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Towards Patient-Friendly Input Signal Design for Optimized Pain Treatment Interventions ⋆

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Abstract: 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. Standard clinical trials, while providing some useful information, are not the most suitable vehicle for understanding the dynamic response of dosage changes to participant response. Meanwhile, much of the work in classical input design, even that which incorporates "plant-friendly" considerations, may not result in clinically acceptable trials for human participants. In this paper, we describe 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. Numerical examples are shown to illustrate the proposed method with a hypothetical clinical trial of the drug gabapentin for the treatment of neuropathic pain.

Keywords: Optimal experiment design; biomedical systems; medical applications; optimization problems.

1. INTRODUCTION

Input signal design is the key step for generating informative experimental data to be used in system identification. There is an increasing interest in examining system identification problems, including issues in experimental design, for applications in health and medicine [Galvanin et al., 2011, Bombois et al., 2011]. However, embarking upon this task requires care, as many input design methods, even the state-of-the-art, may not incorporate human participant requirements that extend beyond commonplace issues relevant in industrial applications. Ultimately, the goal of the dynamic modeling task is to obtain a useful model that enables closed-loop personalized treatment or a similar end-use application [Rivera et al., 2007b].

We illustrate these ideas with a previously conducted clinical trial of naltrexone, an opiate antagonist, as a treatment for a pain disorder known as fibromyalgia [Younger and Mackey, 2009]. The use of this data for dynamical modeling and subsequent closed-loop control is examined in Deshpande et al. [2011]. Figure 1 shows data for a single participant of the pilot study to determine the efficacy of this drug on fibromyalgia symptoms. In this blind controlled experiment, a unit dose is provided over a long period of time, and corresponding changes in symptom reports (on a scale of $0-100$) are noted over the period of the trial. As shown in Fig. 1, the participant in the trial reports lower overall fibromyalgia symptoms, and improved sleep as a consequence of the drug. However, there are a number of issues regarding using this data for system identification. The single step change in the dosage creates difficulties for conducting crossvalidation, assessing nonlinearity, or distinguishing between the effect of disturbances versus the input, among other considerations.

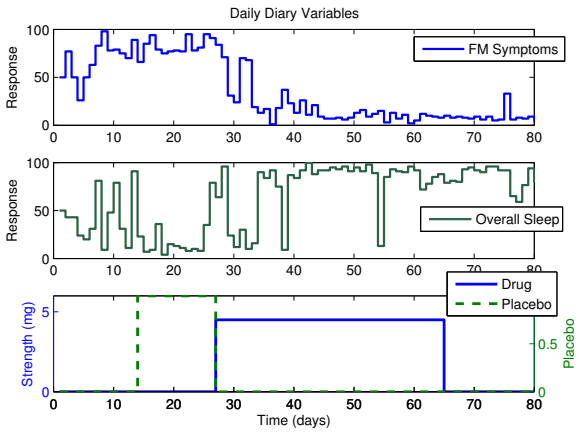

Fig. 1. Variation in pain (FM symptoms) and sleep levels associated with a low dose naltrexone intervention for fibromyagia, shown for a representative participant.

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Prior work on input signal design at Arizona State has considered the concept of "plant friendliness" in input design to address practical time domain constraints that are part of industrial process operation; this includes limits on the signal length, amplitude and its rate of change. Towards this goal, a simultaneous frequency and time domain formulation with plant-friendly constraints was shown in Rivera et al. [2007a, 2009] using multisine signals. The input signals are designed using a predefined discrete power spectrum while the optimization procedure chooses the phases (and some amplitudes) to minimize a desired plant-friendly metric, such as the crest factor. In this paper, our goal is to explore how plant friendliness considerations can be extended for applications in medicine to the concept of "patient-friendly" input design. In addition to the traditional plant-friendly constraints, there may exist additional considerations that arise from clinical practice. Among them is the presence of categorical constraints resulting from the fact that dosage (e.g., number of treatment visits, medications, etc.) cannot be continuously adjusted and can only assume certain discrete values within an interval. Likewise, dosage changes may only occur at certain prescribed time intervals (e.g., weekly) as a result of clinical requirements. Our approach to "patient-friendliness" philosophically parallels, but is distinct from the "human-friendly" concept defined by Lee and Bequette [2009] for patients with diabetes.

