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System Identification Modeling of a Smoking Cessation Intervention

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Abstract:
This paper examines the use of system identification to describe time-varying phenomena in a smoking cessation intervention. The analysis is facilitated by the availability of intensive longitudinal data that enables the application of system identification techniques. Two model structures are considered; one involves the concept of statistical mediation, while the other describes a feedback mechanism. In fitting these models to intensive longitudinal data from a University of Wisconsin clinical trial that studied bupropion and counseling as smoking cessation aids, we focus on the relationship between craving and smoking. Here, we find craving features inverse response and smoking behavior features a dramatic reduction on the quit date, followed by a resumption in smoking. Analyzing the resulting models, we find that they differ in how they describe smoking *resumption*, and the case is made that the feedback mechanism more appropriately describes the relationship between craving and smoking.

Keywords: system identification; social and behavioral sciences; statistical mediation; smoking cessation

1. INTRODUCTION

Behavioral interventions seek to reduce unhealthy behaviors and promote healthy ones through prevention or treatment. Behavioral interventions play an important role in addressing public health concerns such as substance abuse, obesity, sexually transmitted infections, and cancer screening and can be pharmacological or behavioral in nature [Rivera et al., 2007]. Traditionally, these interventions 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 dosage and type of treatment varies according to participant response [Collins et al., 2004]. These interventions can be cast as closed-loop dynamical systems [Rivera et al., 2007].

The rise of mobile and computerized technologies has led to increased access to intensive longitudinal data (ILD), which is loosely defined as quantitative or qualitative measurements recorded at "more than a handful of time points [Walls and Schafer, 2006]," and is often collected via ecological momentary assessment–a variety of methodologies collecting data on a subject's current state over multiple time instances in real-world environments, [Riley et al., 2011, Collins, 2006]. With the rise in availability of ILD comes the opportunity to study an intervention's time-varying effect on behavior change. ILD is used in analysis of the shape, periodicity, and time-dependency (e.g. absolute time-scale versus pubertal time-scale) of an intervention's response; ILD's most significant potential lies in improved analysis of inter- and intra-individual variability [Collins, 2006].

Traditionally, structural equation models (SEM) have been used to statically model relationships in interventions, but the dynamic relationships featured in adaptive interventions and captured in ILD can be described more comprehensively using a dynamical systems modeling approach [Bollen, 1989, Rivera et al., 2007]. Recently, such models have been used for improved evaluation of gestational weight gain and fibromyalgia interventions; these models can potentially be used in conjunction with control theory to optimize time-varying adaptive interventions [Navarro-Barrientos et al., 2011, Rivera et al., 2007, Deshpande et al., 2011]. In this paper, we model the smoking cessation process. An improved ability to inform and evaluate behavioral health interventions warrants construction

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of dynamic models of smoking cessation, as 440,000 premature deaths and $157B in economic loss is attributed to tobacco use in the U.S. annually [Killeen, 2011].

This paper is organized as follows. First, a study of the antidepressant bupropion SR and counseling as aids to smoking cessation, conducted at the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) and funded by the Transdisciplinary Tobacco Use Research Centers (TTURC), is outlined [McCarthy et al., 2008b]. Next, the process of smoking cessation is described in terms of two system identification problems: models for classic mediation are applied to ILD, followed by development and examination of a feedback model. Finally, conclusions and recommendations are briefly presented.

2. SMOKING CESSATION INTERVENTION

Dynamic models are constructed for secondary analysis of a TTURC-funded UW-CTRI study. In this experiment, 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. Although the exact mechanism that makes it an effective smoking cessation therapy is debated, bupropion SR (Zyban SR) acts as a nicotine antagonist, and appears to reduce short- and long-term withdrawal and craving in abstaining smokers [McCarthy et al., 2008a]. 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. Instead 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 1 provides a selection of these items) [McCarthy et al., 2008b].

Table 1. 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

The relationship between *Craving* and *Cigsmked* variables is examined in this paper, 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," "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 1 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).

