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Assessment of Performance Limitations Due to Nonlinearity in a Model of a Human with Diabetes

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***Abstract*— A 19^{th}-order *in silico* patient model is analyzed to determine if nonlinear control is necessary for optimal regulation of blood glucose levels. A numerical measure of nonlinearity is used to assess the open-loop degree of nonlinearity and the results then compared to those from an assessment of the control-relevant nonlinearity. Control-relevant nonlinearity is assessed with a performance metric that uses the system's nonlinear closed-loop operators to calculate bounds on the achievable performance of stabilizing, linear control designs. The results show that the open-loop system is mildly nonlinear in a typical operating region and has a low degree of control-relevant nonlinearity for standard, linear performance specifications. If asymmetric performance is desired, in which negative deviations are rejected more aggressively than positive deviations, the control-relevant nonlinearity grows significantly indicating that nonlinear control is necessary to achieve this task optimally. The results indicate that the primary contributor to the control-relevant nonlinearity is the performance objective and that, for most cases, linear control is sufficient for blood glucose regulation.**

I. INTRODUCTION

The lifestyles of persons living with diabetes may be severely affected by the consequences of the disease. Due to the inability of the pancreas to regulate blood glucose levels, patients are often required to regulate glucose levels manually. This task often involves the patient extracting blood samples to use in measuring glucose levels and then deciding if boluses of insulin beyond those of their daily regimen are required. Due to the infrequent, and possibly imprecise, nature of these measurements, tight glucose self-regulation may only be possible given frequent interactions with a physician. The dangers of widely varying glucose levels are many, including heart and blood vessel disease, kidney disease, blindness, and comas, the consequences of which may be a shortened life span [1]. Glucose deviations below the basal level (hypoglycemic deviations) are considerably more dangerous in the short-term than positive (hyperglycemic) deviations, though both types of deviations are undesirable.

Realizing the inherently problematic nature of self-regulation of glucose, systems researchers have actively pursued automated regulation systems. A closed-loop glucose regulation system requires three components: a glucose sensor, an insulin delivery device, and a control algorithm. A number of practical measurement devices and pumps are commonly-available [2], [3], [4]. For the control algorithm, researchers have investigated a wide-range of designs including simple PID algorithms [5], [6] as well as linear [7] and nonlinear [8] model predictive control (MPC) algorithms. Also, a number of researchers have investigated nonlinear optimal control techniques, e.g. Ollerton [9] and Fisher [10].

In a previous study [11], the authors analyzed the minimal diabetic system model of Bergman *et al.* [12] with the purpose of determining if a nonlinear, or otherwise advanced, control algorithm is necessary to achieve high levels of performance in regulation of glucose through an assessment of the system's degree of control-relevant nonlinearity. Control-relevant nonlinearity is a function of the inherent system nonlinearity, operating region, and performance objective. The assessment techniques involved use of a nonlinearity measure to quantify the degree of nonlinearity of the system's Optimal Control Structure (OCS) [13] as a means to assess the nonlinearity of an approximation to the optimal state-feedback control problem. The results indicate that the system model is only mildly nonlinear in the operating region considered and that, given a standard quadratic performance objective, the system is optimally regulated using linear techniques. When an asymmetric performance objective is considered in which hypoglycemic deviations are penalized more heavily than hyperglycemic deviations due to the greater immediate health concerns associated with hypoglycemic deviations [14], the control-relevant nonlinearity is found to increase with increasing asymmetric weight implying the need for nonlinear control. Due to the nature of the control-relevant nonlinearity effects, nominally linear controller designs with possible nonlinear corrections were found to be the optimal designs. Examples of possible control algorithms meeting these criteria include linear MPC with an asymmetric objective function or gain-scheduled PID control.

Because the model in the previous study contains only three states, many important physiological effects are not explicitly modeled. Possibly, this level of approximation will result in the neglecting of critical nonlinear behaviors that may influence controller design. It is the objective of this study to determine if nonlinear control is needed for the regulation of glucose through control-relevant nonlinearity assessment of the 19^{th}-order metabolic model of Sorensen [15]. Due to the large number of states in this model, the analytical derivation of the system's OCS is lengthy and, therefore, it is better to consider alternate control-relevant nonlinearity assessment techniques.

