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Bio-Behavioral Control, Glucose Variability, and Hypoglycemia-Associated Autonomic Failure in Type 1 Diabetes (T1DM)

Marc D. Breton, Leon S. Farhy, Jennifer K. Penberthy, Boris P. Kovatchev
School of Medicine, University of Virginia

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Abstract

In this paper we present a mathematical model and a computer simulation of the relationship between behavioral control of Type 1 diabetes (T1DM), blood glucose (BG) variability, and hypoglycemia-associated autonomic failure (HAAF). A stochastic behavioral self-control process was coupled with a dynamical system simulation of the dampening effect of counterregulation on BG oscillations. The resulting bio-behavioral control system was able to reproduce characteristics of hypoglycemic events in the field, such as temporal clustering of hypoglycemic episodes associated with HAAF, and occurrence of severe hypoglycemia as a result of periods of HAAF augmented by increased BG variability.

1. Introduction

In health, blood glucose (BG) is tightly controlled by a hormonal network that includes gut, liver, pancreas and brain, ensuring stable fasting BG levels ($\sim 80-100 mg/dl$) and transient postprandial glucose fluctuations. Diabetes is a combination of disorders characterized by absent or impaired insulin action, resulting in hyperglycemia. Intensive insulin and oral medication treatment to maintain nearly normal levels of glycemia markedly reduces chronic complications in both Type 1 (T1DM, [1]) and Type 2 diabetes (T2DM, [2]), but may risk potentially life-threatening severe hypoglycemia (SH) - a result from imperfect insulin replacement, which may reduce warning symptoms and hormonal defenses [3]. Consequently hypoglycemia has been identified as the primary barrier to optimal diabetes management [4]. Thus, people with T1DM and T2DM face a life long behaviorally controlled optimization problem: to maintain strict glycemic control without increasing their risk for hypoglycemia [5]. This struggle for tight glycemic control results in large BG fluctuations over time, a process influenced by many external factors, including the timing and amount of insulin injected, food eaten, physical activity, etc. In other words, BG fluctuations in diabetes are the measurable result of the action of a complex dynamical system influenced by many internal and external factors. The macro (human)-level optimization of this system depends on self-treatment behavior. Because in the autoimmune form of diabetes, T1DM, internal insulin secretion is destroyed, this optimization is entirely dependent on the three feedback processes presented in Figure 1 a: (i) behavioral maintenance, (ii) interaction between exogenous insulin and carbohydrate utilization, and (iii) internal hormonal defenses against hypoglycemia known as hypoglycemia counterregulation. Approached from a systems biology point of view, the bio-behavioral control of T1DM is therefore comprised of: (i) a process of commonly stable glucose fluctuation interrupted by generally random hypoglycemia-triggering behavioral events (e.g. insulin overdose, missed food, or excessive exercise [6, 7]), (ii) an internal processes of glucose uptake depending on a person's insulin sensitivity [8], and (iii) counterregulation that counteracts induced hypoglycemia, but also suffers from occasional depletion of counterregulatory reserves due to repeated hypoglycemia and known as hypoglycemia-associated autonomic failure (HAAF) observed in both T1DM [9] and T2DM [10]. Studies show that the replenishment of counterregulatory reserves can be achieved through avoidance of mild hypoglycemia [11]; the recovery process has been estimated to take several days, likely at least 72 hours [12].

In this paper we propose a model quantifying the interplay between behavior and physiology via integration of previously unrelated concepts: behavioral control of T1DM and HAAF. The model explains key features of the occurrence of hypoglycemia in the field: clustering of hypoglycemic episodes in time [13] and occurrence of SH within periods of increased glucose variability [12]. The model is descriptive, not discussing in detail the specific physiology of glucose-insulin interaction, which is a subject of a number of studies based on the classic minimal model of glucose dynamics [8].

