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Optimized behavioral interventions: what does system identification and control engineering have to offer?

Daniel E. Rivera *

* *Control Systems Engineering Laboratory, School for Engineering of Matter, Transport, and Energy, Arizona State University, Tempe AZ 85287-6106 USA. Email: daniel.rivera@asu.edu*

Abstract: The last decade has witnessed an increasing interest in applying systems science concepts for problems in behavioral health, and using these to inform the design, analysis, and implementation of optimized interventions. How can system identification and control engineering impact interventions for chronic, relapsing disorders such as drug abuse, cigarette smoking and obesity? The paper addresses this question by focusing on the problem of time-varying "adaptive" interventions. In an adaptive intervention, dosages of intervention components are assigned based on the assessed values of *tailoring variables* that reflect some outcome measure (e.g., number of cigarettes smoked, parental function) or adherence (e.g, days abstinent). Because time-varying adaptive interventions constitute closed-loop dynamical systems, they are correspondlngly amenable to control engineering solutions. System identification is enabled by intensive longitudinal data (ILD) that can be obtained in the field via ecological momentary assessment (EMA); this creates the availability of rapidly sampled, continuous-time assessments from which dynamical system behavior can be discerned and modeled. How can system identification and control be applied in this broad setting is demonstrated with a number of illustrative problems: dynamic modeling and hybrid model predictive control of low-dose naltrexone as treatment for fibromyalgia, a chronic pain condition; modeling of a smoking cessation intervention involving bupropion and counseling; constructing a dynamic model of an intervention for preventing excessive weight gain during pregnancy, and Model-on-Demand Model Predictive Control in a hypothetical intervention based on the *Fast Track* program for assigning the frequency of home counseling visits to families with at-risk children.

Keywords: social and behavioral sciences, system identification, control engineering, adaptive behavioral interventions, hybrid model predictive control, experiment design

1. INTRODUCTION

A behavioral intervention can be defined as a program aimed at modifying behavior for the purpose of preventing or treating disease, promoting health, and/or enhancing well-being (Collins, 2012). Behavioral interventions play an important role in addressing many important public health concerns, among them substance abuse, obesity, prevention of sexually transmitted diseases, and cancer. The nature of these interventions can be pharmacological or behavioral in nature, or their combination (Rivera et al., 2007). For instance, a behavioral intervention for drug abusers may include prescribing dosages of an opioid antagonist (e.g., naltrexone) as well as the frequency and type of therapy (e.g., cognitive behavioral therapy, motivational interviewing, or counseling) with the goal of avoiding relapse and ultimately eradicating addictive behavior over time.

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In this paper, our goal is to provide an engineering perspective for how current needs and future trends in the area of behavioral interventions can benefit from a system identification and control engineering approach. Our treatment does not attempt to be comprehensive, but rather, via a set of illustrative examples, seeks to convey these ideas in the language of control engineering; alternatively, the applications in this paper can communicate to individuals outside of control engineering the impact that our field can have in the social and behavioral sciences We begin by noting some enabling technologies and concepts that facilitate the use of system identification and control systems engineering:

(1) *The interest in optimizing interventions by personalizing treatment through adaptation.* The traditional approach to intervention development is that these are "fixed," meaning a single composition and dosage is given to all participants. However, recent efforts in behavioral health center around the development of so-called "adaptive" interventions where the dosage and type of treatment varies according to measures denoting participant response (Collins et al., 2004).

The variables used in determining treatment are referred to as *tailoring variables*; decision rules translate current and previous values of tailoring variables into dosages and forms of treatments at multiple time intervals within the intervention. Prior work has shown that adaptive interventions can be represented as closed-loop dynamical systems (Rivera et al., 2007).

(2) *Increasing access to intensive longitudinal data through computing and mobile technologies such as ecological momentary assessment (EMA), and the opportunity for "closing the loop" in an intervention setting using mobile devices (mHealth).* The rise of mobile and computerized technologies has led to increased access to intensive longitudinal data (ILD) from human participants. ILD is generated in behavioral settings where quantitative or qualitative measurements are recorded at more than a handful of time points (Walls and Schafer, 2006). The diary studies of the past have given way to ILD obtained in the field via ecological momentary assessment (EMA), which consists of a variety of methodologies collecting data on a subject's current state over multiple time instances in real-world environments (Shiffman et al., 2008). With the rise in availability of ILD comes the opportunity to study an intervention's time-varying effect on behavior change, and consequently, the opportunity to estimate dynamical system models that may form the basis for optimized adaptive interventions using control engineering strategies. The mobile devices that accomplish EMA and generate the ILD can be further used to deliver tailored health behavior interventions in an ecological setting; this is an important part of the increasing interest in mobile health (*mHealth*) and ultimately more effective interventions relying on mobile technologies among the medical community (Riley et al., 2011).

(3) *Behavioral theories provide insights that can be helpful for both model and control strategy development.* Access to intensive data enables the application of system identification, with black-box methods the simplest way to start. Conservation and accounting of mass, energy, momentum, and charge underly many traditional applications in system identification; however, when modeling behavior change in human participants, what theoretical constructs are available to guide and inform the use of identification and control approaches? The field of behavioral health has a rich methodological (i.e., quantitative) tradition that has been used to model and understand behavior, albeit from a primarily steady-state perspective, and with the goal of hypothesis testing and crossectional (i.e., between groups or between individuals) understanding of phenomena. In this paper, we will show how path diagrams from structural equation modeling (SEM; Bollen (1989)) which have widespread use in the behavioral and social sciences can be used as a basis for establishing dynamical relationships and model structures amenable to system identification. This includes concepts such as the Theory of Planned Behavior (TPB) and statistical mediation analysis that have been applied for weight change interventions and smoking cessation (Navarro-Barrientos et al., 2011; Timms et al., 2012). Additionally, the well-established concept in psychology of self-regulation (Carver and Scheier, 1998) is grounded on control engineering principles; its usefulness will be illustrated in the paper.

The paper is organized as follows. The first example (discussed in Section 2) considers a pain management intervention for a condition know as fibromyalgia. Section 3 describes a behavioral theory-based dynamical model for an intervention to prevent excessive weight gain in pregnant women. Section 4 in turn describes identification modeling approaches for a smoking cessation intervention, while Section 5 considers a data-centric approach for a preventive adaptive intervention for drug abuse among at-risk children. Section 6 summarizes the main conclusions and some topics for future work and exploration in this important and emerging field.

2. EXAMPLE 1: PAIN MANAGEMENT

Fibromyalgia (FM) is a disorder characterized primarily by chronic widespread pain. Other important symptoms of FM include fatigue, sleep irregularities, bowel abnormalities, anxiety, and mood dysfunction. The causes for FM are uncertain, unknown or disputed; 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 neuroprotective role and may be a potentially effective treatment for FM (Younger and Mackey, 2009; Mattiloi et al., 2010). This section describes salient aspects of the problem as described in Deshpande et al. (2011) and Deshpande (2011), as well as work that is presented separately as part of SYSID 2012 (Deshpande et al., 2012).

The data for this study has been taken from clinical trials conducted by the Systems Neuroscience and Pain Lab in the Stanford University School of Medicine. The study was conducted in two phases: a single blind pilot study on 10 participants and a double blind full study on 30 participants (with longer protocol). The time series is split into baseline, placebo, drug and washout phases with the number of data points ranging from 98 to 154 sampled daily ($T = 1$). Participants entered their responses in a handheld computer to questions like "Overall, how well did you sleep last night?" on a scale of 0-100 as well as visited a clinic every two weeks to undergo a series of physical sensory tests. The daily diary data consists of one primary endpoint "Overall, how severe have your FM symptoms been today?" [FM sym] and 13 secondary endpoints: fatigue, sadness, stress, mood, anxiety, satisfaction with life, overall sleep quality, trouble with sleep, ability to think, headaches, average daily pain, highest pain and gastric symptoms (Younger and Mackey, 2009). Data for a representative participant is shown in Figure 1.