In this paper we pursue the goal of achieving patient-friendliness in two ways. One is to examine how to approximate a "plant-friendly" signal with a"patient-friendly" one without optimization; this is illustrated in the case of multisines. The other approach is to rely on optimization. A formal optimization based procedure in principle should provide better results; however, the problem formulations examined here take the form of challenging nonlinear programming problems. Many methods developed in literature take advantage of the fact that the inverse of parameter error covariance matrix is linear in the spectrum [Ljung, 1999]. Such formulations can be posed as convex optimization problems [Jansson and Hjalmarsson, 2005]; however they have not been shown to explicitly (or with relaxations) consider all patient-friendly constraints required for a clinical trial [Manchester, 2010, Narasimhan and Rengaswamy, 2011].

The paper is organized in following sections: Section 2 describes the input design objective in a health setting. In Section 3, we present the optimization based input signal design formulation and its implications. In Section 4, we show a case study based on the drug gabapentin. Summary and conclusions are presented in Section 5.

2. INPUT SIGNAL DESIGN OBJECTIVES

The aim of the input signal design is to find a realization of the signal, under time domain constraints, such that the signal spectrum ($\Phi_u(\omega)$) approximates a desired spectrum ($\gamma(\omega)$). In many circumstances, very little *a priori* knowledge of the system is available, so a "flat" spectrum over a bandwidth is a reasonable approximation:

$$\Phi_u(\omega) \approx \gamma(\omega) = \begin{cases} \gamma_a & \omega_* \leq \omega \leq \omega^* \\ \gamma_b & \omega > \omega^*, \end{cases} \tag{1}$$

where γ_a and γ_b are real numbers defining the magnitude and ω^* denotes the desired bandwidth. Based on the previous discussion, the following properties are desired from an input signal:

- *Frequency range of interest.* The input signal should be persistently exciting with significant power over the required bandwidth. Since the model may be intended for control design, the signal bandwidth should cover the frequency range of interest for control. Such bounds can be approximately calculated using dominant time constant estimates $(\tau^H_{\text{dom}}, \tau^L_{\text{dom}})$ of the system based on the high (α_s) and low (β_s) frequency information as:
$$\omega_* = \frac{1}{\beta_s \tau^H_{\text{dom}}} \leq \omega \leq \frac{\alpha_s}{\tau^L_{\text{dom}}} = \omega^*, \tag{2}$$
where typically $\alpha_s = 2$ and $\beta_s = 3$ [Rivera et al., 2007a]. For example, information about drug pharmacokinetics metrics such as biological half-life can be used to judge the speed of response.
- *Periodicity.* Applying multiple cycles of a periodic input makes it possible to obtain estimation and validation data sets, thus enabling crossvalidation. Also, a periodic input creates a natural time window for the identification experiment, allowing the user to examine the data while the trial is underway. Hence the input design can be modified after the end of a period to better conform to the observed dynamics.
- *Change in levels.* Having various levels in the input signal can be beneficial, particularly if the plant under study is nonlinear in nature [Ljung, 1999].

In addition to the general properties just mentioned, the variation in (input) drug dosage levels ($u(k)$) has to satisfy the following clinical constraints:

- *Amplitude constraint.* There is a limit on the signal bounds that corresponds to maximum and minimum dosages:
$$u_{\min} \leq u(k) \leq u_{\max}, \tag{3}$$
- *Move size constraint.* Clinically there may exist bounds on the move size of the signal over $|p - q|$ sampling period(s):
$$|u(k+p) - u(k+q)| \leq b, \tag{4}$$
- *Integer constraints.* Dosages can take only discrete or categorical values from a finite set $\mathbb{I} \subset \mathbb{Z}$ or in general:
$$u(k) \in \mathbb{I} = \{u_{-n}, u_{-(n-1)}, \ldots, u_0, \ldots, u_{n-1}, u_n\}. \tag{5}$$
As dosages of medication may be compounded into pills of a standard concentration, any subsequent increase in dosage can be prescribed as an integer multiple of that basic dose,
- *Switching time* (T_{sw}). In a clinical trial setting, patients may have to visit a clinic to pick up their medication. As a result, dosage changes $u(kT_{sw})$ may have to be performed at frequencies other than daily $(T_{sw} = 1)$, such as weekly $(T_{sw} = 7)$.