2. Methods

The mathematical model describing the relationships between self-treatment behavior, hypoglycemia and HAAF is based on the following assumptions grounded in previous research: (i) BG fluctuations in T1DM are driven by insulin-glucose interaction and are dampened down by counterregulatory reserves that protect against extreme hypoglycemic deviations; (ii) Combinations of behavioral events trigger hypoglycemia, which increases the chance of a subsequent hypoglycemic episodes due to depleted counterregulatory reserves; (iii) avoidance of hypoglycemia restores counterregulatory ability. Specifically:

2.1. Behavioral triggers of hypoglycemia:

In order to formally describe the external behavioral process we have previously introduced a stochastic model of self-regulation behavior, which gives a probabilistic description of the pattern: internal condition - perception/awareness - appraisal - self-regulation decision [14]. The idea behind it is that internal events, such as low (or high) BG episodes, are followed by self-regulation behavioral sequences that, if inappropriate, could lead the patient to SH (or extreme hyperglycemia), and if appropriate, lead to avoidance of these extreme situations. In particular, behavioral self-regulation can be approximated by a generally periodic renewal process with a significant random component, which causes downward and upward BG shifts. We model this process as a Wiener process (normally distributed intervals between events). On rare occasions this process escalates into behaviorally induced hypoglycemia, which is a result from the superposition of several low-probability events. Thus, the process of behaviorally induced hypoglycemic events can be approximated by a Poisson process depending on a subject's control and experience. Thus, the probability of having exactly n events (severe hypoglycemia and hyperglycemia) within a time t is given by $P_n(t) = e^{-\lambda t}\frac{(\lambda t)^n}{n!}$.

2.2. Glucose uptake, HAAF and counterregulatory replenishment:

Recurrent hypoglycemia may cause increase of insulin-mediated glucose uptake by increasing insulin sensitivity [15], as well as certain depletion of a person's counterregulatory reserves $P_{CR}(t)$. $P_{CR}(t)$ is fully restored in 72 hours, 24-hours for half restoration. The depletion of $P_{CR}(t)$ changes the characteristics of the insulin-glucose oscillator reducing its dampening capability. Both increased glucose uptake and the depletion of $P_{CR}(t)$ increase the risk for subsequent hypoglycemia and augment the process of behaviorally-induced hypoglycemic events by an additional physiologic component. We use the framework of dynamic systems to model these phenomenon, see Figure 1 b.

The model is based on 3 main equations, see model 1; the first one controls the dynamics of blood glucose via an ideal behavioral loop (first term, right hand side), two superposed stochastic processes (bundled into the *kicks* term) simulate abnormal behaviors like, but not restricted to, meals or exercise, and finally a counterregulatory term (CR). CR (second equation) is both dependent on the available CR pool (P_{CR}) and the level of blood glucose (BG). Finally, the third equation controls P_{CR}, the coefficient r is chosen so replenishment is attained within 72h of the last hypoglycemic episode, with a 50% replenishment at 24h.

$$\begin{aligned}\left(\frac{\partial BG}{\partial t}\right)_t &= -a\,\frac{\left(\frac{BG(t-\tau)}{t_1}\right)^{n_1}}{1+\left(\frac{BG(t-\tau)}{t_1}\right)^{n_1}}BG(t) \\ &\quad +b\,FastBG - kicks(t) + cCR(t) \\ CR(t) &= \frac{\left(\frac{2P_{CR}(t)}{P_{CR_{max}}}\right)^{n_2}}{1+\left(\frac{2P_{CR}(t)}{P_{CR_{max}}}\right)^{n_2}} \times \frac{1}{1+\left(\frac{BG(t)}{t_3}\right)^{n_3}} \\ \left(\frac{\partial P_{CR}}{\partial t}\right)_t &= r(P_{CR_{max}} - P_{CR}(t)) - CR(t)\end{aligned} \quad (1)$$

2.3. Subjects and Data Collection Procedure

The field study recruited 85 with T1DM. The participants in the field study had average age of 44.3 ± 10 years, average duration of diabetes of 26.4 ± 10.7 years; 44 were males. All subjects used LifeScan One Touch BG meters for self-monitoring 3-5 times daily and recorded the date and time of SH episodes in diaries. For each subject, the timing of SH episodes was located in the temporal stream of BG readings recorded by the meter; BG characteristics were computed in 24-hour increments timed from SH.