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In section II, the control-relevant nonlinearity assessment techniques used here are introduced including an open-loop nonlinearity measure and a control-relevant nonlinearity assessment technique based on quantifying performance limitations of linear control designs. In section III, the system model is introduced and open-loop nonlinearity characterization is performed. In section IV, a theoretical assessment of the system's control-relevant nonlinearity is performed for the disturbance rejection task under assumptions of desired linear performance and, separately, asymmetric performance as motivated in the preceding discussion. In section V, the results are summarized and conclusions are presented.

II. NONLINEARITY ASSESSMENT TECHNIQUES

A. Open-Loop Nonlinearity Assessment

To quantify the nonlinearity of the system model used in this work, a measure of open-loop nonlinearity is required. The concept of a measure of nonlinearity was first proposed by Desoer and Wang [16] in demonstrating the linearizing effects of linear feedback. Haber [17] was the first to propose a series of practical, data-driven nonlinearity *tests* used primarily to detect the presence of nonlinearity. Researchers have continued to develop nonlinearity measures based on various quantification principles, including: differences in steady-state gain over an operating region [18], measures of steady-state map curvature [19], norm-based quantification using a novel inner product definition [20], and comparison of empirical and theoretical gramians [21].

For this work, the nonlinearity measure proposed by Allgöwer [22] is used to quantify the degree of open-loop nonlinearity. This measure is directly based on the work of Desoer and Wang [16]. The nominal form of the measure is given as:

$$\phi_N^{\mathcal{U}} = \inf_{G\in\mathcal{G}} \sup_{u\in\mathcal{U}} \frac{\|G[u]-N[u]\|}{\|N[u]\|} \tag{1}$$

where $\mathcal{U}$ is the space of admissible input signals, $N : \mathcal{U} \rightarrow \mathcal{Y}$ is the system operator, $G : \mathcal{U} \rightarrow \mathcal{Y}$ is a linear approximation to N, and $\mathcal{G}$ is the space of linear operators. The norm $\|\cdot\|$ denotes a p-norm defined on the space of output signals, $\mathcal{Y}$. Any admissible norm may be used in computing the measure, but it is prudent to consider a norm that has relevance for the problem under consideration. By definition, $\phi_N^{\mathcal{U}}$ characterizes nonlinearity based on the best linear approximation given the "worst" input signal.

The nonlinearity measure, $\phi_N^{\mathcal{U}}$, will yield results in the range $[0, 1]$ where a value of 0 indicates a linear process (across the set of inputs considered) and values approaching 1 indicate a severely nonlinear process. Nominally, $\phi_N^{\mathcal{U}}$ is well-defined only for bounded-input, bounded-output (BIBO) stable systems. Helbig *et al.* [23] extended the measure definition to consider transient systems by allowing for maximization of the measure over the set of process initial conditions and minimization over the set of linear approximation initial conditions and by limiting the possible definitions of $\|\cdot\|$ to finite-time norms.

As defined in eq. (1), the computation of $\phi_N^{\mathcal{U}}$ involves the solution of an infinite-dimensional min-max problem and is, generally, computationally infeasible. To simplify the problem, the space $\mathcal{U}$ may be limited to a representative set $\mathcal{U}_c \subset \mathcal{U}$. Next, a restricted version of $\mathcal{G}$ is realized through use of a parameterized linear approximation, for example (for a SISO system):

$$G[u(s)] = w_o u(s) + \sum_{i=1}^{N_l} \frac{w_i}{\tau_i s+1} u(s) \tag{2}$$

To compute the nonlinearity measure, one selects the number of basis functions (N_l) and the corresponding set of time constants (τ_i) and then performs a minimization to find the optimal set of weights, w_i, for the $u \in \mathcal{U}_c$ that maximizes the measure. It has been shown that the search for the optimal weight set is convex [22]. Given the above restrictions, the nonlinearity measure approximation can be written as:

$$\phi_N^{\mathcal{U}} \approx \min_{w\in\mathbf{R}^{N_l+1}} \max_{u\in\mathcal{U}_c} \frac{\|G[u]-N[u]\|}{\|N[u]\|} \tag{3}$$

where $G[u]$ is represented by eq. (2).