A cursory examination of the data in Figure 1 shows the presence of lagged dynamics. A more general and important consideration is to specify input and output variables. On the basis of physical insight and other *a priori* considerations, we classify these variables as follows:

Outputs: We are primarily interested in understanding the magnitude and speed at which naltrexone and other external variables affect the various FM symptoms during the

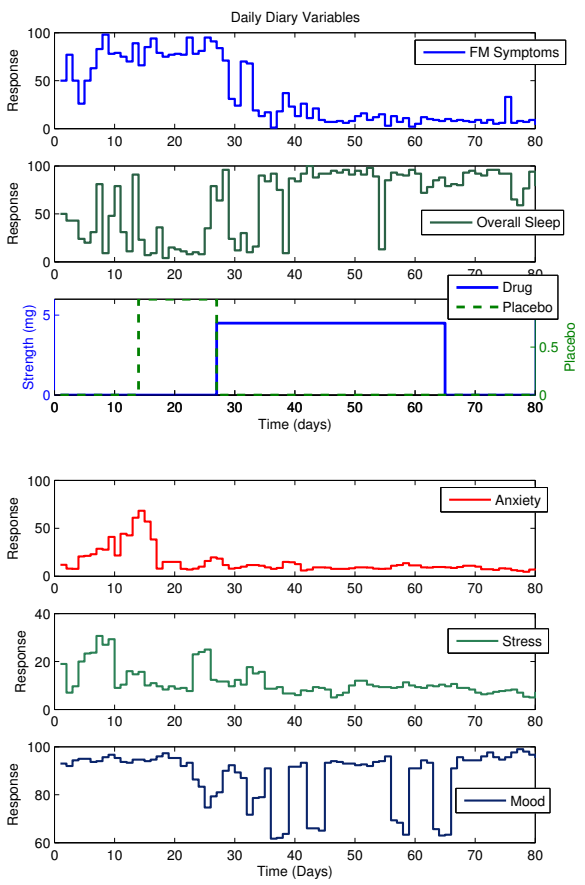

Fig. 1. Selected variables associated with the naltrexone intervention of FM, as shown for a representative participant. Naltrexone drug concentration is 4.5 mg.

intervention. Hence typical symptoms like pain, fatigue, sleep disturbance correspond to dependent variables in the system, which we classify as outputs.

Inputs: Drug and placebo are classified as the primary inputs in this analysis, as they are introduced externally to the system and can be manipulated by the clinician. In addition to these primary inputs, there are other exogenous or disturbance variables affecting the outputs. Variables in the self-reports such as anxiety, stress, and mood are treated as measured disturbance inputs.

2.1 System Identification Procedure

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. To reduce the high frequency content in the time series, a three-day moving average filter is applied.

(2) *Discrete-time modeling using multi-input ARX models.* The filtered data is fitted to a parametric model. We rely on multi-input ARX-$[n_a\ n_b\ n_k]$ models

$$A(q)y(t) = \sum_{i=1}^{n_u} B_i(q)u_i(t - n_{k_i}) + e(t) \qquad (1)$$

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 $A(q) = 1 + \sum_{j=1}^{n_a} a_j q^{-j}$ and $B_i(q) = \sum_{j=1}^{n_{b_i}} b_j q^{-j+1}$ are polynomials in q, the forward shift operator. In our examination of multiple participants, ARX-[4 4 1] models were the highest order needed, and in many cases ARX-[2 2 1] models were suitable, as determined by classical validation criteria.

The protocol applied in this study did not allow for a crossvalidation data set. The procedure for the choice of input signals is to begin with drug and placebo, which are expected to contribute significantly to FM symptoms for all participants. Additional input variables are then introduced sequentially to improve the goodness of fit. Consequently, while increasing the number of inputs improves the overall fit, an exceptionally high fit may not necessarily imply a highly predictive model. Proper judgement on the choice of input variables that adequately describes the data across all participants must be made.

(3) *Simplification to a continuous time model.* The step responses from the ARX model are individually fit to a parsimonious continuous second-order model structure of the form

$$G(s) = \frac{K_p(\tau_a s + 1)}{\tau^2 s^2 + 2\zeta\tau s + 1} \qquad (2)$$

From (2) important dynamical system information such as gain, time constant, overshoot, rise and settling times for each input can be obtained.

2.2 Analysis for a representative participant

The multi-input ARX-[2 2 1] models applied to the representative participant (with respective input(s) and FM symptoms treated as the primary output) are as follows:

(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)

Table 1 summarizes the modeling results for the specific case of the naltrexone drug input. The final model has a gain of -2.47, indicating a nearly 2.5 point drop in the pain report per mg dose of naltrexone. The negative gain for drug allows us to classify this participant as a responder to treatment. A rise time (T_r) of slightly over 5 days, and a 98% settling time (T_s) of nearly 11.5 days characterizes the naltrexone response for this participant. Table 1 further shows how including additional inputs improved the goodness-of-fit. Beyond the five inputs noted, adding more variables did not improve the fit significantly and resulted in overparameterization. For some participants, additional inputs like sadness and headache, as well as ARX models with higher orders gave good fits. Details on the system identification results for all intervention participants can be found in Deshpande (2011).

Table 2 summarizes the transfer functions for all inputs (manipulated and disturbance) for the Model 5 structure. For all these transfer functions the settling times and rise times (with the exception of Mood-FM) are essentially similar. The positive gain for the placebo input indicates that in the case of this participant, the administration

Model	%fit	K_p, τ, ζ, τ_a	T_r(days)	T_s(days)
1	46.5	-12.03, 5.67, 4.14, 21.3	75.5	139.69
2	59.2	-0.91, 3.5, 2.67, 44.4	0.43	75.06
3	64.7	-1.02, 2.09, 1.5, 15.3	0.43	25.6
4	71.8	-3.11, 1.62, 1.24, 0.22	7.53	14.38
5	73.9	-2.47, 1.57, 1.26, 1.96	5.12	11.49

Table 1. Model estimate summary for the drug-FM model. % fit corresponds to the multi-input ARX model structure used.

Model	K_p, τ, ζ, τ_a	T_r(days)	T_s(days)
Drug-FM	-2.47, 1.57, 1.26, 1.96	5.12	11.49
Placebo-FM	45.81, 1.57, 1.26, 1.15	6.59	13.06
Anxiety-FM	0.86, 1.57, 1.26, 0.24	7.45	14.24
Stress-FM	2.29,1.57, 1.26, 0.49	7.31	13.94
Mood-FM	-0.091, 1.57, 1.26, 4.67	0.8	11.93
Drug-OSleep	4.98, 2.13, 1.04, -3.35	7.06	15.83

Table 2. Step response tabulation for various inputs-FM continuous models as well as the drug-overall sleep (Drug-OSleep) model.

of placebo has a detrimental effect. The large magnitude of the placebo gain is in part a consequence of how the input signal is coded (1 when present and 0 when not). Examining the gains for the measured disturbance models (anxiety, stress, and mood), these correspond to 0.86, 2.29, and -0.091, respectively. The positive values for the anxiety and stress gains agree with the clinical observation for how these variables worsen FM symptoms. The low magnitude of the mood gain, coupled with the relatively small contribution of this input to the percent goodness of fit (approximately 2%) indicates the low importance of this variable as a contributor to FM symptoms.

2.3 Novel experimental design

The previous analysis consisted of a secondary analysis of data from a clinical trial that was not designed with a system identification goal in mind. Standard clinical trials, while providing some useful information, are not always the most suitable vehicle for understanding the dynamic response of dosage changes to participant response. The absence of a crossvalidation data set and the limitations imposed by using a constant dosage during the trial are among the reasons why experimental protocols that are more consistent with system identification principles need to be pursued. Meanwhile, much of the work in classical input design in system identification, even that which incorporates "plant-friendly" considerations, may not result in clinically acceptable trials for human participants.

In other work presented at the SYSID 2012 conference (Deshpande et al., 2012), we examine some of the challenges associated with generating input signals for identifying dynamics in pain treatment interventions while imposing "patient-friendly" constraints on the design. The inputs that we consider are periodic in nature (allowing crossvalidation), include multiple dosage levels, and obey clinical constraints regarding the dosage changes that can be imposed (how often, and magnitude) and corresponding anticipated magnitude on the pain report outcome. Deshpande et al. (2012) describes some of the issues involved and suggest various approaches (leading ultimately to optimization-based formulations) to obtain input signals with desired spectral properties under time-domain constraints of importance to clinical practice. An example (shown in Figure 2) illustrates the proposed method with a hypothetical clinical trial of the drug gabapentin for the treatment of neuropathic pain.