3. Results

3.1. Modeling the effects of hypoglycemia:

Figure 2 presents the results of our simulation: In T1DM the natural feedback loop from BG to insulin is disrupted because there is practically no endogenous insulin (and exogenous insulin is not dependent on internal feedback). Thus, the only dampening of the system is exerted by its counterregulatory loop, which contributes to recovery from hypoglycemia. A hypoglycemic episode depletes the counterregulatory response, which, if not fully recovered, increases the risk of a subsequent hypoglycemia and results in a general increase of the magnitude of BG fluctuations:e.g a severely depleted pool (dotted line) resulted in a SH episode at hour 47 (2.5 mmol/L, 4mmol/L in normal P_{CR} conditions)).This effect is augmented by increased glu-

cose uptake following hypoglycemia. The model-derived time course of increasing BG amplitude is close to the time course observed in previous animal studies, suggesting that this model explains realistically the effects of recurrent hypoglycemia [15]. The model also explains the clustering of hypoglycemic episodes in time that has been observed in our previous studies [16].

3.2. BG patterns preceding SH episodes:

The modeling and simulation results were confirmed by the field study that identified a specific glycemic pattern of increased glucose variability and a series of mild hypoglycemic episodes occurring prior to SH. A clear indicator of upcoming SH episode was a highly significant ($p<0.001$) increase in the relative risk for hypoglycemia, e.g. $\frac{LBGI_{24h}}{LBGI_{month}}$. $LBGI_{\tau}$ is related to glucose variability during τ, see [17] for precise definition and validation of LBGI. Once this "system disturbance" occurs, it takes ~ 3 days for the BG level to become normalized. Thus linking the state of the counterregulatory pool to glucose variability(simulation above), and glucose variability to SH episodes (simulation and field study).

4. Conclusions

A combined modeling / computer simulation / data analysis approach explains the relationship between behaviorally induced hypoglycemia, glucose variability and autonomic failure in T1DM. This explanation is valuable not only because it indicates that signs of HAAF can be detected from routine self-monitoring in patients' natural environment, but also because it allows for algorithmic prediction of imminent SH/MH. This latter task is increasingly important, given that automated glucose control is now a high priority in the development of future therapies for T1DM. In particular, the creation of bio-behavioral algorithms predicting the risk of significant glucose control disturbances may prove to be a critical step towards the artificial pancreas of the future.

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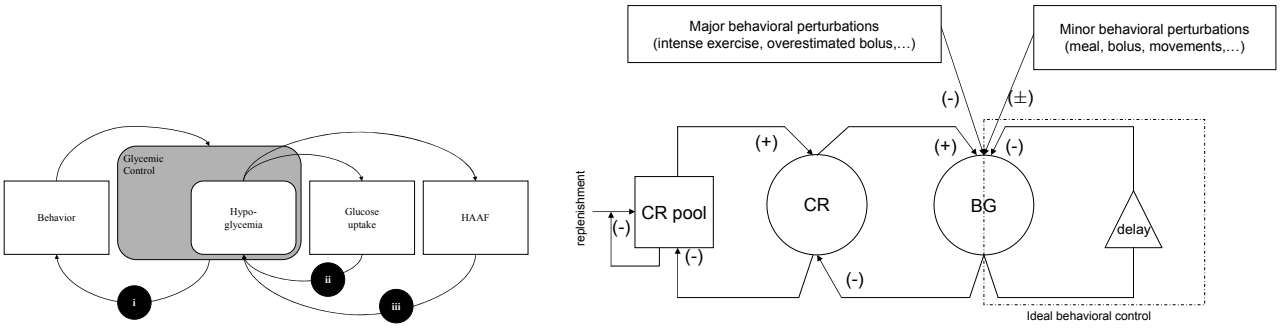