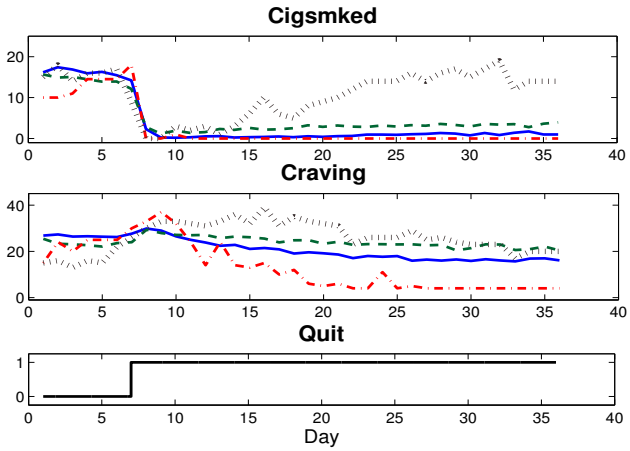

Fig. 1. Plots of two group average (solid blue, AC; dashed green, PNc) and two single subject (dash-dot red, AC; dotted brown, PNc) data sets.

As seen in Figure 1, 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 1, 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.

Both treatment condition average (nomothetic) and single subject (idiographic) analysis are of interest [Molenaar and Campbell, 2009]. Dynamic models are developed for each data set according to a classic mediation model and an alternate feedback model, based on behavioral science concepts. This discussion follows.

3. DYNAMICAL STATISTICAL MEDIATION MODELING

The concept of statistical mediation is broadly applicable in social science and medicine, and is a prominent mechanism in behavioral science. Generally, 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 that is

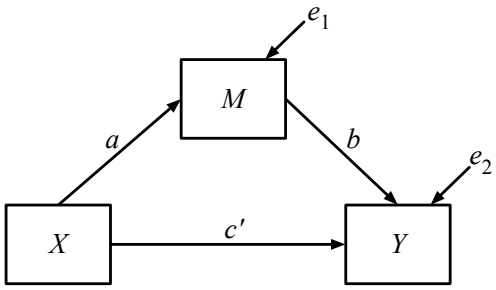

Fig. 2. Path diagram, used in structural equation modeling (SEM) to describe the relationship between variables, for a classic mediational model.

similar to that in 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 [Collins et al., 1998]. 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, respectively.

Behavioral scientists use path diagrams to depict this type of process [MacKinnon, 2008, Bollen, 1989]. A mediational model is depicted in Figure 2: a, b, and c' variables represent gains from X to M, M to Y, and X to Y pathways, respectively [MacKinnon, 2008]. SEM representations of mediation are found in Equations 1 and 2.

$$M = \beta_{0_1} + a\ X + e_1 \tag{1}$$

$$Y = \beta_{0_2} + c'\ X + b\ M + e_2 \tag{2}$$

Prior work [Navarro-Barrientos et al., 2011] established how path diagrams in 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. Drawing from techniques used in production inventory management in supply chains, fluid analogies are used to describe the effect of an intervention on behavior change according to a well-defined behavioral model (which may or may not be represented in SEM form) [Schwartz et al., 2005, Navarro-Barrientos et al., 2011]. These behavioral science models describe structural relationships between variables and the mechanism by which an intervention improves health behaviors [MacKinnon, 2008]. From these fluid analogies, dynamic models can be developed and fit to ILD.

Figure 3 depicts mediation in a fluid analogy, where each pathway in Figure 2 is represented by an inventory. Figure 4 depicts classic mediation in block diagram form where $P_a(s)$, $P_b(s)$, and $P_{c'}(s)$ are the transfer functions–in this case, low order 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

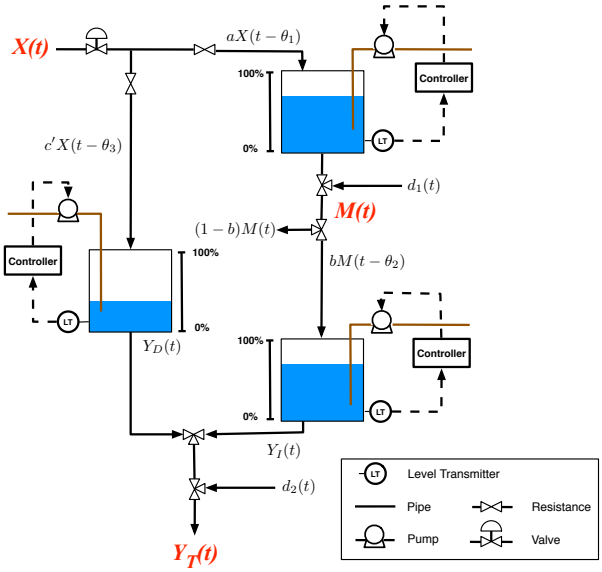

Fig. 3. Fluid analogy for a mediated behavioral intervention developed from production inventory management models in supply chains.