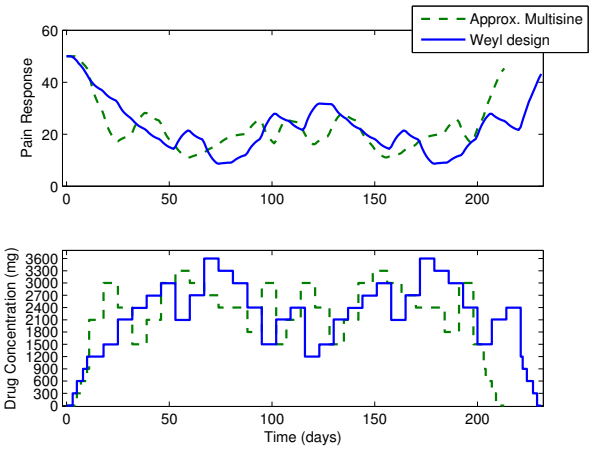

Fig. 2. Two alternative input design protocols for pain interventions constrained to weekly switching intervals ($T_{sw} = 7$), from Deshpande et al. (2012).

2.4 Use of hybrid Model Predictive Control

We use Model Predictive Control (MPC) as the algorithmic framework for making dosage assignments in an adaptive intervention. An important consideration in adaptive interventions is that intervention dosages can assume only discrete levels, and therefore it is necessary to consider hybrid algorithms ; we apply the improved algorithm for hybrid MPC developed by Nandola and Rivera (2012).

In Nandola and Rivera (2012), a Mixed Logical Dynamical (MLD) framework is used to represent linear hybrid systems which are systems with real and integer states, inputs and constraints (Bemporad and Morari, 1999):

$$x(k+1) = Ax(k) + B_1u(k) + B_2\delta(k) + B_3z(k) + B_dd(k) \quad (3)$$

$$y(k) = Cx(k) + d'(k) + \nu(k) \quad (4)$$

$$E_2\delta(k) + E_3z(k) \leq E_5 + E_4y(k) + E_1u(k) - E_dd(k) \quad (5)$$

x and u represent states and inputs of the system. y is the output and d, d' and ν represent measured disturbances, unmeasured disturbances and measurement noise signals respectively. δ and z are discrete and continuous auxiliary variables that are introduced in order to convert logical/discrete decisions into their equivalent linear inequality constraints. The effect of all unmeasured disturbances is lumped as d' in the measurement equation.

Details of the controller formulation examined in this work (both continuous and hybrid) can be found in Nandola and Rivera (2012). The controller relies on a three-degree-of-freedom (3 DoF) approach for tuning. The 3 DoF tuning methodology enables performance requirements associated with setpoint tracking, anticipated measured disturbance rejection and unmeasured disturbance rejection to be adjusted independently (Lee and Yu (1994); Wang and Rivera (2008)) 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 filter ($f(q, \alpha_i)$) as

$$f(q, \alpha_i) = \frac{(1-\alpha_i)q}{q-\alpha_i} \quad \forall \alpha_i \in [0,1), i = \{r, d\} \tag{6}$$

which supplies a *filtered* signal to the controller (for setpoint tracking (α_r) and measured disturbance rejection (α_d)) or adjust the observer gain (K_f) as

$$K_f = \begin{bmatrix} 0 & (f_a)^2 & f_a \end{bmatrix}^T \quad \forall f_a \in (0,1] \tag{7}$$

for unmeasured disturbance rejection. Hence the controller can be tuned for slower rejection of measured disturbances, e.g., by more extensive filtering of the disturbance signals.

The cost function used in this application consists of:

$$\min_{\{[u(k+i)]_{i=0}^{m-1},\, [\delta(k+i)]_{i=0}^{p-1},\, [z(k+i)]_{i=0}^{p-1}\}} J \tag{8}$$

where J, a quadratic objective,

$$J \triangleq \sum_{i=1}^{p} \|(y(k+i) - y_r)\|_{Q_y}^2 \tag{9}$$

is minimized such that mixed integer constraints of (5) hold true and:

$$y_{\min} \leq y(k+i) \leq y_{\max},\ 1 \leq i \leq p \tag{10}$$
$$u_{\min} \leq u(k+i) \leq u_{\max},\ 0 \leq i \leq m-1 \tag{11}$$
$$\Delta u_{\min} \leq \Delta u(k+i) \leq \Delta u_{\max},\ 0 \leq i \leq m-1 \tag{12}$$

p is the prediction horizon, m is the control horizon, y_r is the reference and Q_y is the penalty weight on the error.

We demonstrate the action of the hybrid MPC controller using the models from the representative participant. The continuous model from the estimated ARX Model 5 is used as the nominal model. The drug dosages $u(k)$ lie at eight levels between 0 and 13.5 mg. For comparison, we evaluate both hybrid and continuous solutions to the problem. The controller horizons are $p = 25$ and $m = 15$, $Q_y = 1$ and the sampling time is $T = 1$ day. The 3 DoF tuning parameter values are $(\alpha_r, \alpha_d, f_a) = (0.5, 0.5, 0.5)$ Closed-loop responses are shown in Fig. 3. The control system aims at performing the following three functions:

(1) *Setpoint tracking.* Drug dosages are assigned to take an outcome of interest (FM symptoms in Fig. 3) to a desired reference value or goal (40% in Fig. 3).
(2) *Measured disturbance rejection.* The controller manipulates drug dosages to mitigate the effect from *reported* external influences (anxiety in Fig. 3) relying on the estimated disturbance models.
(3) *Unmeasured disturbance rejection.* The controller manipulates drug dosages to mitigate the effect of unknown and unmodeled external influences.

In a real-life setting, participants would enter their daily diary reports to an information system which can supply endpoint values in real-time to the controller. Using the language of adaptive interventions, the *tailoring variables* are the self-reported FM symptoms (the controlled variable) and anxiety (a measured disturbance); the hybrid MPC controller *operationalizes* the decision process that assigns naltrexone over time.

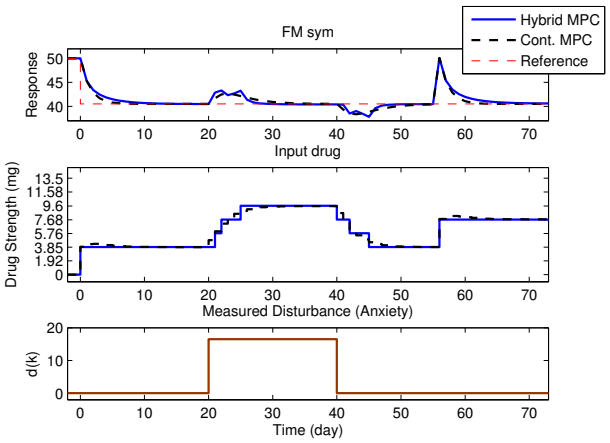

Fig. 3. Performance of hybrid MPC (eight levels) with tuning parameters $((\alpha_r, \alpha_d, f_a) = (0.5, 0.5, 0.5))$ compared to continuous MPC for models from the representative participant, fibromyalgia intervention.

3. EXAMPLE 2: EXCESSIVE GESTATIONAL WEIGHT GAIN

High pre-pregnancy body mass index (BMI) and excessive gestational weight gain (GWG) have become increasingly important public health issues. Over 60% of women of childbearing age in the United States are currently classified as overweight or obese (BMI $\geq$ 25 kg/m^2 and BMI $\geq$ 30 kg/m^2 respectively; Abrams and Rasmussen (2011)). High pre-pregnancy BMI and gaining weight in excess of the 2009 Institute of Medicine (IOM) GWG guidelines contributes to maternal complications (e.g., gestational diabetes, preeclampsia), postpartum weight retention, and subsequent obesity, type 2 diabetes, and cardiovascular disease later in life (Institute of Medicine, 2009; Fraser et al., 2011). Even more importantly, they are independent predictors of infant macrosomia, accelerated weight gain in the first year of life, and childhood obesity (Institute of Medicine, 2009; Oken et al., 2007). Thus, preventing high GWG during pregnancy can impact the etiology of obesity development for offspring at a critical time in the life cycle.

