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Determination of personalized diabetes treatment plans using a two-delay model

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HIGHLIGHTS

- We use a two-delay model to investigate personalized treatment options for diabetes.
- The model describes maintenance of T2D oscillations with exercise and medication.
- Insulin therapy and an additional hour of exercise reduces need for sulfonylureas.
- These strategies could be of immediate use in the design of an artificial pancreas.

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ABSTRACT

Diabetes cases worldwide have risen steadily over the past few decades, lending urgency to the search for more efficient, effective, and personalized ways to treat the disease. Current treatment strategies, however, may fail to maintain oscillations in blood glucose concentration that naturally occur multiple times per day, an important element of normal human physiology. Building upon recent successes in mathematical modeling of the human glucose–insulin system, we show that both food intake and insulin therapy likely demand increasingly precise control over insulin sensitivity if oscillations at a healthy average glucose concentration are to be maintained. We then model and describe personalized treatment options for patients with diabetes that maintain these oscillations. We predict that for a person with type II diabetes, both blood glucose levels can be controlled and healthy oscillations maintained when the patient gets an hour of daily exercise and is placed on a combination of Metformin and sulfonylurea drugs. We note that insulin therapy and an additional hour of exercise will reduce the patient's need for sulfonylureas. Results of a modeling analysis suggest that, with constant nutrition and controlled exercise, the blood glucose levels of a person with type I diabetes can be properly controlled with insulin infusion between 0.45 and 0.7 μU/ml min. Lastly, we note that all suggested strategies rely on existing clinical techniques and established treatment measures, and so could potentially be of immediate use in the design of an artificial pancreas.

1. Introduction

The number of cases of diabetes in the United States has doubled since 2000 and more than tripled since 1990, with current figures estimating about 25.8 million cases (Centers for Disease Control and Prevention, 2011, 2012). The term “diabetes” refers to a range of conditions, varying in origin and severity, characterized by chronic high levels of glucose in the blood, which can lead to peripheral neuropathy, cardiovascular disease, blindness, and even death (American Diabetes Association, 2003; Boulton, 1998; Kannel and Mcgee, 1979). Type I diabetes (T1D) is caused by autoimmune attack on the insulin-producing pancreatic β-cells. Its onset is largely dictated by genetic factors, and the disease is usually present from early in life (Daneman, 2006). Type II diabetes (T2D) is characterized by decreased sensitivity to insulin, making it more difficult for muscle and adipose cells to utilize glucose and eventually impairing insulin secretion by pancreatic β-cells (Stumvoll et al., 2005). While generally less severe, T2D is also much more common and possesses many risk factors ranging from genetics and disease to obesity and environment. Each case is unique and no two people have the same ability to utilize glucose, the same insulin production rate, or the same

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lifestyle; it is therefore of great importance for an individual's treatment plan to be tailor-made for his or her specific condition.

The American Diabetes Association (ADA) recommends a combination of diet, exercise, medication, and insulin therapy to treat diabetes. These treatments are used to lower blood glucose concentration (BGC) to a healthy level (American Diabetes Association, 2013). However, another important factor is often overlooked: blood glucose levels in individuals without diabetes also fluctuate by about 10% every two hours or so. These so-called *ultradian oscillations* (i.e., taking place multiple times each day) were first noted by Hansen in 1923, and various studies since have underlined their prominence and functional importance in regulating glucose concentration (Drozdov and Khanina, 1995; Hansen, 1923; Simon et al., 1987, 2000). The root cause of these oscillations is not fully understood, though evidence suggests that delayed feedback between insulin-producing pancreatic β-cells and the liver may be a significant contributing factor (Li et al., 2006a). As these oscillations are natural and observed in healthy glucose and insulin dynamics, any effective model of disease or therapy should aim to maintain these oscillations.

With no known cure for diabetes, lifelong treatment is generally the only option. This treatment is often strenuous; most patients with diabetes take medications regularly and must closely monitor their exercise levels and dietary intake. Persons with T1D or advanced T2D must additionally check their blood glucose levels and inject insulin multiple times per day. Because of this, much interest has recently developed around creating devices that automate day-to-day control of diabetes (Cobelli et al., 2011). Such a device – often referred to as an *artificial pancreas* – can respond to physical activity and changes in blood glucose concentration by injecting fast-acting insulin analogs and alerting patients when they must take their medication. This, in turn, has great potential to reduce the personal burden on those living with diabetes.