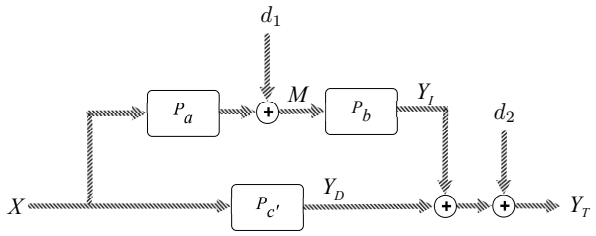

Fig. 4. Block diagram of a classic mediation structure.

and Y_D are the contributions of the mediated and direct pathways to the outcome, respectively. Figure 4 highlights mediation's parallel-cascade nature. Equations 3 and 4 are the corresponding Laplace domain models.

$$M(s) = P_a(s)X(s) + d_1(s) \tag{3}$$

$$Y(s) = P_{c'}(s)\ X(s) + P_b(s)\ M(s) + d_2(s) \tag{4}$$

In fitting the models to the clinical trial data, we use a prediction-error approach to estimate continuous-time linear models from sampled data [Ljung, 2009]. In this approach, we utilize Matlab's *idproc* command; preliminary analysis of these data indicated relatively simple and low order transfer functions accurately capture the observed dynamics. A flexible GUI was built for examination of model structure adequacy and candidate structural and signal relationships. Model predictive ability is evaluated on a 0 to 100% scale and is calculated as:

$$Fit\ [\%] = 100\left(1 - \frac{||y(t) - \tilde{y}(t)||_2}{||y(t) - \bar{y}||_2}\right) \tag{5}$$

where $y(t)$ is the data to which the model is fit, $\tilde{y}(t)$ is the simulated output, and $\bar{y}$ is the average of all y values. In parameter estimation of the group average and single subject models, each candidate transfer function structure and signal relationship was assessed for predictive ability, concern for parsimony, and model realizability.

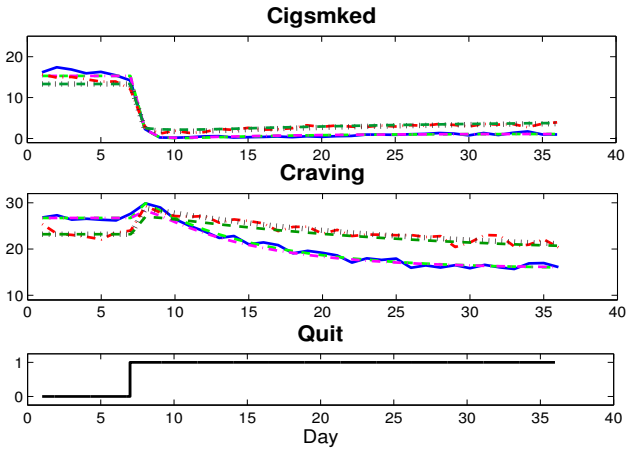

Fig. 5. *Craving* and *Cigsmked* data and models for AC and PNc group averages (solid blue, AC data; dashed light green, AC mediation model; dash-dot magenta, AC feedback model; dash-dot red, PNc data; dotted brown, PNc mediation model; dashed dark green, PNc feedback model).

