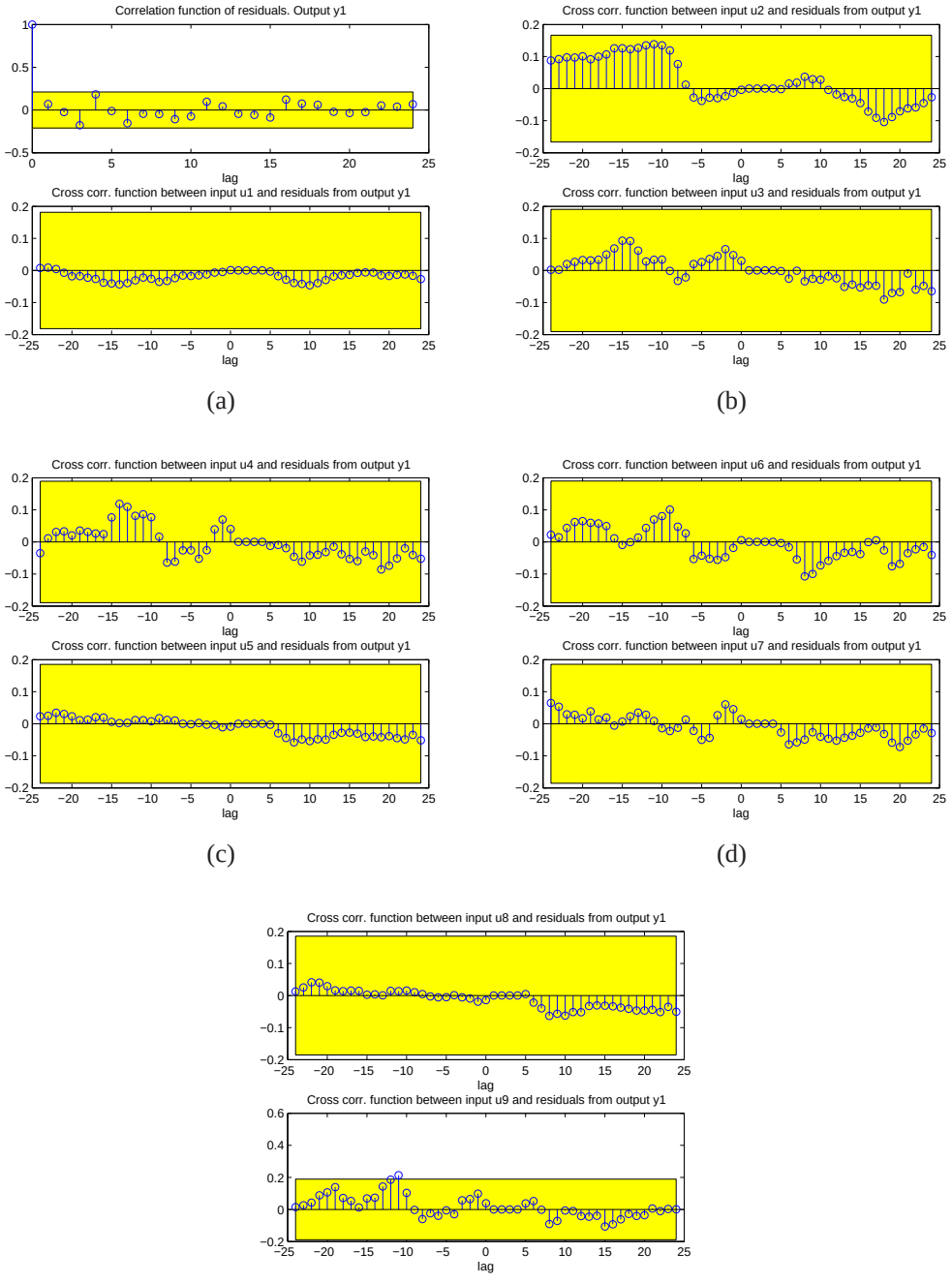
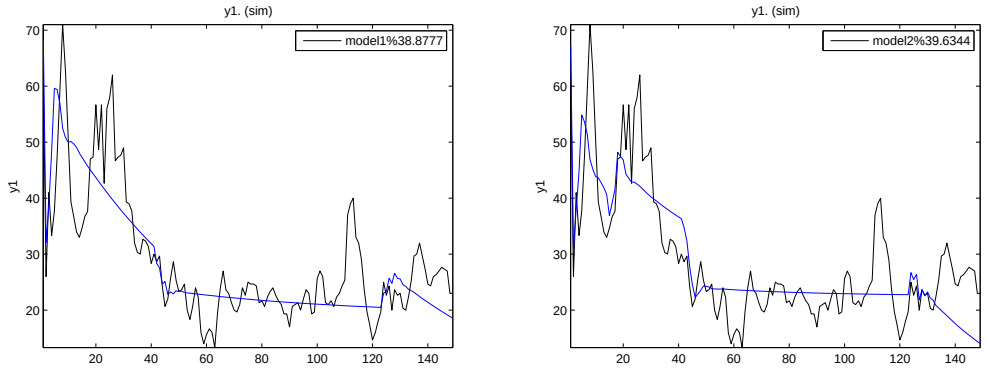
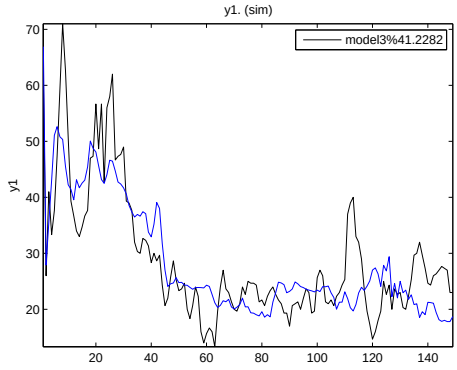


Figure 3.39: Classical correlation analysis test on residuals (with 99% confidence intervals) using model 9 for Participant 38.

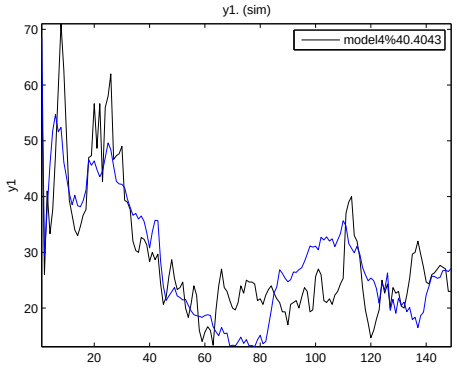


(a) Model 1

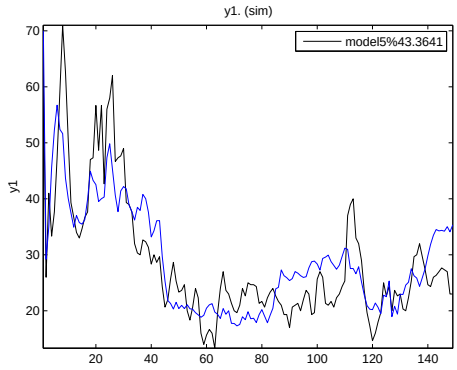
(b) Model 2



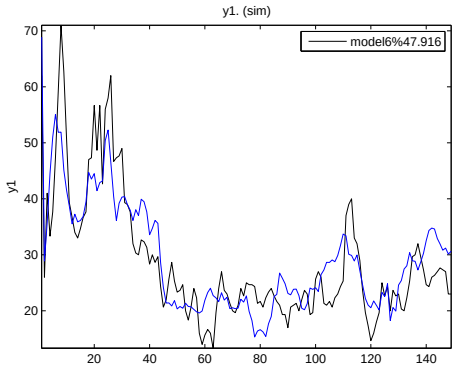
(c) Model 3



(d) Model 4

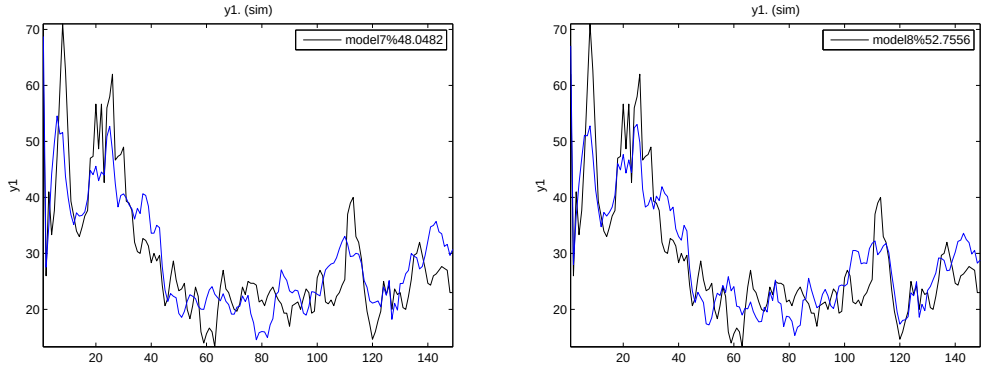


(e) Model 5



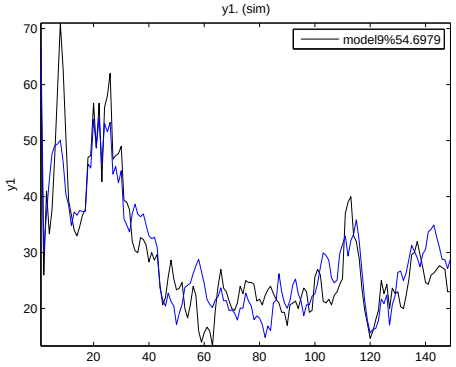
(f) Model 6

Figure 3.40: Estimated model (1-6) output vs. actual (FM sym) output using ARX [4 4 1] for Participant 38.



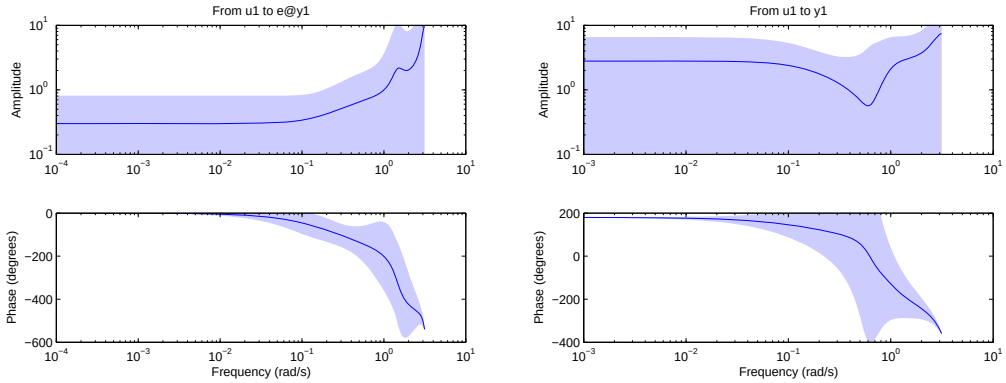
(a) Model 7

(b) Model 8



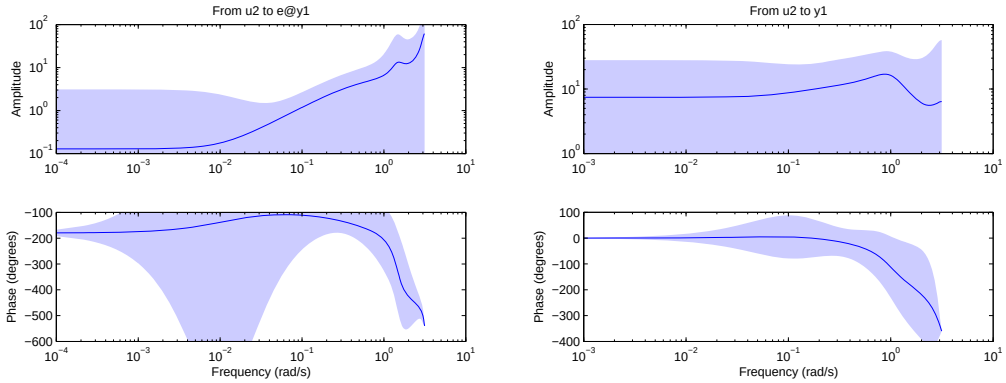
(c) Model 9

Figure 3.41: Estimated model (6-9) output vs. actual (FM sym) output using ARX [4 4 1] for Participant 38.



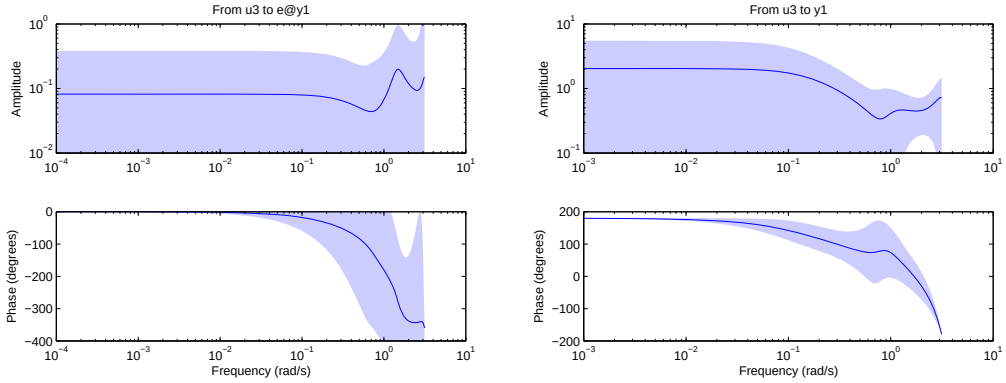
(a) Drug to *e*

(b) Drug to FM



(c) Placebo to *e*

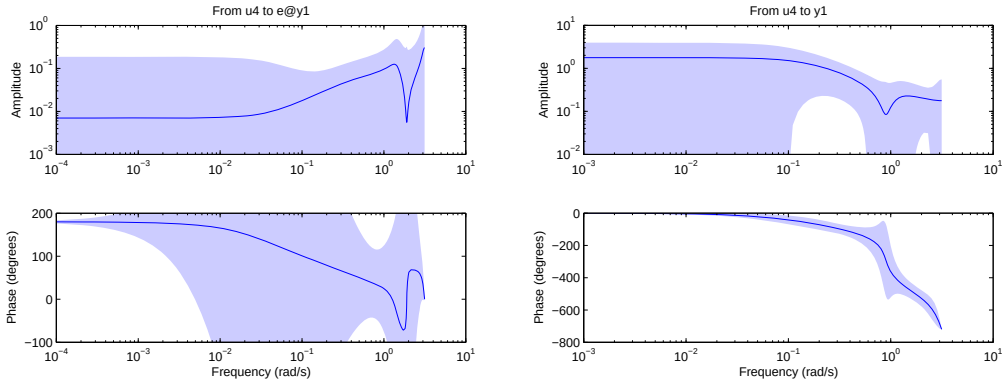
(d) Placebo to FM



(e) Anxiety to *e*

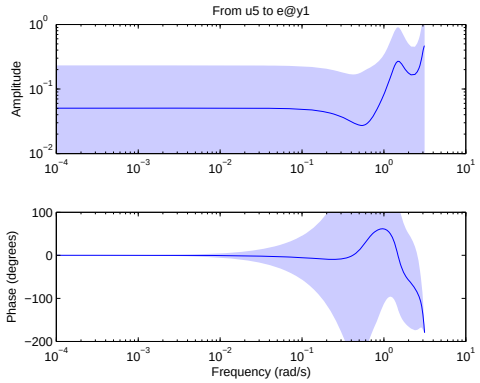
(f) Anxiety to FM

Figure 3.42: Bode plots for the model error model and nominal model (with 95% confidence interval) of estimated ARX model using model 9, for participant 38.

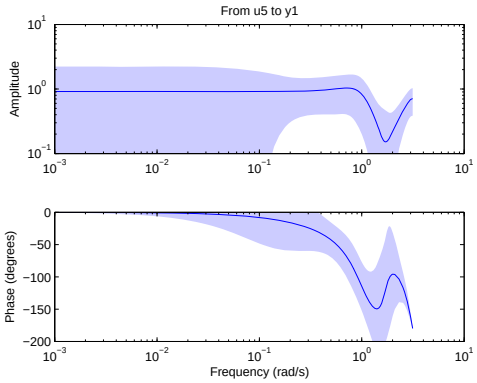


(a) Stress to *e*

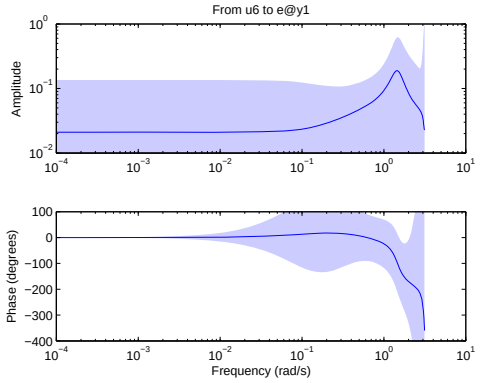
(b) Stress to FM



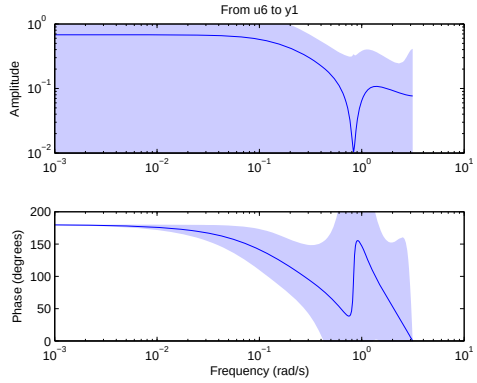
(c) Mood to *e*



(d) Mood to FM

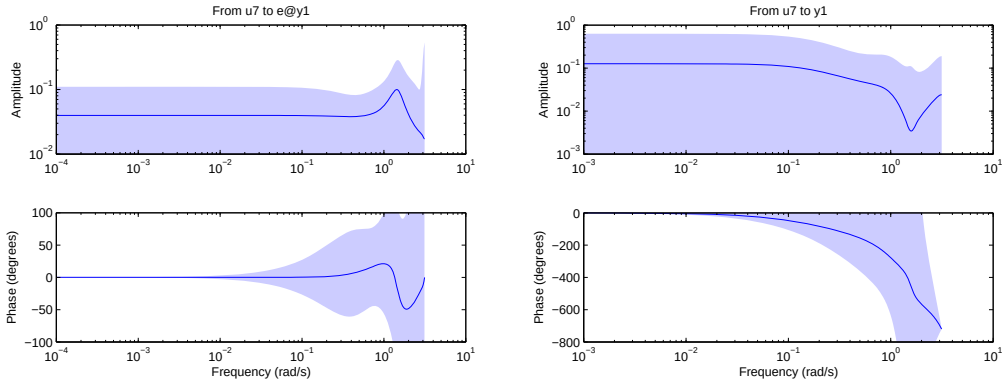


(e) Gastric to *e*



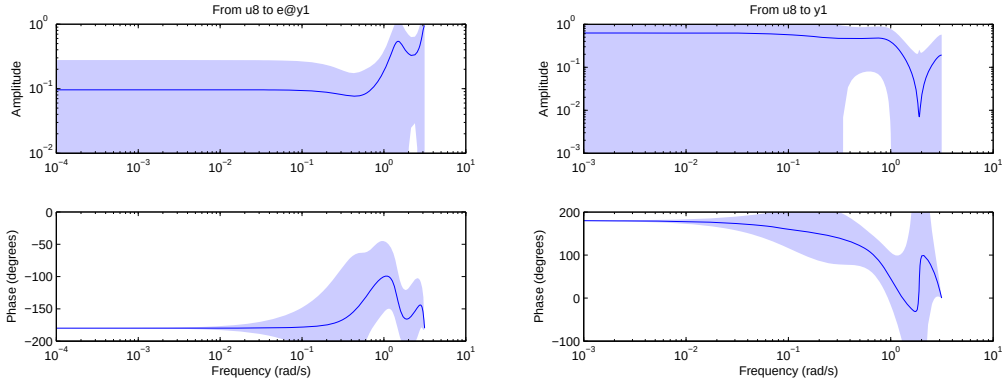
(f) Gastric to FM

Figure 3.43: Bode plots for the model error model and nominal model (with 95% confidence interval) of estimated ARX model using model 9, for participant 38.



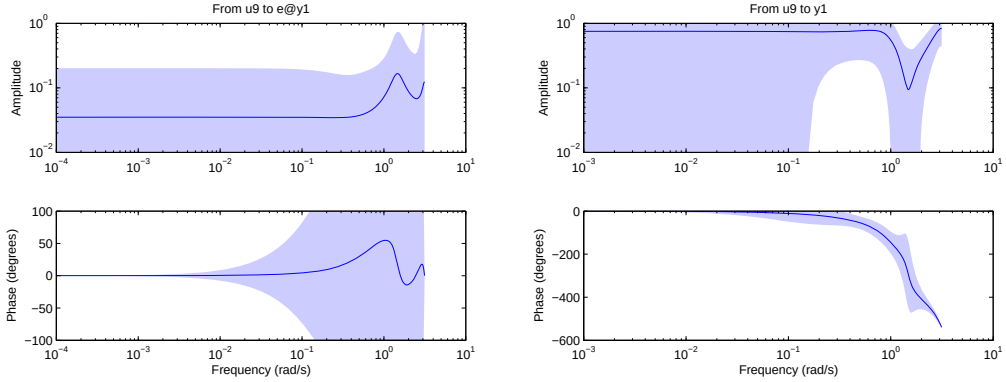
(a) Headache to *e*

(b) Headache to FM



(c) Life to *e*

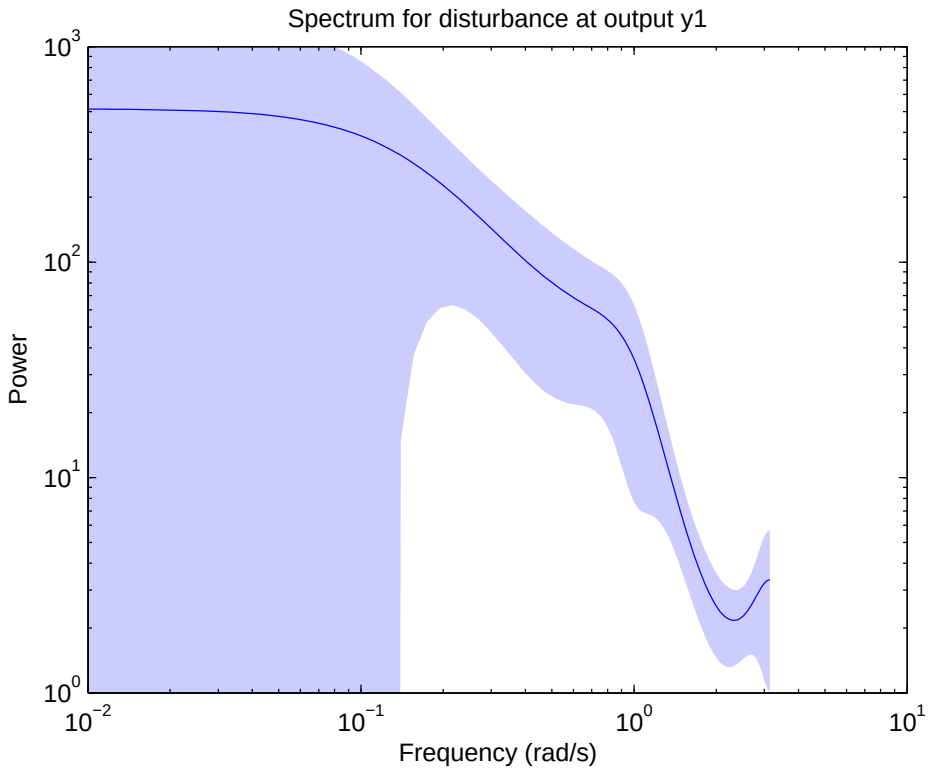
(d) Life to FM



(e) Sadness to *e*

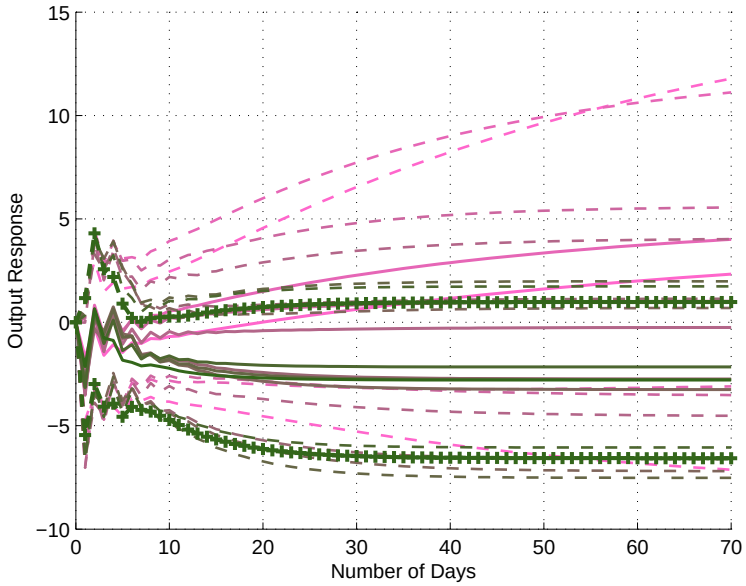
(f) Sadness to FM

Figure 3.44: Bode plots for the model error model and nominal model (with 95% confidence interval) of estimated ARX model using model 9, for participant 38.

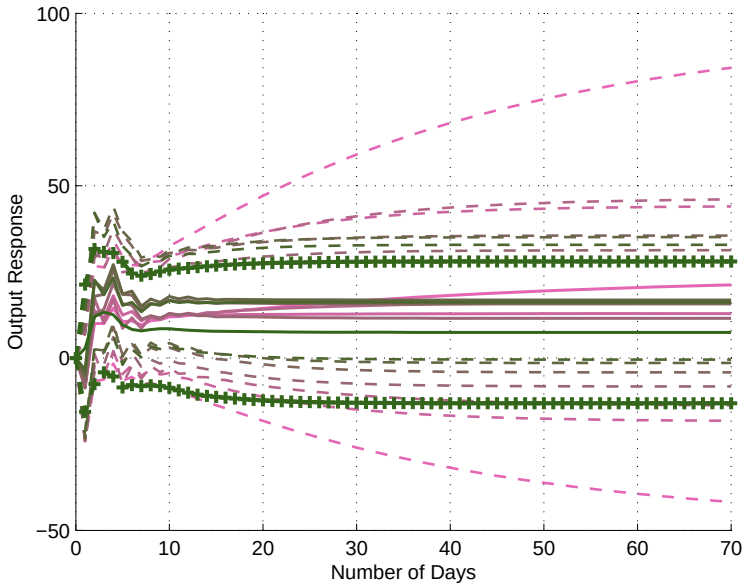


(a) Frequency response of estimated ARX model noise transfer function

Figure 3.45: Frequency magnitude plot (with 95% confidence intervals) of noise model of model 9, for Participant 38.



(a) Drug to FM



(b) Placebo to FM

Figure 3.46: Step responses with 95% confidence intervals (marked by '+') of model 9 of drug-FM and placebo-FM pairs for Participant 38.

As a part of final process, step responses and tabulations of individual inputs from model 9 estimated using an ARX [4 4 1] model structure are shown in Figures 3.47-3.56. For case of drug-FM model, it can be observed how adding extra inputs causes the change in direction of model gain as noted in Table 3.11 (model 3 to model 4).

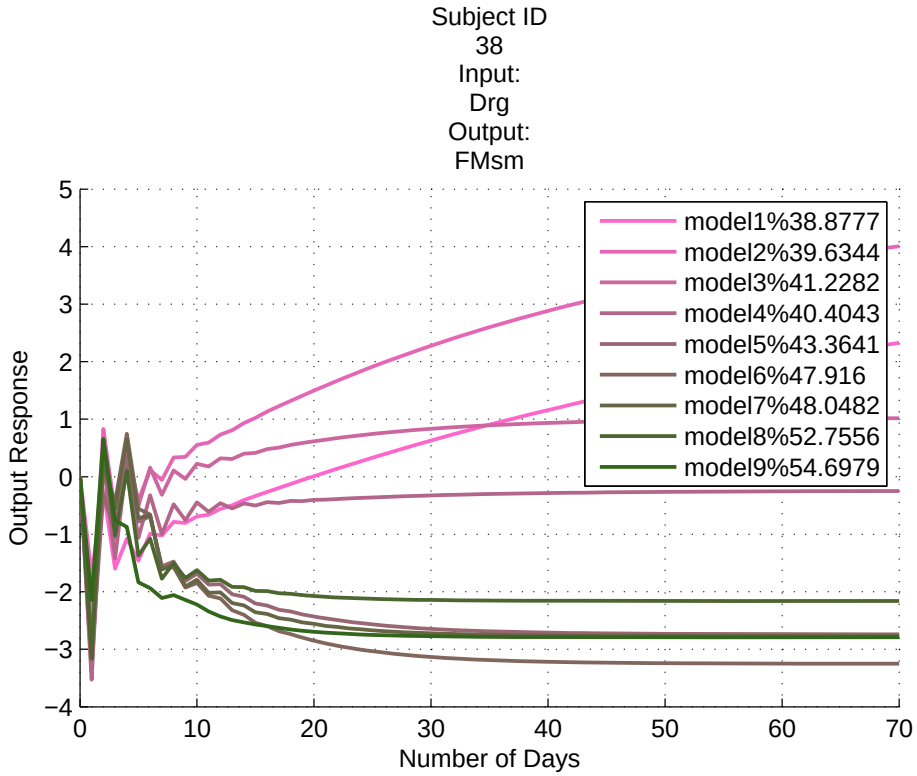


Figure 3.47: Step response of drug-FM model for Participant 38.