There could also exist toxicity constraints based on how much drug has accumulated in the body and has yet to be metabolized by the patient. Considerations such as these are common in cancer/chemotherapy trials, but will not be further considered in this paper. In addition to requirements on the input, there is a clinical interest in

corresponding changes in symptoms and outcomes due to the input (drug) intake. For example, in a pain treatment setting the pain magnitude (measured on a scale of $0-100$) should be varied within certain limits for patient comfort and safety. To address this requirement, the following constraints should be considered:

$$y_{\min} \leq y(k) \leq y_{\max} \tag{6}$$
$$|y(k+l) - y(k+m)| \leq c, \tag{7}$$

where c is a bound on output changes.

In general, problem formulations which result in a signal realization with desired spectral properties do not necessarily produce input (or output) signals which are well distributed in time over the signal span. Among the metrics that can be used to quantify this distribution is crest factor [Godfrey, 1993] which can be defined as:

$$\mathrm{CF}(x) = \frac{x_{\text{peak}}}{x_{\text{rms}}} = \frac{\max_k |x(k)|}{\sqrt{\frac{\sum_k x(k)^2}{N}}}, \tag{8}$$

where $x = u$ or y is a signal of length N. The crest factor varies as $1 \leq \mathrm{CF}(x) < \infty$ such that a low crest factor implies a fully even distribution of the signal. Another metric is the Performance Index for Perturbation Signals (PIPS) [Godfrey et al., 1999], which is defined as:

$$\mathrm{PIPS}(\%) = 200 \times \frac{\sqrt{x_{\text{rms}}^2 - x_{\text{mean}}^2}}{\max(x) - \min(x)}. \tag{9}$$

PIPS is expressed in percent form ($0\% \leq \mathrm{PIPS}(x) \leq 100\%$) which has an intuitive appeal. In practice, a high PIPS value corresponds to a signal which is evenly distributed and has low crest factor. In addition to these two metrics, Weyl's criteria:

$$\lim_{N\to\infty} \frac{1}{N} \sum_{k=0}^{N-1} e^{(2\pi l x(k))i} = 0 \quad \forall l \in \mathbb{Z} - \{0\}, \tag{10}$$

gives the necessary and sufficient condition for a sequence to be uniformly distributed in $[0, 1)$ [Rivera et al., 2007a].

3. INPUT SIGNAL DESIGN FORMULATIONS

The mathematical optimization problem aims to address:

- frequency-wise bounds on the spectrum, and
- a desired distribution metric (e.g. Weyl's critria),

and can be written as:

$$\min_{u\in\mathcal{U}} \quad \text{Objective} \tag{11}$$

where the set $\mathcal{U}$ is defined by the clinical constraints:

$$\mathcal{U} = \{u \in \mathbb{R}^{\mathbb{N}} | (3), (4) \text{ and } (5)\ \forall k\}. \tag{12}$$

Equation 11 represents, in general, a mixed-integer nonlinear constrained optimization formulation which is directly solved in the variable u.

3.1 Input spectrum parametrization

The infinite dimensional variable ($\Phi_u(\omega)$) has to be parameterized to be used by the optimization procedure. Consider a real signal $u \in \mathbb{R}^{\mathbb{N}}$. The discrete-time Fourier transform (DTFT) of the signal is given as:

$$U(\omega) = \sum_{k=0}^{N-1} u(k) e^{-j\omega k}, \quad \omega \in [0, \pi]. \tag{13}$$

Since the signal is finite and bounded, the Fourier transform always exists. Next, we define the spectrum of u as the square of the magnitude of the DTFT as:

$$\Phi_u(\omega) = |U(\omega)|^2 = |\sum_{k=0}^{N-1} u(k) e^{-j\omega k}|^2. \tag{14}$$

A linear relation can be found using the Wiener-Khinchin theorem as:

$$\Phi_u(\omega) = |U(\omega)|^2 = \sum_{k=-\infty}^{\infty} r(k) e^{-j\omega k} \geq 0, \tag{15}$$

where $r(k)$ are the autocorrelation coefficients from a finite signal. However, it is difficult to formulate the problem using (15) with time domain constraints. Hence, we use the relation shown in (14) as the parametrization in the remainder of the paper. For the case of weekly switching, the system is sampled on a daily basis and the weekly input change is produced using move blocking:

$$\sum_{j=1}^{T_{sw}} |u(k) - u(k+j)| = 0 \quad \forall k \in \{0, \ldots, N - T_{sw} - 1\}. \tag{16}$$

In addition to switching time, there are practical limitations on the overall length of the clinical trial. It is desirable if N were chosen such that multiple periods of the signal can be implemented in the trial.