B. Control-Relevant Nonlinearity Assessment

As the authors have shown previously [24], it is generally insufficient to base controller design decisions on assessment of only the degree of open-loop nonlinearity of a system. Control-relevant nonlinearity is the feature that places limitations on the achievable performance of control designs for nonlinear systems. For example, the performance of a linear controller on a system with severe control-relevant nonlinearity should be expected to be very poor. With this intuition, the following is a description of a control-relevant nonlinearity assessment technique that bases its analysis on a measure of achievable performance [25]. Because the primary objective of a glucose controller is to reject external glucose disturbances, focus is placed on assessment of control-relevant nonlinearity in terms of performance is disturbance rejection.

Given a closed-loop system composed of nonlinear operators, as shown in Figure 1, the closed-loop operator, H_{yd_y}, that relates the effect of output disturbances, $d_y \in \mathcal{D}_y$, on the loop output, $y \in \mathcal{Y}$, when $r = d_u = 0$ is defined as follows:

$$H_{yd_y} = (I - GC(-I))^{-1} G_d \tag{4}$$

One can specify desired performance in disturbance rejection through the choice of a reference operator, $H^*_{yd_y}$, whose form specifies the ideal closed-loop output for a given input, d_y. For the purposes of this work, a controller design problem will be said to be well-posed if the following metric is equal to 0:

$$P_{\mathcal{D}_y} = \inf_{C\in\mathcal{C}} \sup_{d_y\in\mathcal{D}_y} \frac{\left\|H_{yd_y}(G,C)d_y - H^*_{yd_y}d_y\right\|}{\left\|H^*_{yd_y}d_y\right\|} \tag{5}$$

where G is a stable process operator and $\mathcal{C}$ is the space of causal, stabilizing controllers. The measure, $P_{\mathcal{D}_y}$, is a measure of the difference between the output of the loop operator and that of the ideal operator given the "worst" disturbance and the best stabilizing controller. If the performance specified by $H^*_{yd_y}$ is achievable, $P_{\mathcal{D}_y} = 0$.

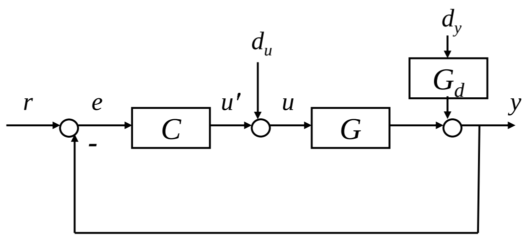

Fig. 1. General closed-loop system. G = process operator, C = controller, G_d = disturbance operator. All operators are assumed to be nonlinear, casual, and stable.

To use eq. (5) to assess control-relevant nonlinearity, one can consider recasting the measure in terms of only linear controllers, i.e.:

$$\Lambda_{\mathcal{D}_y} = \inf_{C \in \mathcal{C}_L} \sup_{d_y \in \mathcal{D}_y} \frac{\left\| H_{yd_y}(G, C)d_y - H^*_{yd_y} d_y \right\|}{\left\| H^*_{yd_y} d_y \right\|} \tag{6}$$

where $\mathcal{C}_L$ is the space of causal, stabilizing *linear* controllers. Therefore, there is no guarantee that, for a well-posed, nonlinear process, $\Lambda_{\mathcal{D}_y} = 0$. Non-zero values for $\Lambda_{\mathcal{D}_y}$ imply that linear control cannot meet the desired performance as specified by $H^*_{yd_y}$ and that, therefore, the system has a non-trivial degree of control-relevant nonlinearity.

To compute $\Lambda_{\mathcal{D}_y}$, the space $\mathcal{C}_L$ can be approximated by considering linear controllers given by the Youla parameterization [26]:

$$C(s) = Q(s)\left(I - L(s)Q(s)\right)^{-1} \tag{7}$$

where L is a linear process operator and Q is a stable filter. Since the process considered here is assumed to be nonlinear, its linearization is used in eq. (7) and it will be understood that global stability is not guaranteed. Thus, for computation of $\Lambda_{\mathcal{D}_y}$, a representative set of input disturbances ($\mathcal{D}_{yc} \subset \mathcal{D}_y$) is chosen and Q in eq. (7) is parameterized using an expression similar to eq. (2). It is easily seen that, similar to the computation of $\phi^{\mathcal{U}}_N$ (1), the optimization problem is reduced to finding the set of weights that minimizes $\Lambda_{\mathcal{D}_y}$.