Table 3.11: Step response tabulation of drug-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
1	38.88	4.39 , 70.14	4.28 , 3.63 , 8.75 , -22.64	112.40	175.81
2	39.63	5.02 , 40.78	5 , 24.36 , 1.12 , 103.28	92.88	136.69
3	41.23	0.89 , 0.00	1.03 , 0.84 , 4.13 , -11.58	36.50	41.39
4	40.40	-0.24 , 17.50	-0.26 , 0.00 , 68.40 , 2517.15	0.06	34.32
5	43.36	-2.74 , 9.94	-2.73 , 5.18 , 0.97 , -12.03	0.69	34.64
6	47.92	-3.26 , 11.29	-3.24 , 5.86 , 0.96 , 0.59	0.86	34.24
7	48.05	-2.78 , 9.57	-2.76 , 5.51 , 0.90 , 0.92	0.76	28.42
8	52.76	-2.16 , 6.52	-2.15 , 4.08 , 0.89 , -7.04	0.55	23.56
9	54.70	-2.79 , 6.23	-2.79, 3.73 , 1.03 , 1.63	13.37	23.11

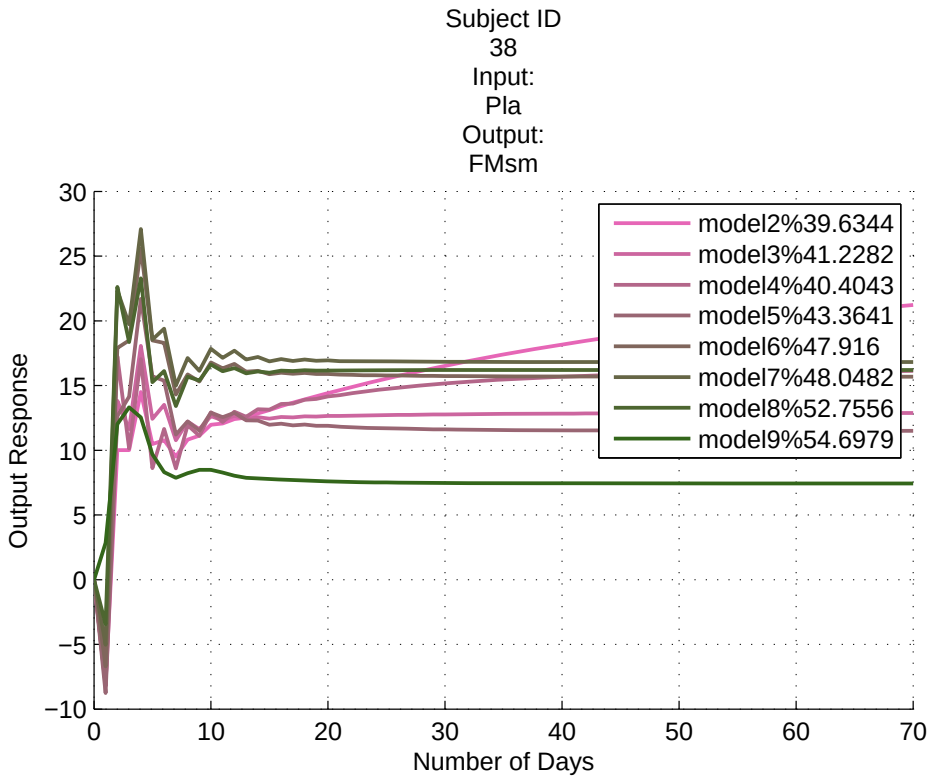


Figure 3.48: Step response of placebo-FM model for Participant 38.

Table 3.12: Step response tabulation of placebo-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
2	39.63	23.54 , 30.88	23.90 , 22.76 , 1.24 , -43.49	71.83	122.36
3	41.23	12.87 , 1.91	12.86 , 0.00 , 96.53 , -55.94	0.47	16.19
4	40.40	16.00 , 6.09	16.21 , 6.16 , 1.57 , 12.96	0.51	41.90
5	43.36	11.65 , 1.44	11.65 , 0.87 , 0.34 , -1.34	0.43	19.82
6	47.92	15.79 , 1.38	15.78 , 0.80 , 0.39 , -1.06	0.51	15.03
7	48.05	16.92 , 1.23	16.92 , 0.32 , 0.65 , -3.41	0.49	13.65
8	52.76	16.23 , 1.21	16.23 , 0.31 , 0.59 , -4.03	0.50	11.05
9	54.70	7.56 , 0.65	7.49 , 1.72 , 0.51 , 3.03	1.16	21.02

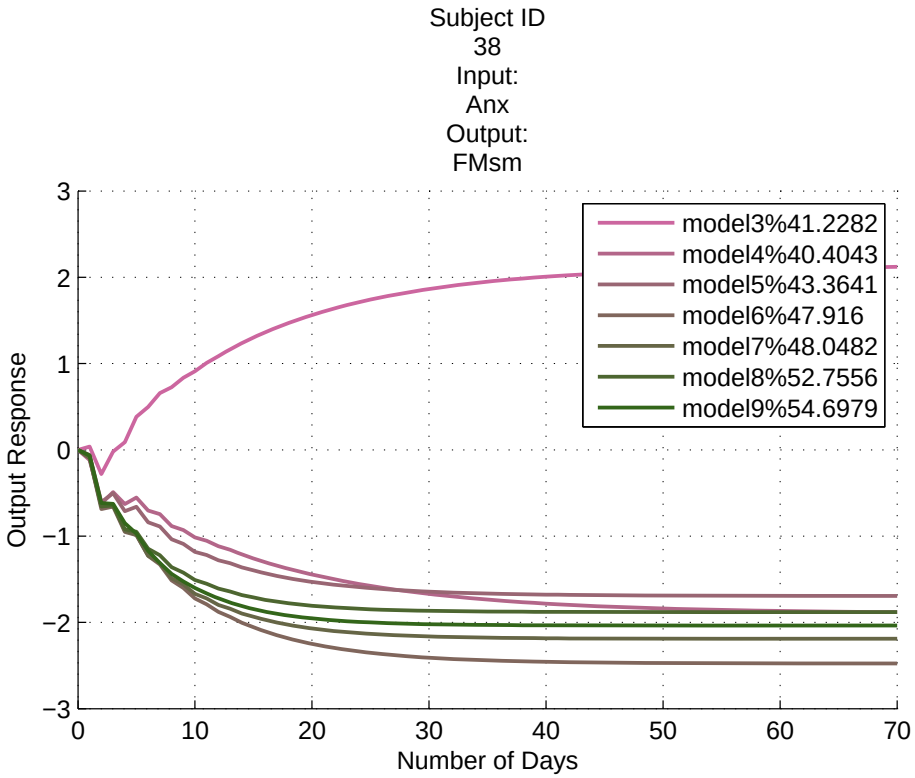


Figure 3.49: Step response of anxiety-FM model for Participant 38.

Table 3.13: Step response tabulation of anxiety-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
3	41.23	2.14 , 14.42	-7.09 , NaN , 1931.40 , NaN	28.66	53.81
4	40.40	-1.90 , 14.31	-1.90 , 22.33 , 1.09 , 0.43	31.44	56.92
5	43.36	-1.69 , 8.55	-1.69 , 7.73 , 1.01 , 7.01	18.48	34.30
6	47.92	-2.48 , 8.59	-2.48 , 5.71 , 1.06 , 3.56	18.08	33.56
7	48.05	-2.19 , 7.24	-2.19 , 3.76 , 1.16 , 1.59	14.73	27.79
8	52.76	-1.88 , 6.38	-1.88 , 1.94 , 1.71 , 0.39	13.15	25.12
9	54.70	-2.04 , 6.57	-2.04 , 1.29 , 2.45 , -0.26	13.35	25.28

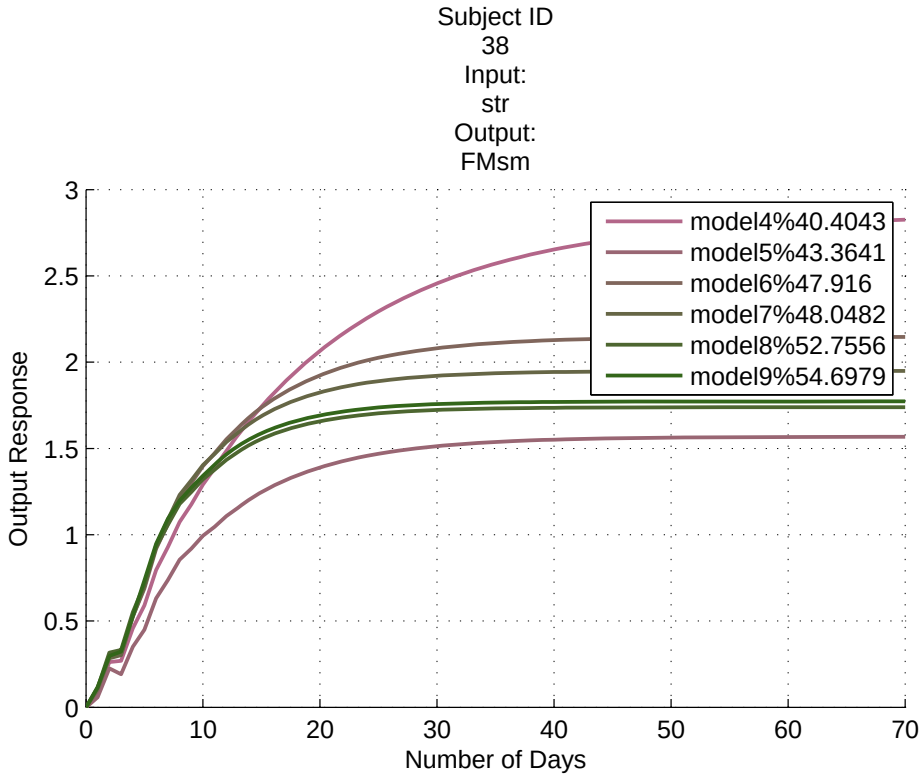


Figure 3.50: Step response of stress-FM model for Participant 38.

Table 3.14: Step response tabulation of stress-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
4	40.40	2.85 , 15.20	2.85 , 4.80 , 1.66 , 0.24	31.61	59.04
5	43.36	1.57 , 9.58	1.57 , 3.97 , 1.26 , 0.09	19.50	35.71
6	47.92	2.15 , 9.21	2.15 , 3.72 , 1.30 , 0.12	18.75	34.57
7	48.05	1.95 , 7.89	1.95 , 3.50 , 1.17 , 0.03	15.49	28.77
8	52.76	1.74 , 7.16	1.74 , 3.33 , 1.14 , 0.25	14.06	26.15
9	54.70	1.78 , 7.15	1.77 , 3.26 , 1.14 , 0.11	13.93	25.94

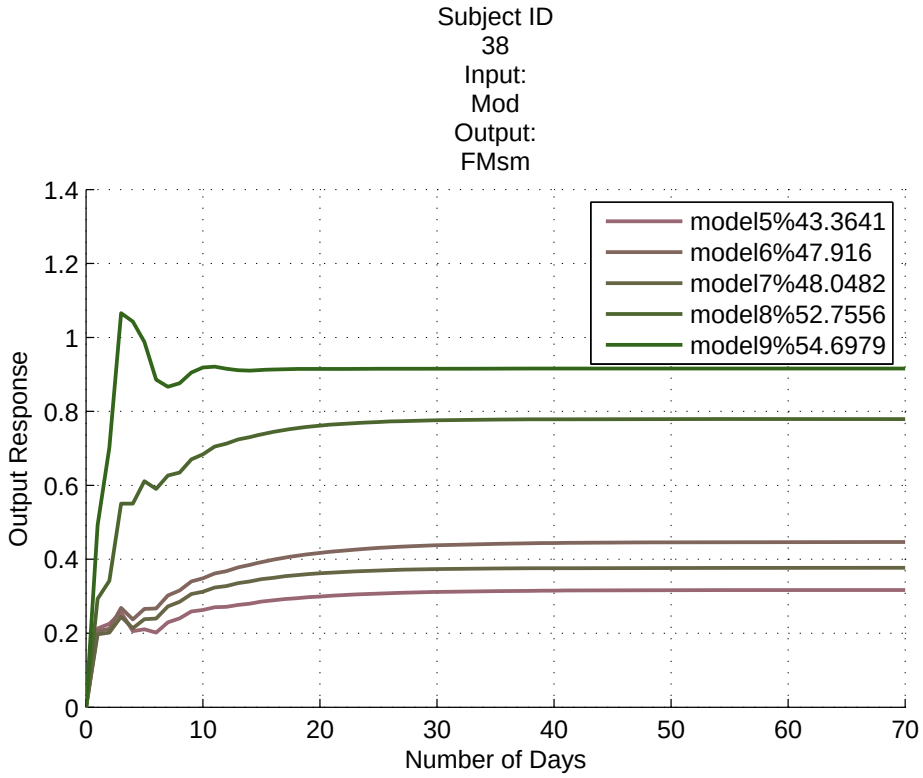


Figure 3.51: Step response of mood-FM model for Participant 38.

Table 3.15: Step response tabulation of mood-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
5	43.36	0.31 , 3.33	0.32 , 1.22 , 4.41 , 6.37	14.80	29.56
6	47.92	0.45 , 6.82	0.45 , 1.14 , 3.83 , 3.10	16.32	30.77
7	48.05	0.38 , 5.51	0.38 , 1.03 , 3.62 , 2.96	13.63	25.45
8	52.76	0.78 , 3.52	0.78 , 2.91 , 1.39 , 4.04	10.56	21.84
9	54.70	0.92 , 1.05	0.91 , 1.13 , 0.54 , 0.42	2.15	9.73

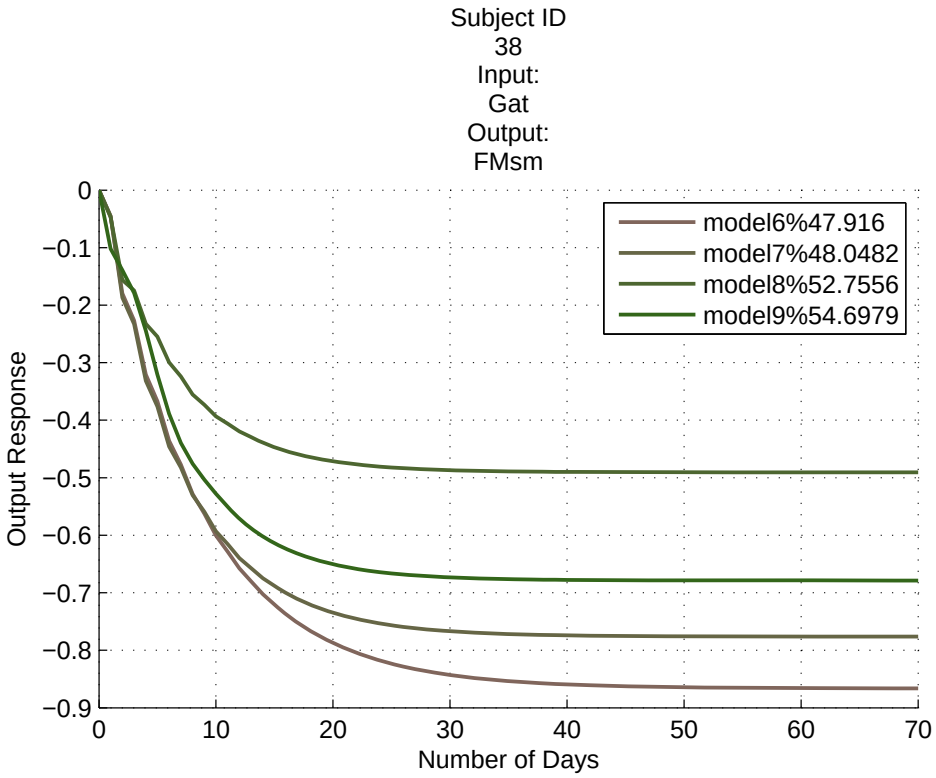


Figure 3.52: Step response of gastric-FM model for Participant 38.

Table 3.16: Step response tabulation of gastric-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
6	47.92	-0.87 , 8.40	-0.87 , 2.05 , 2.08 , 0.18	17.97	33.50
7	48.05	-0.78 , 6.95	-0.78 , 1.40 , 2.41 , -0.15	14.59	27.62
8	52.76	-0.49 , 6.32	-0.49 , 4.61 , 1.03 , 3.21	13.27	25.05
9	54.70	-0.68 , 6.96	-0.68 , 3.58 , 1.09 , 0.71	14.06	25.43

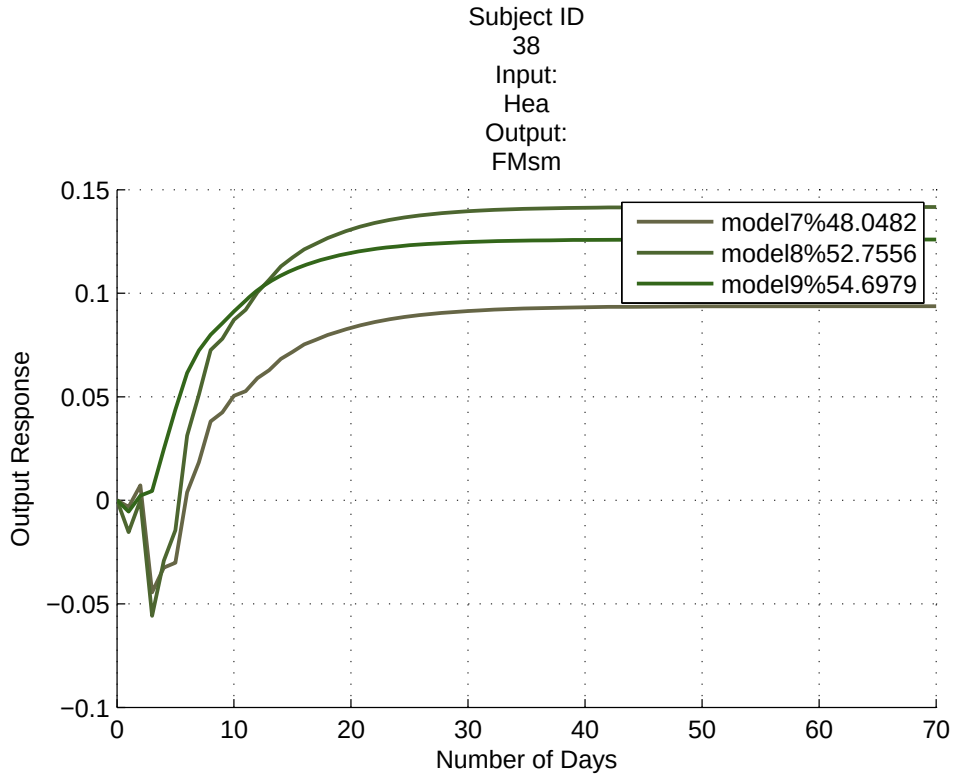


Figure 3.53: Step response of headache-FM model for Participant 38.

Table 3.17: Step response tabulation of headache-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
7	48.05	0.09 , 10.72	0.09 , 4.09 , 0.98 , -4.81	14.37	29.90
8	52.76	0.14 , 9.41	0.14 , 3.55 , 1.02 , -3.86	12.77	27.13
9	54.70	0.13 , 7.61	0.13 , 2.75 , 1.25 , -1.41	12.59	26.42

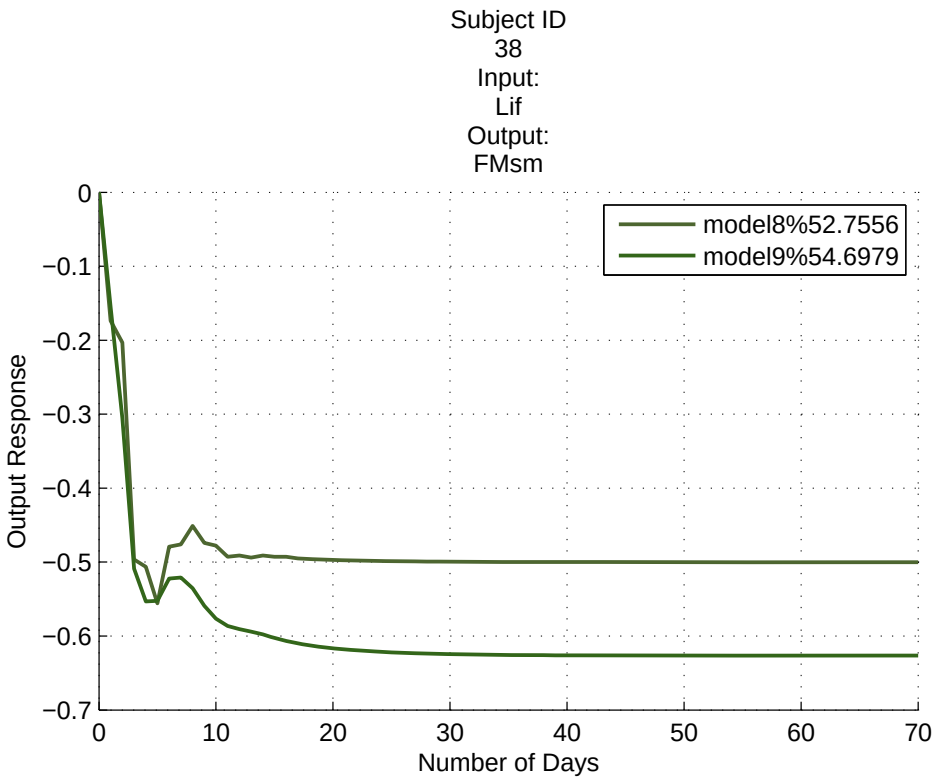


Figure 3.54: Step response of life-FM model for Participant 38.

Table 3.18: Step response tabulation of life-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
8	52.76	-0.50 , 1.85	-0.50 , 1.13 , 0.74 , -0.02	2.55	11.82
9	54.70	-0.62 , 2.67	-0.62 , 0.66 , 1.94 , 0.01	8.86	19.62

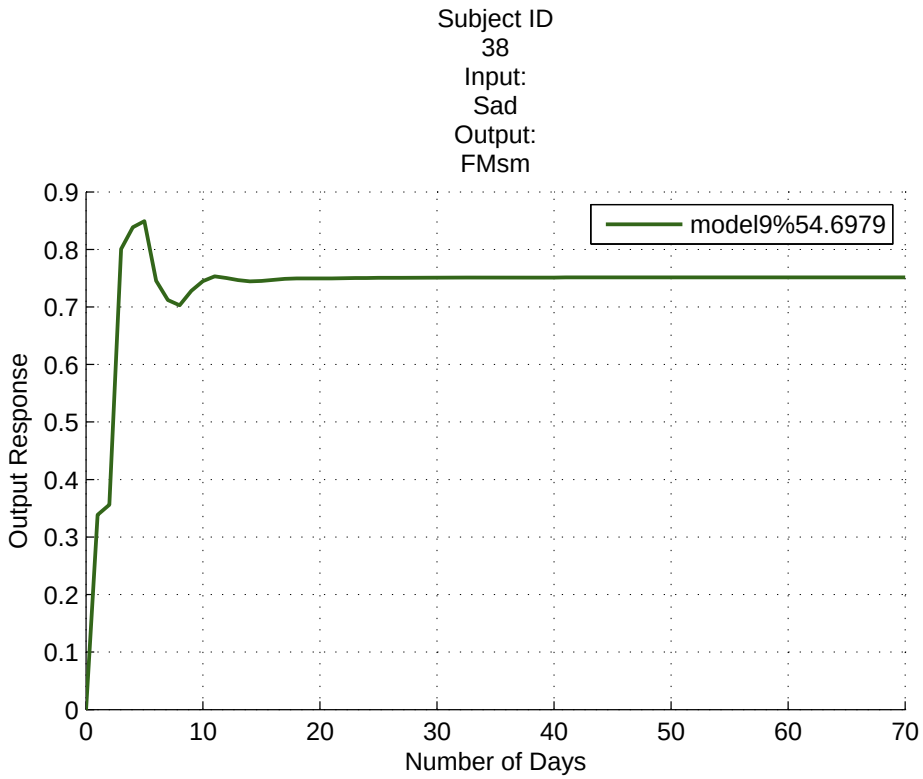


Figure 3.55: Step response of sadness-FM model for Participant 38.

Table 3.19: Step response tabulation of sadness-FM model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
9	54.70	0.75 , 1.50	0.75 , 1.24 , 0.57 , 0.18	2.50	10.49

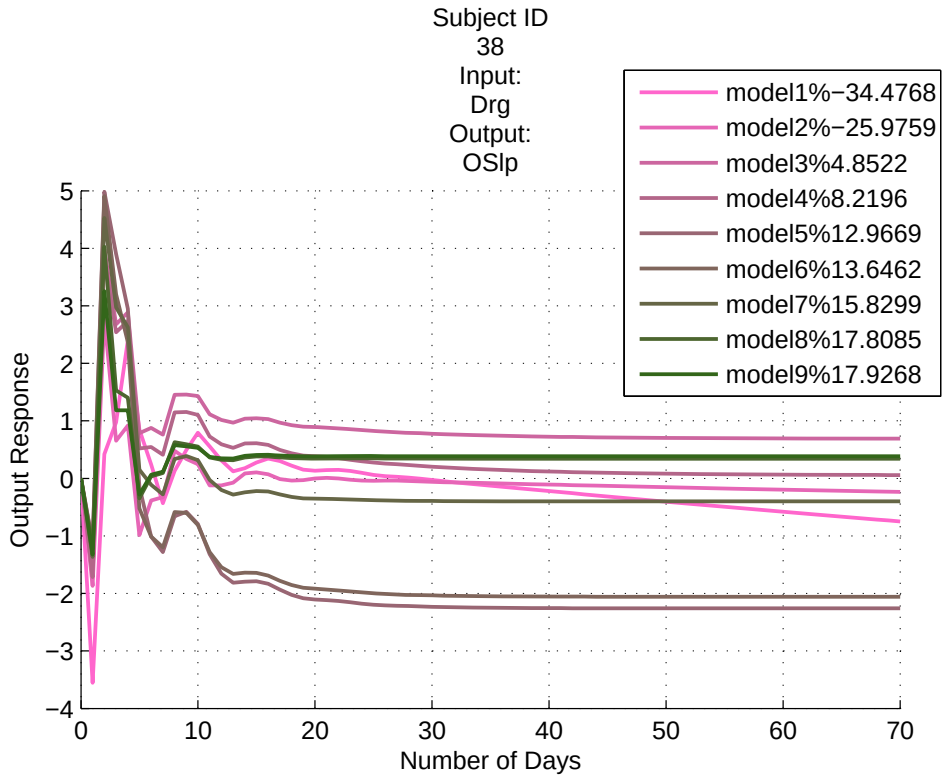


Figure 3.56: Step response of drug-overall sleep model for Participant 38.

Table 3.20: Step response tabulation of drug-overall sleep model for Participant 38.

