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Optimized treatment of fibromyalgia using system identification and hybrid model predictive control

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ABSTRACT

The term *adaptive intervention* is used in behavioral health to describe individually tailored strategies for preventing and treating chronic, relapsing disorders. This paper describes a system identification approach for developing dynamical models from clinical data, and subsequently, a hybrid model predictive control scheme for assigning dosages of naltrexone as treatment for fibromyalgia, a chronic pain condition. A simulation study that includes conditions of significant plant-model mismatch demonstrates the benefits of hybrid predictive control as a decision framework for optimized adaptive interventions. This work provides insights on the design of novel personalized interventions for chronic pain and related conditions in behavioral health.

1. Introduction

With rising health care costs, there is an increasing interest in the medical community towards developing improved strategies for treating chronic diseases (Collins, 2010; Wellstead, Bullinger, Kalamatianos, Mason, & Verwoerd, 2008). 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 and has been proposed as an enabler for more efficacious treatments that minimize waste, increase compliance, and enhance the intervention potency (Deshpande, Rivera, Younger, & Nandola, 2014; Riley et al., 2011; Rivera, Pew, & Collins, 2007; Zafra-Cabeza, Rivera, Collins, Ridao, & Camacho, 2011).

Traditional medical practice is based on treatment protocols designed for a standard response that do not necessarily incorporate individual characteristics or optimization procedures. Many of these dosage strategies are aimed at acute disorders and in spite of effective drugs, they are not necessarily efficient for relapsing, chronic disorders. The use of adaptive approaches, in which dosages are adjusted based on participant response over time, is the key motivation for use of control systems engineering principles. This paper demonstrates how control engineering principles can impact the treatment of chronic, relapsing disorders by examining a pain condition known as fibromyalgia (FM) (Boissevain & Mccain, 1991a,b; Deshpande, Nandola, Rivera, & Younger, 2011; Younger & Mackey, 2009). The examination is based on secondary analysis of information collected from a previously conducted clinical trial using naltrexone for the treatment of FM. This problem is approached from a systems and controls point-of-view: first, system identification techniques are applied to develop dynamical models from daily diary reports completed by intervention participants. These diary reports include self-assessments of outcomes of interest (e.g., general pain symptoms, sleep quality) and additional external variables that affect these outcomes (e.g., stress, anxiety, and mood). These dynamical system models serve as the basis for applying model predictive control as a decision algorithm for dosage selection of naltrexone. The categorical/discrete-event nature of the dosage assignment process calls for hybrid model predictive control (HMPC) schemes. Instead of relying on conventional tuning of HMPC using weight matrices, a multiple degree-of-freedom formulation is evaluated in this paper that enables the user to adjust the speed of setpoint tracking, measured disturbance rejection and unmeasured disturbance rejection independently in the closed loop system. Simulation results depicting realistic conditions are presented to illustrate the benefits of the proposed control scheme in addressing hybrid dynamics, clinical constraints and plant-model mismatch typically present in such applications.

The paper is organized according to the following sections: Section 2 briefly describes the intervention and nature of the associated clinical data. Section 3 discusses the procedure for

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building parsimonious models using system identification. The HMPC formulation used for dosage assignment is presented in Section 4, with Section 5 demonstrating the application of HMPC for delivering adaptive interventions under conditions of disturbances and model uncertainty. The paper ends with a summary and conclusions in Section 6.

2. Naltrexone intervention for fibromyalgia

Fibromyalgia (FM) is a disorder characterized primarily by chronic widespread pain. The characteristic symptoms of FM are diffuse musculoskeletal pain and sensitivity to mechanical stimulation at soft tissue tender points (Wolfe et al., 1990, 2010). Other important symptoms of FM include fatigue, sleep irregularities, bowel abnormalities, anxiety, and mood dysfunction. 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 (Perrot, 2008), although the condition is suspected to involve central sensitization of pain processing (Lee, Nassikas, & Clauw, 2011). As the causes of FM are unknown, it has been difficult to single out a specific type of treatment for this chronic disease. Depending on different approaches for the mechanisms of FM, there have been experiments with various drugs. There is a good evidence to suggest that naltrexone, an opioid antagonist, has a neuroprotective role and may be a potentially effective treatment for diseases like FM (Mattiloi, Milne, & Cahill, 2010; Younger & Mackey, 2009). The data for this paper has been taken from clinical trials of a low dose naltrexone (LDN) intervention conducted by Dr. Jarred Younger and colleagues at the Stanford Systems Neuroscience and Pain Lab (SNAPL), Stanford University School of Medicine (Younger & Mackey, 2009; Younger, Noor, McCue, & Mackey, 2013).