In this section, we consider a hypothetical intervention whose goal is to help pregnant women in the obese/overweight category meet recommended targets for GWG established in a 2009 IOM report. Specifically, we summarize efforts described in Dong et al. (2012) to develop a dynamical system model for a behavioral intervention for reducing excessive gestational weight gain that relies on the integration of behavioral and energy balance models. The list of intervention components for this hypothetical intervention is summarized in Table 3. The intervention components can be classified according to two types. The first consists of manipulated variables whose magnitude or "dosage" can be changed over time; examples include healthy eating (HE) and physical activity (PA) education (I_1 and I_5), HE and PA weekly plans (I_2 and I_6), HE active learning (I_3), goal setting (I_4) and PA sessions (I_7). The second type of intervention component consists of signals that are used by either the closed-loop decision rules or influence the participant's self-regulation

(described in more detail in the ensuing subsection). The intervention components include daily weighing ($I_8(y_1$ dietary records ($I_9(y_2)$), and physical activity monitori ($I_{10}(y_3)$). The role these components play as either inpu or outputs in the model are depicted in Figure 4.

Table 3. Intervention components for hypothetical GWG intervention.

	Description	Frequency
I_1	Healthy Eating Education	weekly
I_2	Healthy Eating Weekly Plan	weekly
I_3	Healthy Eating Active Learning	weekly
I_4	Goal Setting	weekly
I_5	Physical Activity Education	weekly
I_6	Physical Activity Weekly Plan	weekly
I_7	Physical Activity Sessions	bi-weekly
$I_8(y_1)$	Daily Weight Scale	daily
$I_9(y_2)$	Dietary Record	daily
$I_{10}(y_3)$	Physical Activity Monitoring	daily

The overall simulation model for GWG developed in tl paper can be divided into four main segments (Fig. a two-compartment energy balance (EB) model that pı dicts changes in body mass as a result of energy inta (EI) and physical activity (PA), two Theory of Planned Behavior (TPB) models that describe how EI and PA, respectively, are affected by behavioral variables, an intervention delivery module that relates the magnitude and duration of intervention components to the inflows of the TPB models, and two self-regulation modules that model how success expectancies during the intervention influence a participant's motivation to achieve a goal. The overall model can play a useful role in the evaluation of decision policies in an adaptive intervention or in the development of advanced control strategies, which constitutes current efforts in this research. The two-compartment energy balance model is described in Thomas et al. (2012); our focus lies then in the presentation of the Theory of Planned Behavior (TPB) and self-regulation models.

3.1 Dynamic Theory of Planned Behavior (TPB) Model

The Theory of Planned Behavior (TPB; Ajzen and Madden (1986)) is a general social-cognitive theory that can be used to describe human behavior. Figure 5 shows the path diagram for TPB which originates from the field of Structural Equation Modeling (Bollen, 1989) and depicts the steady-state relationships between variables. η_i represents endogenous variables, ξ_i exogenous variables, β_{ij} and γ_{ij} are regression weights and ζ_i are disturbance variables. In TPB, behavior η_5 is determined by intention η_4 and perceived behavioral control (PBC) η_3. Intention, meanwhile, is influenced by attitude towards the behavior η_1, subjective norms η_2 and PBC η_3. The exogenous inflow variables are expressed as follows,

$$\xi_1 = b_1 \times e_1; \quad \xi_2 = n_1 \times m_1; \quad \xi_3 = c_1 \times p_1 \tag{13}$$

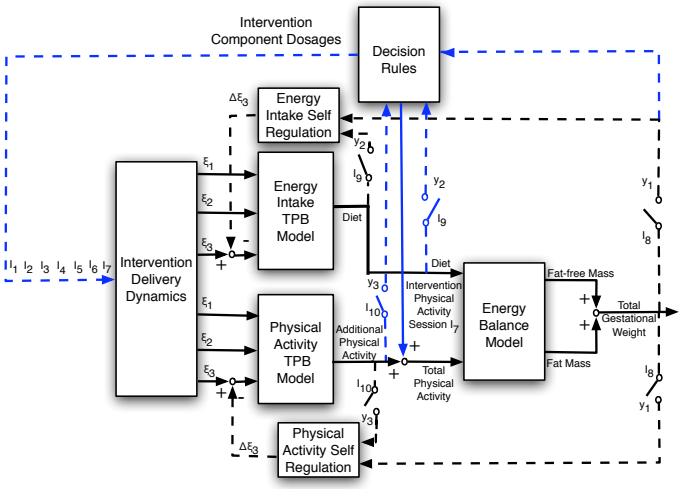

Fig. 4. Overall schematic representation for an adaptive gestational weight gain (GWG) intervention.

b_1 represents the strength of beliefs about the outcome, e_1 the evaluation of the outcome, n_1 the strength of normative beliefs, m_1 the strength of the motivation to comply to the different normative beliefs, c_1 the strength of the control belief and p_1 the perceived power of the control factor. Other efforts examining TPB in a control context includes the work of Vanderwater and Davison (2011).

A dynamic TPB model can be postulated as a fluid analogy (Navarro-Barrientos et al., 2011) in which each endogenous variable in the TPB path diagram is represented by an inventory, as depicted in Fig. 6, with inflows corresponding to the exogenous variables ξ_1, ξ_2, and ξ_3. To generate the dynamical system description, the principle of conservation of mass is applied to each inventory, from which a system of differential equations can be obtained:

$$\tau_1 \frac{d\eta_1}{dt} = \gamma_{11}\xi_1(t-\theta_1) - \eta_1(t) + \zeta_1(t) \tag{14}$$

$$\tau_2 \frac{d\eta_2}{dt} = \gamma_{22}\xi_2(t-\theta_2) - \eta_2(t) + \zeta_2(t) \tag{15}$$

$$\tau_3 \frac{d\eta_3}{dt} = \gamma_{33}\xi_3(t-\theta_3) - \eta_3(t) + \zeta_3(t) \tag{16}$$

$$\tau_4 \frac{d\eta_4}{dt} = \beta_{41}\eta_1(t-\theta_4) + \beta_{42}\eta_2(t-\theta_5) + \beta_{43}\eta_3(t-\theta_6) - \eta_4(t) + \zeta_4(t) \tag{17}$$

$$\tau_5 \frac{d\eta_5}{dt} = \beta_{54}\eta_4(t-\theta_7) + \beta_{53}\eta_3(t-\theta_8) - \eta_5(t) + \zeta_5(t) \tag{18}$$

τ_i are time constants, θ_i time delays, and ζ_i disturbances. In this dynamical representation, the regression weights β_{ij} and γ_{ij} from the structural equation model correspond to gains of the system. Higher-order derivatives with corresponding parameters can be used to enhance the model in (14) - (18) to capture underdamped responses, inverse response, and the like. For reasons of brevity these are not considered further in this paper, but are discussed in work describing weight change interventions with non-pregnant individuals (Navarro-Barrientos et al., 2011).

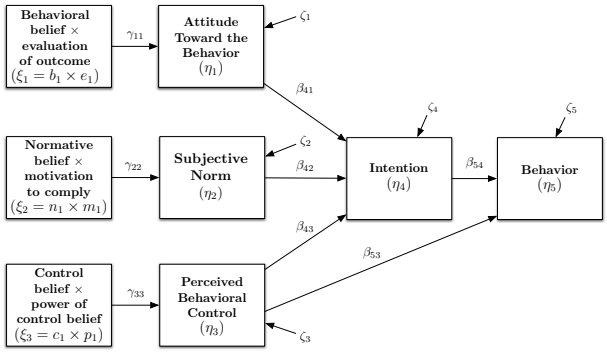

Fig. 5. Path diagram for the Theory of Planned Behavior (TPB) obtained from Structural Equation Modeling

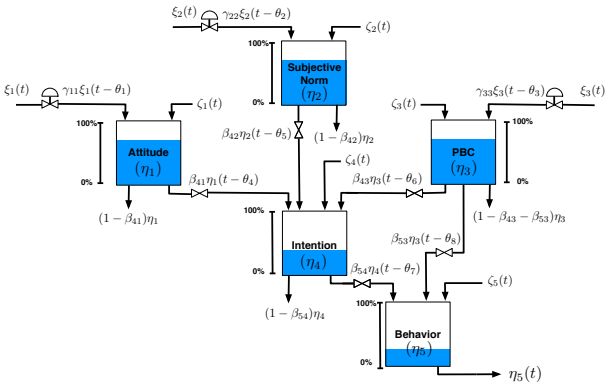

Fig. 6. Fluid Analogy for the Theory of Planned Behavior.