An alternative approach to control-relevant nonlinearity assessment based on eq. (5) is to solve for the controller, C^*, that results in $P_{\mathcal{D}_y} = 0$ and to characterize its nonlinearity with a nonlinearity measure such as eq. (1). In this case, higher controller nonlinearity implies a higher degree of control-relevant nonlinearity for the process and performance objective. This type of analysis is consistent with optimal control-based characterization techniques, such as analysis of the system's OCS, and is not pursued here due to the analytical burden in deriving C^* for the high-order system model that will be analyzed.

III. SYSTEM MODEL AND OPEN-LOOP CHARACTERIZATION

The diabetic system model considered in this work is the metabolic model developed by Sorensen [15]. This 19^{th}-order model represents a compartmentalized view of the human body with a focus on the tissues that are relevant to the body's glucose and insulin dynamics. As compared to the single bilinear term in the model of Bergman *et al.*, the metabolic model considered in this work contains a large number of nonlinear features including several instances of the inverse tangent function. At steady-state, the model receives a baseline insulin feed of 22.33 mU/min and has a basal glucose concentration of 87.65 mg/min. To model the effects of external glucose delivery (i.e., meals) and the dynamics of glucose absorption, the meal model of Lehmann and Deutsch [27] is used.

To provide a baseline for the control-relevant nonlinearity assessment that will be performed in the next section, the system's open-loop nonlinearity is characterized using the nonlinearity measure $\phi^{\mathcal{U}}_N$ (1) over glucose concentrations in the range 70-150 mg/dL. Using a set of 28 positive and negative insulin pulse deviations, a subset of which is shown in Figure 2 along with the resulting glucose trajectories, the nonlinearity measure is computed using the linear approximation in eq. (2) with $N_l = 20$ and $\tau_i \in [2.5, 600]$ min resulting in a value of $\phi^{\mathcal{U}}_N = \mathbf{0.10}$. This low value of the nonlinearity measure implies a very low degree of system nonlinearity. In the next section, it will be shown how these results compare to the system's degree of control-relevant nonlinearity.

IV. CONTROL-RELEVANT NONLINEARITY ASSESSMENT

The focus of the control-relevant nonlinearity characterization will be the system's performance in rejecting external glucose disturbances. To begin, performance will be assessed given meals ranging in size from 12.5-50 g. These meal sizes are representative of typical breakfast, lunch, and dinner glucose quantities. The exogenous glucose infusion rate for a 50 g meal is shown in the solid line in Figure 3. The selected form for $H^*_{yd_y}$ is given as follows:

$$H^*_{yd_y} = \frac{35.03s}{(150s+1)^2} \tag{8}$$

Figure 4 is a plot of the output of eq. (8) given a 50 g meal disturbance as well as the system's open-loop response to that same disturbance. Eq. (8) is selected as it represents a decrease in the peak glucose value of greater than 50% and

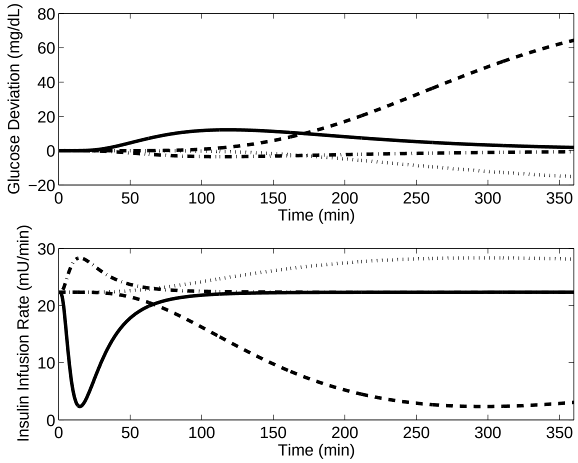

Fig. 2. Subset of the outputs (top) and inputs (bottom) used to compute the open-loop nonlinearity of the system model. Insulin delivery amounts: Solid = -670 mU, Dashed = -4500 mU, Dash-dotted = 200 mU, Dotted = 1350 mU.