Model	%fit	K_p, τ	K_p, τ, ζ, τ_a	T_r	T_s
1	-34.48	NaN , NaN	-1.09, 0.43 , 0.48 , 3.10	0.53	189.02
2	-25.98	-2.62 , 757.46	-0.29 , 0.33 , 0.28 , 19.30	0.25	164.05
3	4.85	0.75 , 0.70	0.76 , 0.39 , 0.35 , -4.88	0.10	34.42
4	8.22	0.15 , 0.66	0.16 , 0.38 , 0.32 , -22.03	0.01	39.54
5	12.97	-2.28 , 9.54	2.18 , NaN , 1214.93 , NaN	17.93	21.88
6	13.65	-2.07 , 9.32	-2.04 , 2.44 , 0.97 , -9.45	17.79	20.97
7	15.83	-0.41 , 10.82	-0.31 , 0.39 , 0.26 , 8.07	0.23	18.56
8	17.81	0.36 , 0.61	0.36 , 0.39 , 0.27 , -8.10	0.05	11.72
9	17.93	0.39 , 0.71	0.4 , 0.38 , 0.30 , -7.41	0.07	11.57

3.5 Summary for Full Study

There were a total of 30 participants in the full study. Overall, the response of participants to naltrexone was not as strong when compared with cases in the pilot study. The following inferences make use of data tabulated in Tables 3.21-3.24. Some of our findings from secondary analysis on the full study data are as follows:

- The goodness of fit is determined by the percent variance in the output variable described by the ARX model for a given model structure. In the full study, this varies from 2.19 % (Participant # 29) to 66.41 % (Participant # 48) for FM symptoms (as noted in Figures 3.57-3.60) and from 17.93 % (Participant # 38) to 72.5 % (Participant # 17) for Overall Sleep.

- The strength of response to drug on FM symptoms is noted by the gain of the drug-FM model. The gain varies from -11.66 (Participant # 33) to 4.09 (Participant # 29) for participants subjected to the Placebo-Drug protocol. Similarly, the gain varies from -7.23 (Participant # 34) to 2.17 (Participant # 37) for the Drug-Placebo protocol.

- The strength of response to drug on overall sleep is noted by the gain of the drug-overall sleep model. The gain varies from 6.23 (Participant # 46) to -4.89 (Participant # 35) for participants in the Placebo-Drug protocol. Similarly, the gain varies from 9.7 (Participant # 18) to -4.08 (Participant # 27) for the Drug-Placebo protocol.

- The settling time for most the participants responding to drug for both output cases (FM symptoms and overall sleep) was under 30 days on average.

- The strength of response to placebo on FM symptoms is noted by the gain of the placebo-FM model. The gain varies from -67.83 (Participant # 42) to 41.48 (Participant # 17) for participants with the Placebo-Drug protocol. Similarly, the gain varies from -61.62 (Participant # 18) to 72.44 (Participant # 48) for Drug-Placebo protocol.

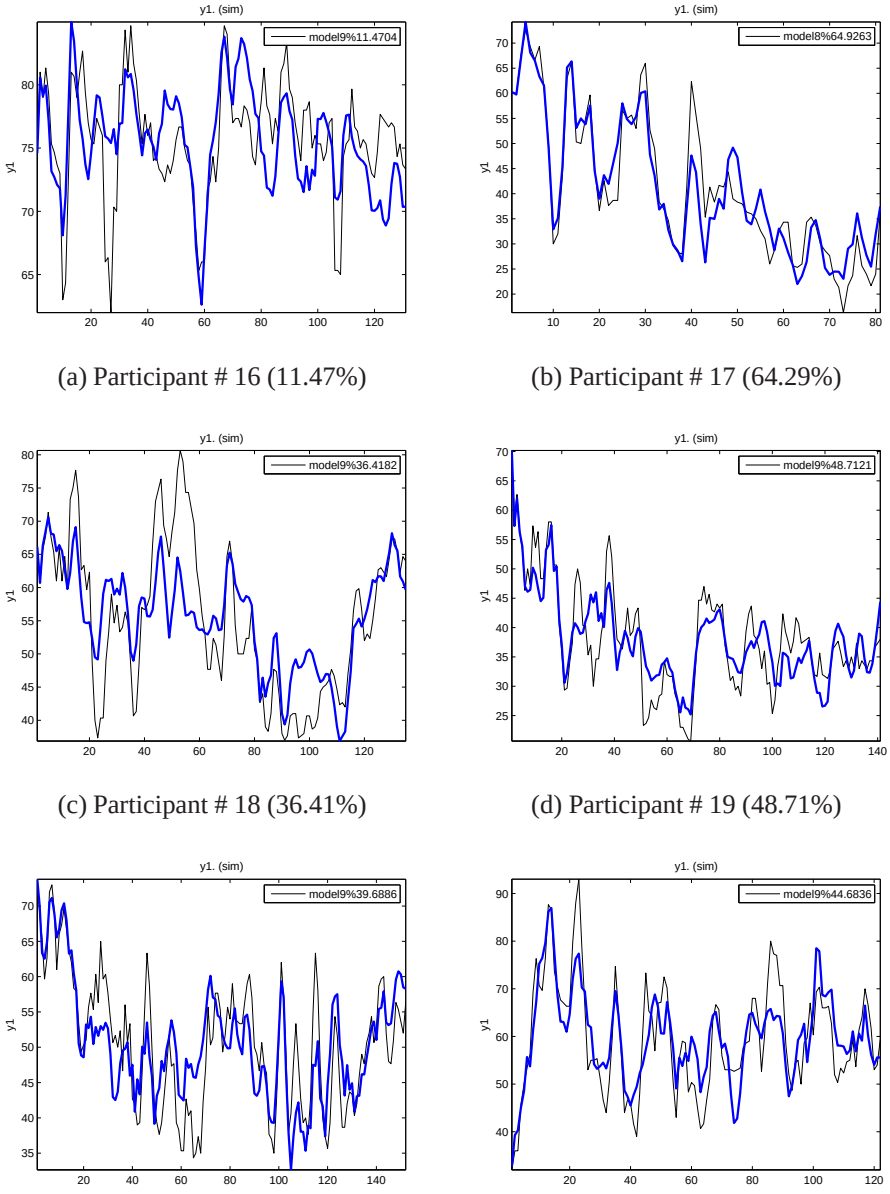
- The strength of response to placebo on overall sleep is noted by the gain of the placebo-overall sleep model. The gain varies from 37.37 (Participant # 46) to -30.87 (Participant # 35) for Placebo-Drug protocol. Similarly, the gain varies from 102.52 (Participant # 18) to -15.13 (Participant # 45) for Drug-Placebo protocol.

- Based on the estimated gains for the drug-FM model, we classify the following participants as responders : **# 16, 17, 18, 19, 22, 28, 30, 32, 33, 34, 35, 38, 39, 40, 42, 45, 50 and 52** (total 18) and the remainder as non responders. Similarly, based on the estimated gains for the drug-overall sleep model, we classify the following participants as responders : **# 16, 18, 19, 28, 30, 33, 34, 37, 38, 43, 44, 45, 46, 47, 48, 50, and 52** (total 17) and the other participants as responders. Consider the gains for both outputs (FM symptoms and overall sleep) we have following common responders : **#16, 18, 19, 28, 30, 33, 34, 38, 45, 50 and 52** (total 11).

- Placebo effects on FM symptoms are substantial in this study. It was observed that a much greater percentage of participants display a negative gain for drug-FM model (indicating beneficial effects of placebo) than were observed in the pilot study. Of the 11 common responders (displaying beneficial effects to both FM symptoms and overall sleep from drug), eight display a beneficial effect from placebo. The magnitude of the average effect (as reflected by the

nominal gain values) is similar to that obtained from the drug. It seems to indicate that most participants who respond to drug respond similarly as well to placebo and there seems to be no benefit from naltrexone treatment under these circumstances.

- We tabulate the standard deviations of the estimated gain estimates for each participant. It was observed that for most the participants (including many responders), the estimated gain interval crosses over the zero gain threshold.



(a) Participant # 16 (11.47%)

(b) Participant # 17 (64.29%)

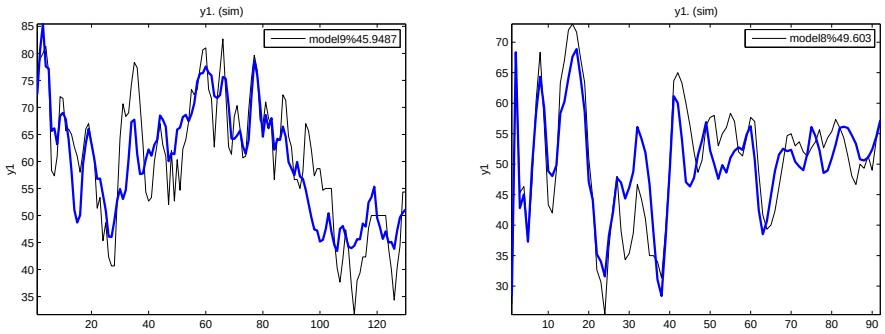
(c) Participant # 18 (36.41%)

(d) Participant # 19 (48.71%)

(e) Participant # 22 (39.68%)

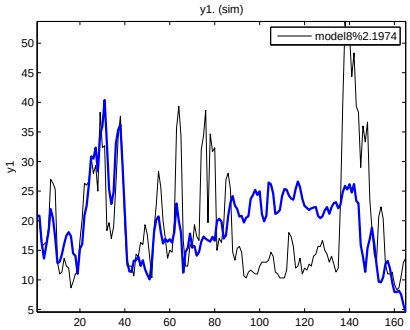
(f) Participant # 25 (44.68%)

Figure 3.57: Estimated model output vs. actual output (FM sym), using an ARX $[4\,4\,1]$ structure per model 9 (unless otherwise mentioned) for the participants of full study. Model fits are mentioned in parenthesis.

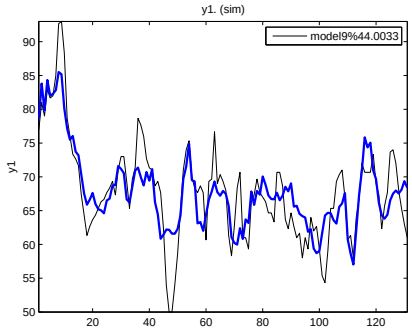


(a) Participant # 27 (45.94%)

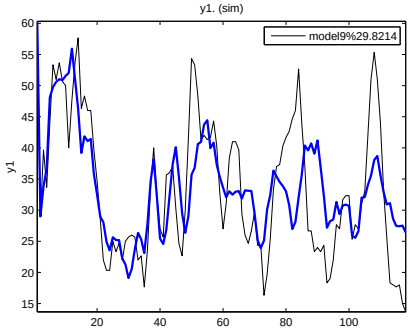
(b) Participant # 28 (49.6%)



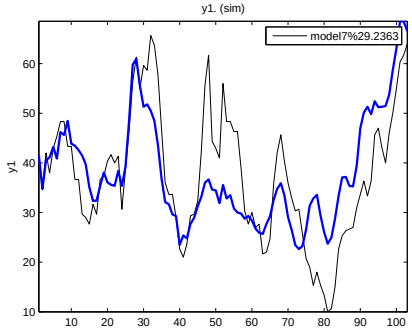
(c) Participant # 29 (2.19%)



(d) Participant # 30 (44%)

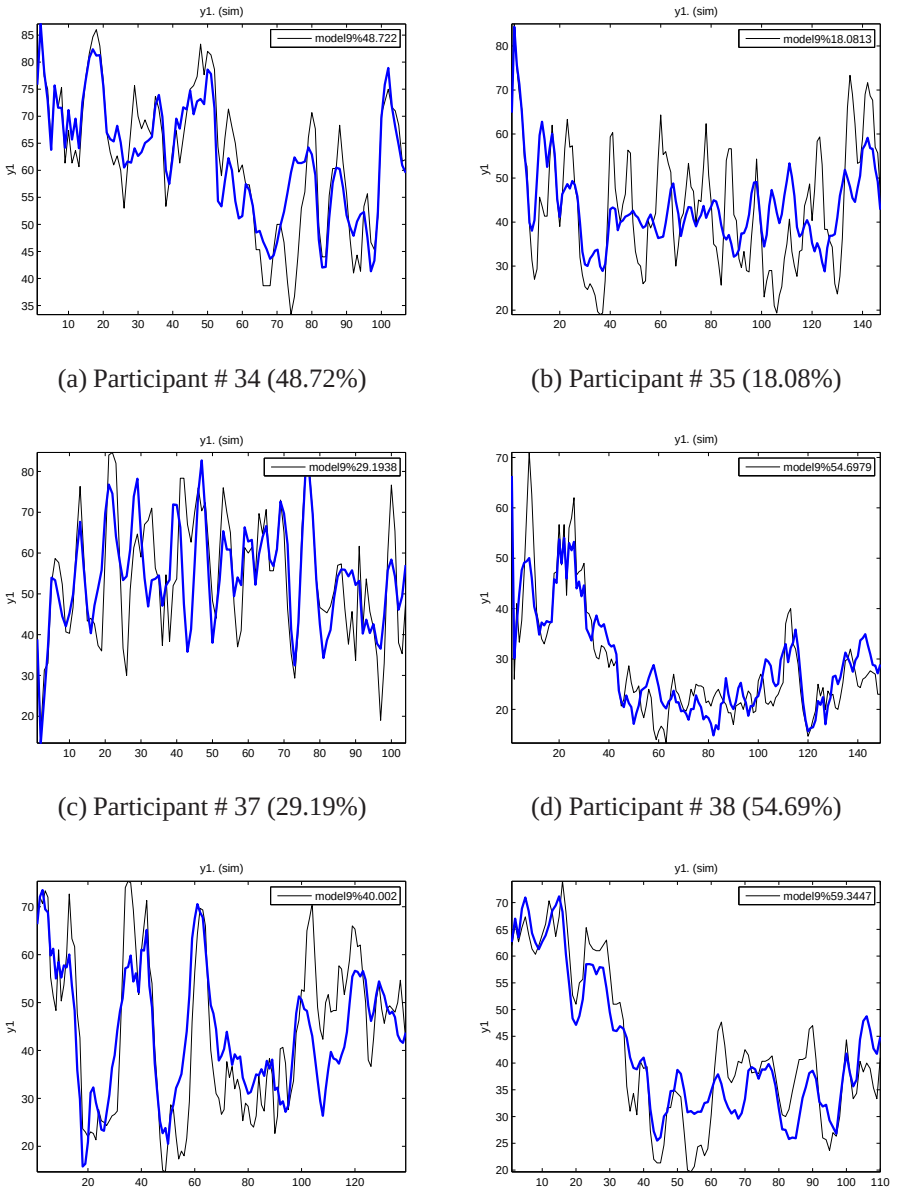


(e) Participant # 32 (29.82%)



(f) Participant # 33 (29.23%)

Figure 3.58: Estimated model output vs. actual output (FM sym), using an ARX $[4\,4\,1]$ structure per model 9 (unless otherwise mentioned) for the participants of full study. Model fits are mentioned in parenthesis.



(a) Participant # 34 (48.72%)

(b) Participant # 35 (18.08%)

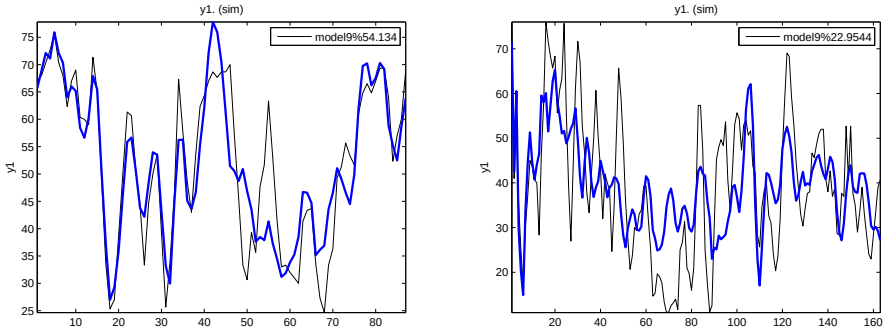
(c) Participant # 37 (29.19%)

(d) Participant # 38 (54.69%)

(e) Participant # 39 (40%)

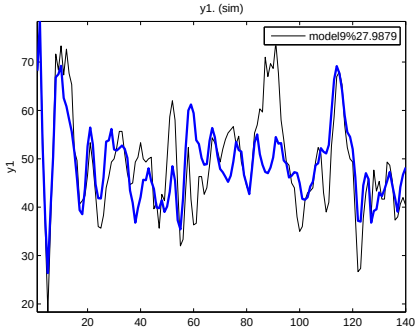
(f) Participant # 40 (59.34%)

Figure 3.59: Estimated model output vs. actual output (FM sym), using an ARX $[4\,4\,1]$ structure per model 9 (unless otherwise mentioned) for the participants of full study. Model fits are mentioned in parenthesis.

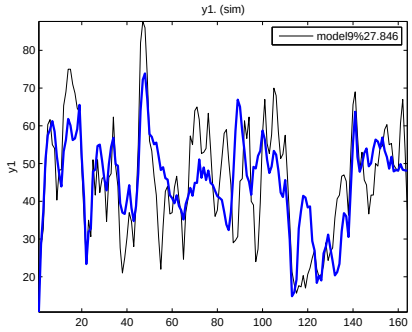


(a) Participant # 42 (54.13%)

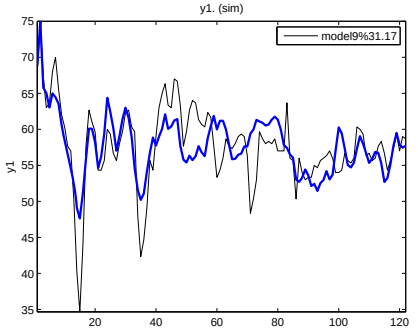
(b) Participant # 43 (22.95%)



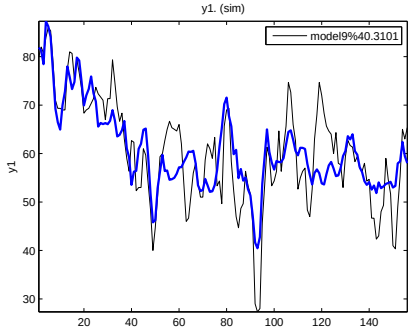
(c) Participant # 44 (27.98%)



(d) Participant # 45 (27.84%)

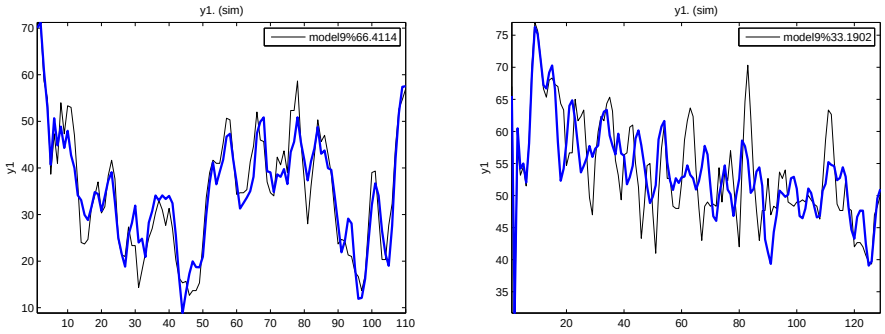


(e) Participant # 46 (31.17%)



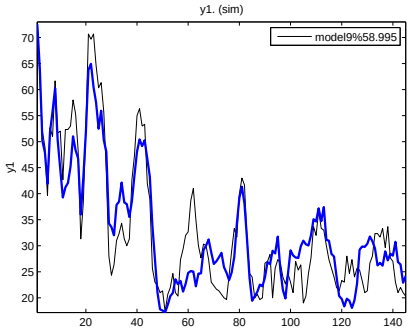
(f) Participant # 47 (40.31%)

Figure 3.60: Estimated model output vs. actual output (FM sym), using an ARX $[4\,4\,1]$ structure per model 9 (unless otherwise mentioned) for the participants of full study. Model fits are mentioned in parenthesis.

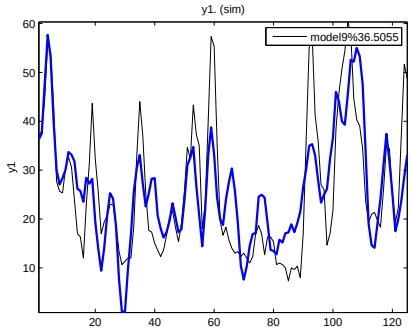


(a) Participant # 48 (66.41%)

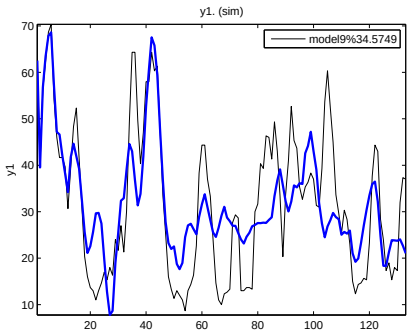
(b) Participant # 49 (33.19%)



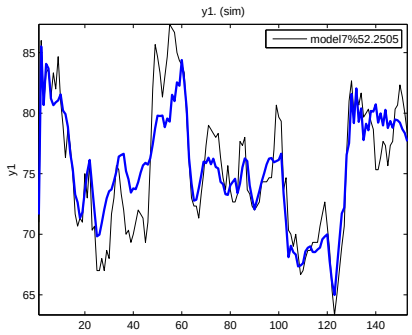
(c) Participant # 50 (58.99%)



(d) Participant # 52 (36.5%)



(e) Participant # 54 (34.57%)



(f) Participant # 24^{λ} (52.25%)

Figure 3.61: Estimated model output vs. actual output (FM sym), using an ARX $[4\,4\,1]$ structure per model 9 (unless otherwise mentioned) for the participants of full study. Model fits are mentioned in parenthesis.

Legend

- The system responses are grouped into four cases: **DFM** or Drug FM response, **DS** or Drug overall sleep response, **PFM** or Placebo FM response and **PS** or Placebo overall sleep response
- K_p **(DFM/DS)** is the gain (units of change in outcome per unit dose of LDN) and T_s**(.)** is the settling time (in days) of system response.
- **ESR** (Erythrocyte Sedimentation Rate) values for each participant
- Two protocols have been followed: **PD** (Placebo followed by Drug) and **DP** (Drug followed by Placebo)
- Goodness of fit of estimated models is shown by **% fit**
- **"Average values"** are the mean of data in respective columns
- * : Model using {Drug, Placebo, Anxiety, Stress, Mood, Life, Sadness and Gastric} and λ using {Drug, Placebo, Anxiety, Stress, Mood, Life and Headache} as inputs
- μ : Model 7 formed using {Drug, Placebo, Anxiety, Stress, Mood, Gastric and Headache}
- β : Model 9 using ARX [221] structure
- The standard deviation (σ) on data is shown by $\pm$. Please note that σ values in rows corresponding to each participant is the variability on estimated gains (from system identification) where as σ values in rows corresponding to average values is the deviation of mean of each participant's response.
- In some case due to large amount of missing data, a conclusive model was not formed and this is represented by $-$.

Table 3.21: Tabulation of system responses to drug for Placebo-Drug protocol.

Responders

#	Sub.	ESR	Pro.	% fit(DFM)	K_p(DFM)	T_s(DFM)	% fit(DS)	K_p(DS)	T_s(DS)
1	17	10	PD	64.92*	-4.70*±7.67	23.23*	72.50	-3.28±6.98	27.24
2	19	19	PD	48.71	-0.66±1.15	15.28	35.19	0.668±1.52	16.12
3	32	15	PD	29.82	-0.6±1.71	15.89	23.17	-2.83±4	45.55
4	33	0	PD	29.23^{μ}	$-11.66^{\mu}\pm$ 12.36	67.01^{μ}	28.89	1.59±2.7	13.02
5	35	4	PD	18.08	-0.83±2.3	10.51	29.87	-4.89±3.7	20.39
6	38	10	PD	54.70	-2.79±1.88	23.11	17.93	0.4±2.77	11.57
7	39	10	PD	40.00	-2.27±3.99	27.1	43.38	-0.92±1.16	17.19
8	42	10	PD	54.13	-8.44±5.12	12.63	64.55	-1.88±1.46	19.11
9	50	2	PD	59.00	-0.112±0.83	16.04	44.58	2.27±0.77	13.05
Average Values (std. deviation for nominal gain only)									
—	—	8.88	—	44.28±15.8	-3.56±4	23.42±17.2	40±18.4	-0.98±2.4	20.36±10.5
Non Responders									
10	25	2	PD	44.68	3.96±3	33.05	—	—	—
11	29	11	PD	2.19*	4.09*±3.96	39.21*	20.57	-2.53±2.47	15.54
12	44	7	PD	27.99	0.82±1.73	30.37	38.45	1±1.16	17.8
13	46	20	PD	31.17	1.94±2.07	34.97	22.47	6.23±4.94	42.46
14	47	8	PD	40.31	0.37±1.24	16.24	26.7	0.85±1.33	22.67
15	54	6	PD	34.57	1.17±2.85	15.4	49.14	0±1.16	18.34
Average Values (std. deviation for nominal gain only)									
—	—	9	—	30.15±14.9	2.06±1.6	28.2±10	31.46±12	1.11±3.17	23.62±10.9
Total Average Values (std. deviation for nominal gain only)									
—	—	8.94	—	38.63±16.5	-5.91±19.2	25.33±14.5	36.95±16.4	-0.23±2.77	21.43±10.4

Table 3.22: Tabulation of system responses to drug for Drug-Placebo protocol.

#	Sub.	ESR	Pro.	% fit(DFM)	K_p(DFM)	T_s(DFM)	% fit(DS)	K_p(DS)	T_s(DS)
Responders									
1	16	15	DP	11.47	-0.008±2.5	34.23	35.73	3.2±9.70	2.15
2	18	3	DP	36.42	-5.33±5.93	47.34	58.61	9.70±6.08	53.94
3	22	15	DP	39.69	-2.01±2.05	36.14	23.80	4.11±6.23	72.4
4	24	13	DP	52.25	-3.43±1.77	21.39	—	—	—
5	28	5	DP	49.60*	-6.25*±7.14	54.13*	34.09	0.75± 1.69	20.09
6	30	36	DP	44.00	-1.68±1.3	26.15	37.72	0.63±5.06	45.23
7	34	20	DP	48.72	–7.23±7.57	5.96	34.85	4.06±3.3	23.37
8	40	13	DP	59.34	-2.39±3.15	9.39	52.92	-1.5±1.45	15.44
9	45	25	DP	27.85	-4.99±1.82	14.16	18.44	0.008±1.43	15.49
10	52	8	DP	36.51	-1.54±1.61	20.83	34.28	3.18±1.66	21.31
Average Values (std. deviation for nominal gain only)									
—	—	15.3	—	40.58±13.7	-3.48±2.35	26.97±15.89	33.04±16.5	2.41±3.2	28.77±21.6
Non Responders									
11	27	13	DP	45.95	1.78 ± 3.28	19.97	31.98	-4.08±3.78	19.94
12	37	20	DP	29.19	2.17 ± 1.53	17.14	25.78^{β}	-0.1313^{β} ±1.11	12.13^{β}
13	43	10	DP	22.95	0.35 ± 1.64	22.38	36.24	3.74±1.53	17.8
14	48	5	DP	66.41	2.10 ± 1.31	11.92	33.34	6.42±2.76	11.64
15	49	15	DP	33.19	0.24 ± 0.8	28.85	34.38	-0.99±4.24	21.88
Average Values (std. deviation for nominal gain only)									
—	—	12.6	—	39.53±17.2	1.33±0.93	20.05±6.2	34.40±1.8	0.96±4.11	16.67±4.6
Total Average Values (std. deviation for nominal gain only)									
—	—	13.9	—	40.23±14.34	-1.88±3.05	24.66±13.6	33.49±13.3	1.94±3.44	24.74±18.4

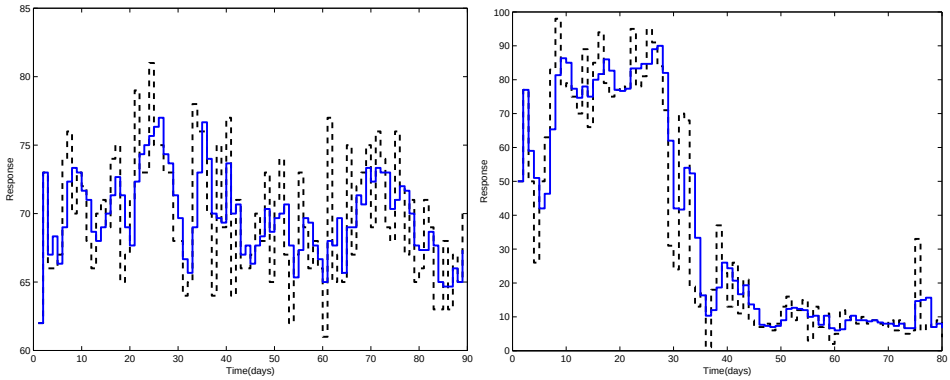
Table 3.23: Tabulation of system responses to placebo for Placebo-Drug protocol.

