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A PID Control Algorithm for a Post-Prandial Hypoglycemic Clamp Study*

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Abstract— **Post-prandial hypoglycemia occurs 2-5 hours after food intake, in not only insulin-treated patients with diabetes but also other metabolic disorders. For example, postprandial hypoglycemia is an increasingly recognized late metabolic complication of bariatric surgery (also known as PBH), particularly gastric bypass. Underlying mechanisms remain incompletely understood to date. Besides excessive insulin exposure, impaired counter-regulation may be a further pathophysiological feature. To test this hypothesis, we need standardized postprandial hypoglycemic clamp procedures in affected and unaffected individuals allowing to reach identical predefined postprandial hypoglycemic trajectories. Generally, in these experiments, clinical investigators manually adjust glucose infusion rate (GIR) to clamp blood glucose (BG) to a target hypoglycemic value. Nevertheless, reaching the desired target by manual adjustment may be challenging and possible glycemic undershoots when approaching hypoglycemia can be a safety concern for patients. In this study, we developed a PID algorithm to assist clinical investigators in adjusting GIR to reach the predefined trajectory and hypoglycemic target. The algorithm is developed in a manual mode to permit the clinical investigator to interfere. We test the controller in silico by simulating glucose-insulin dynamics in PBH and healthy non-surgical individuals. Different scenarios are designed to test the robustness of the algorithm to different sources of variability and to errors, e.g. outliers in the BG measurements, sampling delays or missed measurements. The results prove that the PID algorithm is capable of accurately and safely reaching the target BG level, on both healthy and PBH subjects, with a median deviation from reference of 2.8% and 2.4% respectively.**

Clinical relevance— **This control algorithm enables standardized, accurate and safe postprandial hypoglycemic clamps, as evidenced in silico in PBH patients and controls.**

I. INTRODUCTION

Postprandial hypoglycemia refers to hypoglycemia that occurs after a meal — usually within 2-5 hours after eating. While this is a very common form of hypoglycemia in insulin-treated individuals with diabetes, it can also occur in other metabolic conditions. A prime example are postprandial hypoglycemic episodes that occur in patients who underwent bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB). The condition is also known as postbariatric hypoglycemia (PBH) and is increasingly recognized as a late metabolic complication of bariatric surgery, affecting up to 30% of operated individuals [1]. Patients with PBH show a distinct postprandial glycemic pattern, with a sharp glycemic rise reaching peak levels after 30 min, followed by a rapid decline leading to hypoglycemia 90-120 min after eating [2].

The underlying mechanisms are incompletely understood and most likely multi-factorial [3]. Besides excess insulin exposure (i.e. as a consequence of enhanced enteroinsulinar signaling), impaired counter-regulation to hypoglycemia is increasingly proposed to be involved in PBH physiology. Testing this hypothesis requires exploration of counter-regulatory hormones, cardiovascular responses and symptom perception in affected and unaffected individuals. To assess the role of counter-regulation independently from other factors, both cases and controls should follow the same glycemic trajectory to reach a standardized blood glucose (BG) target.

This can be achieved by using a hypoglycemic clamp experiment, in which continuous intravenous insulin infusions and variable glucose infusions (GIR) are guided by frequent BG measurements to track a desired glycemic target [4]. There are two main categories of algorithm-directed glucose clamp techniques: manual systems require the investigator to execute the suggested GIR following entry of BG measurements. In fully automated systems, both operations are managed automatically by closed-loop algorithms, without the need for user input. Whereas the latter offers the highest level of convenience, the former allows for dose adjustment based on clinical reasoning.

Accurately controlling glycemia is as prerequisite for high quality clamp experiments due to the following reasons. First, driving glucose levels to the desired target in cases and control is important for obtaining results of high validity. Second, activation of counter-regulatory responses requires BG levels to be at sufficiently low levels (e.g. 2.5 mmol/L), meaning that possible undershoots of target BG may be hazardous for patients. Third, this experimental technique is time-consuming, resource-intensive and burdensome to participants and must therefore operate smoothly. Thus, the need for accurate, reproducible and convenient experiments should prompt clinical researcher to use of automated clamp techniques. However, automated clamp technique require dedicated tools and infrastructure, need to be validate and follow state of the art principles [4].