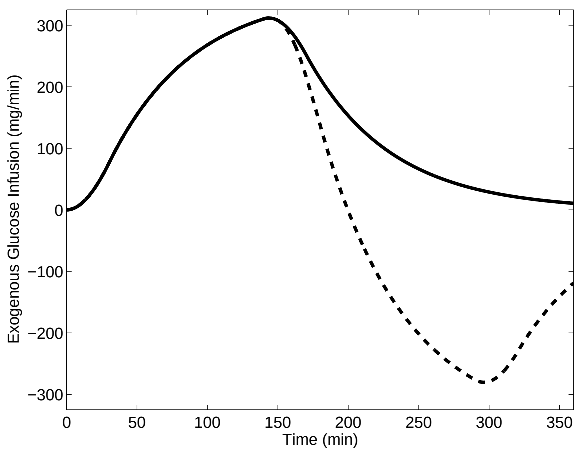

Fig. 3. 50 g meal disturbance profile (solid) and 50 g meal disturbance followed by a comparable negative deviation at $t = 150$ min (dashed).

includes an allowance for negative glucose deviations at the end of the trial due to possibly imprecise control action.

To compute $\Lambda_{\mathcal{D}_y}$, the input space, $\mathcal{D}_y$ is restricted to a set of four meals with magnitudes of 12.5-50.0 g. The stable filter, Q, in eq. (7) is parameterized as in eq. (2) where $N_l = 10$ with logarithmically-spaced $\tau_i \in [2.5, 126]$ min. The optimization is performed using Matlab's *fminunc* algorithm to a final time of 360 min (6 h). Given the performance criteria in eq. (8) and the considered meal sizes, the computed value of $\Lambda_{\mathcal{D}_y}$ is **0.10** indicating that the system can approximately meet this linear performance specification under linear control. Figure 5 compares the output of the closed-loop system under the optimized linear controller to that of eq. (8). The results show that the outputs of the closed-loop system do not quite meet the precise form of the outputs of eq. (8). There is no significant evidence of nonlinear effects. Therefore, the results imply low control-relevant nonlinearity (in agreement with the

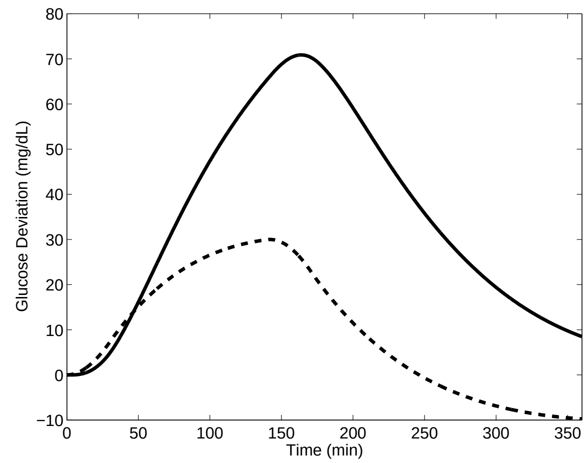

Fig. 4. Comparison of the open-loop system output (solid) and the ideal closed-loop response (dashed) given by eq. (8) for a 50 g meal disturbance.

open-loop nonlinearity assessment) and do not indicate a need to consider nonlinear control for this task.

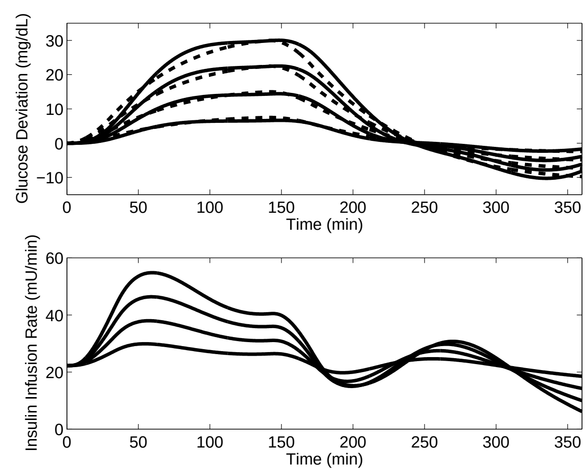

Fig. 5. Comparison of the closed-loop system output (top, solid) under optimized linear control and the ideal closed-loop response (top, dashed) given by eq. (8) for 12.5, 25, 37.5, and 50 g meal disturbances. Closed-loop insulin inputs are shown in the bottom plot.

While performance in rejecting a meal disturbance is critical in glucose control design, what is, perhaps, even more important is control during hypoglycemic deviations as these are more acutely dangerous to a patient if they reach large magnitudes. Therefore, a second qualitative type of disturbance is considered that includes both positive and negative components, an example of which is shown as the dashed line in Figure 3. Physically, this disturbance can be thought of as, perhaps, a meal followed by an excessive bolus of insulin. The system's open-loop response to this disturbance is shown in Figure 6 along with the output of eq. (8). It can be seen that a disturbance of this magnitude results in a significant negative deviation in glucose. In fact, a deviation of this magnitude is physically undesirable, but will be used as a worst-case for future comparison.