Figure 1. a: Feedback Loops **b:Behaviorally controlled BG system**

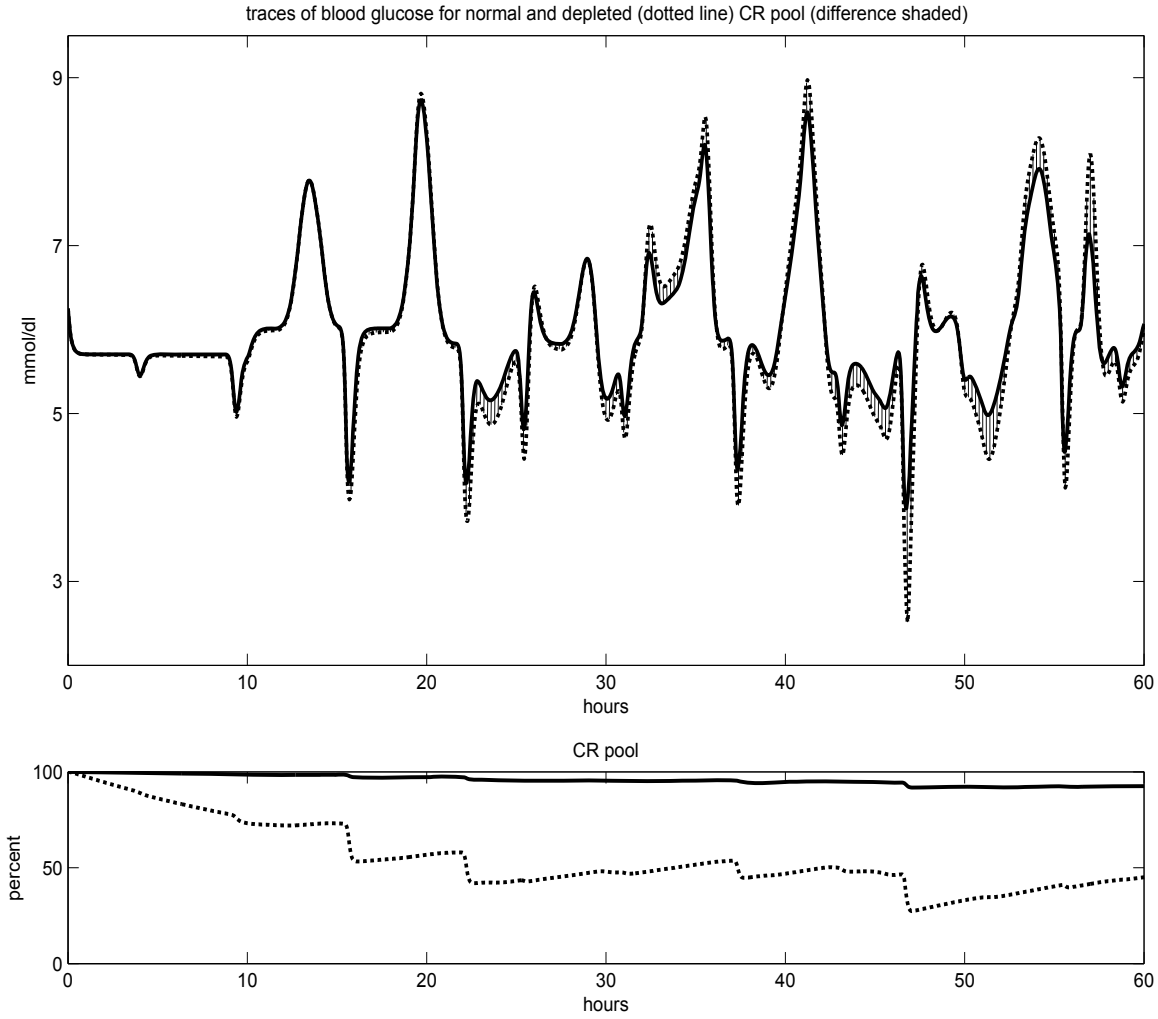

Figure 2. Effect of decreased CR pool on glucose variability and hypoglycemia.