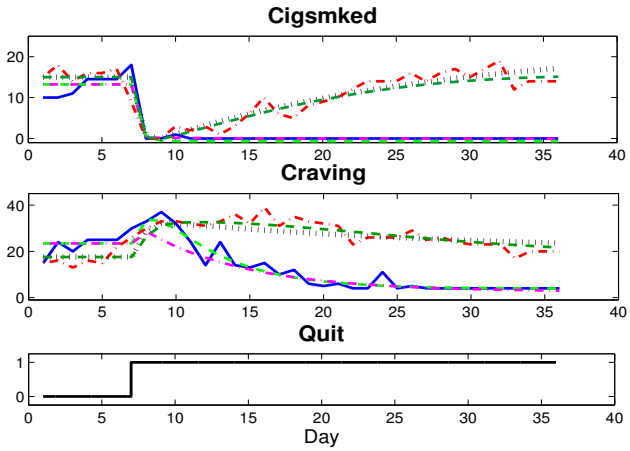

Fig. 6. *Craving* and *Cigsmked* data and models for AC and PNc single subject examples (solid blue, AC data; dashed light green, AC mediation model; dash-dot magenta, AC feedback model; dash-dot red, PNc data; dotted brown, PNc mediation model; dashed dark green, PNc feedback model).

For parameter estimation in the classic mediational model, a single day is set as the sampling time; P_a parameter estimates are found by defining a single-input single-output (SISO) system where quitting is the input and *Craving* the output; P_b and $P_{c'}$ parameter estimates are found by defining a multiple-input single-output (MISO) problem, where the mediator and *Quit* signals are the inputs and *Cigsmked* the output.

Table 2 contains the parameter estimates, settling times (in days), and goodness-of-fits for the mediated structure; ILD and model outputs are shown in Figures 5 and 6. The following transfer function structures were found to adequately describe the signals:

$$P_a(s) = \frac{a\,(\tau_{a_1} s + 1)}{(\tau_1 s + 1)\,(\tau_2 s + 1)} \tag{6}$$

$$P_b(s) = \frac{b}{(\tau_3 s + 1)} \tag{7}$$

$$P_{c'}(s) = \frac{c'}{(\tau_5 s + 1)} \tag{8}$$

The models feature high fit percentages for the group averages. Use of low-order transfer functions suggests the good fits are not the result of over-parameterizing. The high signal-to-noise ratios of the group average data sets is conducive to such good fits, regardless of the different structures. The lower mediator fit value for the PNc condition supports this assertion, as this measured craving signal appears to have a lower signal-to-noise ratio than its counterparts. As indicated by the negative system zeroes, the group average craving signals feature pronounced inverse response; the net decrease in *Craving* is greatest in the AC group, smallest in the PNc, and follows a logical relationship to treatment condition (a is -11.20 for AC, -8.85 for ANc, -7.17 for PC, and -5.05 for PNc). For the group average *Cigsmked* models, there is a dramatic quit-date drop in smoking followed by a relatively small and slow resumption. The magnitude of the initial drop, c', is largest for the AC treatment, -15.50, and follows a logical relationship to the treatment condition. The settling times (in days) for both the craving and cigsmked signals are comparable for each of the four cohorts, taking almost the entire ILD-gathering protocol to settle.

Table 2. Mediation model parameter estimates and goodness-of-fits.

Treatment	AC	ANc	PC	PNc	AC	PNc
Data Set	Avg	Avg	Avg	Avg	Sgl	Sgl
Med.						
Fit [%]	87.70	79.02	77.72	53.16	70.84	43.32
Out.						
Fit [%]	91.70	86.09	91.12	87.34	77.09	52.51
ab	0.98	1.96	1.48	1.11	-0.2	14.9
$ab + c'$	-14.55	-12.91	-11.94	-10.72	-13.3	-1.4
Med.						
Set. T.	35.69	35.91	35.82	35.90	26.34	33.87
Out.						
Set. T.	34.56	35.26	35.60	35.29	10.64	33.86
a	-11.20	-8.85	-7.17	-5.05	-19.61	2.64
τ_{a_1}	-3.20	-5.32	-15.40	-20.25	-5.02	123.48
τ_1	7.70	11.02	18.29	17.04	4.64	0.86
τ_2	0.30	0.15	0.17	0.00	1.02	20.41
b	-0.10	-0.22	-0.21	-0.22	0.01	5.65
τ_3	1.10	3.29	0.41	0.63	0.74	82.64
c'	-15.50	-14.87	-13.42	-11.83	-13.06	-16.36
τ_5	0.50	0.24	0.36	0.08	0.00	0.41

In the mediational model, the dramatic quit-date smoking reduction is modeled by the c' pathway while the resumption is modeled by the mediated pathway. Comparing ab values, the mediated pathway gains, and $ab + c'$ values, the net gains, we see that the mediated pathway's contribution to the net effect is consistently small for the group averages. The mediated pathways' *relative* contribution to the outcome, however, does not follow the previously described intuitive relationship to treatment; the mediated pathway's contribution to the outcome is 6.3% for the AC group, 13.2% for ANc, 11.0% for PC, and 9.4% for PNc. The speed of resumption of smoking also does not strictly adhere to this intuitive relationship: the ANc group features the largest τ_3 and the PC group has the smallest.