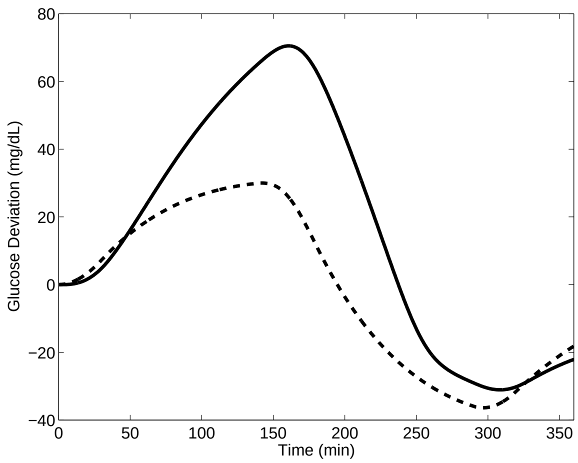

Fig. 6. Comparison of the open-loop system output (solid) and the ideal closed-loop response (dashed) given by eq. (8) for a 50 g meal disturbance followed by a comparable negative disturbance as shown in Figure 3.

Using four different magnitudes of the disturbance, the calculated value of $\Lambda_{\mathcal{D}_y}$ is **0.13**. Figure 7 includes the closed-loop outputs under the optimized linear controller and the corresponding outputs of eq. (8). Again, the results show that the system is not quite able to meet the precise shape of the output of $H^*_{yd_y}$, but, in general, the difference is acceptable. Based on the value of $\Lambda_{\mathcal{D}_y}$, the system still demonstrates low control-relevant nonlinearity as linear control approximately meets the desired performance. It is important to note that the system responses tend to approach the lower constraint on insulin infusion rate, thus adding a degree of nonlinearity to the system behavior.

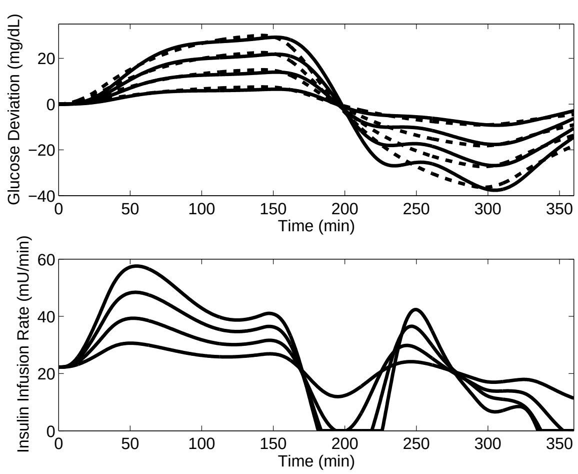

Fig. 7. Comparison of the closed-loop system output (top, solid) under optimized linear control and the ideal closed-loop response (top, dashed) given by eq. (8) for 12.5, 25, 37.5, and 50 g meal disturbances followed by comparable hypoglycemic deviations. Closed-loop insulin inputs are shown in the bottom plot.

As discussed above, the negative glucose deviations seen in Figures 6 and 7 are unacceptable for the largest disturbances, but the positive deviations are within an acceptable range. Therefore, it is investigated how closely the system can be brought to the performance of an asymmetric objective that yields a more desirable negative response, e.g.:

$$H^{*'}_{yd_y} = \begin{cases} \frac{35.03s}{(150s+1)^2} & H^*_{yd_y} d_y \geq 0 \\ \frac{35.03(1-\alpha)s}{(150s+1)^2} & H^*_{yd_y} d_y < 0 \end{cases} \tag{9}$$

The parameter, $\alpha \in [0, 1]$, in eq. (9) controls the degree of asymmetry of $H^{*'}_{yd_y}$. As α is increased, the magnitude of the desired negative response decreases. Clearly, this is nonlinear behavior that should not be achievable using linear control on this essentially linear system, but it is worth quantifying how close the output can be brought to this type of behavior under linear control to help gauge the need for nonlinear control.