#	Sub.	ESR	Pro.	% fit(PFM)	K_p(PFM)	T_s(PFM)	% fit(PS)	K_p(PS)	T_s(PS)
Responders									
1	17	10	PD	64.92*	41.48*±28.10	15.62*	72.50	8.48±28.19	24.42
2	19	19	PD	48.71	-6.29 ± 7.38	14.17	35.19	16.36±10.03	14.72
3	32	15	PD	29.82	-14.34 ± 9.80	15.82	23.17	-1.45±22.70	23.61
4	33	0	PD	29.23^{μ}	-33.61^{μ}±47.24	66.49^{μ}	28.89	-11.57±23.37	13.74
5	35	4	PD	18.08	-4.65 ± 12.71	14.16	29.87	-30.87±19.80	20.81
6	38	10	PD	54.70	7.49 ± 10.29	21.02	17.93	-2.45±15.99	19.45
7	39	10	PD	40.00	-30.23 ± 29.26	26.23	43.38	5.02±8.42	16.85
8	42	10	PD	54.13	-67.83 ± 28.61	13.59	64.55	4.91±7.79	19.01
9	50	2	PD	59.00	15.56 ± 5.12	14.14	44.58	5.21±4.55	16.24
Average Values (std. deviation for nominal gain only)									
—	—	8.88	—	44.3±15.8	-10.26±31.6	22.36±17	40±18.4	-0.7±13.7	18.76±3.7
Non Responders									
10	25	2	PD	44.68	-9.34±16.86	28.24	—	—	—
11	29	11	PD	2.19*	7.64*±17.49	36.64*	20.57	-5.99±13.53	20.21
12	44	7	PD	27.99	6.67 ± 14.93	28.68	38.45	-7.17±9.70	22.99
13	46	20	PD	31.17	7.38 ± 14.26	38.36	22.47	37.37±33.61	41.08
14	47	8	PD	40.31	11.62 ± 7.91	16.42	26.7	2.26±8.54	23.11
15	54	6	PD	34.57	-6.16 ± 13.07	15.32	49.14	-6.53±5.31	18.81
Average Values (std. deviation for nominal gain only)									
—	—	9	—	30.15±14.9	2.96±8.5	27.27±9.7	31.46±12	3.98±19	25.24±9
Total Average Values (std. deviation for nominal gain only)									
—	—	8.94	—	38.63±16.3	-7.04±22.3	25.35±14.2	36.95±16.4	0.97±15.2	21.07±6.6

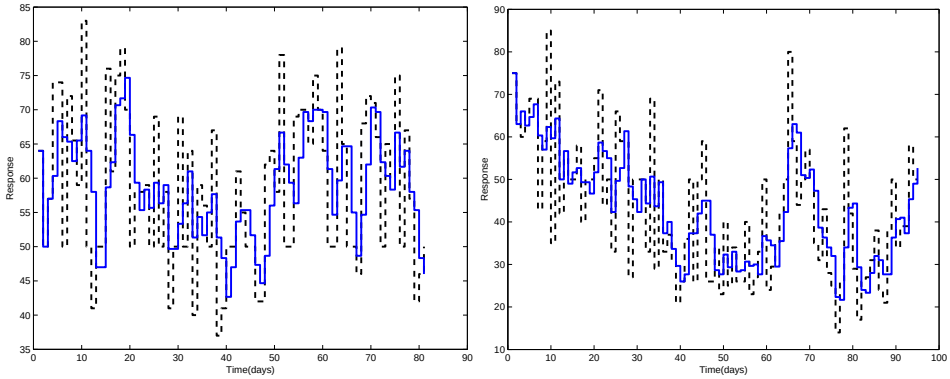
Table 3.24: Tabulation of system responses to placebo for Drug-Placebo protocol.

Responders

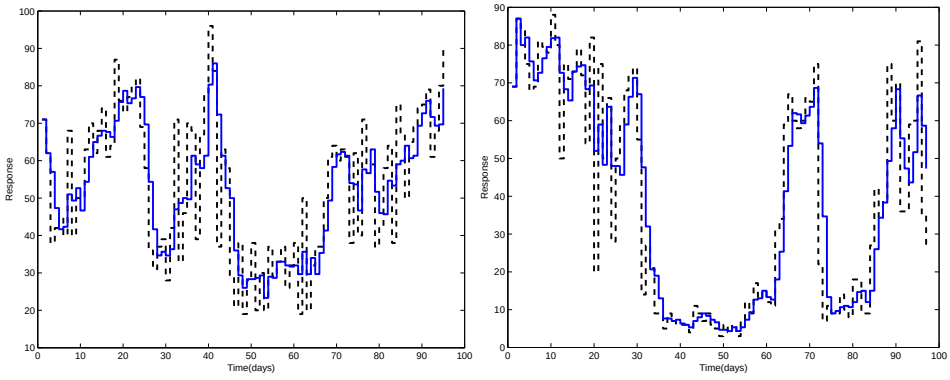
#	Sub.	ESR	Pro.	% fit(PFM)	K_p(PFM)	T_s(PFM)	% fit(PS)	K_p(PS)	T_s(PS)
1	16	15	DP	11.47	-4.31±13.07	35.04	35.73	6.18±9.37	23.35
2	18	3	DP	36.42	-61.62±44.46	44.47	58.61	102.52±56.32	55.44
3	22	15	DP	39.69	-6.41±10.97	40.48	23.80	20.22±29.17	71.47
4	24	13	DP	52.25	-26.14±12.93	23.25	—	—	—
5	28	5	DP	49.6*	-6.23*±19.48	52.04*	34.09	8.24±7.41	21.28
6	30	36	DP	44.00	-12.49±5.99	19.15	37.72	-3.13±30.17	29.88
7	34	20	DP	48.72	-52.44±51.23	10.04	34.85	14.12±19.76	23.14
8	40	13	DP	59.34	-55.01±33.36	49.49	52.92	-1.64±12.40	14.71
9	45	25	DP	27.85	-33.08±7.40	17.17	18.44	-15.13±6.04	13.81
10	52	8	DP	36.51	5.97±8.27	21.54	34.28	5.11±8.53	18.29
Average Values (std. deviation for nominal gain only)									
—	—	15.3	—	40.58±13.7	-25.17±24.27	30.85±15.56	36.71±12.5	13.64±32.7	27.13±21
Non Responders									
11	27	13	DP	45.95	-11.04±13.11	29.46	31.98	18.31±14.04	14.3
12	37	20	DP	29.19	-0.18±11.17	14.66	25.78^{β}	-6.76^{β}±6.65	12.50^{β}
13	43	10	DP	22.95	-1.67±11.13	21.49	36.24	7.49±8.95	16.28
14	48	5	DP	66.41	72.44±37.22	12.46	33.34	73.58±74.02	10.43
15	49	15	DP	33.19	-0.72±5.48	29.51	34.38	5.85±30.78	37.28
Average Values (std. deviation for nominal gain only)									
—	—	12.6	—	39.5±17.2	11.76±34.2	21.51±8	34.40±1.8	19.70±31.4	18.15±10.9
Total Average Values (std. deviation for nominal gain only)									
—	—	13.95	—	40.23±14.34	-12.86±32.21	27.74±13.95	35.89±9.9	15.66±31.2	24.14±18.3



(a) 3 (b) 5

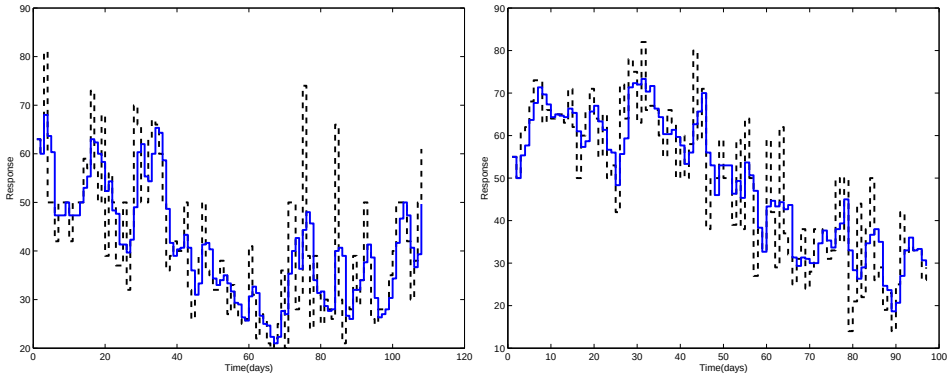


(c) 6 (d) 7

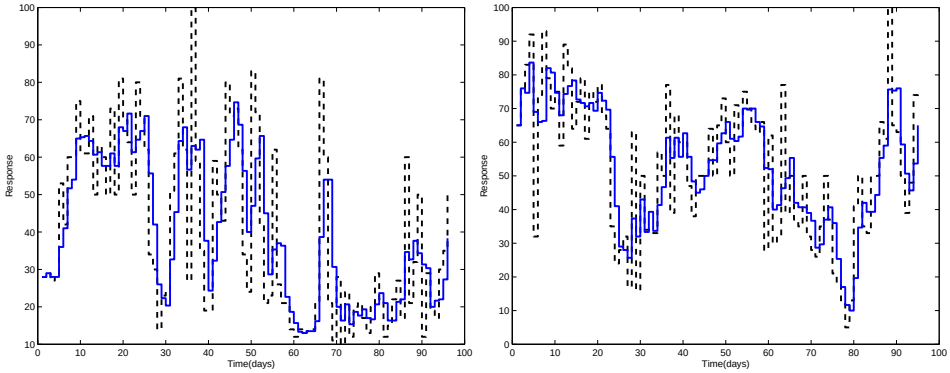


(e) 8 (f) 9

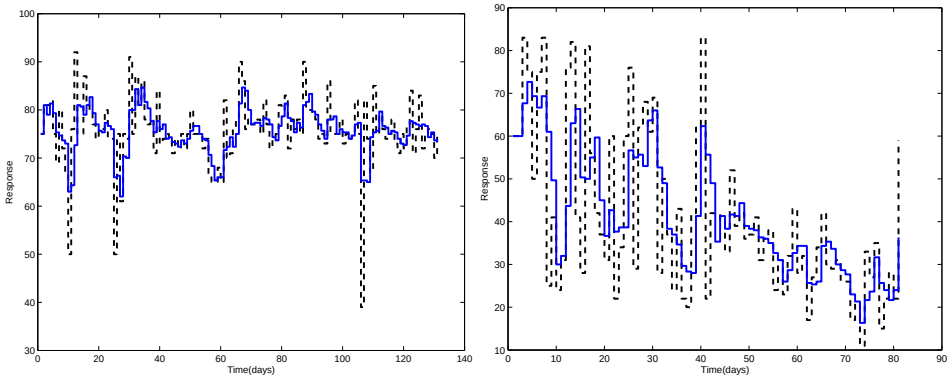
Figure 3.62: Original data time series (dashed) with three day moving averaged data (solid) of FM sym variable for participants 3 through 9.



(a) 10 (b) 11

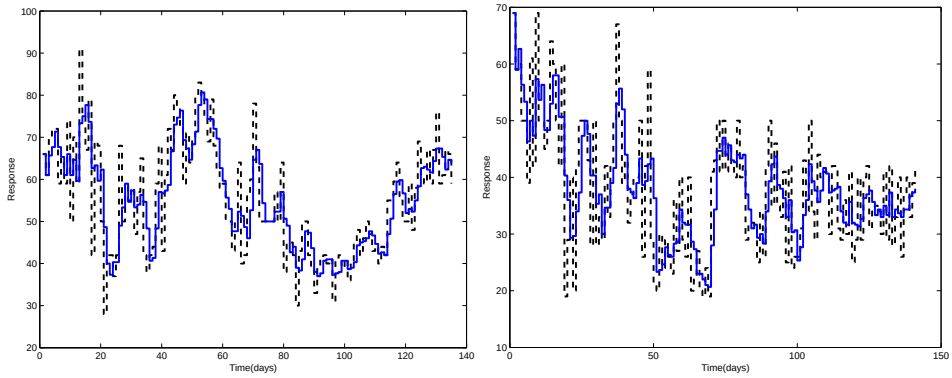


(c) 12 (d) 14



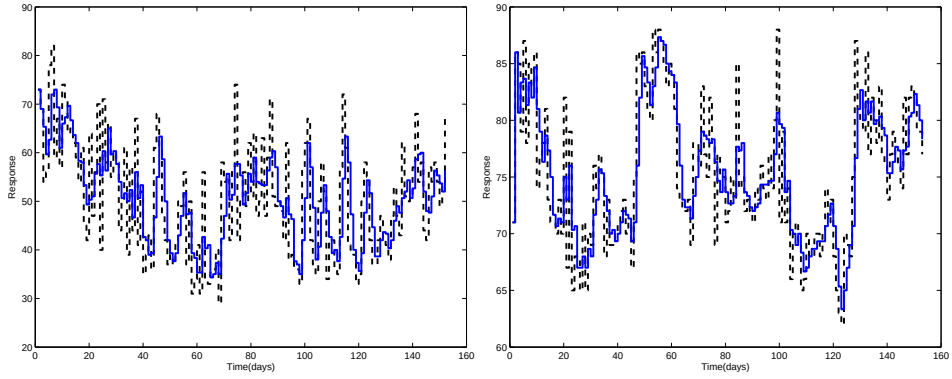
(e) 16 (f) 17

Figure 3.63: Original data time series (dashed) with three day moving averaged data (solid) of FM sym variable for participants 10 through 17.



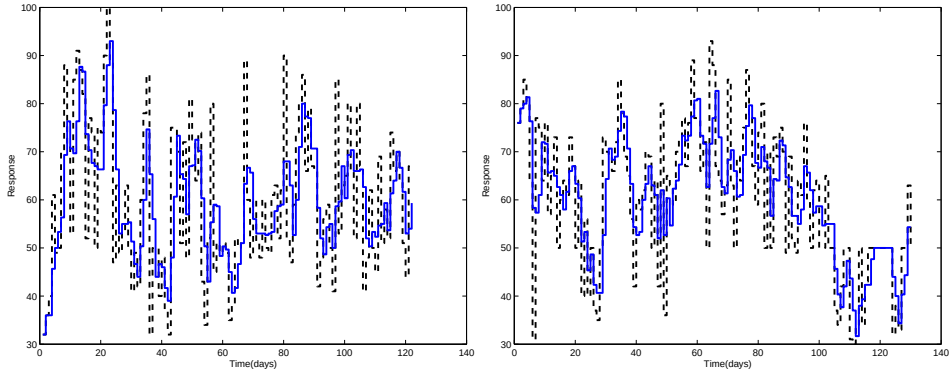
(a) 18

(b) 19



(c) 22

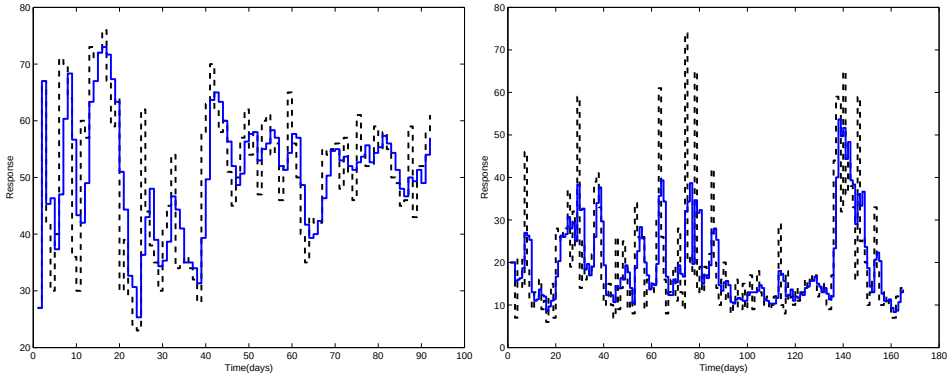
(d) 24



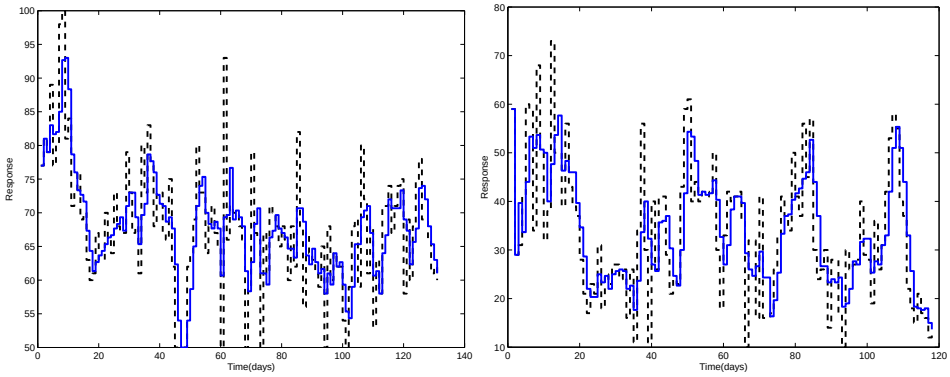
(e) 25

(f) 27

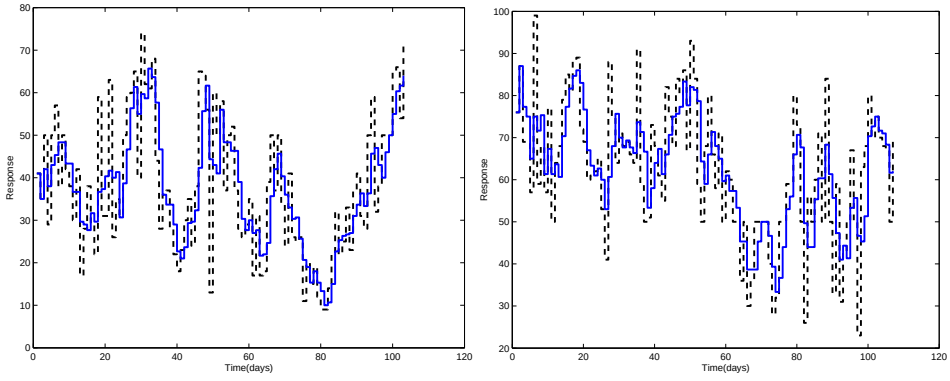
Figure 3.64: Original data time series (dashed) with three day moving averaged data (solid) of FM sym variable for participants 18 through 27.



(a) 28 (b) 29

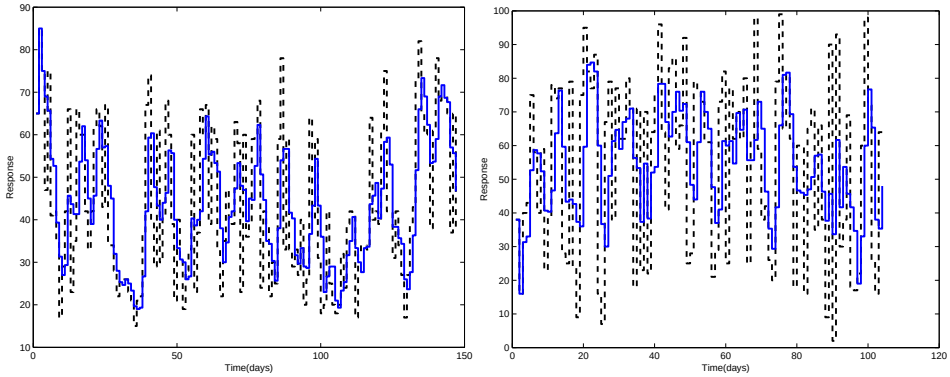


(c) 30 (d) 32

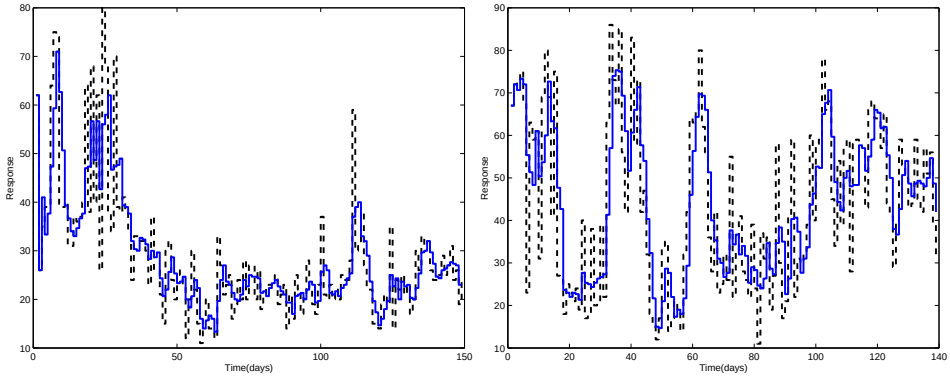


(e) 33 (f) 34

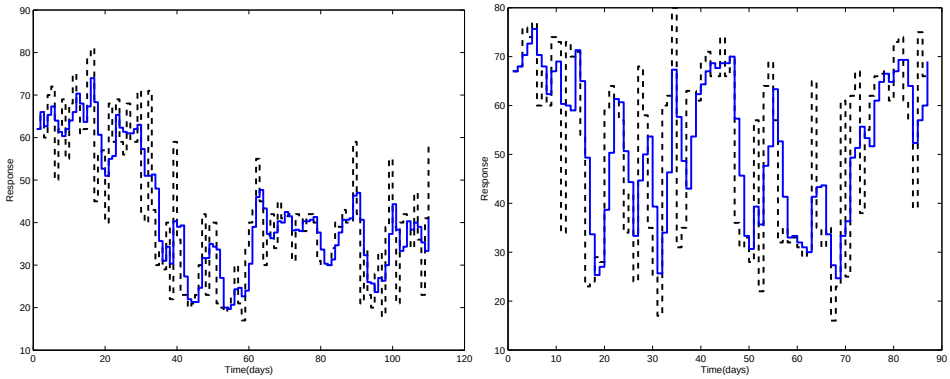
Figure 3.65: Original data time series (dashed) with three day moving averaged data (solid) of FM sym variable for participants 28 through 34.



(a) 35 (b) 37

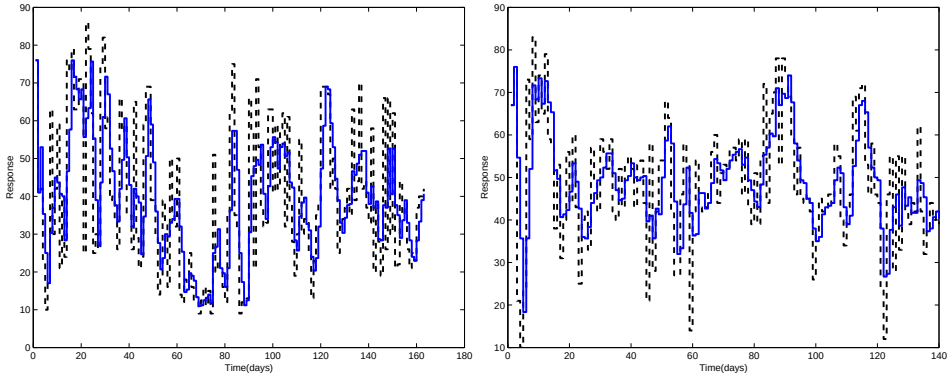


(c) 38 (d) 39

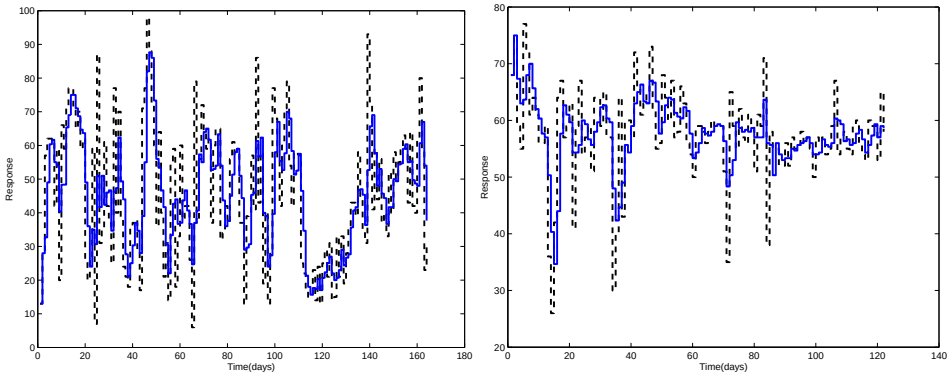


(e) 40 (f) 42

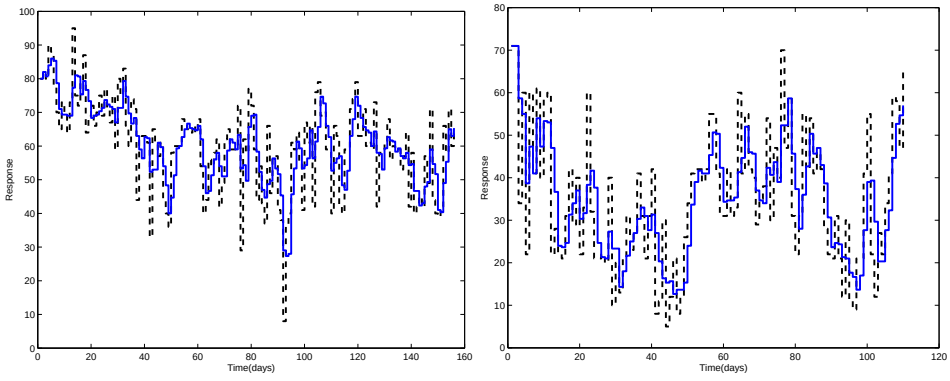
Figure 3.66: Original data time series (dashed) with three day moving averaged data (solid) of FM sym variable for participants 35 through 42.



(a) 43 (b) 44

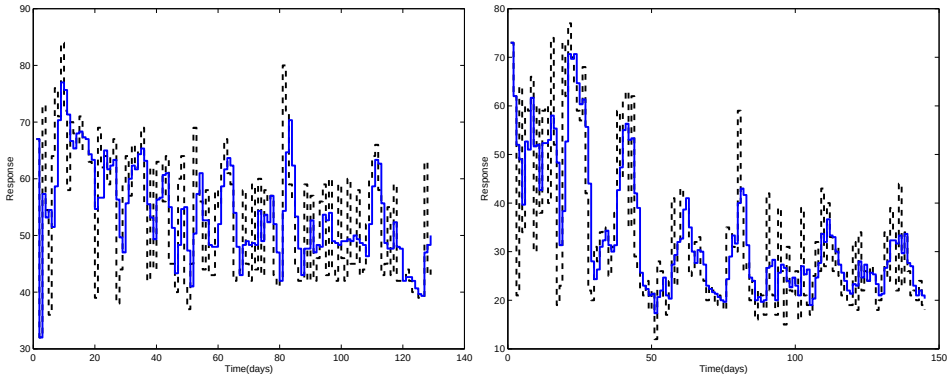


(c) 45 (d) 46

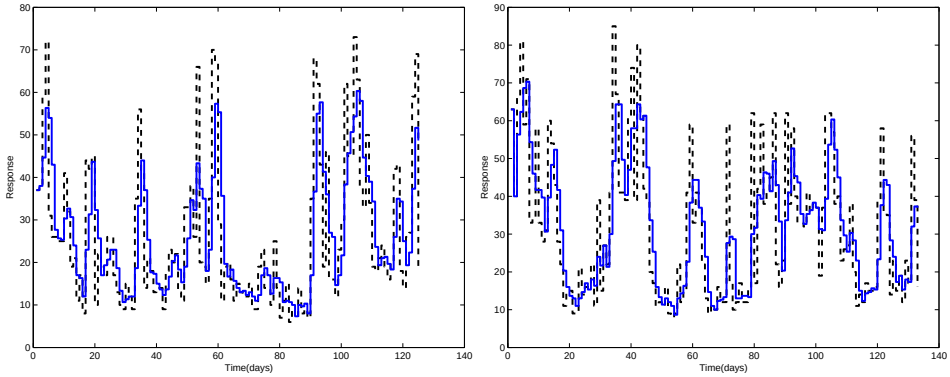


(e) 47 (f) 48

Figure 3.67: Original data time series (dashed) with three day moving averaged data (solid) of FM sym variable for participants 43 through 48.



(a) 49 (b) 50



(c) 52 (d) 54

Figure 3.68: Original data time series (dashed) with three day moving averaged data (solid) of FM sym variable for participants 49 through 54.

3.6 Summary

The full study featured a longer protocol as compared to the pilot study. In addition, the full study featured a double blind study as compared to single blind in the pilot study. Looking at the response, we observe that the full study is inconclusive to the question of whether the drug is effective or not. In a controlled experiment, it is important to not only recognize any significant effect of a drug but that effect has to be significant than the used experimental control (which is placebo in this clinical trial). It is observed, based on this analysis, that many participants, particularly from the full study, did not show conclusive response when comparing response from drug with response from placebo.