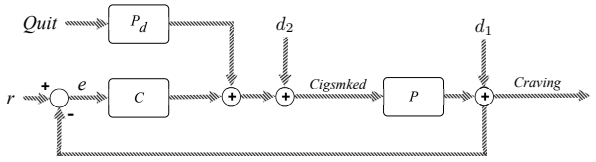

Fig. 7. Block diagram depicting a smoking cessation feedback model relating *Craving* and *Cigsmked*.

For the single subject examples, the models are generally less accurate. This can be attributed to greater variance in the single subject data; single subject data quality issues pose a challenge in developing reliable idiographic models in general. From the PNc single subject model, τ_{a_1} is positive, as is a, indicating this subject departs from the trend seen in the group averages. Similarly, the AC single subject appears to successfully quit shortly after the quit-date, as indicated by the short mediator and outcome settling times and small ab (-0.2, and the mediated pathway has only a 1.5% contribution to the outcome).

4. FEEDBACK MODEL

One of the proposed uses for ILD is to describe self-regulatory phenomena in behavioral interventions [Collins, 2006]. This is incorporated into the Nicotine Regulation Model (NRM), and conceptually similar models. 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 [Velicer et al., 1992, Walls and Rivera, 2009]. Expansion of the classic mediational model to include simple feedback produces a structure conceptually similar to the previously described mechanisms. This alternate model, depicted in block diagram form in Figure 7, describes a feedback loop in which a controller, $C(s)$, responds to the deviation, e, 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*. Computationally, $P(s)$ parameter estimates are found by defining a SISO system where *Cigsmked* is the input and *Craving* the output; $C(s)$ and $P_d(s)$ parameter estimates are found by defining a MISO system where e and *Quit* signals are the respective inputs and *Craving* is the output. These are the associated Laplace-domain expressions:

$$Craving = \left(\frac{PC}{1+PC}\right) r + \left(\frac{PP_d}{1+PC}\right) Quit \quad (9)$$

$$Cigsmked = \left(\frac{C}{1+PC}\right) r + \left(\frac{P_d}{1+PC}\right) Quit \quad (10)$$

Based on an r equal to the pre-quit baseline craving value, the parameter estimates and goodness-of-fit percentages are tabulated for the treatment group averages and the single subjects in Table 3; the corresponding model outputs are depicted in Figures 5 and 6. After following this iterative procedure, we found the step and controller transfer functions are described by:

$$P_d(s) = \frac{K_d}{(\tau_d s + 1)} \quad (11)$$

$$C(s) = \frac{K_c}{(\tau_c s + 1)} \quad (12)$$

For the AC single subject example, the $P(s)$ transfer function structure behaves as a semi-proper function:

$$P(s) = \frac{K_1 (\tau_a s + 1)}{(\tau_1 s + 1)} \quad (13)$$

while a second order transfer function with a zero term is appropriate for the other data sets:

$$P(s) = \frac{K_1 (\tau_a s + 1)}{(\tau_1 s + 1)(\tau_2 s + 1)} \quad (14)$$

Table 3. Feedback model parameter estimates and goodness-of-fits.