3.2 Realization of input signal with an exact spectrum

We consider the condition expressed in (1), i.e. when a particular spectrum is exactly desired. This Chebychev type of problem [Wu et al., 1996] can be stated as

$$\min \quad |\Phi_u(\omega) - |\gamma(\omega)||, \tag{17}$$

and can be reformulated by using an auxiliary variable t, as:

$$|\Phi_u(\omega) - |\gamma(\omega)|| \leq t \tag{18}$$
$$\text{or}, -t \leq \Phi_u(\omega) - |\gamma(\omega)| \leq t \tag{19}$$
$$\text{or}, -t + |\gamma(\omega)| \leq \Phi_u(\omega) \leq t + |\gamma(\omega)|. \tag{20}$$

In addition to this optimization being mixed-integer nonlinear constrained problem, (20) makes the problem semi-infinite due to the continuous variable $\omega \in [0, \pi]$. A numerical way to handle this is to use a discretized spectral space [Reemtsen and Rückmann, 1998] on finite (M) numbers. Consequently, the optimization problem can be stated as:

$$\begin{aligned} \min \quad & t \\ \text{s.t.} \quad & -t + |\gamma(\omega_j)| \leq \Phi_u(\omega_j) \leq t + |\gamma(\omega_j)| \\ & 0 \leq \omega_j \leq \pi, j = 1, \ldots, M \\ & u_{\min} \leq u(k) \leq u_{\max} \\ & |u(k+p) - u(k+q)| \leq b \\ & u(k) \in \mathbb{I}. \end{aligned} \tag{21}$$

We noted earlier that there is a clinical interest in corresponding changes in symptoms due to the input (drug) intake. If an *a priori* model for the intervention dynamics is available, for example:

$$y = \left(\frac{K_p}{\tau_p s + 1}\right) u, \tag{22}$$

then (6)-(7) with any of the following constraints can be added to the optimization problem (21):

$$200 \times \frac{\sqrt{x_{\text{rms}}^2 - x_{\text{mean}}^2}}{\max(x) - \min(x)} \geq \kappa_x \quad x = u \text{ or } y, \tag{23}$$

where κ_x is a minimum PIPS metric or,

$$\mathrm{Re}\left\{\frac{1}{N}\sum_{k=0}^{N-1} e^{(2\pi l x(k))i}\right\} \leq \delta \quad \forall l \in \mathbb{L} \subset \mathbb{Z} - \{0\} \qquad (24)$$

$$\mathrm{Im}\left\{\frac{1}{N}\sum_{k=0}^{N-1} e^{(2\pi l x(k))i}\right\} \leq \delta \quad \forall l \in \mathbb{L} \subset \mathbb{Z} - \{0\}, \qquad (25)$$

where δ is a relaxation parameter used to approximately satisfy Weyl's criteria (given that only finite data points are available) using integers from a finite set $\mathbb{L}$.

3.3 Polynomial Relaxation

The mixed integer nonlinear (and nonconvex) programs are, in general, NP-hard and computationally very difficult to solve. This problem can be posed as nonlinear optimization by reformulating the integer constraints as follows: $u(k) \in \mathbb{I}$ can be replaced by a polynomial which has roots at the desired integer points, and can be further relaxed as:

$$|\prod_{i\in\mathbb{I}}(u(k)-i)| \leq \epsilon \quad \forall k, \qquad (26)$$

where ϵ is the parameter used for accuracy.

4. NUMERICAL EXAMPLES

We illustrate a case study for input signal design using a hypothetical clinical trial to treat neuropathic pain. The drug used in this study is gabapentin which has a broad therapeutic window [Siler et al., 2011]. This implies that it is possible to vary the drug dosages over time and to observe corresponding changes in reported pain condition. Some of the features of the proposed trial are:

- Typical dosage: $1200 - 3600$ mg,
- Length of protocol : $3 - 8$ months or $90 - 240$ days,
- Dosage change size : $100, 300, 600, 900$ mg,
- Switching time: 1 day to 7 days.