3.2 Self-Regulation

Self-regulation theory in psychology has been largely influenced by the work of Carver and Scheier (1998) who propose that human behavior is goal-directed and regulated by feedback control processes. A depiction of Carver and Scheier's self-regulation model as a feedback control system is shown in Figure 7. Self-regulation reflects the innate capacity of individuals to alter the behavior, enabling people to adjust actions to a broad range of social and situational demands. Individuals tend to engage in activities they believe they can succeed in; this confidence in performance success influences an individual's perceived behavioral control, which reflects the individual's perception of their ability to perform a given behavior.

Self-regulation is enabled by measurement; in the context of a weight gain intervention, the act of daily weighing, combined with information regarding will trigger a self-regulatory response. However, it is a challenge to identify the various components of the self-regulation process.

The combination of the TPB and self-regulation is shown in Figure 4. There are self-regulation loops associated with meeting dietary intake and physical activity guidelines; there are additional self-regulation loops resulting from gestational weight gain monitoring. In the general schematic representation, self-regulation influences perceived behavioral control (ξ_3) although it could affect other inflows to the TPB model. These theoretical concepts from behavioral science provide candidate model

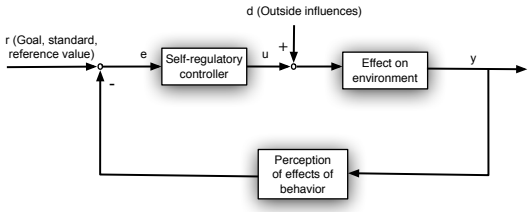

Fig. 7. Behavior and perception as elements of a feedback loop guiding human action per the self-regulation theory of Carver and Scheier (1998).

structures for parameter estimation, thus helping to define a semiphysical identification problem. Estimating the parameters of this semiphysical model from observational trials represents a challenge, leading to the need for novel and judicious experimental designs for this problem.

4. EXAMPLE 3: SMOKING CESSATION

In this section, we consider a smoking cessation intervention. Effective smoking cessation interventions are an important element to public health, as 440,000 premature deaths and $157B in economic loss is attributed to tobacco use in the U.S. annually (Killeen, 2011).

This section represents a summary of the paper by Timms et al. (2012) that is also part of the SYSID 2012 program. We consider using identification methods to construct dynamical models from secondary analysis of a smoking cessation study conducted by the University of Wisconsin's Center for Tobacco Research and Intervention (McCarthy et al., 2008b). In this trial, participants receive either bupropion SR, a nicotine antagonist (known commercially as Zyban), counseling, or their combination. 98 subjects received both bupropion and counseling as treatment (the "AC" group), 101 received only bupropion ("ANc"), 98 received a placebo and counseling ("PC"), and 99 received a placebo and no counseling ("PNc"). Bupropion becomes effective only after it has built up in an individual's system, so those receiving the active drug took 150 mg per day starting one week prior to the quit date (hereafter referred to as quit), and 300 mg daily for four days immediately prior to quit, on the quit date, and for eight weeks following quit. Subjects receiving counseling completed two pre-quit counseling sessions, one quit-date session, and five sessions over the following four weeks. Sessions focused on preparation, coping, motivation, and relapse prevention. In lieu of counseling, the ANc and PNc groups spoke with study operators about medication use adherence and encouragement (McCarthy et al., 2008b).

Among other measurements, self-reported data were collected in daily Evening Reports (ER) through personal digital assistants from two weeks prior to quit to four weeks after quit. The ER featured questions on a 10 point Likert scale covering topics such as withdrawal, positive and negative affect, and motivation Table 4 provides a selection of these items.

Timms et al. (2012) examines the relationship between *Craving* and *Cigsmked* variables, as was done in a statistical study of the same ILD by McCarthy et al. (2008a). *Craving* is defined as a sum of "Urge," "Cigonmind,"

Table 4. Continuously-measured raw evening report variables examined.

Code	SINCE LAST ER	Scale
Urge	Bothered by urges?	1-11 points
Cigonmind	Cigarettes on my mind?	1-11 points
Thinksmk	Thinking about smoking a lot?	1-11 points
Bother	Bothered by desire to smoke?	1-11 points
Cigsmked	No. of cigarettes smoked	0-99
Enthus	Enthusiastic?	1-11 points
Food	Thinking about food a lot?	1-11 points

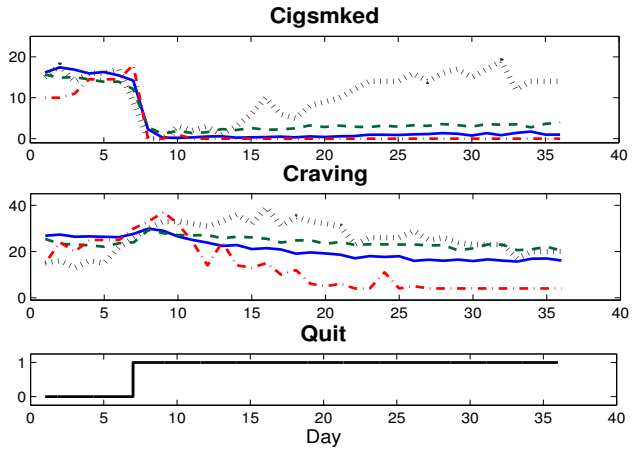

Fig. 8. Plots of two group average (solid blue, AC; dashed green, PNc) and two single subject (dash-dot red, AC; dotted brown, PNc) data sets.

"Thinksmk," and "Bother." Models are constructed for a 36 day data set: one week prior to quit, the quit date, and four weeks immediately following quit. Models are developed from both group average and single subject perspectives. For the group averages, each signal is averaged across all members in a group for the 36 days; for the single subject examples, one from the AC group and one from the PNc group, missing data was interpolated by averaging adjacent measured values or extending the adjacent measured value to the appropriate boundary; eight days of data points are imputed for the AC subject and seven for the PNc subject. Figure 8 are plots of the *Craving* and *Cigsmked* raw data for two group averages (solid blue, AC; dash-dot red, PNc) and two single subject examples (dashed green, AC; dotted brown, PNc).

As seen in Figure 8, the group average *Craving* signals feature distinct inverse response upon quit; the group average *Cigsmked* signals feature a dramatic quit-day drop, followed by a relatively small and slow resumption of smoking. The single subject data sets display greater variability. In Figure 8, the PNc single subject does not feature a net reduction in craving; the AC subject has little resumption in smoking–reflecting quit success–while the PNc subject has significant resumption and approximately reaches pre-quit smoking levels.

Dynamic models are developed in this case using classic statistical mediation models (MacKinnon, 2008) and an alternate feedback model, based on self-regulation (Carver and Scheier, 1998). The concept of statistical mediation is broadly applicable in social science and medicine, and is a prominent mechanism in behavioral science. Generally,

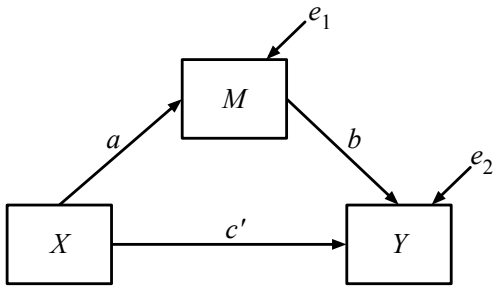

Fig. 9. Path diagram from structural equation modeling for a classic mediational model.

mediation is described by an independent variable ($X(t)$) affecting a mediator ($M(t)$) and an outcome ($Y(t)$), with $M(t)$ also contributing to $Y(t)$ (MacKinnon, 2008). In this work we adhere to a more general definition of mediation in the spirit of Collins et al. (1998). Collins et al. (1998) underscores the temporal relationship between X, M, and Y, describing mediation as a process in which a change in an independent variable results in lagged changes in the mediator and outcome. In adhering to this definition, we seek to describe the *process* of smoking behavior change, characterizing how bupropion and counseling influence the behavior change resulting from a change in an independent quit variable. In this model development, the independent variable input is a unit step occurring on the quit date, corresponding to a transition from not attempting to quit smoking to attempting to quit (which we refer to as *Quit*); *Craving* and *Cigsmked* are treated as the mediator and outcome (M and Y), respectively.