The aim of this work is to present a proportional-integrative-derivative (PID) control algorithm for manual hypoglycemic clamp experiments to explore counter-regulatory responses in patients with suspected neuroendocrine dysregulations (e.g. PBH) and control subjects. The algorithm should

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assist clinical investigators in achieving accurate, safe and convenient control of BG concentrations by suggesting the correct GIR. The algorithm is tested in silico to assess its performances in achieving an accurate control of glucose levels, as well as its robustness to noise, outliers and delayed or missed BG measurements.

II. Methods

A. Problem formulation

We will indicate the time grid as $t_1, t_2, \ldots, t_N$, with t_k being the current sampling instant. Ideally, BG measurements and control actions would be sampled with sampling period (T_s) of 5 min. Nevertheless, we assume possible sampling jitter due to non-automatic measurement.

The measured output we aim to control is patient's blood glucose (BG) level, $y(t_k) \in \mathbb{R}$ (mmol/l). BG concentration may be perturbed by oral glucose intake, $d(t_k) \in \mathbb{R}$ (g), or by external insulin administration, $i(t_k) \in \mathbb{R}$ (ml/min). Glucose intake is expected to cause a rise of BG concentration, eventually followed by an abrupt decrease if the subject is affected by PBH. Insulin will instead lower glucose concentration, regardless of the population under exam.

The manipulated variable in this control problem is glucose infusion rate, $g(t_k) \in \mathbb{R}$ (ml/min). It is adjusted in order to guarantee patient's safety and to adhere to a desired reference value, $r(t_k) \in \mathbb{R}$ (mmol/l).

B. Controller

For the control algorithm, we chose to adopt a classical PID formulation. The suggested glucose infusion rate is therefore computed by the controller as

$$g(t_k) = g_P(t_k) + g_I(t_k) + g_D(t_k), \tag{1}$$

where

$$g_P(t_k) = K_P \cdot e(t_k), \tag{2}$$

$$g_I(t_k) = g_I(t_{k-1}) + K_I \cdot e(t_{k-1}) T_s, \tag{3}$$

$$g_D(t_k) = -K_D \cdot \frac{y(t_k) - y(t_{k-1})}{t_k - t_{k-1}}. \tag{4}$$

and

$$e(t_k) = r(t_k) - y(t_k) \tag{5}$$

is the tracking error.

In other words, $g_P(t_k)$, corresponds to a control action that is proportional to $e(t_k)$. The action $g_I(t_k)$ is proportional to the integral of e until time t_k, which is discretized via forward Euler formulation. This action is initialized at $g_I(t_1) = 0$. The last term in (1), $g_D(t_k)$, corresponds to an action that is proportional to the derivative of y at time t_k, which is approximated on the last two measurements of BG. The parameters K_P, K_I and $K_D \in \mathbb{R}^+$ weight the trade-off between the different terms of the transfer function. These values were tuned by trial and error, testing the impact of different parameters combinations on the final control achieved in virtual subjects, simulated by means of the simulator described in section III-A (in silico manual tuning). Their values were set to $K_P = 30$, $K_I = 1$ and $K_D = 1$.

We aim to reach a hypoglycemic target of 2.5 mmol/l, which implies that glycemic undershoots may lead to a safety risk for patients. To decrease the risk of undershoots, we designed the reference $r(t_k)$ to smoothly decrease towards hypoglycemia as follows:

$$r(t_k) = \begin{cases} 3.885 & \text{if } \Delta t \leq 25 \\ 3.885 - 0.037(\Delta t - 25) & \text{if } 25 \geq \Delta t < 55 \\ 2.775 - 0.018(\Delta t - 55) & \text{if } 55 \geq \Delta t < 70 \\ 2.5 & \text{if } \Delta t \geq 70 \end{cases} \tag{6}$$

with Δt being the difference between the current instant t_k and the instant when the operator activated the control algorithm, t_{PID}.

A main concern in this control problem is that control actions are not actuated automatically, but are triggered whenever clinicians ask the controller for a suggestion. Although we expect the operator to respect the sampling period for most of the experiment, some specific foresight needs to be taken in order to guarantee the robustness of the controller to missing measurements and non-compliance to the sampling period. Therefore, specific corrections to the control actions are imposed downstream of the computation of the various components of (1) to increase the robustness and safety of the algorithm.