These time domain requirements can be translated as constraints into the optimization-based formulation shown in (21). It is important that the drug dosage should be gradually increased to and from 1200 mg level. This is achieved by padding the input signal with 'baseline' and 'washout' dosages. In addition, it is desired that the drug dosages do not change too abruptly between two samples and hence a maximum input move size of 900 mg is applied. The input signal was first generated on a magnitude of -4 to 4 and then scaled up to the desired drug concentrations of $1200 - 3600$ mg. Corresponding output was constrained and then scaled using a first order system with gain $K_p = -0.01235$ per mg of drug. Time constant was assumed to be $\tau = 5$ days. The simulation results are shown for two periods and nine levels of the input signal, with added baseline and washout periods. Corresponding parameters used for simulation are as follows:

- $N = 100$, $M = 50$,
- $n = 4$, $\mathbb{I} = \{-n, 1-n, \ldots, 0, \ldots, n-1, n\}$ (9 levels),
- $\omega^* = 0.4$: (based on dominant time constant $\tau = 5$),
- $u_{\max} = n$, $u_{\min} = -n$,
- $p = l = 1$, $q = m = 0$, $u_{\text{move}} = b = 3$, $c \to \infty$,
- (Section 4.2) $\gamma_a = 3500$, $\gamma_b = 35$, $y_{\max,\min} = \pm 15$, $\mathbb{L} = \{-15, \ldots, 15\}$, $\delta = 0.5, \epsilon = 1$.

Table 1. Performance Indices for Different Input Signals

Signal	x	CF(x)	PIPS(x)	max(Δx)
Section 4.1 ($T_{sw} = 1$)	u	1.74	57.21	600 mg
	y	1.91	54.82	2.64%
Section 4.1 ($T_{sw} = 4$)	u	1.96	57.91	900 mg
	y	2.08	51.7	2.78%
Section 4.1 ($T_{sw} = 7$)	u	1.61	61.59	1500 mg
	y	2.03	51.5	3.39%
Section 4.2 (Weyl, $T_{sw} = 1$)	u	1.84	53.77	900 mg
	y	1.88	54.45	2.55%
Section 4.3 (Weyl, $T_{sw} = 7$)	u	1.82	54.66	900 mg
	y	1.82	57.46	2.16%

- (Section 4.3) $y_{\max,\min} = \pm 20$, $\mathbb{L} = \{-10, \ldots, 10\}$, $\epsilon = 20$

The formulations were written in the AMPL modeling language, with KNITRO as the solver. To overcome potentially poor local minima solutions, the solver was initiated with the 'multistart' option to enable a more global search.

4.1 Approximated Multisine

Before discussing the optimization based results, we briefly consider (integer) approximated multisine signals. The desired properties of input design can also be satisfied by multisine signals which are deterministic, periodic signals designed to contain specific frequency information:

$$u(k) = \sum_{i=1}^{n_s} a_i cos(\omega_i kT + \phi_i), \qquad (27)$$

where n_s is the number of harmonics, T is the sampling time, ω_i are specified by the user and a_i, ϕ_i are selected by an algorithm. These multisines can be designed to reach a desired plant friendly metric such as the crest factor under time domain constraints [Rivera et al., 2009]. But since the amplitude at a give time k is expressed only as a sum of finite sinusoids, it may be infeasible for the signal to take only categorical values. A practical way to archive this goal is to approximate average of the multisine signal over predetermined switching time (T_{sw}) to the nearest integer. This can be written as:

$$\bar{u}(k : k + T_{sw}) = u_I^*, \quad \forall k \in \{0, \ldots, N - T_{sw} - 1\} \qquad (28)$$

$$\text{s.t.} \quad \arg\min_{u_I}\{|\frac{\sum_{i=k}^{k+T_{sw}} u(i)}{T_{sw}} - u_I|\}, \quad u_I \in \mathbb{I} \qquad (29)$$

where N is the signal length, u_I^* is the nearest integer value, u is the original multisine and $\bar{u}$ is the approximated signal. Clearly, this approximation is more accurate when the number of categorical levels is large and the switching time is short. This can be now shown for the gabapentin trial. The number of signal levels are assumed to be nine (i.e. minimum dosage size of 300 mg). Dynamic simulation of pain response to an integer approximated Schroeder-phased multisine signal is shown in Fig. 2 with two periods of 96 data points. Fig. 4 shows comparison of the discrete power spectrum with increase in T_{sw} from daily to weekly. It can be noticed that increasing T_{sw} results in an unavoidable loss of power at frequencies close to the desired bandwidth.