We can also infer that the cases in which model fit or quality is very poor is primarily because hardly any change is seen in the reported pain symptoms (See Figures 3.62-3.68) and not necessarily due to shortcomings in the parametric identification. In other words, it means that there is little dynamics in the data to be modeled; such trends indicate that the intervention did not have any significant effect on pain reports, for example. In comparison, the cases where relatively strong response was observed (as in participant 5), the model was able to capture some of those dynamics.

In summary, most of the pilot study participants were adequately modeled with model 5 using the ARX [2 2 1] structure (unless otherwise noted) and in the full study with model 9 using the ARX [4 4 1] structure (unless otherwise noted). Some of the following conclusions are in agreement with the results obtained from data analysis from both the pilot and full study:

- For some participants, models obtained from using only drug and placebo as inputs had good fit and high magnitude gain. This implies that the primary

inputs (drug and placebo) have major impact on the outputs (FM symptoms and overall sleep),

- As additional inputs are added in the model, the goodness of fit was observed to improve. Five inputs (consisting of {Drug, Placebo, Anxiety, Stress and Mood}) were shared in both the pilot and full studies.

- Adding typical output variables such as sleep and fatigue as inputs results in overparametrization of the estimated model. In model structures 10 to 14, more inputs such as sleep, fatigue and toleration of medicine are included. Adding sleep as an input generally resulted in no significant improvement in the goodness of fit for most of the participants. Adding toleration and side effects in many cases caused marked changes in the model estimates, among them unstable models. During the pilot study analysis we felt that these additional variables reflected outputs more than inputs, and while their inclusion in the model may increase the goodness-of-fit, in the absence of crossvalidation data this does not necessarily imply that a better predictive model has been obtained. Distinguishing between input and output variables is important in this study, particularly in how it relates to overfitting models and the absence of predictive ability in the estimated models.

The following two points have been a major shift for full study from the results obtained in pilot study:

- The pilot data analysis was done with an ARX model of lower order ($[2\,2\,1]$) than the full study ($[4\,4\,1]$). Also the standard deviation bounds on estimated gain from the pilot study are much closer as compared to the bounds obtained from the full study. As a result, the distinction between responders and non-

responders can become vague for borderline cases, and more so for the full study.

- A major change over the pilot study is the response to placebo as input. We have observed that a large group of participants can be classified as responders to placebo based on the gain of the placebo-FM model response including many participant which had responded to the drug; this was consistent across both protocols (PD and DP). It was also noted that based on classification on average values, nonresponders (i.e., to drug) are (generally) nonresponders to placebo as well.

In conclusion, we observe that not many participants show large change in pain reports on the introduction of drug and in general, it was inconclusive as to whether the drug naltrexone was, in many cases, stronger or effective than placebo. Despite this general conclusion on this naltrexone intervention, the proposed methodology provides a more detailed characterization of the response, and forms the basis for adapting the intervention using control engineering approaches as described in the next chapter.

Chapter 4

CONTROL DESIGN FOR AUTOMATED DOSAGE ASSIGNMENTS

4.1 Overview

This chapter explores the problem of drug dosage assignment using techniques from control system engineering. In this work, we implement an adaptive intervention using the estimated models from system identification and a model predictive control (MPC) framework. The aim of the control design is two fold: *a*) to calculate a control move so as to assign a (discrete-level) drug dosage for nominal control performance, i.e. setpoint tracking with measured and unmeasured disturbance rejection; *b*) to implement a control formulation which is robust enough to handle model uncertainties due to plant-model mismatch. The control results are shown for case of a representative participant ('participant 5') to demonstrate the nominal and robust performance using a three-degree-of-freedom (3 DoF) formulation of MPC as described by Nandola and Rivera [31, 61] and Wang and Rivera [62]. The control system aims at functionally performing the following three tasks:

- **Setpoint tracking.** Drug dosages are assigned to take an outcome of interest (such as FM symptoms or overall sleep quality) to a desired goal. For example, clinician may decide on a goal or setpoint of 45% reduction in general pain symptoms within two weeks of drug administration.

- **Measured disturbance rejection.** The controller manipulates drug dosages to mitigate the effect from *reported* external influences (e.g., anxiety) using estimated disturbance models. For instance, if some external event which can lead to stress is known *a priori*, then dosages can be adjusted to compensate that disturbance.

- **Unmeasured disturbance rejection.** The controller manipulates drug dosages to mitigate the effect of unknown and un-modeled external influences. For example, any sudden event which leads to increased anxiety and thus worsening pain condition. In such cases, the controller adjusts dosages for mitigate the disturbance.

As was noted in Chapter 3, the plants are estimated using ARX [2 2 1] or ARX [4 4 1] model structure and simplified to a second order continuous model with zero (mostly LHP zeros). The system under consideration, for participant 5, is a 5 input-1 output dynamical model with one manipulated variable (drug), four disturbance variables (placebo, anxiety, stress and mood) and one output (FM symptoms). The nominal performance of this control scheme is shown using different scenarios of setpoint tracking. For the robustness case, we consider different parametric uncertainties on the estimated models to generate scenarios for plant-model mismatch. We showcase robustness as a proof-of-concept since a formal robustness treatment for used hybrid MPC is beyond the scope of this thesis. The rest of the chapter is organized as following. Section 4.2 deals with hybrid dynamics and Mixed Logical Dynamical (MLD) representation. In Section 4.3 we introduce the model predictive controller and tuning for MPC using the three-degree-of-freedom formulation. In Sections 4.4 and 4.5, we discuss the aspects of nominal and robust performance respectively. We conclude with summary in Section 4.6.

4.2 Hybrid Dynamical Systems

Hybrid dynamical systems can be considered to be a superset for classes of dynamical systems. They can be identified by interacting continuous and discrete events and their behavior can be described by the differential (or difference) equation describing their physical process and logic describing their binary or categorical be-

havior. The binary constraints can be a part of the state, output or input as shown below in three simple cases:

1. *A piecewise linear dynamical system* is when the state equation update depends on a binary variable e.g.,

$$x(k+1) = \begin{cases} A_1 x(k) + B_1 u(k) & \text{if } \delta = 0 \\ A_2 x(k) + B_2 u(k) & \text{if } \delta = 1 \end{cases} \tag{4.1}$$

$$y(k) = Cx(k) + Du(k) \tag{4.2}$$

2. *Output Nonlinearity* is the case where the output from a linear system may be under conditions like saturations, for example. In other words, y can take only certain values which can be then described in terms of boolean logic. An example is shown below (for simplicity, $D = 0$)

$$x(k+1) = Ax(k) + Bu(k) \tag{4.3}$$

$$y(k) = \begin{cases} C_1 x(k) \geq 1 & \text{if } \delta = 0 \\ C_2 x(k) \leq -1 & \text{if } \delta = 1 \end{cases} \tag{4.4}$$

3. *Discrete Inputs* is the case where the input u may be required to take only specific values in its domain under given circumstances e.g.,

$$x(k+1) = Ax(k) + Bu(k) \tag{4.5}$$

$$u(k) = \begin{cases} u_1 & \text{if } \delta = 0 \\ u_2 & \text{if } \delta = 1 \end{cases} \tag{4.6}$$

where δ is a discrete variable. It can be noted that since the inputs are produced by the controller, the controller formulation should account for discrete inputs (in

contrast, the output discreteness may be due to the system dynamics). In this work, the system exhibits hybrid characteristics due to the presence of categorical decision making where drug dosage (or inputs) can only be assigned to discrete levels. All states and output of the system are continuous i.e. none involve discrete/categorical events. More detailed examples and explanations on hybrid dynamical systems can be noted in [63, 64].

4.2.1 State Space Representation

In this work, we consider the following discrete time state space system

$$x(k+1) = Ax(k) + B_1 u(k) + B_d d(k) \tag{4.7}$$

$$y(k+1) = Cx(k+1) + d'(k+1) + v(k+1) \tag{4.8}$$

where x and u represent states and inputs (e.g., drug) of the system. y represents the output (e.g., FM sym) and d, d' and v represent measured disturbances (e.g., anxiety), unmeasured disturbances and measurement noise signals, respectively. It can be noted that the effect of measured disturbance has been assumed on the state equation and the effect of unmeasured disturbance has been assumed on the measurement equation. The reason for measured disturbance in the state equation can be understood from the system dynamics. Consider a system with n_s states and m_s inputs then in that case the resulting 'B' matrix is $n_s \times m_s$ where some variables will correspond to the manipulated input and will determine B_1 and some variables will be disturbance (measured) and will determine B_d. We use a nomenclature of B_1 so that we can incorporate other B matrices due to hybrid dynamics. The unmeasured disturbance, in reality, can be affect both state and the output although it is common to lump the effect in the measurement equation. One of the primary reason for this is that the MPC formulation requires future predictions of outputs (not states) and hence it is sufficient that this is modeled as described.

Also consider a stochastic disturbance model

$$x_w(k+1) = A_w x_w(k) + B_w w(k)$$
$$d'(k+1) = C_w x_w(k+1) \tag{4.9}$$

where w is an *integrated* white noise and x_w is the state of the noise term. This model is motivated from process control where disturbances may be non-stationary and hence this offers a general representation for a large class of scenarios. In this work, $B_w, C_w = I$ and $A_w = 0$. It can also be argued that the unmeasured disturbance term can be modeled from estimated noise model from system identification e.g., $d' = H(q)e(t)$ where $H(q)$ is the noise model and $e(t)$ is white noise sequence (as is $\Delta w(k)$). In addition to stochastic disturbances, unmeasured disturbances can also be deterministic in character.

4.2.2 Mixed Logical Dynamical (MLD) systems

The most common hybrid system representations are piece wise affine (PWA) systems [65], mixed logical dynamical (MLD) systems [64] and linear complementary (LC) systems [63]. These forms can be proved to be equivalent to each other under certain assumptions [66]. The specific choice of hybrid system representation in many ways depends on the intended use. In this work, the models are used for predictive control techniques. It can be noted that predictive control like MPC requires explicit prediction of the system output (which will also be a function of discrete or binary events). Hence we use the MLD type representation for hybrid systems as it effectively combines the continuous and discrete dynamics. The key idea is to convert boolean logic into linear inequalities involving integer and real variables [67].

Extending on the general state space representation as shown in 4.7-4.8, the

MLD systems model can be written as

$$x(k+1) = Ax(k) + B_1u(k) + B_2\delta(k) + B_3z(k) + B_dd(k) \tag{4.10}$$

$$y(k+1) = Cx(k+1) + d'(k+1) + v(k) \tag{4.11}$$

$$E_2\delta(k) + E_3z(k) \leq E_5 + E_4y(k) + E_1u(k) - E_dd(k) \tag{4.12}$$

where, in general, $x = [x_c^T\ x_d^T]^T$, $x_c \in \mathbb{R}^{n_x^c}$, $x_d \in \{0,1\}^{n_x^d}$ and $u = [u_c^T\ u_d^T]^T$, $u_c \in \mathbb{R}^{n_u^c}$, $u_d \in \{0,1\}^{n_u^d}$, $n_u \triangleq n_u^c + n_u^d$ represent states (both discrete and continuous) and inputs (both discrete and continuous) of the system. $y \in \mathbb{R}^{n_y}$ is a vector of outputs, and d, d' and v represent measured disturbances, unmeasured disturbances and measurement noise signals, respectively as mentioned earlier. $\delta \in \{0,1\}^{n_d}$ and $z \in \mathbb{R}^{n_z}$ are discrete and continuous auxiliary variables that are introduced in order to convert logical/discrete decisions into their equivalent linear inequality constraints. Discussion on stability of MLD systems can be noted in [64].

The logical constraints used can be explained using an example. For illustration, let the drug dosages be $u(k) \in \{0, 4.5, 9, 13.5\}$ mg i.e. drug can take only stipulated four values. These discrete inputs (4 levels) that be represented logically as:

$$\delta_1(k) = 1 \Leftrightarrow z_1(k) = 13.5; \delta_2(k) = 1 \Leftrightarrow z_2(k) = 9 \tag{4.13}$$

$$\delta_3(k) = 1 \Leftrightarrow z_3(k) = 4.5; \delta_4(k) = 1 \Leftrightarrow z_4(k) = 0 \tag{4.14}$$

$$\sum_{i=1}^{4} \delta_i(k) = 1 \tag{4.15}$$

$$u(k) = \sum_{i=1}^{4} z_i(k) \tag{4.16}$$

It can be noted that on using the two summation conditions, we make sure that only *one* input level is selected. In this example each 'state' of the input was assigned using a discrete variable. As an alternative, we can define these four levels using

only two discrete variables and boolean logic. Also in a similar way, more categorical levels (z) can be defined using less discrete variables (δ) by the use of boolean logic.

4.2.3 Prediction

MPC uses a p step ahead prediction (called as prediction horizon) which can be called as open loop response to the calculated input $u(t)$. This can be obtained by starting from initial condition at $t = k$ and propagating through the state and measurement equations (and using the linear inequalities) to obtain the output $y(k+1)$. The process is repeated for remaining $p-1$ steps and hence finally $y(k+1)$ to $y(k+p)$ is obtained. The prediction vectors can be represented as:

$$\mathscr{Y}(k+1) = \begin{bmatrix} y^T(k+1) \\ \vdots \\ y^T(k+p) \end{bmatrix} \mathscr{U}(k) = \begin{bmatrix} u^T(k) \\ \vdots \\ u^T(k+m-1) \end{bmatrix} \bar{\delta}(k) = \begin{bmatrix} \delta^T(k) \\ \vdots \\ \delta^T(k+p-1) \end{bmatrix} \tag{4.17}$$

$$\mathscr{Z}(k) = \begin{bmatrix} z^T(k) \\ \vdots \\ z^T(k+p-1) \end{bmatrix} \mathscr{D}(k) = \begin{bmatrix} {d_{flt}}^T(k) \\ \vdots \\ {d_{flt}}^T(k+p-1) \end{bmatrix} \tag{4.18}$$

where $\mathscr{Y}(k+1)$, $\mathscr{U}$, $\bar{\delta}$, $\mathscr{Z}$ and $\mathscr{D}$ are future values of outputs, inputs, auxiliary binary variables, auxiliary continuous variables and filtered measured disturbances. The vector $\mathscr{U}$, $\bar{\delta}$, $\mathscr{Z}$ are calculated from the MPC problem where as the $\mathscr{D}$ is available beforehand. It can be noted that $\mathscr{D}$ is a function of *filtered* disturbance d_{flt} that is the filtered value of the measured disturbance obtained using a discrete time filter and will be discussed in Section 4.3.2.

Equations 4.10-4.12 can be used to obtain the prediction vector. But before we proceed with prediction, the MLD system is augmented with the disturbance model, as shown in Equation 4.9 and this will be used for prediction instead. It is written in *difference form* ([68] for more information) as follows

$$X(k) = \mathscr{A}X(k-1) + \mathscr{B}_1\Delta u(k-1) + \mathscr{B}_2\Delta\delta(k-1) + \mathscr{B}_3\Delta z(k-1) + \mathscr{B}_d\Delta d(k-1) + \mathscr{B}_w\Delta w(k-1) \tag{4.19}$$

$$y(k) = \mathscr{C}X(k) + \nu(k) \tag{4.20}$$

where,

$$X(k) = [\Delta x^T(k) \quad \Delta x_w^T(k) \quad y^T(k)]^T$$

$$\mathscr{A} = \begin{bmatrix} A & 0 & 0 \\ 0 & A_w & 0 \\ CA & A_w & I \end{bmatrix};\ \mathscr{B}_i = \begin{bmatrix} B_i \\ 0 \\ CB_i \end{bmatrix},\ i = 1,2,3,d;\ \mathscr{B}_w = \begin{bmatrix} 0 \\ I \\ I \end{bmatrix};$$

$$\mathscr{C} = [0 \quad 0 \quad I]$$

and hence use Equations 4.19-4.20 to write the prediction equation which calculates the vector $\mathscr{Y}(k+1)$ as:

$$\mathscr{Y}(k+1) = \Phi X(k) + \mathscr{H}_1\mathscr{U}(k) + \mathscr{H}_2\bar{\delta}(k) + \mathscr{H}_3\mathscr{Z}(k) + \mathscr{H}_d\mathscr{D}(k) - H_{11}u(k-1) - H_{21}\delta(k-1) - H_{31}z(k-1) - H_{d1}d_{flt}(k-1) \tag{4.21}$$

$$\mathscr{E}_5 \geq \mathscr{E}_2\bar{\delta}(k) + \mathscr{E}_3\mathscr{Z}(k) + \mathscr{E}_1\mathscr{U}(k) + \mathscr{E}_4X(k) + \mathscr{E}_d\mathscr{D}(k) - \mathscr{E}_{41}u(k-1) - \mathscr{E}_{42}\delta(k-1) - \mathscr{E}_{43}z(k-1) - \mathscr{E}_{4d}d_{flt}(k-1) \tag{4.22}$$

where Φ, $\mathscr{H}_*$, H_*, $\mathscr{E}_*$ and $\bar{E}_*$ are the appropriate coefficients matrices that can be generated using (4.12), (4.19) and (4.20) as shown:

$$\Phi = \begin{bmatrix} \mathscr{C}\mathscr{A} \\ \mathscr{C}\mathscr{A}^2 \\ \vdots \\ \mathscr{C}\mathscr{A}^p \end{bmatrix} \tag{4.23}$$

$$H_{i1} = \begin{bmatrix} \mathscr{C}\mathscr{B}_i \\ \mathscr{C}\mathscr{A}\mathscr{B}_i \\ \mathscr{C}\mathscr{A}^2\mathscr{B}_i \\ \vdots \\ \mathscr{C}\mathscr{A}^{p-1}\mathscr{B}_i \end{bmatrix} \; i = 1,\, 2,\, 3,\, d \tag{4.24}$$

$$\bar{E_i} = \text{diag}\{E_i, \cdots, E_i\},\; i = 2,\, 3,\, d \tag{4.25}$$

$$\bar{E_4} = \text{diag}\{-E_4, \cdots, -E_4\} \tag{4.26}$$

$$\bar{E_5} = [E_5 \quad E_5 \; \cdots \; E_5]^T \tag{4.27}$$

$$\bar{E_1} = \begin{bmatrix} -E_1 & 0 & \cdot & 0 \\ 0 & \ddots & \cdot & \vdots \\ \vdots & \cdots & \cdot & -E_1 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & \cdot & -E_1 \end{bmatrix} \tag{4.28}$$

$$\mathscr{E}_i = (\bar{E_4}\bar{\mathscr{H}_i} + \bar{E_i}),\; i = 1,\, 2,\, 3,\, d \tag{4.29}$$

$$\mathscr{E}_4 = \bar{E_4}\bar{\Phi} \tag{4.30}$$

$$\mathscr{E}_{4i} = \bar{E_4}\bar{\mathscr{H}_{i1}},\; i = 1,\, 2,\, 3,\, d \tag{4.31}$$

$$\mathscr{E}_5 = \bar{E_5} \tag{4.32}$$

$$\mathscr{H}_1 = \begin{bmatrix} \mathscr{C}\mathscr{B}_1 & 0 & \cdots & 0 & 0 \\ \mathscr{C}\mathscr{A}\mathscr{B}_1 - \mathscr{C}\mathscr{B}_1 & \mathscr{C}\mathscr{B}_1 & \cdots & 0 & 0 \\ \mathscr{C}\mathscr{A}^2\mathscr{B}_1 - \mathscr{C}\mathscr{A}\mathscr{B}_1 & \mathscr{C}\mathscr{A}\mathscr{B}_1 - \mathscr{C}\mathscr{B}_1 & \ddots & \vdots & \vdots \\ \vdots & \vdots & \ddots & \mathscr{C}\mathscr{B}_1 & \vdots \\ \mathscr{C}\mathscr{A}^{m-1}\mathscr{B}_1 - \mathscr{C}\mathscr{A}^{m-2}\mathscr{B}_1 & \mathscr{C}\mathscr{A}^{m-2}\mathscr{B}_1 - \mathscr{C}\mathscr{A}^{m-1}\mathscr{B}_1 & \cdots & \mathscr{C}\mathscr{A}\mathscr{B}_1 - \mathscr{C}\mathscr{B}_1 & \mathscr{C}\mathscr{B}_1 \\ \mathscr{C}\mathscr{A}^{m}\mathscr{B}_1 - \mathscr{C}\mathscr{A}^{m-1}\mathscr{B}_1 & \mathscr{C}\mathscr{A}^{m-1}\mathscr{B}_1 - \mathscr{C}\mathscr{A}^{m-2}\mathscr{B}_1 & \cdots & \mathscr{C}\mathscr{A}^2\mathscr{B}_1 - \mathscr{C}\mathscr{A}\mathscr{B}_1 & \mathscr{C}\mathscr{A}\mathscr{B}_1 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \mathscr{C}\mathscr{A}^{p-1}\mathscr{B}_1 - \mathscr{C}\mathscr{A}^{p-2}\mathscr{B}_1 & \mathscr{C}\mathscr{A}^{p-2}\mathscr{B}_1 - \mathscr{C}\mathscr{A}^{p-1}\mathscr{B}_1 & \cdots & \mathscr{C}\mathscr{A}^{p-m+1}\mathscr{B}_1 - \mathscr{C}\mathscr{A}^{p-m}\mathscr{B}_1 & \mathscr{C}\mathscr{A}^{p-m}\mathscr{B}_1 \end{bmatrix} \tag{4.33}$$

$$\mathscr{H}_i = \begin{bmatrix} \mathscr{C}\mathscr{B}_i & 0 & \cdots & 0 & 0 \\ \mathscr{C}\mathscr{A}\mathscr{B}_i - \mathscr{C}\mathscr{B}_i & \mathscr{C}\mathscr{B}_i & \cdots & 0 & 0 \\ \mathscr{C}\mathscr{A}^2\mathscr{B}_i - \mathscr{C}\mathscr{A}\mathscr{B}_i & \mathscr{C}\mathscr{A}\mathscr{B}_i - \mathscr{C}\mathscr{B}_i & \cdots & \vdots & \vdots \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ \mathscr{C}\mathscr{A}^{p-1}\mathscr{B}_i - \mathscr{C}\mathscr{A}^{p-2}\mathscr{B}_i & \mathscr{C}\mathscr{A}^{p-2}\mathscr{B}_i - \mathscr{C}\mathscr{A}^{p-3}\mathscr{B}_i & \cdots & \mathscr{C}\mathscr{A}\mathscr{B}_i - \mathscr{C}\mathscr{B}_i & \mathscr{C}\mathscr{B}_i \end{bmatrix}, \; i = 2,\, 3,\, d \tag{4.34}$$

$$\bar{\mathscr{H}_j} = \begin{bmatrix} [0]_{n_y} \\ \mathscr{H}_j(1:(p-1)n_y,:) \end{bmatrix}$$

$$j = 1,\ 2,\ 3,\ d,\ 11,\ 21,\ 31,\ d1 \tag{4.35}$$

$$\bar{\Phi} = \begin{bmatrix} \mathscr{C} \\ \Phi(1:(p-1)n_y,:) \end{bmatrix} \tag{4.36}$$

Here n_y is number of outputs,$[0]_{n_y}$ denotes matrix with n_y rows that has all the elements 0 and $*(1:(p-1)n_y,:)$ is matrix's $(*)$ row 1 to row $(p-1)n_y$ with all the columns.

4.3 Model Predictive Control

MPC solves a finite horizon optimal control problem using the model prediction to obtain the control move over a finite horizon (under given constraints). After this, only the first value of control is applied and the same procedure is repeated for the next sampling instant. MPC can be contrasted with other optimal control approaches [69, 70, 71]. Traditionally, these use an infinite prediction horizon of an unconstrained system where the control law can be precomputed. In contrast in MPC, a finite horizon optimal control problem (possibly, a constrained problem i.e. the admissible states and controls are bounded) is solved where the control is calculated on-line at each sampling instant. Calculating the control move at each instant and applying only the first calculated move makes sure that the controller is more responsive to disturbances and hence this receding horizon strategy provides closed loop robustness to the system.

In general, the prediction horizon is smaller than the control horizon. When the disturbances are 'measured', they are part of the prediction and hence MPC can effectively implement the feedback-feedforward control. As an example for

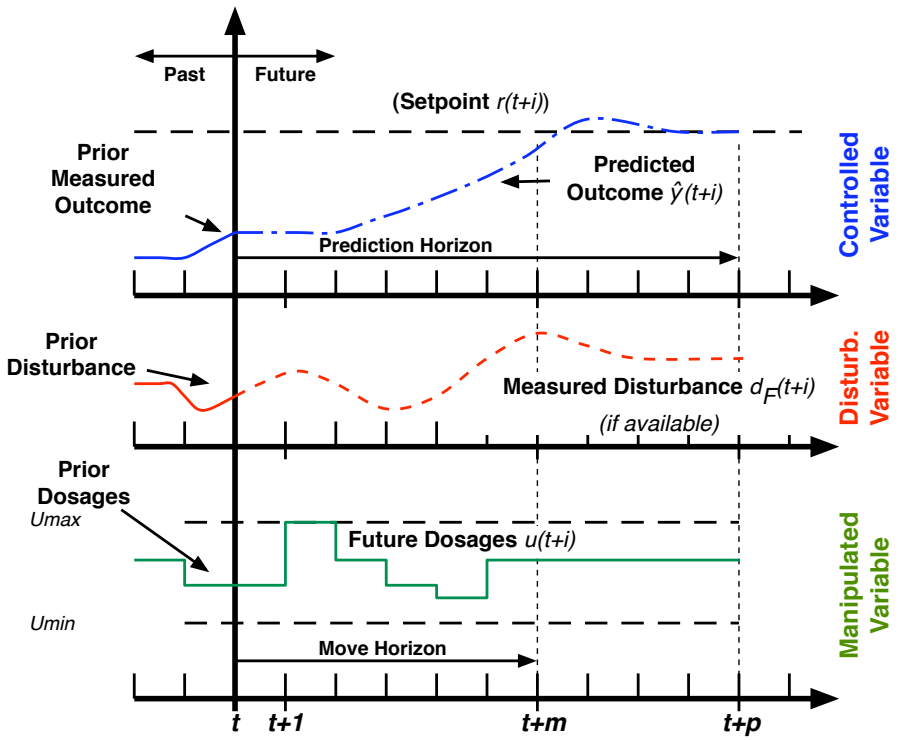


Figure 4.1: Receding Horizon Control Strategy. The control moves are calculated over control horizon of length m and only the first calculated move is implemented. This process is repeated at each sampling instant.

the control strategy, we show a representative diagram explaining the process in Figure 4.1. The first subplot represents the evolution of the system output as per the prediction over p steps. The second subplot represents the plot of a *measured* disturbance which will be a part of the prediction equation. Finally, in the third subplot we show a calculated control move such that the goal is reached in m steps. Some of the salient features of MPC are:

- Naturally suited for multi input multi output (MIMO) systems *with constraints*
- Effectively combines the feedback-feedforward control action

- Applies a receding horizon strategy which can be summarized as

    1. Calculating a system prediction.
    2. Solving an optimization problem over a horizon.
    3. Applying *only* the control move corresponding to current sampling time.
    4. Going to the next sampling instant and repeating the process.

It is to be noted that the control moves are calculated such that after m steps, there is no more control action or $\Delta u(i) = 0$ for $i \geq m$.

4.3.1 Hybrid MPC's Control Move

Under constraints (by limits on the domain for signals as well as by the hybrid dynamics), we cannot write a state feedback control law directly as $u = Kx$ where K is the gain matrix. A standard quadratic cost function, through the l_2-norm, is used to calculate the decision vector as described below

$$\min_{\{[u(k+i)]_{i=0}^{m-1},\,[\delta(k+i)]_{i=0}^{p-1},\,[z(k+i)]_{i=0}^{p-1}\}} J \stackrel{\triangle}{=} \sum_{i=1}^{p} \|(y(k+i)-y_r)\|_{Q_y}^2 + \sum_{i=0}^{m-1} \|(\Delta u(k+i))\|_{Q_{\Delta u}}^2 + \sum_{i=0}^{m-1} \|(u(k+i)-u_r)\|_{Q_u}^2 + \sum_{i=0}^{p-1} \|(\delta(k+i)-\delta_r)\|_{Q_d}^2 + \sum_{i=0}^{p-1} \|(z(k+i)-z_r)\|_{Q_z}^2 \tag{4.37}$$

such that

$$y_{\min} \leq \quad y(k+i) \quad \leq y_{\max},\ 1 \leq i \leq p \tag{4.38}$$

$$u_{\min} \leq \quad u(k+i) \quad \leq u_{\max},\ 0 \leq i \leq m-1 \tag{4.39}$$

$$\Delta u_{\min} \leq \quad \Delta u(k+i) \quad \leq \Delta u_{\max},\ 0 \leq i \leq m-1 \tag{4.40}$$

and also subjected to state, output and mixed integer constraints as shown in Equations 4.10-4.12 where p is the prediction horizon and m is the control horizon. The

vector 2-norm are weighted by matrix Q_* as in Q_y, $Q_{\Delta u}$, Q_u, Q_d, and Q_z are the penalty weights on the error, move size, control signal, auxiliary binary variables and auxiliary continuous variables, respectively. It is to be noted that the problem is formulated as a *tracking* control system (as contrasted with a state regulator) using references y_r, u_r, δ_r and z_r for output, input, discrete and continuous auxiliary variables, respectively.