Two possible kinds of corrections are applied to the integral action depending on how much time Δ_{last} has passed since the last measurement. If $\Delta_{last} \geq 9$ min and $\Delta_{last} \leq 20$ min, the formula in (3) for the update of the accumulated error is temporarily replaced with a more accurate estimate of the integral, i.e. via trapezoidal rule:

$$g_I(t_k) = g_I(t_{k-1}) + K_I \cdot \frac{1}{2}(e(t_k) - e(t_{k-1}))(t_k - t_{k-1}). \tag{7}$$

On the other hand, if $\Delta_{last} \geq 20$ min, then $g_I(t_k)$ is set to 0 in order to avoid abrupt increases of the integral action.

When $\Delta_{last} \leq 2$ min, the derivative action $g_D(t_k)$ is set to 0 in order to avoid possibly over-aggressive derivative actions due to measurement errors or outliers. Similarly, when $\Delta_{last} \geq 15$ min, $g_D(t_k)$ is set to 0 in order to avoid aggressive actions due to large changes in y.

A second aspect to consider in this control problem is that the manipulated variable $g(t_k)$ cannot result in negative values. In order to avoid possible integrator wind-up, we implemented an anti-windup scheme and any negative value of g_I is set to 0. Furthermore, possible negative GIR suggestion are saturated to 0.

III. Experimental set-up

A. Simulator

The control algorithm has been tested in silico by means of two large-scale computer models that mimic the metabolisms of the populations under study. For the healthy subjects of the control group, i.e. intact gastro-intestinal tract, we used the healthy subject simulator of glucose-insulin dynamics presented in Dalla Man et al. [5]. Due to space limitations, we refer the reader to the original paper [5] for a comprehensive presentation of the model equation and of its parameters.

The PBH group was simulated using the same model structure, but modifying the values of the parameters associated to the gastro-intestinal subsystem. PBH subjects are characterized by increased emptying rate of liquid phase glucose from gastric pouch into the intestine [2]. In view of this, the parameter k_{empt} in [5] was increased to better emulate PHB data previously collected, resulting in a final increase of 20 times.

Both simulators are equipped with a cohort of 100 different virtual subjects, i.e. 100 different sets of parameters of the insulin-glucose model, which well represent the inter-subject variability observed in real patients.

We also designed a model for BG measurement. We supposed that samples are obtained with YSI analyzer [6], that is, one of the most widely accepted BG measuring systems, and applied a white Gaussian noise with standard deviation 0.1 mmol/l to the measurements $y(t_k)$. Despite of the accuracy of the instrumentation, measurements are also susceptible to errors due to the sampling process and to the operator. We assume that any measurement may be affected, with a probability p_{out}, by a larger error sampled from a Gaussian distribution with mean -0.5 mmol/l and standard deviation 0.2 mmol/l.

Since measurements are manually sampled, we also assumed the sampling period will – most likely – slightly vary between measurements. We simulated this sampling jitter by applying a delay

$$delay(t_j) = \left\lfloor n(t_j) \cdot T_s \right\rfloor \tag{8}$$

to the j-th measurement, $\forall j \in \{1,\dots,N\}$, with $n \in \mathscr{U}([0,1])$. Moreover, one sample may be missed with probability p_1 and two consecutive samples may be missed with probability p_2, as it will be described in Section III-C.

B. Experimental protocol

The aim of the experiment is to drive BG concentration to a hypoglycemic plateau of 2.5 mmol/l. The plateau should start at minute 160 and last 20 min.

Experiments last 4 hours. At minute 0, patients will consume 15 grams of oral glucose. Hypoglycemia will be induced by means of a primed insulin infusion, starting at minute 90 of the experiment. The primed insulin infusion consists of a priming insulin bolus of 0.05 ml/Kg $\cdot BW$, where BW is patient's body weight (Kg), and a constant insulin infusion rate of 0.04 ml/m^2/min$\cdot BSA$, where BSA (m^2) is the patient's body surface area. Together with insulin infusion, GIR suggestions will also be activated at $t_{\text{PID}} = 90$.