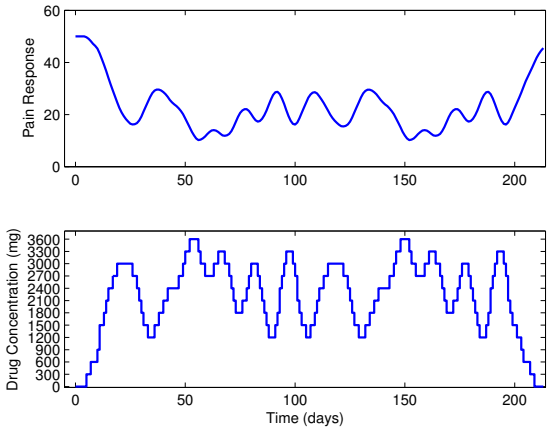

Fig. 2. Dynamic simulation of pain response (from baseline 50) to a nine-level integer approx. Schroeder-phased multisine with daily switching ($T_{sw} = 1$).

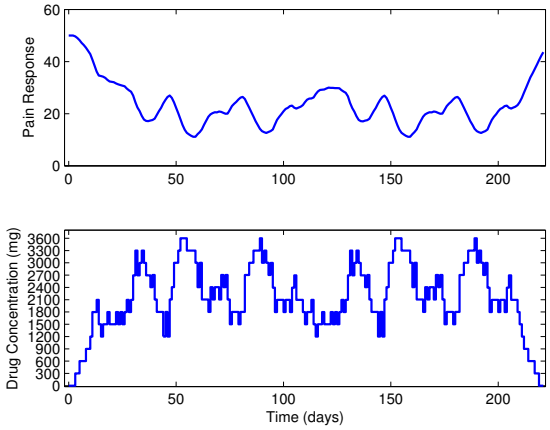

Fig. 3. Dynamic simulation of pain response (from baseline 50) to a nine-level input signal under output Weyl's criteria constraints with daily switching ($T_{sw} = 1$) .

4.2 Joint input-output design with Weyl's criteria

In the joint input-output design, the aim is to obtain a signal that produces uniform changes in the output, while respecting input constraints. Using the formulation (21), Weyl's criteria on the output is imposed as a constraint as shown in (24-25), while satisfying spectrum and other time domain constraints on the input and output. The condition expressed in (26) is used for (relaxed) integer constraints. Fig. 3 shows the dynamic simulation of pain response to the corresponding input signal with the obtained input signal spectrum shown in Fig. 4. The dosage is varied between $1200 - 3600$ mg with maximum move size of 900 mg as noted in Table 1. To ascertain the distribution of output, we can observe the spread of y to the corresponding changes in y or $\Delta y = y(k+1) - y(k)$. In Fig. 5, the integer constrained optimization based method can be contrasted with the approx. multisine result (with daily switching and on neglecting transients), where we observe a more uniform spread of y with corresponding uniform changes in Δy, under integer constraints, for the Weyl design.

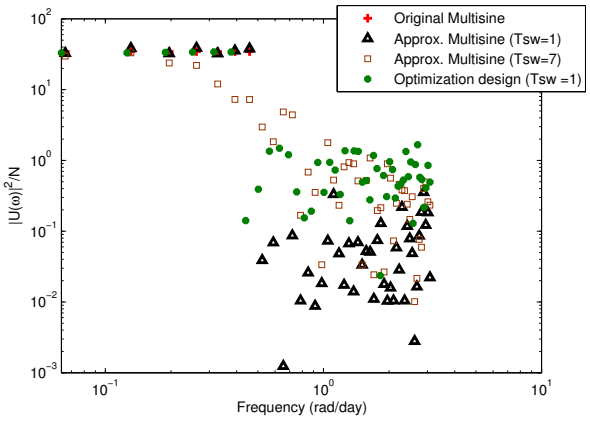

Fig. 4. Comparison of periodogram of the original multisine with approx. multisine signals and Weyl optimization design.