The path diagram for mediation is depicted in Figure 9: a, b, and c' variables represent gains from X to M, M to Y, and X to Y pathways, respectively (MacKinnon, 2008). As illustrated in the previous section, Navarro-Barrientos et al. (2011) established how path diagrams in structural equation modeling (SEM) correspond to steady-state process models; from these, a fluid analogy can be constructed which leads to a dynamical system amenable to estimation via system identification techniques. Figure 10 depicts the fluid analogy for mediation, where each pathway in Figure 9 is represented by an inventory. Figure 11 depicts classic mediation in block diagram form where $P_a(s)$, $P_b(s)$, and $P_{c'}(s)$ are the transfer functions for the independent variable to mediator, mediator to outcome, and independent variable to outcome pathways, respectively. d_1 and d_2 are mediator and outcome disturbances, and Y_I and Y_D are the contributions of the mediated and direct pathways to the outcome, respectively. From these fluid analogies, dynamic models can be developed and parameter estimation methods from system identification can be fit to the intervention data.

An alternate representation of the smoking process is based on the Nicotine Regulation Model (NRM) (Velicer et al., 1992; Walls and Rivera, 2009) which is conceptually derived from self-regulation. These models suggest a blood nicotine concentration or *Urge* set point is regulated by smoking, which itself is influenced by environmental factors and/or emotional states. This model, depicted in block diagram form in Figure 12, describes a feedback loop in which a controller, $C(s)$, responds to the deviation, e,

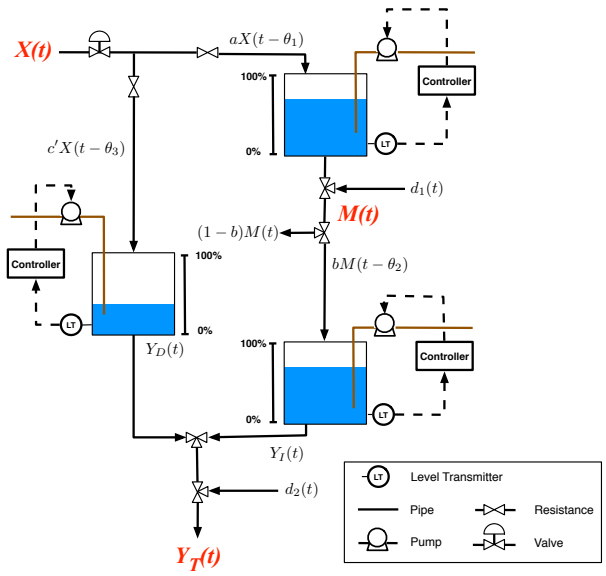

Fig. 10. Fluid analogy for a mediated behavioral intervention. In the smoking cessation intervention, X is the quit attempt, M represents craving, and Y_i, $i = D, T$ represents cigarettes smoked.

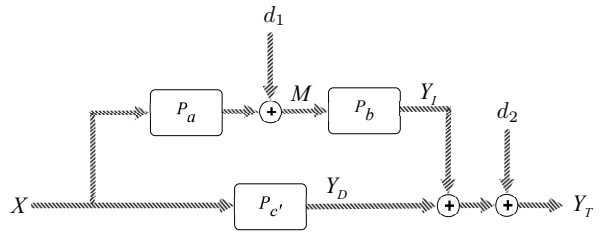

Fig. 11. Block diagram for a mediational model structure.

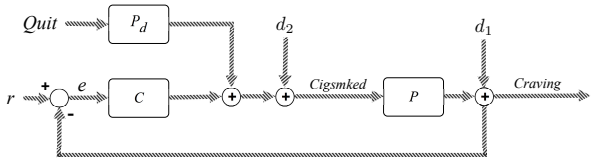

Fig. 12. Block diagram depicting a self-regulation model for smoking behavior.

between a craving set point, r, and the actual measured craving signal ($Craving$); the smoking behavior signal ($Cigsmked$) is a sum of the outputs from the controller and the intervention step, $P_d(s)$; $Cigsmked$ then acts as an input for $P(s)$, producing $Craving$. As shown in Timms et al. (2012), truncated series expansions of the closed-loop transfer functions from self-regulation model can be shown to correspond to a mediation model structure, indicating a fundamental relationship between these two theoretical constructs. We can estimate continuous-time linear models from the data shown in Figure 8 utilizing Matlab's *idproc* command; as described in Timms et al. (2012), identification results show that relatively simple and low order transfer functions accurately capture the observed dynamics.

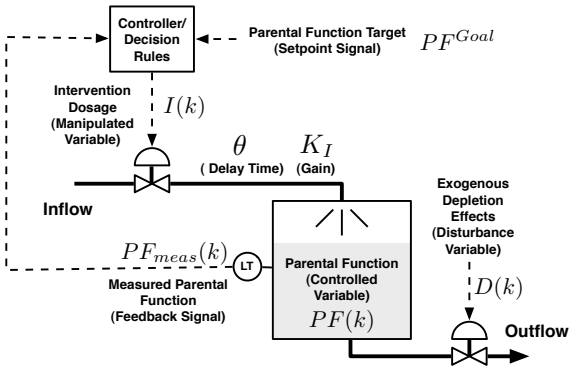

Fig. 13. Fluid analogy corresponding to a hypothetical preventive adaptive intervention inspired by the *Fast Track* program, a preventive intervention for conduct disorder in at-risk children.

5. EXAMPLE 4: AN ADAPTIVE PREVENTIVE INTERVENTION

Our final example is based on the simulation of a time-varying adaptive behavioral intervention inspired by the *Fast Track* program (Conduct Problems Prev. Res. Group, 1992). *Fast Track* was a multi-year, multi-component program designed to prevent conduct disorders in at-risk children. Youth showing conduct disorder are at increased risk for incarceration, injury, depression, substance abuse, and death by homicide or suicide. In *Fast Track*, some intervention components were delivered universally to all participants, while other specialized components were delivered adaptively. In this section we focus on a slightly modified version of the hypothetical adaptive intervention described in Collins et al. (2004) for assigning family counseling, which was provided to families on the basis of parental functioning. There are several possible levels of intensity, or doses, of family counseling. The idea is to vary the doses of family counseling depending on the needs of the family, in order to avoid providing an insufficient amount of counseling for very troubled families, or wasting counseling resources on families that may not need them or be stigmatized by excessive counseling. The decision about which dose of counseling to offer each family is based primarily on the family's level of functioning, assessed by a family functioning questionnaire completed by the parents. Family functioning is reassessed at monthly intervals, at which time the intervention dosage may change. This goes on for four years with 48 opportunities for a dose of family counseling to be assigned.

Rivera et al. (2007) analyzed the intervention by means of a fluid analogy, represented in Figure 13. Parental function $PF(k)$ is treated as fluid in a tank, which is depleted by exogenous disturbances $D(k)$. The tank is replenished by the intervention $I(k)$, which is the manipulated variable. The use of fluid analogy enables developing a mathematical model of the open-loop dynamics of the intervention using the principle of conservation of mass. This model can be described by nonlinear difference equations which relates parental function $PF(k)$ with the intervention $I(k)$ as follows:

$$PF(k+T) = PF(k) + K_I(k)I(k-\theta) - D(k) \qquad (19)$$

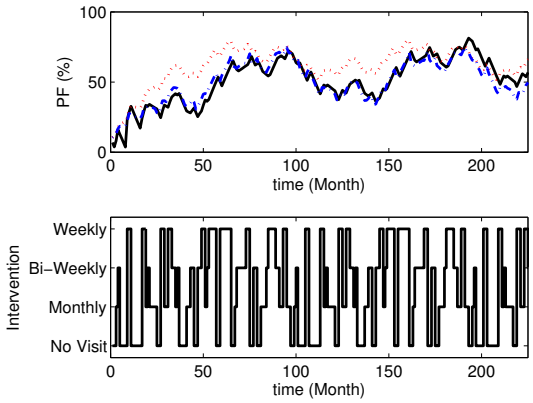

Fig. 14. Comparison with open-loop simulation using MoD model (dashed line) and linear ARX model (dotted line) with nonlinear systems (solid line).