C. Simulation scenarios and robustness tests

In order to test the robustness of the control algorithm, its performances are evaluated in three different scenarios with increasing sources of variability and errors:

- Scenario 1: No measurement errors or sampling jitter.
- Scenario 2: Measurement noise, $p_{\text{out}} = 1\%$, no sampling jitter and no missed samples.
- Scenario 3: Measurement noise, $p_{\text{out}} = 1\%$, sampling jitter and missing samples ($p_1 = 10\%$ and $p_2 = 2.5\%$).

D. Metrics

There are two main categories of metrics that we consider for this study: those associated to the performances of the controller and those associated with patients' safety. Concerning the first category, we will consider the mean and standard deviation of glucose levels during the expected hypoglycaemic plateau (μ_{plateau} and σ_{plateau}), i.e. between minute 160 and 180 of the experiment. For what it concerns subjects' safety, we will consider the minimal glucose level and the percentage of time spent in three increasingly dangerous hypoglycemic regions: BG $\in$ [1.6-2.2] mmol/l (HR1); BG $\in$ [1.1-1.6] mmol/l (HR2); BG $<$ 1.1 mmol/l (HR3).

IV. Results

Table I reports the results obtained in simulation, stratified by population (PHH vs control) and scenarios.

Regardless of the scenario, the average glucose level during the hypoglycemic plateau is in median equal to 2.44 mmol/L with PBH patients and 2.43 mmol/L with control patients, i.e. 2.4% and 2.8% less than the desired reference of 2.5 mmol/l, respectively. The range [5$^{\text{th}}$, 95$^{\text{th}}$] percentile highlights the differences among populations and scenarios. Generally, the controller achieve a very tight control for PBH patients, which only slightly worsen with the increase of variability. The percentile range spans from [2.39, 2.48] mmol/l in Scenario 1, i.e. [-4.4%, -0.8%] than the reference, to [2.32, 2.62] mmol/l in Scenario 3, i.e. [-7.2%, +4.8%] than the reference. Control subjects are instead less susceptible to these sources of variability and show very marginal differences among different scenarios. On the other hand, they show a larger variability between subjects, with the 95$^{\text{th}}$ percentile reaching up to 3.04 mmol/l in Scenario 2, i.e. +21.6% than the desired target but still in severe hypoglycemia. This may be due to a wider variability of insulin sensitivity in this virtual population.

Standard deviations of BG at the targeted hypoglycemic plateu highlight a larger glycemic variability when the sources of errors and variability increase: in Scenario 1 and 2, PBH patients and controls have a standard deviation of 0.04 mmol/l in median; this value increases in Scenario 3, up to 0.05 and 0.06 mmol/l, respectively. Noticeably, the 95$^{\text{th}}$ percentile increases from 0.04 mmol/l in Scenario 1 to 0.36 mmol/l in Scenario 3 with PBH subjects and from 0.14 mmol/l in Scenario 1 to 0.22 mmol/l in Scenario 3 with control subjects. The intervals mean $\pm$ standard deviation of BG are reported in Fig. 1, Fig. 2 and Fig. 3.

Similar to the previous metrics, those related to patients' safety are also affected by the variability of the different scenarios. The minimal glucose level in PBH subjects is in median 2.42, 2.41 and 2.35 mmol/l in scenarios 1, 2 and 3 respectively. For the control group, it is 2.4, 2.39 and 2.35 mmol/l. Despite of the increased variability and realism of the testing scenarios, the control algorithm is capable of achieving a safe glucose control. In median, the time spent in HR1 is 0 in every scenario and for both populations. The 95$^{\text{th}}$ percentile is 15 minutes in PHH subjects and 7 minutes in the control group. HR2 and HR3 are never reached.

TABLE I

RESULTS FOR THE VARIOUS METRICS, STRATIFIED BY POPULATION AND SCENARIO, REPORTED AS MEDIAN [5TH PERCENTILE, 95TH PERCENTILE].