Treatment	AC	ANc	PC	PNc	AC	PNc
Data Set	Avg	Avg	Avg	Avg	Sgl	Sgl
Craving Fit [%]	84.79	78.42	71.96	59.13	60.65	53.62
Cigsmked Fit [%]	91.64	86.05	91.03	87.47	77.09	61.23
Craving Set. T.	35.69	35.91	35.82	35.90	26.34	33.87
Cigsmked Set. T.	34.56	35.26	35.60	35.29	10.64	33.86
$P(s)$ K_1	0.76	0.65	0.52	0.45	1.57	-2.20
$P(s)$ τ_{a_1}	-2.10	-4.25	-12.98	-17.47	-3.05	6.76
$P(s)$ τ_1	8.04	12.30	18.61	19.73	6.88	17.43
$P(s)$ τ_2	0.00	0.00	0.00	0.00		0.54
$C(s)$ K_c	0.09	0.22	0.21	0.22	-0.01	-5.65
$C(s)$ τ_c	1.10	3.29	0.41	0.63	0.74	82.64
$P_d(s)$ K_d	-15.53	-14.87	-13.42	-11.83	-13.06	-16.36
$P_d(s)$ τ_d	0.51	0.24	0.36	0.09	0.00	0.41

As before, the goodness-of-fits are high for the group averages. Here, the P_d model corresponds to the initial quit-day reduction in *Cigsmked*, and the magnitude of this drop follows an intuitive relationship to the treatment condition. For these four models, the controller–which models the resumption in *Cigsmked*–features relatively simple dynamics and provides a small contribution to *Cigsmked*. The ANc, PC, and PNc group models provide comparable contributions to the *Cigsmked* model, as indicated by consistent gains of 0.22, but the AC group's controller contribution is much smaller, indicated by a $C(s)$ gain of only 0.087 (60% smaller than in the three other group average models). The $P(s)$ transfer function accurately captures craving's inverse response, and the magnitude of craving reduction follows an intuitive relationship to treatment condition: K_1 equal to 0.76 for AC, 0.65 for the ANc, 0.52 for the PC, and 0.45 for the PNc.

Some basic analysis can be used to relate the mediation and feedback models. Assuming $|PC| < 1 \; \forall \; \omega$ (Small Gain Theorem), and truncating leads to the approximation:

$$\frac{1}{1+PC} \cong 1 - PC \quad (15)$$

Substituting and rearranging Equations 9 and 10 leads to:

$$Cigsmked \cong P_d(s)Quit - C(s)Craving \quad (16)$$

Here, $P_{c'} = P_d$ and $P_b = -C$. The values in Tables 2 and 3 are congruent with these approximations. Because *Quit* affects *Craving*, Equation 16 denotes that *Craving* mediates *Cigsmked*. The complementary expression is also true:

$$Craving \cong P(s)P_d(s)Quit + P(s)Cigsmked \quad (17)$$

Additional data analysis (not shown for reasons of brevity) entailed development of mediational and feedback models for the "reversed" *Craving-Cigsmked* scenario. In this case, high goodness-of-fits were obtained for the mediation structure, but less so for the feedback structure. These results seem to indicate that feedback is an appropriate description and that mediation is more of an approximation of the relationship. Additional intervention experiments could be constructed to support this hypothesis.

5. CONCLUSIONS AND RECOMMENDATIONS

Drawing from intensive longitudinal data collected in a clinical trial of bupropion and counseling as aids to smoking cessation, system identification models are developed for four treatment group averages and two single subjects according to two candidate models for describing the process of smoking cessation: a classic mediation model and a feedback model. Ultimately, these models differ in how they describe resumption of smoking. The mediated pathway models resumption in the classic structure and the feedback pathway models resumption in the alternate structure. Based on analysis of models for "reversed" *Craving-Cigsmked* relationships, we find that the feedback model appears to more appropriately describe the process of smoking cessation. Regardless of structure, varying parameter values estimated from the group average data, which are signals with high signal-to-noise ratios, suggest both bupropion and counseling have some effect on craving and reduction of smoking behavior.

We have effectively shown system identification is useful in analysis of smoking cessation interventions and for comprehensively describing the process of smoking cessation. The dynamical modeling strategy used here could be applied to this clinical trial data further in order to study alternate signal relationships and behavioral mechanisms, but the generalizability of the models is limited due to the secondary nature of this analysis. For optimal use of system identification and control engineering techniques in behavioral applications, the models generated in this and similar studies can help inform the design of novel experimental protocols that draw from system identification principles. This poses a significant challenge in terms of "plant-friendliness," as protocols must adhere to practical resource limitations, healthcare policies, and ethical boundaries. A novel protocol addressing the challenge of experimental design for a fibromyalgia intervention is presented in Deshpande et al. [2011], but additional methods must be developed and validated for expanded use of system identification in behavioral health.

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