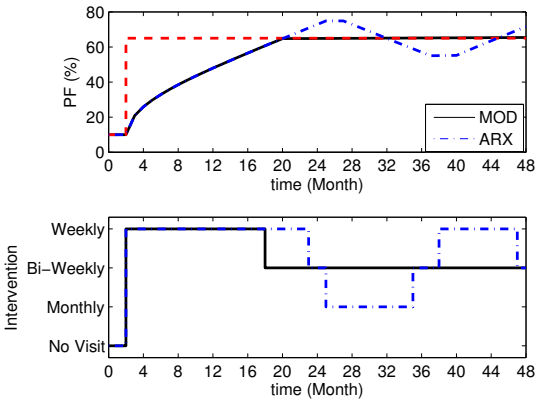

Fig. 15. Comparison of controller performance using the proposed MoD-MPC formulation (solid line) and the MPC formulation relying on linear ARX model (dashed-dotted line). A setpoint change from 10% to 65% parental function with simultaneous step disturbance $D(k) = 4$ are evaluated with tuning parameter $Q_y = 1$, $Q_{\Delta u} = 0.1$, $Q_u = Q_d = Q_z = 0$, $(\alpha_r,\ f_a) = (0,\ 0.3)$, $p = 40$ and $m = 10$.

$$D(k) = \sum_{i=1}^{n_d} D_i(k) \tag{20}$$

$$PF_{meas}(k) = PF(k) + N(k) \tag{21}$$

$PF(k)$ is parental function, $I(k)$ refers to the intervention dosage (frequency of counselor home visits), $K_I(k)$ is the time-varying intervention gain, T represent the review period or sampling time (=1 month), $\theta(k)$ represents the time-varying time delay between intervention and its effect on parental function, $PF_{meas}(k)$ is the parental function measurement. $D(k)$ is the source of parental function depletion and $N(k)$ represents the measurement noise. Here we consider both nonlinear gain and delay relationships. The gain, K_I varies with parental function $PF(k)$ as follows,

$$K_I(k) = be^{-aPF(k)} + c \tag{22}$$

where $c = K_{max} - b$ and $b = \frac{(K_{min} - K_{max})}{(e^{-a}-1)}$. The delay θ varies with parental function $PF(k)$ per the following rules:

$$\theta = \begin{cases} 0; & 0 \le PF(k) \le 25 \\ 1; & 25 < PF(k) \le 50 \\ 2; & 50 < PF(k) \le 75 \\ 3; & 75 < PF(k) \le 100 \end{cases} \tag{23}$$

Moreover, the intervention $I(k)$ has a restriction on the frequency of counselor visits, which requires imposing a restriction on the intervention $I(k)$ such that it takes only four values: 0, I^{weekly}, $I^{biweekly}$ and $I^{monthly}$. Hence the problem has inherent discreteness that can be classified as non-autonomous (deterministic) discrete events in addition to the continuous dynamics. Thus, system can be characterized by the nonlinear hybrid dynamical system.

We consider the application of Model-on-Demand (MoD) and Model-on-Demand MPC (MoD-MPC) in this problem setting (Stenman, 1999; Braun, 2001; Braun et al., 2001). We summarize the results shown in Nandola and Rivera (2010), who present a hybrid controller extension to the problem. Model-on-Demand estimation is appealing because of its data-centric nature, in which a local linear model conforming to a user-specified ARX structure is obtained "on demand" based from a database of measurements. The MoD modeling formulation applied for a SISO process follows the approach of Braun et al. (2001). We consider the case shown in Nandola and Rivera (2010) for parameters $K_{max} = 0.3$, $K_{min} = 0.06$, and $a = 10$. The database for MoD estimation can be seen in Figure 14; it corresponds to a multi-level pseudo-random input applied to the nonlinear model structure previously described. We note that, while informative, this input design sequence is likely not to be acceptable in a clinical setting, which motivates additional research on the problem (per the patient-friendly concept described in Deshpande et al. (2012)). In the case study an implicit NARX structure with $[n_a = 2,\ n_b = 2,\ n_k = 1]$ is used in the MoD estimator. A first order local polynomial and database size limit [50 240] is used as additional parameters. This local model is then converted into its equivalent state-space form. In order to capture deterministic discrete events in the intervention, four binary auxiliary variables and four continuous auxiliary variables are introduced to obtain an equivalent MLD model per (3)-(5). This model is generated adaptively (i.e., "on demand") at each time step and used to formulate the MPC problem.

Figure 14 compares the open-loop simulation results using the MoD approach (dashed line) with the open-loop simulation from the actual nonlinear system (19)-(23) (solid line). It can be seen that the MoD approach satisfactorily estimates the dynamic behavior of the system with root mean square (RMS) error 5.62. On the other hand, the simulation result from the linear ARX model using the same model structure as the MoD model (denoted by dotted line in Fig. 14), yields a poor estimation result with RMS error value of 13.68. Figure 15 documents the MPC performance using the MoD approach (solid line) with the linear ARX model approach (dashed-dotted line) in the presence of a setpoint change in parental function to 65% and a simultaneous step unmeasured disturbance $D(k) = 4$. In both the cases, the same MPC tuning parameters are used. From the figure it can be seen that the controller designed using the MoD approach is able

to quickly achieve the desired setpoint, and stabilizes the system at the setpoint. In contrast, the controller relying on the fixed linear ARX model oscillates substantially. Finally, the hybrid MoD-MPC controller achieves less variation in the dosages and displays uniform performance.

6. SUMMARY AND CONCLUSIONS

This paper has presented a series of issues and examples from behavioral health that have illustrated how techniques from system identification and control engineering can be useful for better understanding and ultimately optimizing the performance of behavioral interventions through a time-varying adaptive framework. Some challenges that were noted in working with these problems:

(1) *Difficulties in a priori classifying signals as inputs and/or outputs, and challenges introduced by the lack of validation data in conventional clinical trials.* Secondary analysis of data from trials not designed for identification purposes can be useful initially, but poses many limitations. While behavioral concepts like the Theory of Planned Behavior and self-regulation can provide insights into the relationship between signals and model structure, ultimately it becomes important to rely on careful experimental design to better understand this problem.

(2) *Limitations associated with implementing system-identification oriented-protocols on human subjects.* Behavioral interventions bring a new dimension to the problem of "plant-friendly" input design (Rivera et al., 2009) to one involving "patient-friendly" considerations; this includes liimitations on test duration and variation in the input and output signals that will restrict the information content in the data. Making an assumption of ergodicity, some of these restrictions could be compensated by averaging over multiple participants in a trial (the nomothetic approach); this was the case in the analysis of the smoking cessation intervention. However, behavioral researchers such as Molenaar and Campbell (2009) have indicated that ergodicity may not represent a valid assumption in behavioral settings, and have stressed the need for single subject designs (the idiographic approach). In practice, a combination of both nomothetic and idiographic approaches should be pursued.

(3) *"Patient-friendly" formulations of data-centric Model Predictive Control are needed.* We were able to show that hybrid MPC is essential for this class of problems, and improved formulations such the ones developed by Nandola and Rivera (2010) are useful. The data-centric Model-on-Demand formulation of Nandola and Rivera (2012) shows promise, but (again) demands judicious experimental designs in order to be implemented in practice.

In conclusion, it is hoped that this paper will encourage additional activities from the system identification and control community in this problem, and that advances in topics such as optimal experimental design for identification, identification of alternate model structures such as linear parameter-varying (LPV) models, and efforts to improve and robustify model predictive control will have increasing impact in this important application area.