	Scenario 1		Scenario 2		Scenario 3	
	PHH	Control	PHH	Control	PHH	Control
$\mu_{plateau}$ (mmol/l)	2.44 [2.39,2.48]	2.43 [2.39,3.03]	2.44 [2.39,2.57]	2.43 [2.38,3.04]	2.44 [2.32,2.62]	2.43 [2.36,3.01]
$\sigma_{plateau}$ (mmol/l)	0.04 [0.03,0.04]	0.04 [0.03,0.14]	0.04 [0.03,0.16]	0.04 [0.03,0.16]	0.05 [0.02,0.36]	0.06 [0.03,0.22]
min glucose level (mmol/l)	2.42 [2.36,2.45]	2.40 [2.35,2.44]	2.41 [1.90,2.44]	2.39 [1.75,2.43]	2.35 [1.80,2.44]	2.35 [1.87,2.43]
time spent in HR1 (min)	0 [0,0]	0 [0,0]	0 [0,5]	0 [0,5]	0 [0,15]	0 [0,7]
time spent in HR2 (min)	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]
time spent in HR3 (min)	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]	0 [0,0]

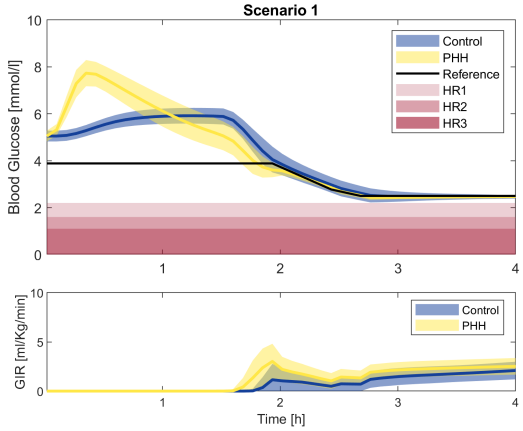

Fig. 1. BG and GIR in Scenario 1. Results are reported as mean (thick line) ± standard deviation over the two populations.

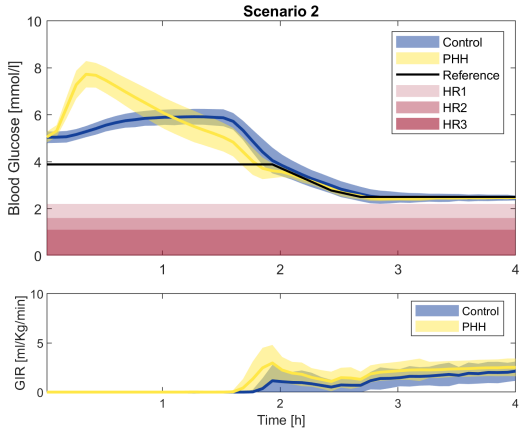

Fig. 2. BG and GIR in Scenario 2. Results are reported as mean (thick line) ± standard deviation over the two populations.

V. CONCLUSIONS

Exploration of counter-regulation to hypoglycemia is key in understanding the pathophysiology of hypoglycemic disorders such as PBH. To this end, comparison of the response to a standardized hypoglycemia in affected and unaffected individual can provide further insights. However, achieving an accurate hypoglycemic clamp by manually adjusting GIR according to clinical judgement is nontrivial, possibly risky and susceptible to investigator bias.

In this work, we propose a PID control algorithm for

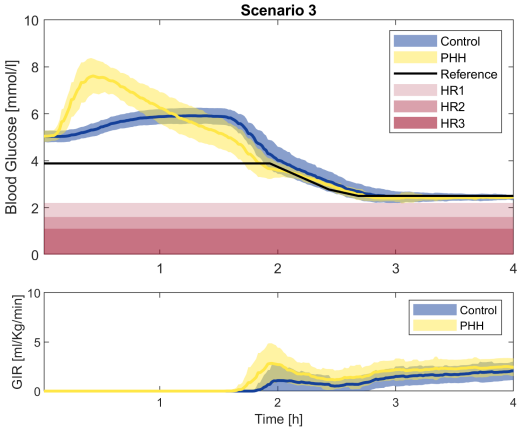

Fig. 3. BG and GIR in Scenario 3. Results are reported as mean (thick line) ± standard deviation over the two populations.

supporting clinical investigators in the decision of the correct GIR during hypoglycemic clamps studies. This PID algorithm has been tested in silico to assess its accuracy and safety in both PBH and healthy subjects and to test its robustness to increasingly more realistic scenarios.

The control algorithm achieved consistently positive results in the two populations despite of the presence of noise, outliers and sampling jitter, with at worst a median deviation from the desired target of 2.4% and 2.8% for the PBH and control group respectively. Furthermore, no safety concerns were raised during the simulations.

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