Using the vector prediction based on the state space model as shown in Equations 4.21-4.22, we can transform the objective function based on summation to the one based on matrices and vectors. This new objective function can be formulated as a inequality constrained mixed integer quadratic program (MIQP) as shown below

$$\min_{\xi} J \stackrel{\triangle}{=} \frac{1}{2}\xi^T \mathscr{H} \xi + \mathscr{G}^T \xi \tag{4.41}$$

$$\mathscr{S}\xi \leq b \tag{4.42}$$

where $\xi = [\mathscr{U}(k)^T \quad \bar{\delta}(k)^T \quad \mathscr{Z}(k)^T]^T$ is the vector of the decision variables. More details of the formulation with respect to the Hessian and gradient matrices can be found in [31, 61]. It should be noted that since the sampling time is equal to one day, the computation time for solving MIQP is a non-issue in this application. Further discussion on optimal control of MLD systems, including computational complexity, can be found in [64].

4.3.2 Tuning for MPC

Setpoint tracking using the nominal model in presence and absence of measured and unmeasured disturbance can be used to define the nominal performance of the controller. For this, the conventional MPC tuning rules rely on changing either p (the prediction horizon), m (the control horizon) or penalty weights such as $Q_{\Delta u}$ (move

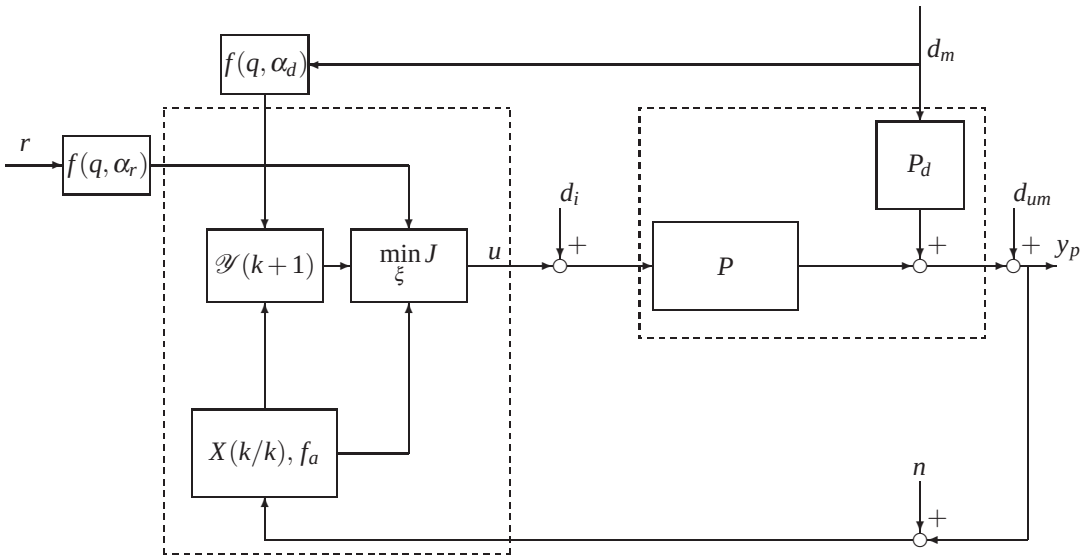


Figure 4.2: Three-degree-of-freedom (3 DoF) controller formulation of model predictive control.

suppression) which may not be very intuitive. We rely on a three-degree-of-freedom (3 DoF) approach to tune our controller which enables performance requirements associated with setpoint tracking, anticipated measured disturbance rejection and unmeasured disturbance rejection to be adjusted independently ([61, 68]) by varying parameters α_r, α_d and f_a respectively. These parameters can be adjusted between values 0 and 1; they in turn alter the response of Type I or Type II filters which supply filtered signals to the controller (for setpoint tracking and measured disturbance rejection) or adjust the observer gain (for unmeasured disturbance rejection). Hence, the controller can be detuned (as controller without filter will be the case where it achieves best possible effect) as per the requirement of the problem. In the Figure 4.2, we show a 3 DoF controller formulation of model predictive control in an extension of the classical control loop (Figure 1.2) where P, P_d are the system plants, $X(k/k)$, f_a is the observer block, $\mathscr{Y}$ is the predictor block, $min J$ is the optimizer block and $f(q,\alpha)$ are the filters for reference and measured disturbance

signals.

- **Setpoint tracking and measured disturbance rejection.**

  In this work, the setpoint tracking corresponds to the feedback action and measured disturbance rejection to the feedforward action. Using a filter, we can detune a controller to vary the closed loop response. Based on the system at hand, we can filter using a Type I filter as shown below

$$f(q,\alpha^j) = \frac{(1-\alpha^j)q}{q-\alpha^j},\ 1 \leq j \leq n_y \tag{4.43}$$

  or a Type II filters as shown in Equation 4.44-4.46

$$f(q,\alpha^j) = (\beta_0 + \beta_1 q^{-1} + \cdots + \beta_\omega q^{-\omega}) \times \frac{(1-\alpha^j)q}{q-\alpha^j} \tag{4.44}$$

$$\beta_k = \frac{-6k\alpha^j}{(1-\alpha^j)\omega(\omega+1)(2\omega+1)},\ 1 \leq k \leq \omega; 1 \leq j \leq n_y \tag{4.45}$$

$$\beta_0 = 1 - (\beta_1 + \cdots + \beta_\omega) \tag{4.46}$$

  where n_y is the number of outputs. In both cases, α can be varied to alter the response. As noted earlier, the tuning parameter to alter the reference trajectory response is denoted by α_r and the tuning parameter for measured disturbance filtering by α_d. The set point or disturbances changes should be asymptotically step or ramp and the choice of the filter depends on the type of the system (integrating, for example) [62, 72]. In this work, we use Type I filter for both cases where both $\alpha_{r,d} \in [0,1)$. Hence the controller can be tuned for slower rejection of measured disturbances, for example, by more extensive filtering of the disturbance signals.

- **State Estimation**

  A parametrized observer is used to handle unmeasured disturbances as discussed in [31, 68]. These disturbances can be applied externally and/or can

originate from the plant-model mismatch. In this formulation, it is necessary to separate the effect of measured and unmeasured disturbance of the state estimation. Reference tracking is not a part of the prediction equation and hence, by definition, is independent of both α_d and f_a. To truly separate this effect, we track the measured disturbance and *filtered* measured disturbance separately. Consider that both measured and unmeasured disturbances are acting on the system and the filtering for respective signals is also initiated. In first step, we obtain state estimation by considering actual measured disturbance (d) using the Kalman filter-based approach as follows,

$$X(k|k-1) = \mathscr{A}X(k-1|k-1) + \mathscr{B}_1\Delta u(k-1) + \mathscr{B}_2\Delta\delta(k-1) + \mathscr{B}_3\Delta z(k-1) + \mathscr{B}_d\Delta d(k-1) \tag{4.47}$$

$$X(k|k) = X(k|k-1) + K_f(y(k) - \mathscr{C}X(k|k-1)) \tag{4.48}$$

where X is the augmented state of the system. This is the state of the system, estimated under unmeasured disturbance only. In the second step, we obtain state estimation using the filtered measured disturbance as shown

$$X_{flt}(k|k-1) = \mathscr{A}X_{flt}(k-1|k-1) + \mathscr{B}_1\Delta u(k-1) + \mathscr{B}_2\Delta\delta(k-1) + \mathscr{B}_3\Delta z(k-1) + \mathscr{B}_d\Delta d_{flt}(k-1) \tag{4.49}$$

$$X_{flt}(k|k) = X_{flt}(k|k-1) + K_f(y(k) - \mathscr{C}X(k|k-1)) \tag{4.50}$$

where X_{flt} is the estimate corresponding to the effect of filtered measured disturbance and unmeasured disturbance. Next, X_{flt} is used in the controller formulation so that it can respond to changes in α_d and f_a. In this it was assumed that there is no plant-model mismatch but even in presence of such mismatch, the net effect will be an unmeasured disturbance.

An optimal value of the filter gain K_f can be found by solving an algebraic Riccati equation which requires estimating the covariance matrices for the unmeasured disturbance. In this work, no such *a priori* information is available. Therefore, following [68], we apply the parametrization of the filter gain shown in general as:

$$K_f = \begin{bmatrix} 0 \\ F_b \\ F_a \end{bmatrix} \tag{4.51}$$

where

$$F_a = \text{diag}\{(f_a)_1, \cdots, (f_a)_{n_y}\} \tag{4.52}$$

$$F_b = \text{diag}\{(f_b)_1, \cdots, (f_b)_{n_y}\} \tag{4.53}$$

$$(f_b)_j = \frac{(f_a)_j{}^2}{1+\alpha_j-\alpha_j(f_a)_j},\ 1 \leq j \leq n_y \tag{4.54}$$

$(f_a)_j$ is a tuning parameter that lies between 0 and 1. As $(f_a)_j$ approaches zero, the state estimator increasingly ignores the prediction error correction and the state estimator tries to compensate for all prediction error as $(f_a)_j$ approaches 1, and hence the controller becomes extremely aggressive. Since we consider asymptotically step inputs, $\alpha_j = 0$. Hence, K_f results in:

$$K_f = \begin{bmatrix} 0 \\ (f_a)^2 \\ f_a \end{bmatrix} \tag{4.55}$$

It can be noted that the parametrization of the observer gain causes correction in the output of the system and not on the state since the first term is zero.

4.3.3 Control Performance

Since the objective of the control system is to produce a desired output y by manipulating the input u, we can define performance requirements. Such performance conditions will be set by the user as per the requirement by using the tuning methods discussed earlier. In the following sections, we look at broadly two set of results: *a*) **Nominal Performance** where the system performance is noted when there is no model uncertainty. It is important to note that we do not strictly specify the performance requirements but rather demonstrate how a 3 DoF formulation gives flexibility and hence can be tuned as per the clinical requirements; *b*) **Robust Performance** where the model is perturbed (thus causing a plant-model mismatch) and hence the controller has to perform under these uncertainties . Deriving strict robustness bounds is challenging for hybrid, constrained control and hence we use model perturbation to simulate uncertainties. Nominal and robust performance are evaluated assuming that the system has nominal and robust stability.

Some of the parameters for simulation are kept constant through out (unless otherwise mentioned) and they are as follows: the controller horizons are p = 25 and m = 15; objective function weights are $Q_y = 1$, $Q_{\Delta u} = Q_u = Q_d = Q_z = 0$, and $T = 1$ day is the sampling time.

4.4 Nominal Performance

The results in this section are broken down into various scenarios. Each of them will be discussed within each sub-headings.

4.4.1 Hybrid vs. Continuous MPC

Since the discrete nature of drug dosages introduce a hybrid constraint, we compare and contrast the performance of the hybrid controller and its continuous controller

(i.e. where u can take any value over its domain). The performance also aims at showcasing a 3DoF result. For reference, we restate the continuous time approximation of estimated 5 input ARX [2 2 1] model as:

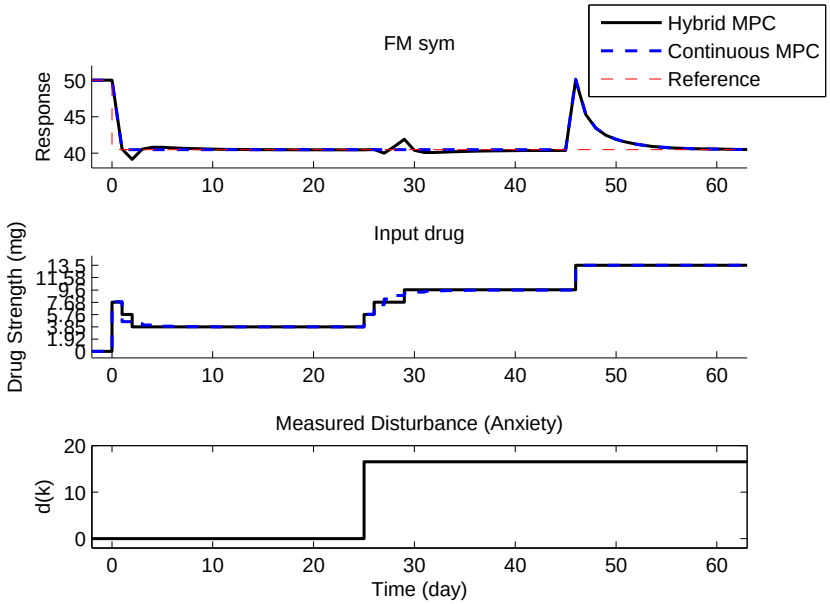
$$\frac{FMsym(s)}{Drug(s)} = G_1(s) = \frac{-2.47(1.96s+1)}{(1.57)^2 s^2 + 2(1.26)(1.57)s + 1} \tag{4.56}$$

$$\frac{FMsym(s)}{Anxiety(s)} = G_3(s) = \frac{0.86(0.24s+1)}{(1.57)^2 s^2 + 2(1.26)(1.57)s + 1} \tag{4.57}$$

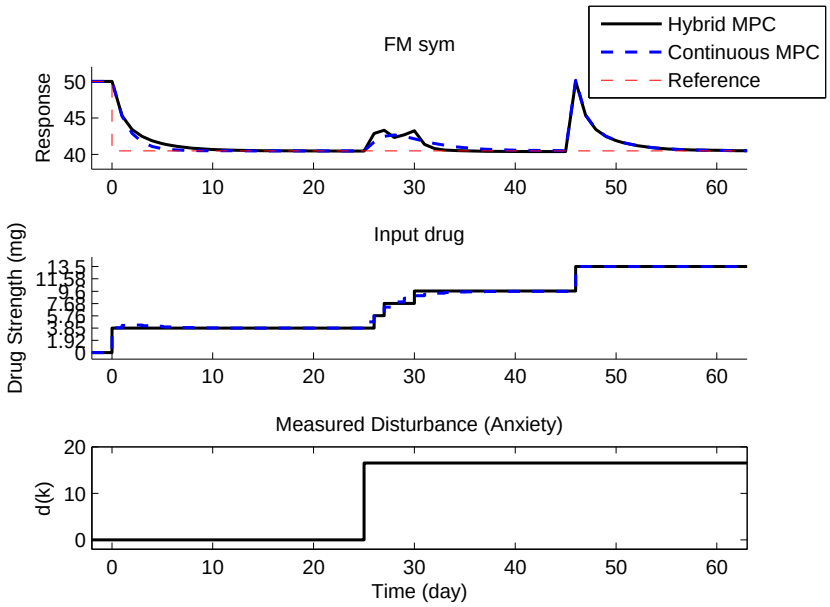
The gain for the drug-FM model is shown in per milligram of dosage.

In this simulation, the setpoint tracking starts at $t = 0$, measured disturbance acts at $t = 25$ and unmeasured disturbance at $t = 45$. The output variable starts with a baseline value of 50 and a change of -9.5 is applied at $t = 0$ as shown by the reference. The results are shown for two sets of tuning parameters as *a*) $(\alpha_r, \alpha_d, f_a) = (0, 0, 1)$, which is the fastest possible setting for the control system; *b*) $(\alpha_r, \alpha_d, f_a) = (0.5, 0.5, 0.5)$ where we de-tune the controller . The hybrid control result is shown using eight drug dosage levels as $u(k) \in \{0, 1.92, 3.85, 5.76, 7.68, 9.6, 11.58, 13.5\}$ mg.

As shown in Fig. 4.3, it can be seen that the 3 DoF formulation allows us to tune the controller independently for setpoint tracking and disturbance rejection. For setpoint tracking, α_r can be adjusted to suit the expected response. Similarly, the response to disturbances can be varied by α_d and f_a to suit the conditions at hand. By increasing filtering action, the dosage assignments are more smoother (and as per clinical requirements) as compared to the unfiltered case and the continuous MPC. For measured disturbances, continuous MPC offers perfect compensation through the use of feedforward action where as in the case of hybrid MPC, the action is less effective due to constraints. At $t = 45$ an abrupt change in the pain report occurs due to an unmeasured disturbance (this change is not a part of model prediction). The controller reacts by increasing the drug dosage to compensate. It should be noted that as a result of maximum dosage restriction, we do not see much



(a)



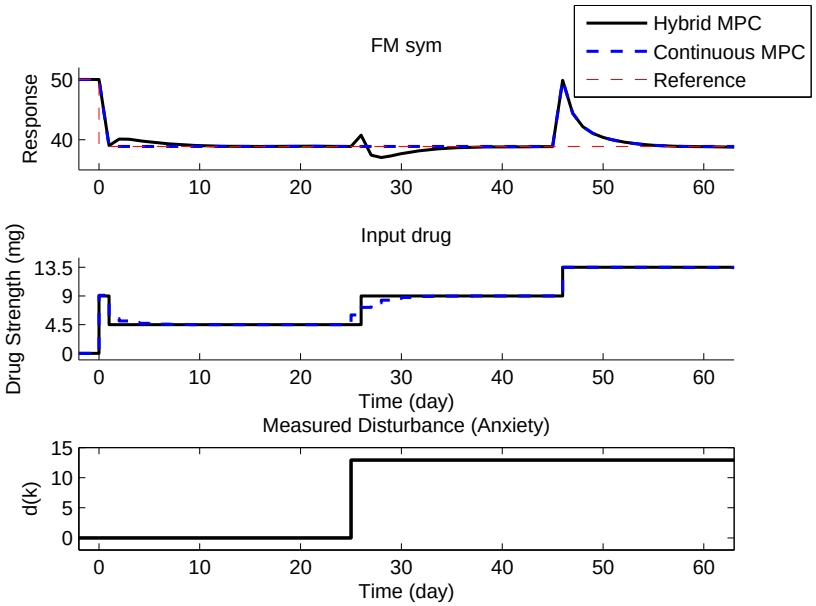
(b)

Figure 4.3: Performance of hybrid MPC (eight levels) with tuning parameters $(\alpha_r, \alpha_d, f_a) = (0, 0, 1)$ (top) and $(\alpha_r, \alpha_d, f_a) = (0.5, 0.5, 0.5)$ (bottom); both cases are compared to their continuous MPC counterparts.

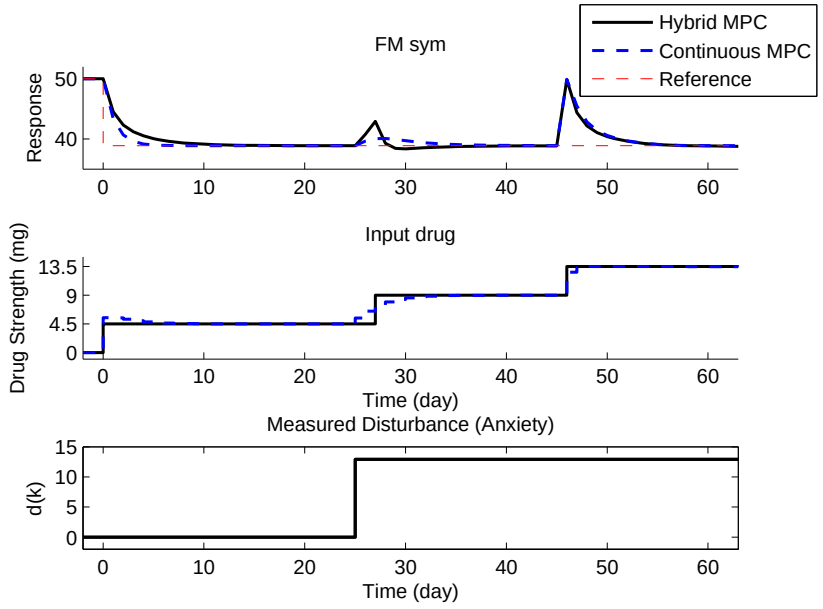
difference on how hybrid and continuous MPC handle unmeasured disturbance in this example.

In Figure 4.4, we show the same scenario with slight change in tuning for performance $(\alpha_r, \alpha_d, f_a) = (0.4, 0.4, 0.4)$) and with the number of discrete levels now dropped to only four, $u(k) \in \{0, 4.5, 9, 13.5\}$ mg. The reference is now set at -11.1 from baseline value of 50; this is done in order to avoid offsets with changed input levels. Due to fewer drug levels, it can be seen that hybrid controller, in this four level scenario, changes dosages in as a 'step' as that is the best possible solution. This can be contrasted to the eight level scenario where due to more options with drug levels, we observe a 'smoother' transition. Even under these limitations, we can observe a comparable performance with the continuous MPC. In both the figures, we have chosen the tuning to represent a typical response where as per the nominal performance requirements, the tuning can be adjusted.

The MPC where $u(t)$ as a continuous variable and with no filtering represents the best possible performance by the controller. Clinically, this can be the first benchmark which can be used to get a sense of treatment regimen from the control system. Next, depending on the clinical constraint of drug dosage levels, a new treatment regimen has to be generated and can be contrasted with the continuous case. In both the mentioned case, the drug dosing may be too aggressive for comfort of a clinician and hence, in that scenario based upon the exact requirements (e.g., pain reduction by 30%) the hybrid controller can be de-tuned. In the next, Section 4.4.2, we come some of the possible scenarios of setpoint tracking.



(a)



(b)

Figure 4.4: Performance of hybrid MPC (four levels) with tuning parameters $(\alpha_r, \alpha_d, f_a) = (0, 0, 1)$ (top) and $(\alpha_r, \alpha_d, f_a) = (0.4, 0.4, 0.4)$ (bottom); both cases are compared to their continuous MPC counterparts.

4.4.2 Setpoint Tracking

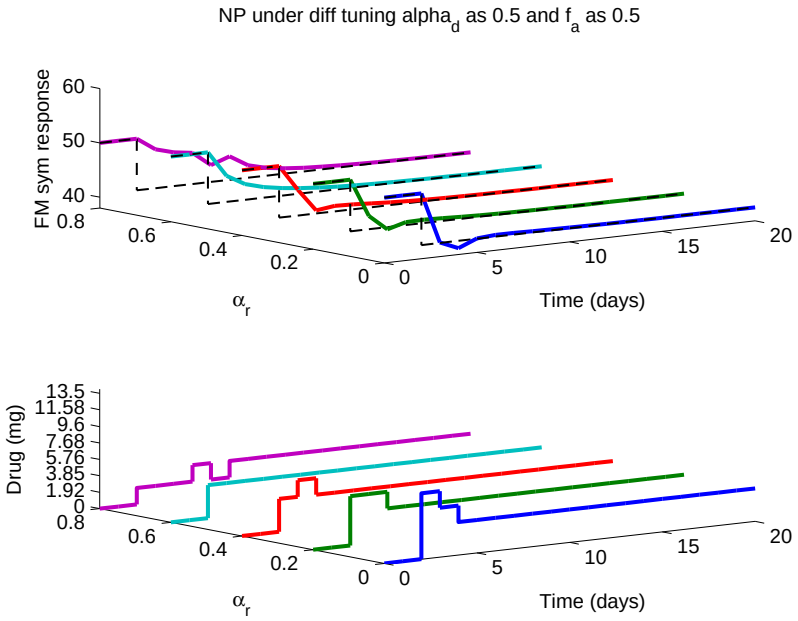
In this section, we analyze how changing tuning parameters modifies performance. In setpoint tracking, the controller keeps track of the goal (e.g., pain reduction) by assigning drug dosages. Since we have three parameters to adjust $(\alpha_r, \alpha_d, f_a)$, there are many possible permutations. For sake of brevity, we narrow it down to following scenarios. In each of these cases, we keep α_d and f_a constant and then different α_r are tried:

- When there is no disturbance at $t = 0$ (Figure 4.5)
- When there is only an unmeasured disturbance acting at $t = 0$ of magnitude 4.72 (Figure 4.6)
- When there is only an measured disturbance (in anxiety report) acting at $t = 0$ of magnitude 11.05 (Figure 4.7)
- When there are both unmeasured and unmeasured disturbance (of magnitude as above) acting at $t = 0$ (Figure 4.8)

For reference, we restate that keeping α_r and α_d near zero will result in the least amount of filtering and vice-versa. For unmeasured disturbance rejection, moving f_a away from one will result in slower rejection. In the previous section, setpoint tracking was disturbance free (as we split the time line to emphasize the 3DoF) but in this section we run through cases where simultaneous disturbances and reference tracking are present. In traditional MPC, move suppression is used to influence the speed of reponse but in this work we use the 3DoF formulation which can produce better results in a more intuitive way as the tuning parameters are directly related to the speed of response. Another interpretation of these tuning results are that since

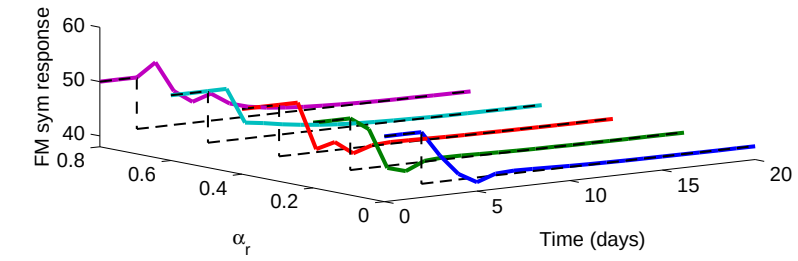
they are shown in time domain, the user can choose the three tuning parameters as per requirement more intuitively.

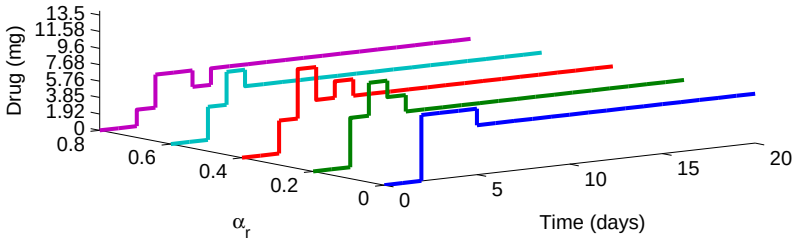
From the results shown in Figure 4.5 through Figure 4.8, we see that by adjusting α_r, it is possible to adjust the speed of setpoint tracking. In general, α_r in vicinity of 0.5 works well for a smoother response. In presence of disturbances, the setpoint tracking is also dependent upon disturbance rejection and then the suitable choice of α_r depends on disturbance tuning (α_d, f_a) as well. In Figure 4.5, there are no disturbances present and decreasing the tuning results in increasing sluggish response. Similar results are seen in Figure 4.6 under the presence of an unmeasured disturbance under two tunings ($f_a = 1$ and $f_a = 0.2$). In case of $f_a = 1$, we see complete disturbance rejection which gives a tighter control. Figure 4.7 shows tracking under measured disturbance from anxiety report with plot corresponding to $\alpha_d = 0.9$ gives a more sluggish response. Finally, Figure 4.8 shows tracking under both measured and unmeasured disturbances where a smoother (but more aggressive) response is obtained for $\alpha_d = 0$ and $f_a = 1$. In all of the cases mentioned before, the variation of α_r from 0 to 0.8 (as seen on the Y-axis) results in more sluggish setpoint tracking speed. It can also be observed in Figure 4.5-4.8 that to compensate the effect of disturbance, more dosage magnitude is required.



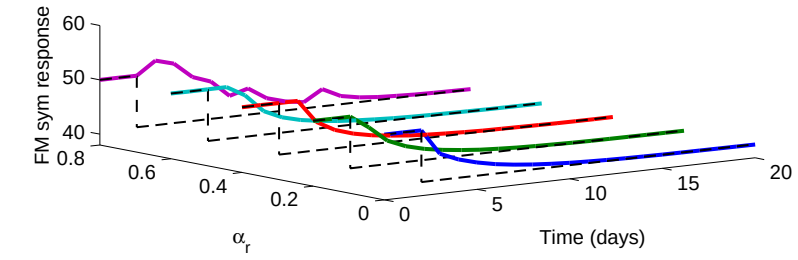
(a)

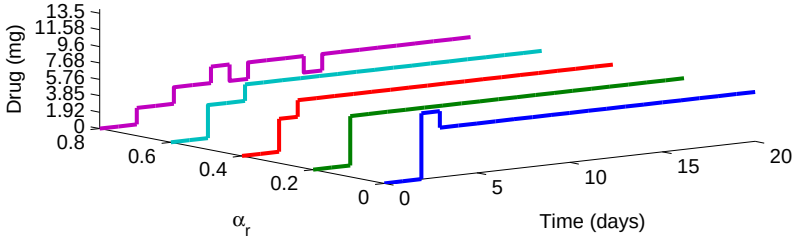
Figure 4.5: Setpoint tracking under no disturbances for various tuning (α_r) values. Setpoint is denoted by dotted lines.