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REFERENCES

B. M. Abrams and K. Rasmussen. GWG and later maternal health: are they related. *Am J Clin Nutr*, 93: 1186–1187, 2011.

I. Ajzen and T.J. Madden. Prediction of goal-directed behavior: attitudes, intentions, and perceived behavioral control. *Journal of Experimental Social Psychology*, 22: 453–474, 1986.

Alberto Bemporad and Manfred Morari. Control of systems integrating logic, dynamics, and constraints. *Automatica*, 35:407–427, 1999.

K.A. Bollen. *Structural Equations with Latent Variables*. Wiley Series in Probability and Mathematical Statistics. John Wiley and Sons, New York, 1989.

M. W. Braun. *Model-on-demand nonlinear estimation and model predictive control: Novel methodologies for process control and supply chain management*. PhD thesis, Arizona State University, USA, 2001.

M. W. Braun, D. E. Rivera, and A. Stenman. A model-on-demand identification methodology for nonlinear process systems. *Int. J. Control*, 74(18):1708 – 1717, 2001.

C. S. Carver and M. F. Scheier. *On the Self-Regulation of Behavior*. Cambridge University Press, 1998.

L. M. Collins, S. A. Murphy, and K. L. Bierman. A conceptual framework for adaptive preventive interventions. *Prevention Science*, 5(3):185–196, 2004.

L.M. Collins. Unpacking the black box: engineering more potent behavioral interventions to improve public health. Evan G. and Helen G. Pattishall Outstanding

Research Achievement Award lecture presented at Penn State University, State College, PA on March 20, 2012.

L.M. Collins, J.W. Graham, and B.P. Flaherty. An alternative framework for defining mediation. *Multivariate Behavioral Research*, 33(2):295–312, 1998.

S. Deshpande, N.N. Nandola, D.E. Rivera, and J. Younger. Control engineering approach for designing an optimized treatment plan for fibromyalgia. *American Control Conference*, pages 4798–4803, 2011.

S. Deshpande, D. E. Rivera, and J. Younger. Towards patient-friendly input signal design for optimized pain treatment interventions. In *Proceedings of the 16th IFAC Symposium on System Identification (SYSID 2012)*, Brussels, Belgium, July 2012.

Sunil Deshpande. A control engineering approach for designing an optimized treatment plan for fibromyalgia. Master's thesis, Arizona State University, 2011.

Y. Dong, D. E. Rivera, D. M. Thomas, J. E. Navarro-Barrientos, D. S. Downs, J. S. Savage, and L. M. Collins. A dynamical systems model for improving gestational weight gain behavioral interventions. In *Proc. of the 2012 American Control Conf.*, Montreal, June 2012.

A. Fraser, K. Tilling, C. Macdonald-Wallis, R. Hughes, N. Sattar, S. M. Nelson, and Debbie. A. Lawlor. Associations of GWG with maternal body mass index, waist circumference, and blood pressure measured 16 y after pregnancy. *Am J Clin Nutr*, 93:1285–1292, 2011.

P.R. Killeen. Markov model of smoking cessation. *PNAS*, 108 Supplement 3(37):15549–15556, 2011.

J. H. Lee and Z. H. Yu. Tuning of model predictive controllers for robust performance. *Comput. Chem. Eng.*, 18(1):15 – 37, 1994. ISSN 0098-1354.

D. MacKinnon. *Introduction to Statistical Mediation Analysis*. Routledge Academic, 2008.

T. M. Mattiloi, B. Milne, and C.M. Cahill. Ultra-low dose naltrexone attenuates chronic morphine-induced gliosis in rats. *Molecular Pain*, 6(22):1–11, 2010.

Conduct Problems Prev. Res. Group. A developmental and clinical model for the prevention of conduct disorders: The *Fast Track* program. *Development and Psychopathology*, 4:509–528, 1992.

Institute of Medicine. *Weight gain during pregnancy: reexamining the guidelines*. National Research Council, The National Academies Press, Washington, DC, 2009.

D.E. McCarthy, T.M. Piasecki, D.L. Lawrence, D.E. Jorenby, S. Shiffman, and T.B. Baker. Psychological mediators of bupropion sustained-release treatment for smoking cessation. *Addiction*, 103(9):1521–1533, 2008a.

D.E. McCarthy, T.M. Piasecki, D.L. Lawrence, D.E. Jorenby, S. Shiffman, M.C. Fiore, and T.B. Baker. A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. *Nicotine and Tobacco Research*, 10(4):717–729, 2008b.

P.C.M. Molenaar and C.G. Campbell. The new person-specific paradigm in psychology. *Current Directions in Psychology*, 18(2):112–117, 2009.

N. N. Nandola and D. E. Rivera. Model-on-demand predictive control for nonlinear hybrid systems with application to adaptive behavioral interventions. In *49th IEEE Conference on Decision and Control*, pages 6113–6118, Atlanta, Georgia, December 2010.

N. N. Nandola and D. E. Rivera. An improved formulation of hybrid model predictive control with application to production-inventory systems. *IEEE Trans. Control Systems Tech.*, 2012. early access.

J. E. Navarro-Barrientos, D. E. Rivera, and L. M. Collins. A dynamical model for describing behavioural interventions for weight and body composition change. *Mathematical and Computer Modelling of Dynamical Systems*, 17(2):183–203, April 2011.

E. Oken, E. Taveras, K. Kleinman, J. W. Rich-Edwards, and M. W. Gillman. Gestational weight gain and child adiposity at age 3 years. *Am J Obst Gynecol*, 196:322.e1–8, 2007.

W. T. Riley, D. E. Rivera, A. A. Atienza, W. Nilsen, S. M. Allison, and R. Mermelstein. Health behavior models in the age of mobile interventions: are our theories up to the task? *Translational Behavioral Medicine*, 1(1):53–71, March 2011.

D.E. Rivera, M.D. Pew, and L.M. Collins. Using engineering control principles to inform the design of adaptive interventions: A conceptual introduction. *Drug and Alcohol Dependence*, 88(Supplement 2):S31–S40, 2007.

D.E. Rivera, H. Lee, H.D. Mittelmann, and M.W. Braun. Constrained multisine input signals for plant-friendly identification of chemical process systems. *Journal of Process Control*, 19(4):623–635, 2009.

S. Shiffman, A. A. Stone, and M. R. Hufford. Ecological momentary assessment. *Annual Reviews in Clinical Psychology*, 18(4):1–32, 2008.

A. Stenman. *Model-on-demand: Algorithms, analysis and applications*. PhD thesis, Linköping University, Sweden, 1999.

D. M. Thomas, J. E. Navarro-Barrientos, D. E. Rivera, S. B. Heymsfield, C. Bredlau, L. M. Redman, C. K. Martin, S. A. Lederman, L. M. Collins, and N. F. Butte. A dynamic energy balance model predicting gestational weight gain. *Am J Clin Nutr*, 95:115–122, 2012.

K. P. Timms, D. E. Rivera, L. M. Collins, and M. E. Piper. System identification modelingof a smoking cessation intervention. In *Proceedings of the 16th IFAC Symposium on System Identification (SYSID 2012)*, Brussels, Belgium, July 2012.

R. Vanderwater and D. E. Davison. Using rewards to change a person's behavior: a double-integrator output-feedback dynamic control approach. In *Proceedings of the 2011 ACC*, pages 1861–1866, 2011.

W.F. Velicer, C.A. Redding, R.L. Richmond, J. Greeley, and W. Swift. A time series investigation of three nicotine regulation models. *Addictive Behaviors*, 17(4): 325–345, 1992.

T.A. Walls and D.E. Rivera. Control engineering-based approaches to modeling substance abuse data. Washington, D.C., May 2009. 17th Annual Meeting of the Society for Prevention Research.

T.A. Walls and J.L. Schafer, editors. *Models for Intensive Longitudinal Data*. Oxford University Press, USA, 2006.

W. Wang and D.E. Rivera. Model predictive control for tactical decision-making in semiconductor manufacturing supply chain management. *IEEE Trans. on Control Systems Tech.*, 16(5):841 –855, Sep. 2008.

J. Younger and S. Mackey. Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. *Pain Medicine*, 10(4):663–672, 2009.