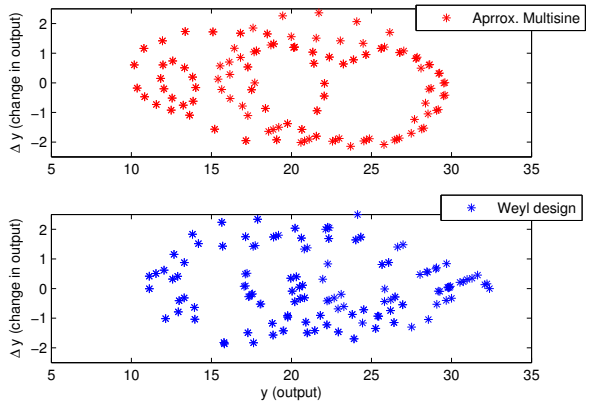

Fig. 5. Comparison of distribution of output and rate of change of output for two signal designs for daily switching ($T_{sw} = 1$).

4.3 Weekly Switching Time

So far, dosage changes have been daily, which may be excessive or impractical in health intervention settings. A weekly dosage change i.e. $T_{sw} = 7$ is examined in this section. The problem in (21) is modified by removing the spectrum constraints while imposing Weyl's criteria on the output (24-25) and solving (min δ) with move blocking as shown in (16). In Fig. 6, the time-domain signals are shown with two periods. Since the optimization-based design results in an input signal which fully covers the useful span, we observe the patient experiencing longer stretches of lower pain as a result of better utilization of the input. The optimization approach avoids the drawback of the approximate multisine where the user has no direct control over the final realization (e.g. large move sizes as noted in Table 1). In Figure 7, the distribution (y vs. Δy) for these two signals is compared where it can be observed that the Weyl design has a larger spread. It should also be noted that the two signals are of slightly different lengths.

5. SUMMARY AND CONCLUSIONS

In this work, we present a time-domain approach for input signal design which is motivated by the requirements of

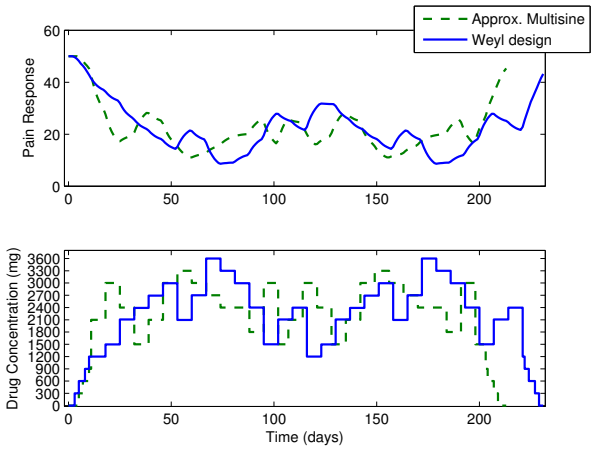

Fig. 6. Dynamic simulation of pain response for input signals constrained to a minimum weekly switching interval ($T_{sw} = 7$).

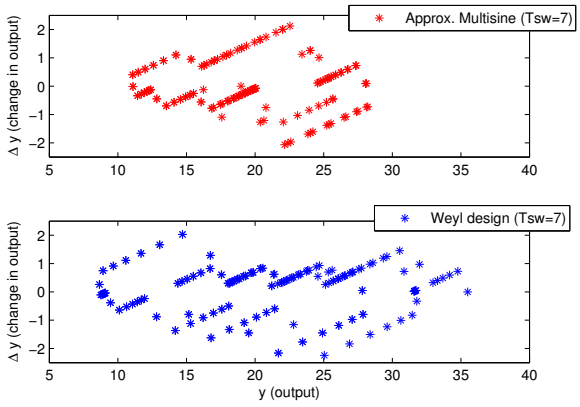

Fig. 7. Comparison of distribution of output and rate of change of output for the approximate multisine and optimization-based signal for weekly switching ($T_{sw} = 7$).

clinical trials for pain treatment intervention. This design considers constraints on signal magnitude, move sizes, and the categorical nature of the input signal. A joint input-output design is presented to achieve a uniform distribution in the output. The resulting optimization problems are integer-constrained nonlinear programming problems. We use a polynomial-based static relaxation for the integer constraints so that the problem can be solved by nonlinear programming. A hypothetical gabapentin-based clinical trial is shown to illustrate the usefulness of the proposed design. Best optimization results in comparison to approximated multisines are obtained when a minimum weekly switching time is required between dosage changes.

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