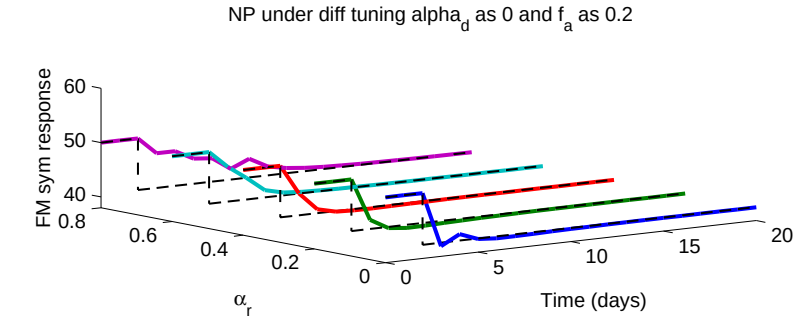
(a) $f_a = 1$

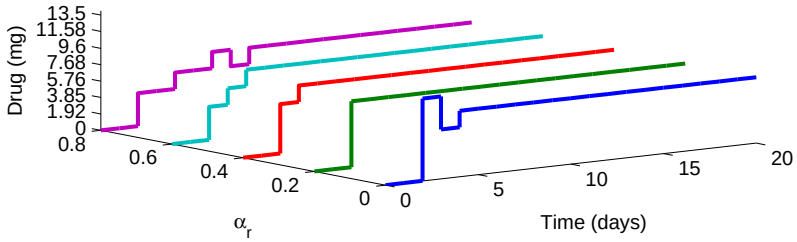




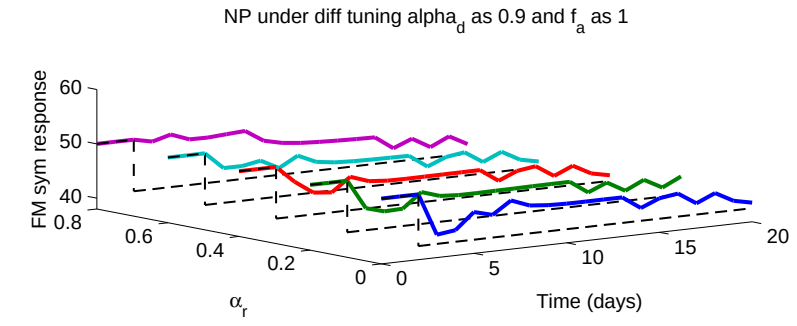
(b) $f_a = 0.2$

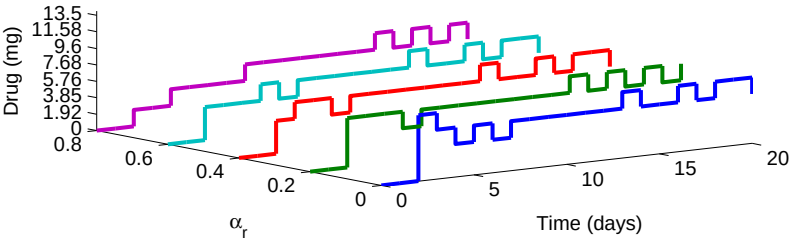
Figure 4.6: Setpoint tracking under unmeasured disturbance for various tuning (α_r) values with two settings for f_a. Setpoint is denoted by dotted lines.





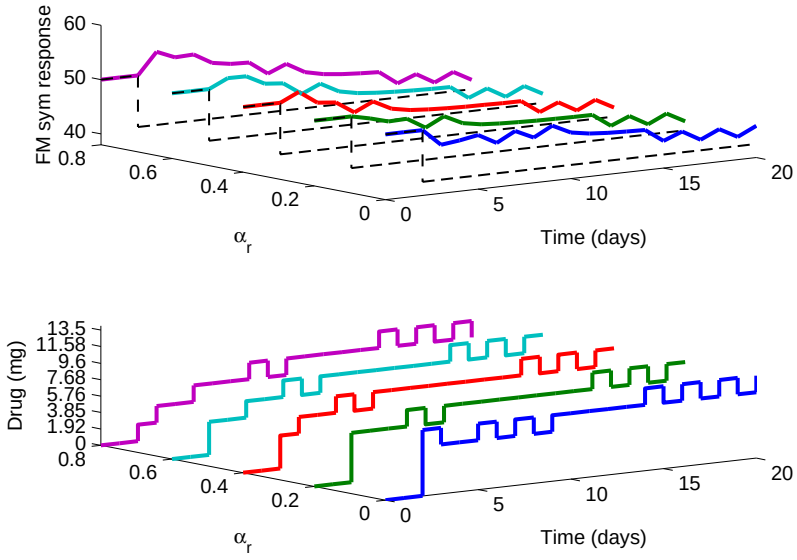
(a) $\alpha_d = 0$



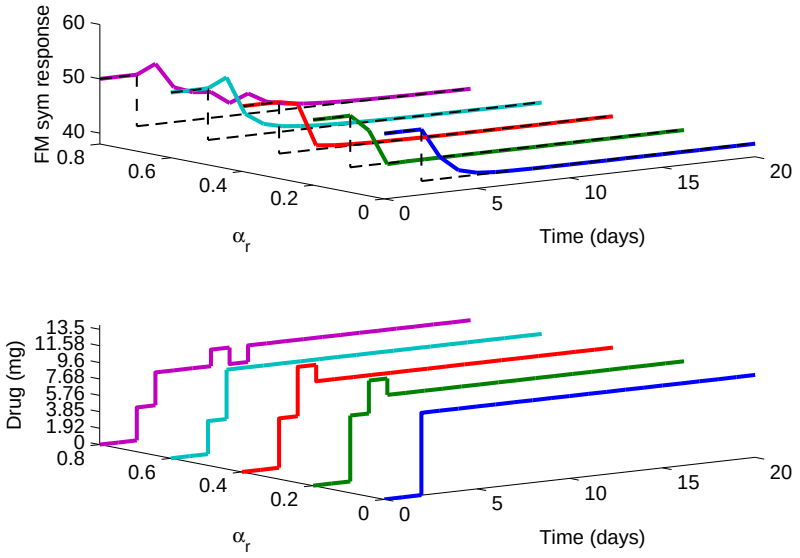


(b) $\alpha_d = 0.9$

Figure 4.7: Setpoint tracking under measured disturbance for various tuning (α_r) values with two settings for α_d. Setpoint is denoted by dotted lines.



(a) $\alpha_d = 0.9,\ f_a = 0.2$



(b) $\alpha_d = 0,\ f_a = 1$

Figure 4.8: Setpoint tracking under both unmeasured and measured disturbance for various tuning (α_r) values with two settings for α_d, f_a. Setpoint is denoted by dotted lines.

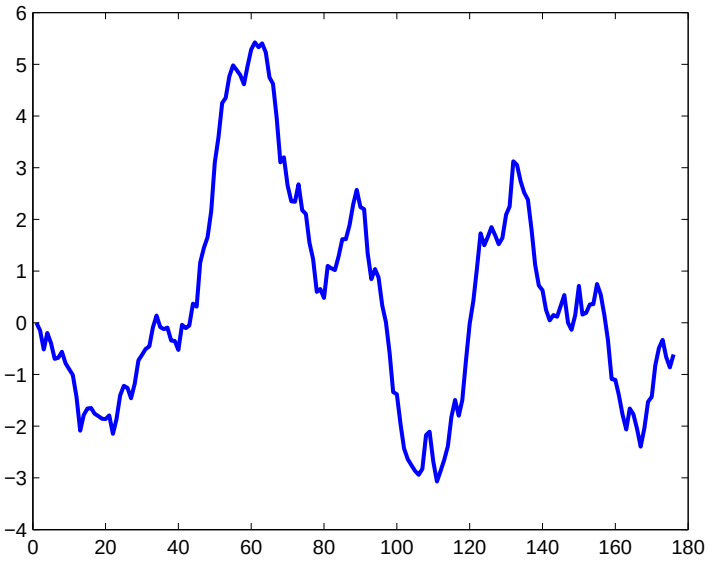
4.4.3 Stochastic Unmeasured Disturbance

So far, a deterministic (step) unmeasured disturbance has been considered. The controller performance can also be evaluated when the disturbance is white or is colored (e.g., Autoregressive moving average (ARMA)). We show only the case where the noise is colored to simulate a disturbance whose average value is changing over time. By changing the observer gain through f_a, it is possible to influence disturbance rejection.

The ARMA model which has a zero at 0.5 and a two poles at 0.9 can be represented as:

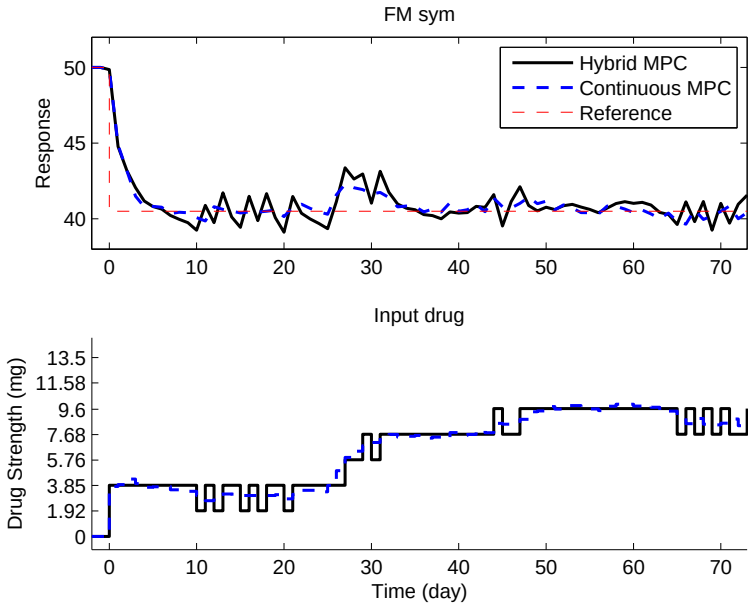
$$d(t) = \frac{(q-0.5)}{(q-0.9)^2} a(t) \tag{4.58}$$

where d, a are discrete signals, q is the forward shift operator. The time series realization as shown in Figure 4.9 using the MATLAB plot command. The original noise $a(t)$ is zero mean with variance 0.1. The two simulation cases are shown in Figure 4.10 and are compared with respective continuous MPC. In the first case, we apply $f_a = 1$ where as in the second case, $f_a = 0.1$ resulting in a sluggish response (and hence a longer realization was shown ($t = 175$) to see the full cycle). A measured disturbance of magnitude 11.05 acts at $t = 25$ (α_r and $\alpha_d = 0.5$ for both cases). Also, the drug dosage levels can take any of the designated eight levels.

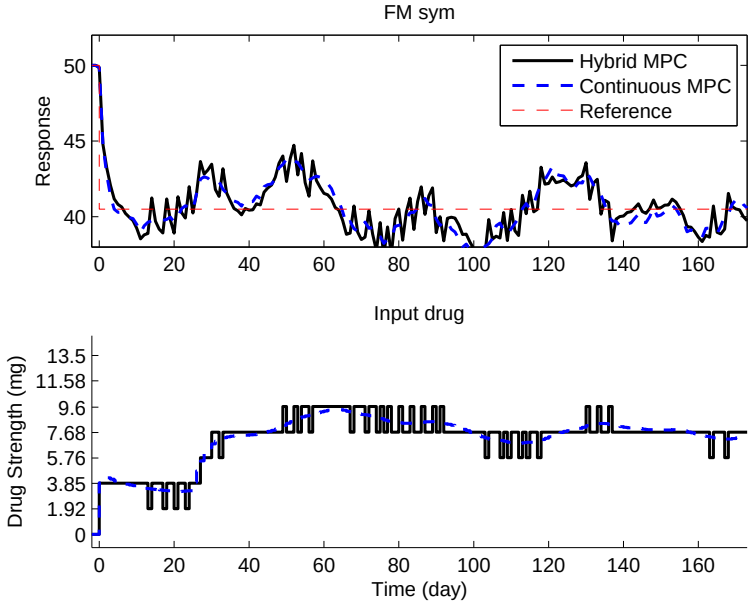


(a)

Figure 4.9: ARMA time series realization.



(a) $f_a = 1$



(b) $f_a = 0.1$

Figure 4.10: Performance of hybrid MPC under different tuning ($f_a = 1, 0.1$) when the unmeasured disturbance is a realization of ARMA noise model.

4.5 Robust Performance

We consider a 5 input 1 output model whose inputs are drug, placebo, anxiety, stress and mood. Robust performance addresses the scenario where a perfect model is not available from identification. Plant-model mismatch will result in some prediction error which can be influenced by the observer through f_a. Modeling errors in drug-FM model will be compensated through the feedback action alone although for modeling errors in anxiety-FM model, for example, will be partially compensated by the feedforward action and what ever signal is not compensated by the anticipation, will enter the feedback loop as unmeasured disturbance. We assume that none of the plant-mismatch scenarios result in plant instability.

We can formulate various scenarios for testing robustness using simulations. For example, consider when the plant is nominal and the disturbance model is perturbed. It is also possible to perturb the plant model but keep it *same or constant* for different disturbance model uncertainties. For simplicity, we perturb only the drug-FM model ('plant model') and the anxiety-FM model ('disturbance model'). We go through different permutations of these cases of which three broad scenarios are as following:

1. Only the plant model is perturbed
2. Only the disturbance model is perturbed
3. Both plant and disturbance models are perturbed

The results are shown in two major groups: first, a tuning parameter is **fixed** and the effect of different uncertainties is observed as is shown in Section 4.5.1. Second, the uncertainty is **fixed** and the effect of tuning (f_a) on the response if observed as shown in Section 4.5.2. For each scenario, we evaluate different uncertainties in

the plant and disturbance models. As mentioned earlier, the plant model is fixed as drug-FM model and disturbance model as anxiety-FM model. It can be observed that when no filtering is imposed, the result is more aggressive controls. Similarly when some uncertainty is fixed, we can see better results from less filtering.

Before describing the results, it is important to mention how robust performance results are grouped. In each simulation figure, we use the following two functional groupings:

1. *When a fixed nominal model is used.* A nominal model is used as a basis for the controller to assign dosages for different plants. This case can be understood in two ways: first, in the classical interpretation where the estimated model is an approximation of the true system and second, when the nominal model represents an average or representative model, with a single, fixed controller assigning dosages to different participants within this population.

2. *When the true plant serves as the nominal model.* For each scenario considered in the previous case, we supply the true plant as the nominal model to the controller. This case can be understood as when accurate modeling (through system identification or otherwise) has been performed for each individual in a population.

Each of these two groups will be demonstrated when examining model uncertainties as shown in Figures 4.11-4.19; each case of model uncertainty is complemented by the scenario where we have a 'correct' model of each uncertainty. The key motivation for this is to get a clinical insight as the user can now compare how the controls will vary under plant-model mismatch (typical robustness scenario) and on the same page, it will help us asses the case when the correct model is available to

the controller. Hence, the user can gauge the resultant change in dosing strategies due to modeling errors.

The uncertainties used for plant model P are

1. Nominal model (no mismatch);
2. $\Delta K_p = (-14.8\%)$;
3. $\Delta K_p = (14.8\%)$;
4. $\Delta K_p, \Delta\zeta_p, \Delta\tau_p = (-14.8\%, -16.6\%, 259\%)$;
5. $\Delta K_p, \Delta\zeta_p, \Delta\tau_p = (14.8\%, 79.3\%, -29.1\%)$

and for the disturbance model P_d, the uncertainities are

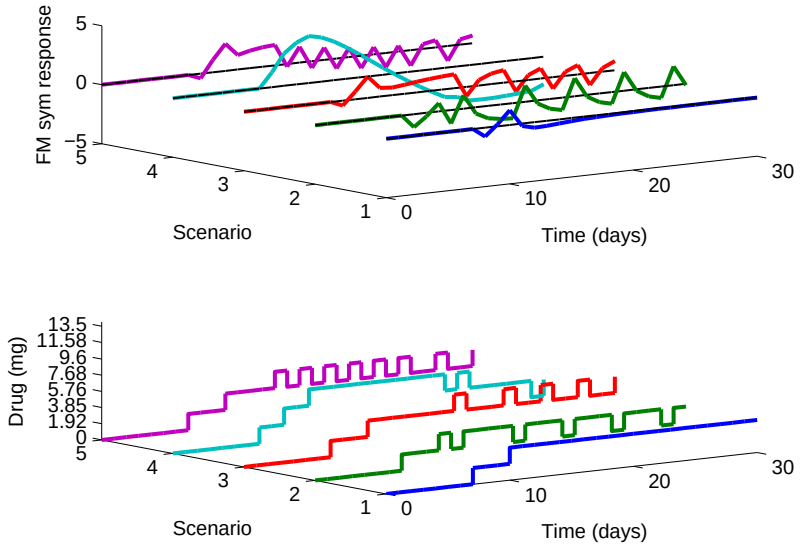
1. nominal model (no mismatch);
2. $\Delta K_d = (-14.8\%)$;
3. $\Delta K_d = (14.8\%)$;
4. $\Delta K_d, \Delta\zeta_d, \Delta\tau_d = (-14.8\%, -16.6\%, 259\%)$;
5. $\Delta K_d, \Delta\zeta_d, \Delta\tau_d = (14.8\%, 79.3\%, 191\%)$

The motivation for choosing these values is to start with gain perturbations and then move to cases where both parameters of the characteristic equation are changed along with the gain. The gain change direction is in both positive and negative direction.

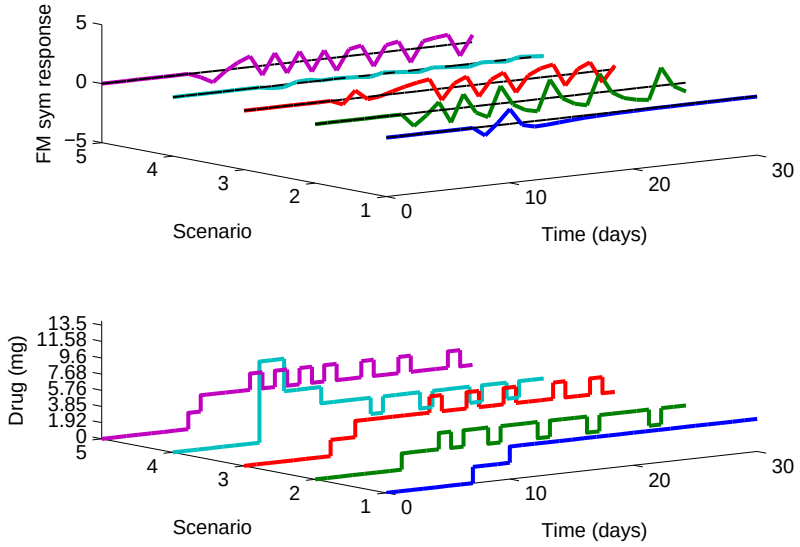
4.5.1 Robustness Evaluated under Fixed Tuning

In this subsection, the controller tuning is fixed and then different uncertainties are evaluated. It is to be noted that $\alpha_r = 0$ and $\alpha_d = 0$ and hence we only vary f_a. The setpoint is kept constant at 0 and a measured disturbance is applied at $t = 5$ of magnitude 11.05. The plant-model mismatch will contribute to unmeasured disturbance so it is not applied *externally* in the simulation.

In Figures 4.11-4.16 each scenario ('Y' axis) represents one of the five cases of uncertainty as mentioned above. We show the three cases (plant model only perturbed, disturbance model only perturbed and both plant and disturbance models perturbed) in six figures, two for each cases. It can be seen that as f_a moves from $f_a = 0.2$ to $f_a = 1$ we get tighter control but it may result in overshooting. All the cases are compared with respective scenarios where a correct nominal model is available and it can be observed that the control is better as expected. In Figures 4.11 and 4.12, only plant model is perturbed. In Figures 4.13 and 4.14, only disturbance model is perturbed. Finally, in Figures 4.15 and 4.16 both plant and disturbance models are perturbed. With addition of more uncertainty as shown in Figures 4.11-4.16 requires higher dosage of drug for corresponding compensation. It is also to be noted that scenario 1 in all plots is the case of nominal model where there is no steady state error.

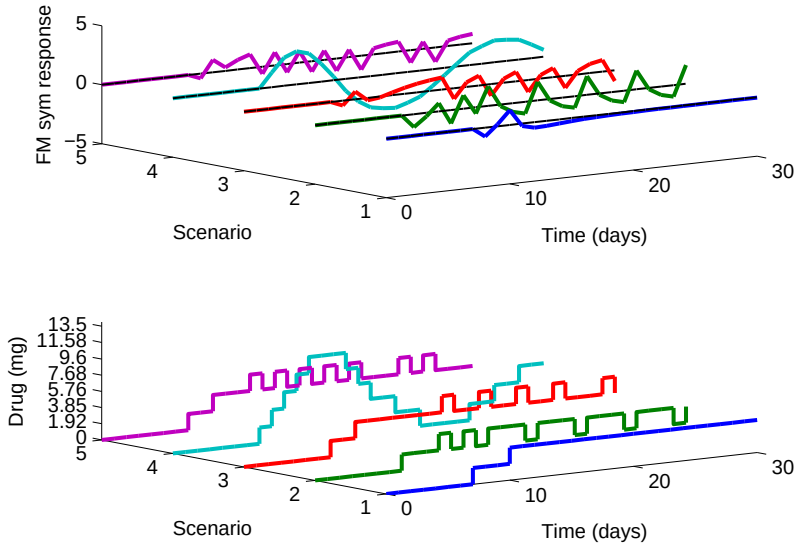


(a) Closed loop response with plant model mismatch where scenario 1 represents the nominal model

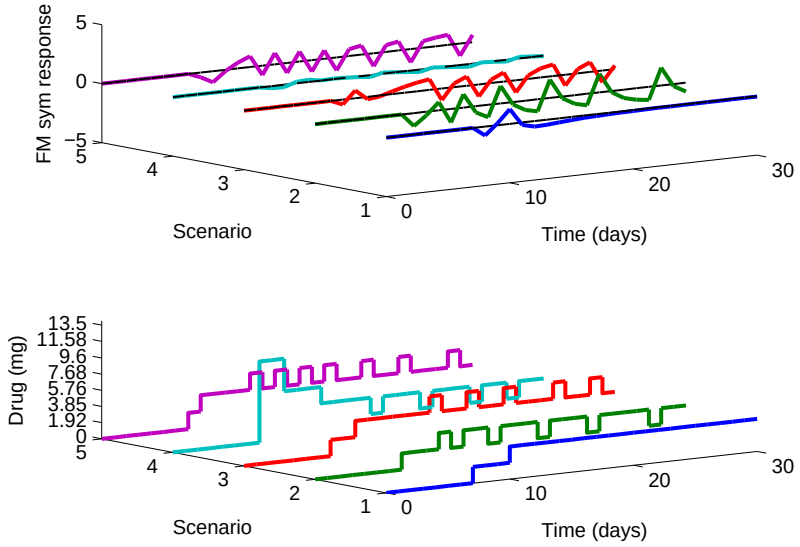


(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.11: Robustness evaluation when only plant model (drug-FM) is perturbed under tuning $f_a = 0.2$.

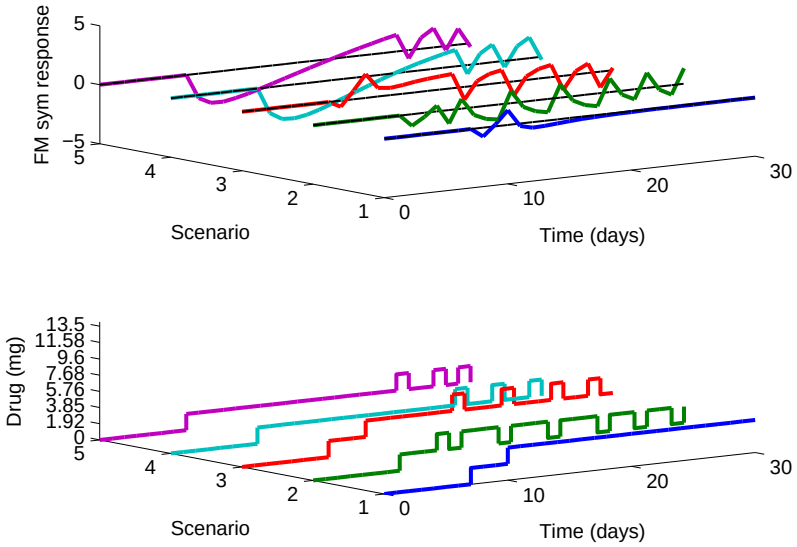


(a) Closed loop response with plant model mismatch where scenario 1 represents the nominal model

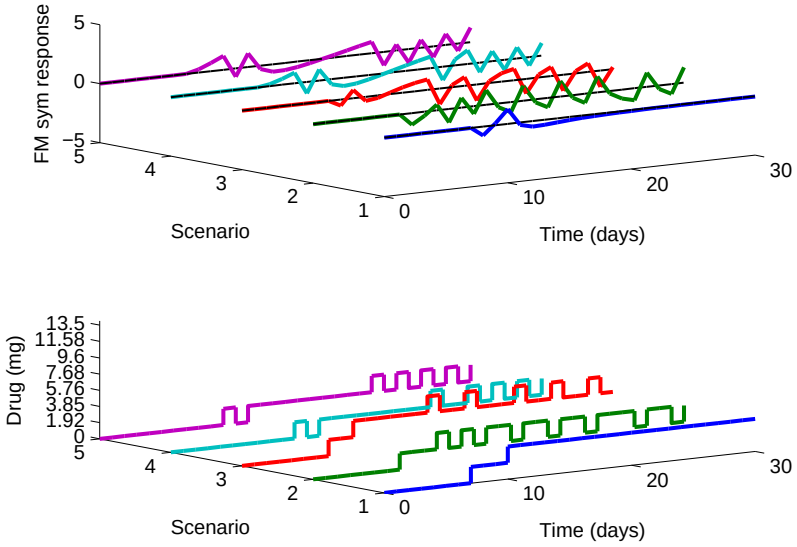


(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.12: Robustness evaluation when only plant model (drug-FM) is perturbed under tuning $f_a = 1$.

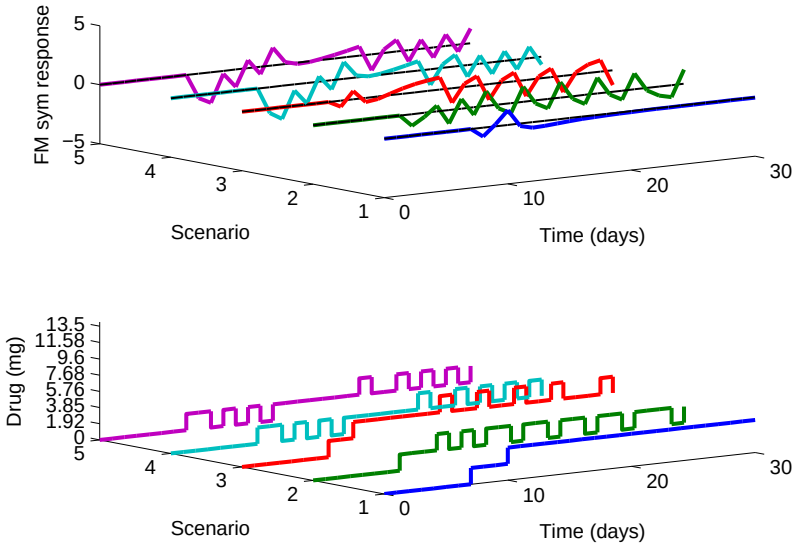


(a) Closed loop response with plant model mismatch where scenario 1 represents the nominal model

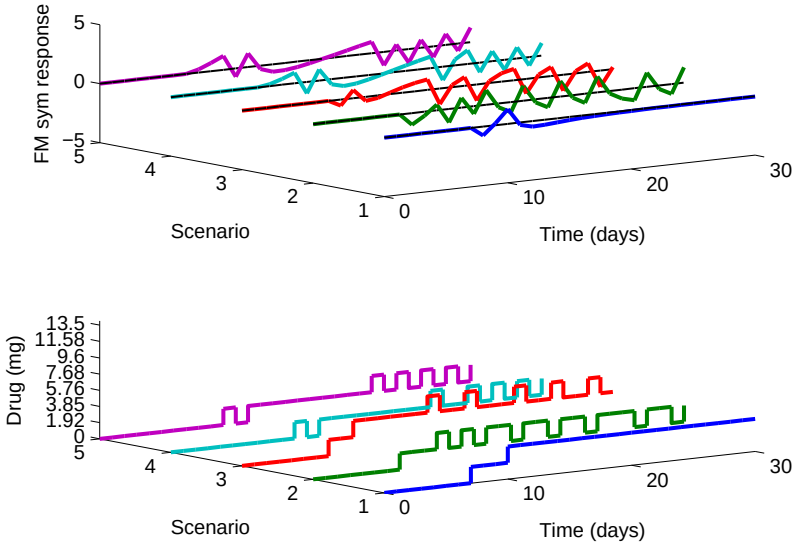


(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.13: Robustness evaluation when only disturbance model (anxiety-FM) is perturbed under tuning $f_a = 0.2$.