For the same disturbances used in obtaining the results in Figure 7, $\Lambda_{\mathcal{D}_y}$ was calculated given the performance specification in eq. (9) as a function of α. The results, as shown in Figure 8, demonstrate that $\Lambda_{\mathcal{D}_y}$ increases with increasing α. The discontinuity that appears in Figure 8 near $\alpha = 0.80$ appears to be related to an increase in the influence of constraints. Given that the maximum value of $\Lambda_{\mathcal{D}_y}$ is 0.53 at the extreme value of $\alpha = 1$ (i.e., no hypoglycemic deviation), the results show that linear control performs well across the majority of the range of α values.

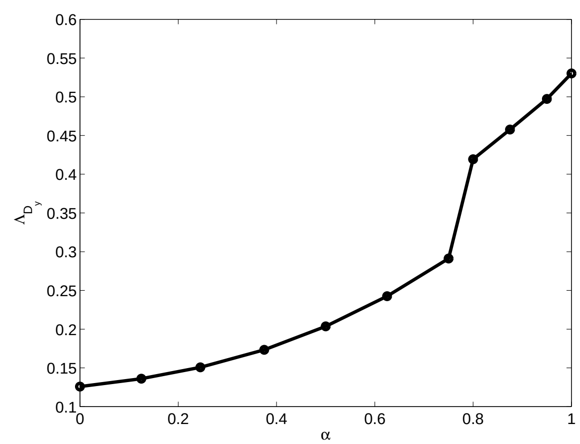

Fig. 8. Linear performance metric for the system with desired performance specified by $H^{*'}_{yd_y}$ in eq. (9) as a function of the asymmetric performance parameter, α.

To exactly demonstrate how the best-possible linear controller performs in trying to mimic the behavior of eq. (9), Figure 9 contains the closed-loop outputs for the optimized linear controllers given a set of varying α values. As the earlier results imply, the system can easily obtain the desired performance for the positive portion of the disturbance, but the performance in rejecting the negative disturbance is limited by the impact of constraints. Still, except in the region $200 \leq t \leq 250$ min, the responses closely match the desired behavior for most values of α. For the largest values of α (e.g., the $\alpha = 0.95$ result in Figure 9), the impact of constraints and the overly-aggressive reference function result in the optimal linear control response having decreased performance at early times. Based on the set of obtained $\Lambda_{\mathcal{D}_y}$ values, there is little room for improvement through the use of nonlinear control.

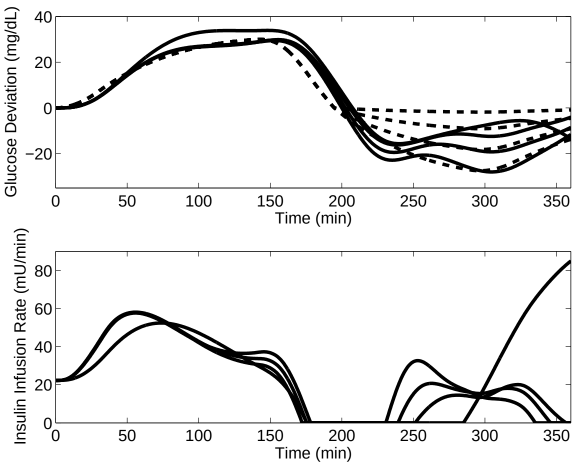

Fig. 9. Comparison of the closed-loop system output (top, solid) under optimized linear control and the ideal closed-loop response (top, dashed) given by eq. (9) for a 50 g meal disturbance followed by a comparable hypoglycemic deviation for $\alpha = 0.25, 0.5, 0.75, 0.95$. Closed-loop insulin inputs are shown in the bottom plot.

V. CONCLUSIONS

For physically-relevant performance specifications, the results provide no significant motivation for the use of nonlinear control for glucose regulation. Even in the case of an asymmetric performance objective, linear control was found to yield satisfactory levels of performance. If nonlinear control is investigated, the most likely source of significant improvement would be in the incorporation of constraint handling techniques in a linear algorithm. In general, the results of this study agree with those of the previous analysis of the model of Bergman *et al.* using different techniques.

In terms of the best design of linear controller to be used, a linear MPC algorithm with constraint handling is likely to be the best choice. The additional robustness properties of linear MPC algorithms make them preferable over less-complex algorithms (e.g., PID) for this system since the system dynamic properties are likely to change significantly over both short and long-term periods. Due to the low degree of open-loop and control-relevant nonlinearity, it is not expected that any significant changes in the model's nonlinearity would occur that would necessitate changing the controller design itself.

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