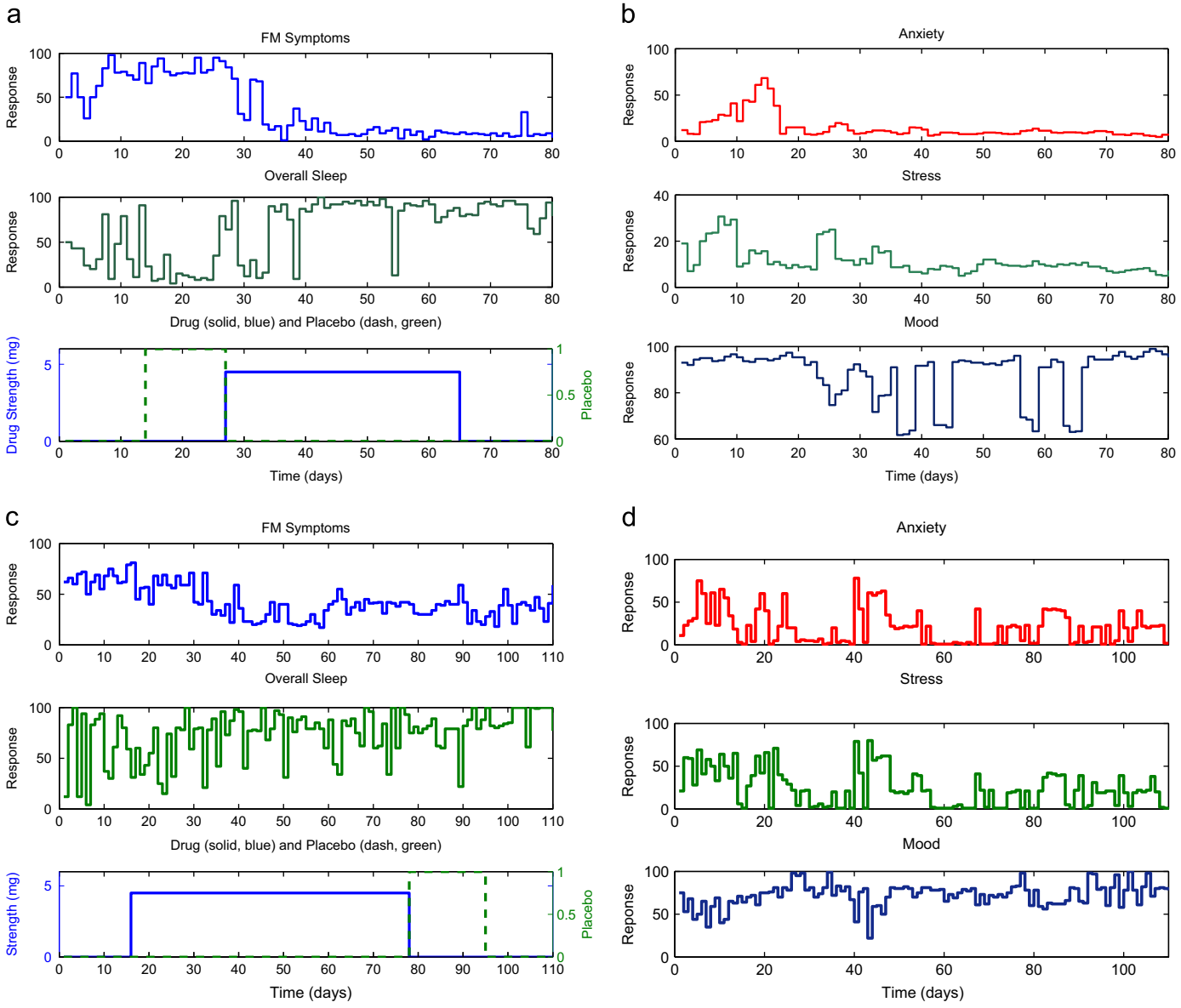

Fig. 1. Primary self-report variables associated with naltrexone intervention of fibromyalgia as shown for two representative participants: one participant from the pilot study with placebo–drug (P–D) protocol ((a) and (b)) and a participant from the full study with drug–placebo (D–P) protocol ((c) and (d)). With the introduction of naltrexone, there is a significant decrease in FM symptoms and increase in sleep quality over time for both participants.