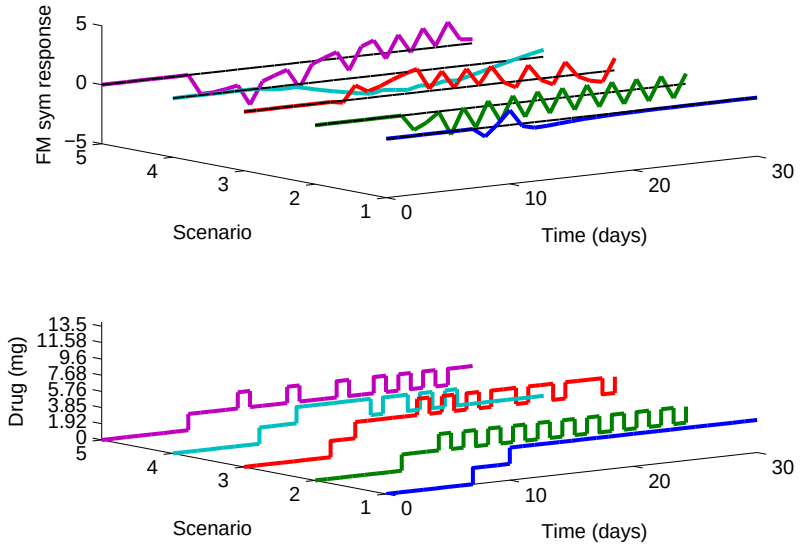


(a) Closed loop response with plant model mismatch where scenario 1 represents the nominal model

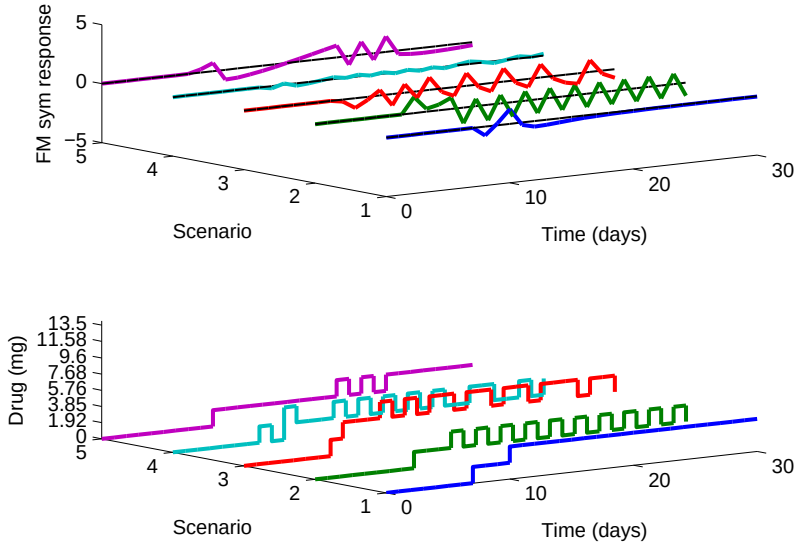


(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.14: Robustness evaluation when only disturbance model (anxiety-FM) is perturbed under tuning $f_a = 1$.

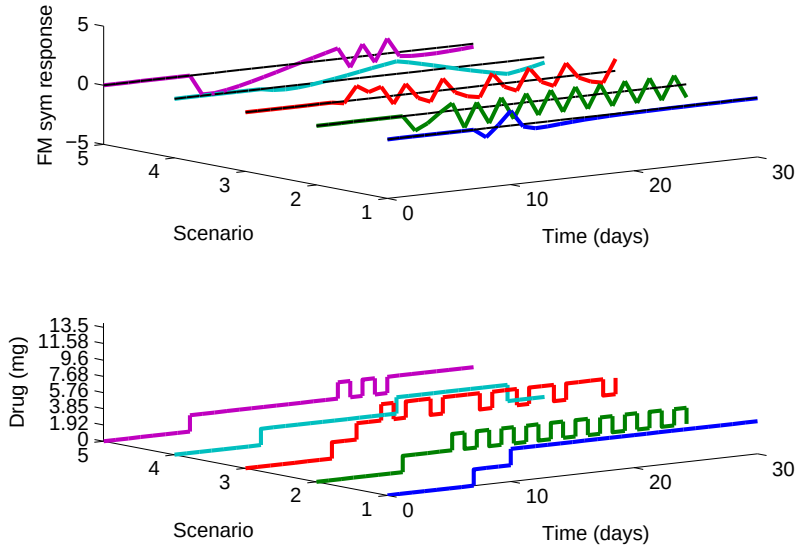


(a) Closed loop response with plant model mismatch where scenario 1 represents the nominal model

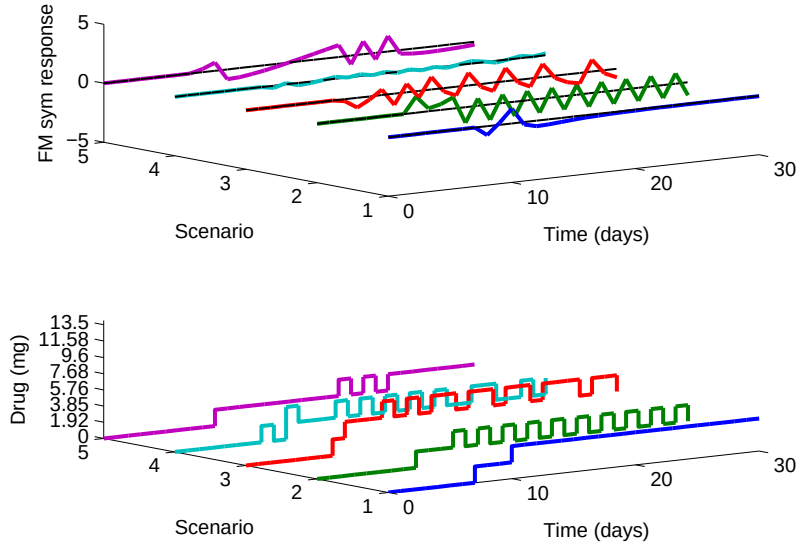


(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.15: Robustness evaluation when both disturbance model (anxiety-FM) and plant model (drug-FM) are perturbed under tuning $f_a = 0.2$.



(a) Closed loop response with plant model mismatch where scenario 1 represents the nominal model



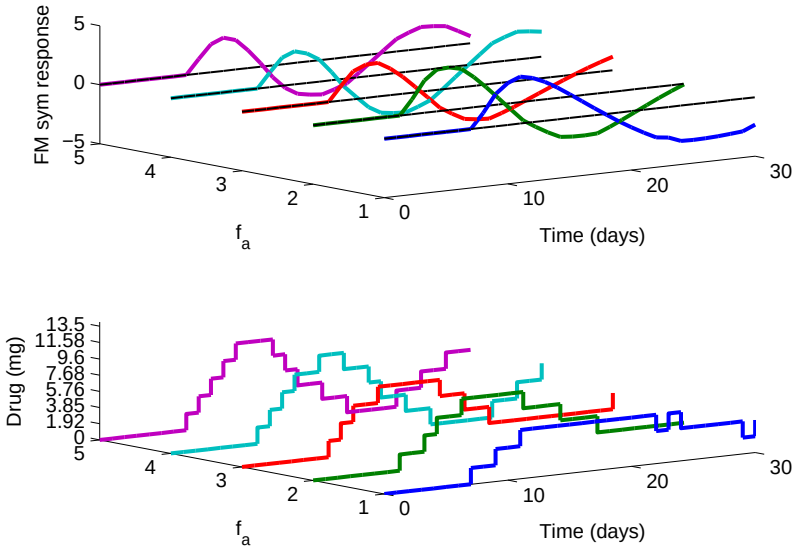
(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.16: Robustness evaluation when both disturbance model (anxiety-FM) and plant model (drug-FM) are perturbed under tuning $f_a = 1$.

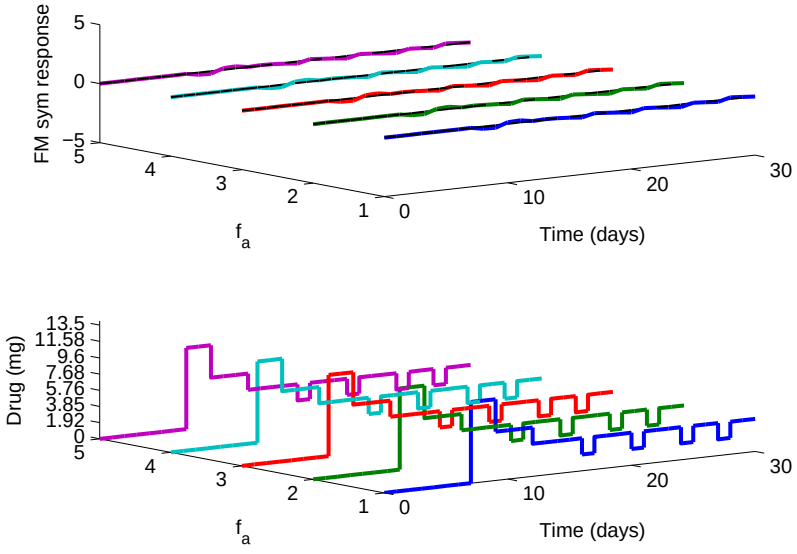
4.5.2 Robustness Evaluated under Fixed Uncertainty

In this subsection, the tuning of the controller is varied with a fixed uncertainties in the plant model, disturbance model combination. Each scenario on the 'Y axis' represents a case for f_a: scenario 1 is for $f_a = 0.2$ and scenario 5 is for $f_a = 1$. Hence, as we move away from $f_a = 1$ along the axis, we see less and less disturbance rejection.

In Figures 4.17-4.19 we show how the tuning affects the performance more precisely than previous section as we now fix the uncertainty. In each case, $f_a = 1$ results in more aggressive control. As earlier, each control is compared with the case where a correct nominal model is available where the control is better as expected. If the user has some sense for the expected modeling uncertainties, we can see different control inputs under different tunings. A clinician can then choose certain tuning parameters which can then prescribe best possible treatment regimens.

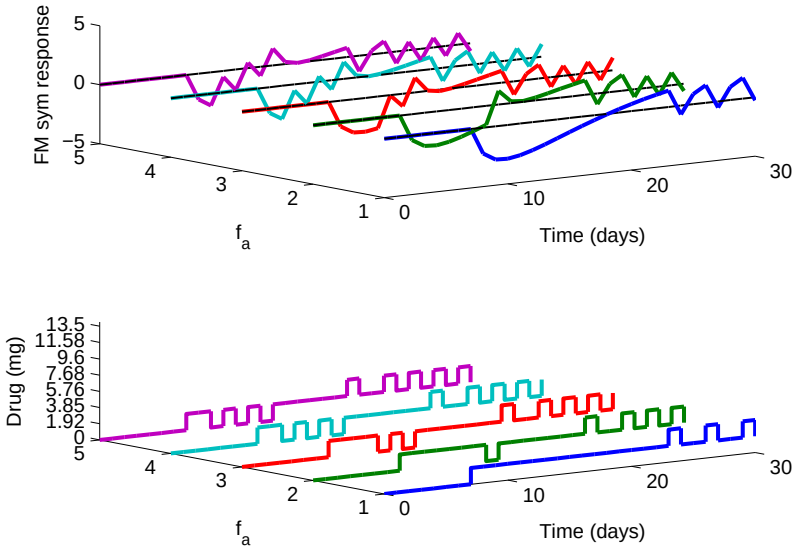


(a) Closed loop response with plant model mismatch

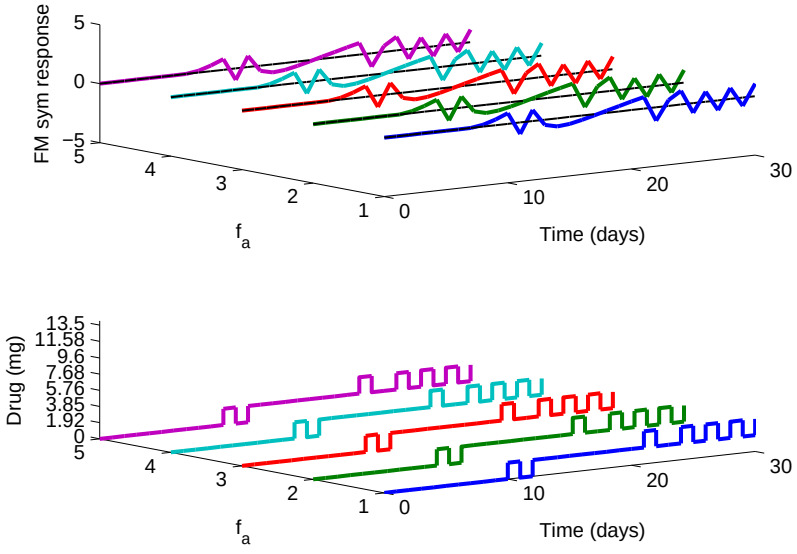


(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.17: Robustness evaluation under different f_a (with $\alpha_r = \alpha_d = 0$) when only plant model (drug-FM) is perturbed using plant uncertainty case number 4 as $\Delta K_p, \Delta\zeta_p, \Delta\tau_p = (-14.8\%, -16.6\%, 259\%)$.

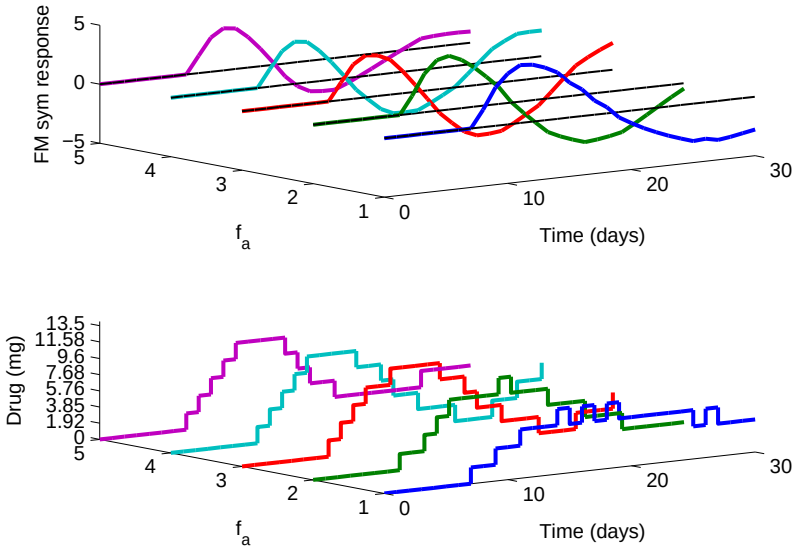


(a) Closed loop response with plant model mismatch

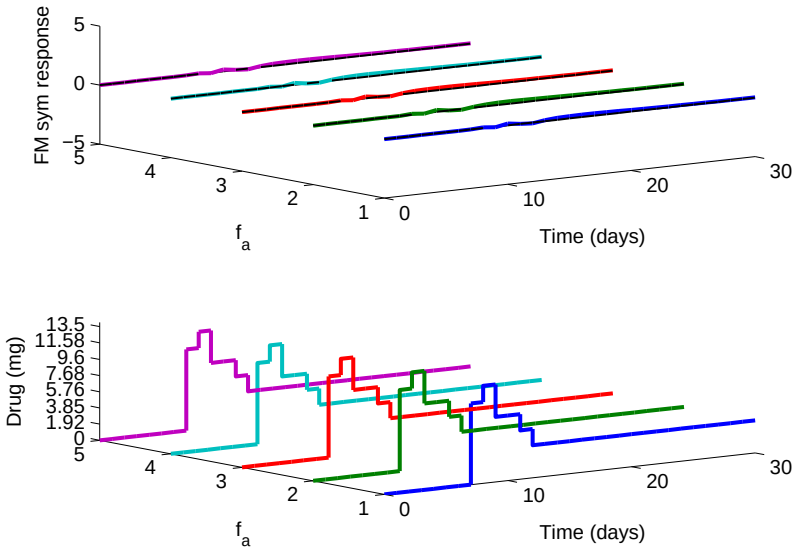


(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.18: Robustness evaluation under different f_a (with $\alpha_r = \alpha_d = 0$) when only disturbance model (anxiety-FM) is perturbed using disturbance uncertainty case number 4 as $\Delta K_d, \Delta\zeta_d, \Delta\tau_d = (-14.8\%, -16.6\%, 259\%)$.



(a) Closed loop response with plant model mismatch



(b) Closed loop response where true plant serves as the nominal model (no plant model mismatch)

Figure 4.19: Robustness evaluation under different f_a when both plant model (drug-FM) and disturbance model (anxiety-FM) are perturbed using plant uncertainty case number 4 as $\Delta K_p, \Delta\zeta_p, \Delta\tau_p = (-14.8\%, -16.6\%, 259\%)$ and using disturbance uncertainty case number 3 as $\Delta K_d = (14.8\%)$.

4.6 Summary

The aim of this chapter is to demonstrate how a control system framework can be used in an adaptive intervention for fibromyalgia. We use a representative participant from the clinical trial and using estimated models from system identification, we show how a model predictive controller can be used to assign dosages in presence of disturbances and model uncertainties. The control results are shown using simulation and are broadly classified under nominal performance and robust performance. Under nominal performance it is shown how by varying the three parameters (α_r, α_d, f_a), we can achieve independent tuning for setpoint tracking (taking pain report to a goal), measured and unmeasured disturbance rejection. We also demonstrate how different settings of these parameters will lead to different time responses and demonstrate the usefulness for both deterministic and stochastic disturbances.

In the robust performance evaluation, we perturb the model parameters to create conditions of a plant-model mismatch which is then used by the controller. In this scenario, we run two broad cases: one where controller tuning is fixed and the effect of different uncertainties are noted and second, when the plant uncertainty is fixed and the effect of tuning is evaluated on the resulting response. Due to constraints on the input drug dosage levels, the plant uncertainties were not chosen arbitrarily very large and it can be noted that in such a scenario, an unconstrained MPC can achieve much higher mismatches where as constrained control will saturate.

In all the responses pertaining to the nominal and robust performance of the controller as noted in many of the Figures 4.5-4.19, we observe that the hybrid controller tries its best to track the goal under given constraints and that may result in an oscillatory input drug assignment. This treatment regimen would be the best pos-

sible result under given models and clinical constraints. Hence, it is demonstrated that even under considerable uncertainty and since the modeling effort is always lacking, an acceptable performance is achieved.

Chapter 5

CONCLUSIONS

5.1 Summary

In this thesis, we have demonstrated how techniques from system identification and hybrid model predictive control (HMPC) can be used to evaluate and design an adaptive intervention. We showcase the case of drug dosage levels assignment of naltrexone for the treatment of fibromyalgia as a proof of concept. The work in this thesis can be broadly divided into two areas: dynamical modeling and control.

We performed a secondary data analysis of data obtained from a clinical study to estimate parsimonious dynamical system models. The modeling procedure was split into three parts: first part deals with the preprocessing of the data for removing high frequency content as well as handling issues of missing data. In the primary second step, we fit the estimation data to parametric ARX model of order [2 2 1] or higher. The model is then validated using standard residual analysis as well a sense of model uncertainty is obtained through the model error model approach and using bounds on the step response of estimated models. During this process of parametric modeling, we systematically look at the two sources of errors in system identification: bias error and variance errors. We also note that the experimental data can be considered to be generated in a closed loop experiment (and as observed by correlated variables) and hence a prediction-error framework works as a good initial choice. After working through the data for all 40 participants, we observed that ARX [2 2 1] or ARX [4 4 1] proved to be sufficient without resulting in a case of over parametrization. These multi-input models best described the output variance among give choice of inputs. The inputs were selected such that they have minimum cross correlation and will result in minimum bias errors. Since the intervention aims

at testing the efficacy of the drug (low dose naltrexone), drug is always included as the primary input. Also since the experimental design for this clinical trails used a placebo as an experimental control, placebo is also included as input. Working further from these two inputs, we found that many other variables reported in the daily diary data such as anxiety, stress, mood can be potentially added as input helping improve the fit of the dynamical models. Most of the participants of the pilot study conformed to a model structure which used drug, placebo, anxiety, stress and mood as inputs and most of the participants in the full study conformed to a model which adds gastric, headache, life and sadness to variables in the pilot data study.

In the final step of our system identification procedure, we approximate the estimated discrete time parametric model with a second order continuous models with a zero. We found that this structure was adequate to represent the observed dynamics. This model is then used to extract useful information about the effect of drug on pain symptoms, for example, through gain of the model and other parameters affecting the time response. These parameters are represented in the step response tabulation for multi input models. Based on the nominal gain of the drug-FM sym model, we can classify participants as *responders* (the model gain K_p will be negative) or in other words whose pain reports go down with drug intervention and as *non-responders* (the model gain K_p will be positive) whose pain reports stay the same or go up with drug intervention. Since in clinical trails, the aim is to separate the drug response from the placebo response, we note the gain of placebo-FM sym model and which has to be, ideally, positive (implying increase in pain) or in lesser magnitude than the drug response. Based on these criteria, we classify a large group of participants as responders (total 26, see Tables 3.8-3.9 and Tables 3.21-3.24) although many of these cases lie on the borderline. Similar classification of gain can

be made in the case when 'overall sleep' is used as the output where a positive gain would imply improvement in sleep quality with drug intervention and hence the participant is a responder in that sense. Chapter 2 and 3 cover the modeling aspect of this work.

As a conclusion to dynamic modeling, we revisit questions raised in Chapter 2, Section 2.7 regarding the effectiveness of this clinical intervention.

- *Does a participant respond to the drug?*

  The participants are classified as responders and responders based on models from system identification. Very few participants showed a strong response to drug (e.g., participant 5) while in most of the cases, the response ranged from mild to no response.

- *If yes, then how fast does the drug cause a measurable effect?*

  We observed a large variability in settling time values from model step responses. On an average over pilot and full study, we can say that the drug took over $2-3$ weeks to show full effect.

- *How does the response compare for different outcomes?*

  In the pilot study, the response of FM sym and overall sleep variables to drug for responders are similar which means that those who had relief from pain generally enjoyed better sleep qualities. In the case of responders in the full study, this relationship was not observed. In case of non-responders from both studies, some showed improvement in sleep.

- *How does the participant respond to placebo?*

  Ideally, for responders to drug it is expected that the response to placebo is increase in pain. This was not observed for all responders; many of the par-

ticipants in both pilot and full studies who had been classified as responders based on the drug-FM model were also 'responders' to placebo. The placebo response was stronger in the full study as compared with the pilot study.

- *How can the response of two different participants be compared?*
  It is difficult to compare the response *quantitatively* between participants because the data is obtained through self-reports though we can qualitatively compare that one participant shows as stronger response to drug than the other for example, participant 5 has a stronger response than participant 40 (both responders).

The dynamical model describing the effect of drug, placebo, anxiety, stress and mood on FM sym can now be used by the controller. In a typical clinical setting, the physician may use patient characteristics (e.g., vital signs, pathological information) to make a dosage change; in case of naltrexone intervention the self-reports completed by the participants can be used as patient characteristics (which can be better described by the dynamical model). Additionally, successful handling of disturbances or external influences is critical from a standpoint of an effective treatment plan. It is likely obvious to the reader that the traditional method is not systematic, and is neither robust nor optimal. In this approach of using control systems, greater efficacy can be obtained. To assign drug dosages, a hybrid model predictive control approach, as shown in [31, 61, 73], has been utilized which can allow independent tuning for disturbance free setpoint tracking, measured disturbance rejection and unmeasured disturbance rejection. The physician may set a certain goal both in terms of magnitude of response expected and the time frame of the treatment (setpoint tracking). The controller will prescribe a dosage regiment based on those requirements. Since the MPC control law is updated on every

sampling instant based on the 'feedback' from self-reports, the control law will be updated in case of a disturbance (measured and unmeasured disturbance rejection). These requirements can be grouped under nominal performance of the controller and through simulations, we show how this hybrid control framework can be used tune the system response as specified by the clinical requirements.

Since any modeling effort will not result in an exact description of the real system, the controller formulation should be robust enough to handle plant-model mismatch and unknown disturbances. From simulation results, we show that this MPC setup maintains the outcome variable at goal in presence of disturbance and uncertainties. A physician can get a sense of the drug dosage regiment prescribed by the controller in case of modeling errors and hence can get information on how aggressive or sluggish the regiment may become due to mentioned mismatches. The Chapter 4 covers the discussion on control for naltrexone intervention. The approach described in this work generates models from experimental data and considers hybrid dynamics in an MLD framework. It offers a broad-based methodology that can be applied in an similar application setting involving adaptive interventions.

5.2 Future Work

Many goals of adaptive interventions, personalized medicine and control engineering converge to a common factor emphasizing the extraction of the maximum possible potential of the underlying system while using minimum resources. Modeling of biological phenomena as dynamical systems will not only result in greater understanding of the process but will allow systematic use by the controller to optimize the process. The future research thrust will be towards methods for modeling and control of systems to be used in an adaptive intervention.

An area of future work is the design of experimental protocols. As the informa-

tion content of the used input signal for system excitation is crucial for the success of system identification, design of protocols for plant-friendly and informative data set is required. Clinical trials are primarily designed with a fixed dosage strategy (a binary input) and hence the data set may not necessarily very informative. Further, a input signal exceeding two (binary) levels is required for finding nonlinearities. In addition, the experimental design has to be as per given clinical constraints e.g., the drug levels should not change abruptly from lowest dosage to highest dosages. An experimental design can be suggested which would involve a deterministic periodic signal dosage, e.g., multilevel pseudo random sequence as shown in Figure 5.1, designed such that it has persistence of excitation in the bandwidth of interest based on some *a priori* information.

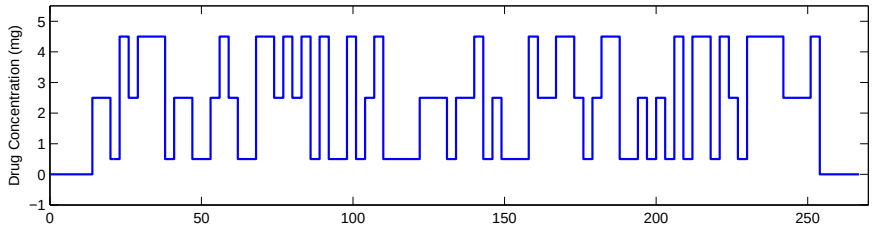


Figure 5.1: A Multilevel pseudo random sequence altering between drug dosages of $0.5 - 2.5 - 4.5$ mg with a 14 day baseline and washout period.

Further computational approaches for local modeling are required to work with finite date set and hence as a part of nonlinear identification, approaches such as Model-on-Demand (MoD) [74, 75] can be utilized on the collected informative data set from these new protocols. These new databases can also be organized for multiple participants to generate models for large cohorts. Apart from modeling issues related to input signal quality and parametric identification, there is also a need to better understand the underlying feedback mechanism of complex biological systems from experimental data.

The presented formulation of hybrid model predictive controller can be modified such that it is more suited for adaptive interventions by further integration of treatment related constraints. First, since MPC only requires explicit output/state predictions near operating conditions, the local models from MoD utilizing the informative dataset can be used for more precise future predictions. Next, it is more practical to allow setpoint bands for tracking as compared to a strict setpoint value where a clinician can choose a band of pain level for example; this will also lead to less aggressive dosing. Finally, ideas from robust control can be used for the uncertainty set obtained from system identification procedures. In conclusion, the motivation is to improve existing tools for effective system identification and control as well as to develop new methods which can guarantee robust performance under given clinical constraints.

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