With these points in mind, our goal is to develop a systematic strategy to model and formulate a personalized treatment plan for lowering the BGC of a person with diabetes to within the ADA-specified range (between 70 and 130 mg/dl before meals (American Diabetes Association, 2008)). This treatment plan should retain the ultradian glucose oscillations observed in healthy individuals and should rely on existing standard treatment measures, i.e. diet, exercise, insulin therapy, and/or medication. It should be straightforward enough to be programmed into a medical device such as an artificial pancreas. Finally, the information necessary to personalize the treatment plan should be readily available from existing clinical procedures. To accomplish these goals we will study a mathematical model of the human glucose–insulin system that explicitly accounts for the treatment methods proposed by the ADA.

This work builds upon a foundation of previous models of the human glucose and insulin system. Of particular note are those by Sturis et al. (1991), who presented the foundational model of the system; Drozdov and Khanina (1995) who first incorporated a time delay to account for the lag in hepatic glucose production; and Li et al. (2006a) who incorporated a second time delay to account for the lag in insulin release, and who established the model most closely associated with the one we present here. Makroglou et al. (2006) provide a detailed summary of these and other important models in the field. The work we present marks a shift in focus from much of what precedes it; the existing literature largely emphasizes the effect of the two time delays on system's stability, but little has been done to explicitly analyze the effects of medication and exercise (Giang et al., 2008; Li and Zheng, 2010; Pei et al., 2010). By explicitly accounting for these factors, we hope to shrink the gap between theoretical models and clinical practice, providing individualized information that can inform clinical care, and to help guide the production of personalized medical technology.

We present the model in Section 2. In Section 3 we identify the conditions under which a person's BGC will reach an acceptable range and will oscillate. To illustrate how this method can be put into practice, we perform a hypothetical case study in Section 4, in which we set forth viable plans to treat persons with T1D and T2D. We conclude with our results in Section 5 and propose areas for further research (Table 1).

2. Model presentation

We begin with a schematic model of the human glucose–insulin system, illustrated in Fig. 1. We first note that glucose concentration (G) can increase via two pathways: (1) ingestion and (2) endogenous production. For simplicity, we only model glucose release from the liver, commonly called *hepatic production*. We first consider ingestion, which we represent by the glucose intake rate G_{in}. We make this term constant because, if it were instead periodic (as in the case of multiple daily meals), ultradian glucose oscillations would automatically be induced. Simon et al. (1987) demonstrated that ultradian glucose oscillations exist in healthy individuals even when ingesting glucose at a constant rate, and we want to ensure that our model accounts for this behavior.

We next consider hepatic glucose production, described by $f_1(I(t-\tau_2))$. The equation for f_1 is given in Table 2 and its shape in Fig. 2. Insulin inhibits hepatic production, so it makes sense that f_1 would be a decreasing function of insulin concentration. Furthermore, there is a well-documented time delay between when insulin reaches the liver and when the liver responds by adjusting glucose production rate (Li et al., 2006a). We denote this delay as τ_2, the amount of time (in minutes) required for a change in insulin concentration to affect hepatic glucose production.

Glucose concentration can also decrease via two pathways, namely (1) utilization by the central nervous system and (2) utilization by muscle and fat cells. Glucose utilization by the central nervous system (CNS) does not depend on insulin concentration; these cells will use all of the glucose available to them up to a

Table 1
Parameter values for model equations (1) and (2).

Parameters	Units	Range	Meaning
β	–	0–1	Relative pancreatic β-cell function
γ	–	0–1	Relative insulin sensitivity
G_{in}	mg/dl min	0–1.08	Glucose intake rate
I_{in}	μU/ml min	0–2	Insulin infusion rate
K_M	μU/ml	2300	Insulin degrading enzyme's half-saturation concentration
m	min	0–120	Daily minutes of physical activity
m_b	min	60	Baseline minutes of physical activity
s	1/min	0.0072	Rate of insulin sensitivity increase per minute of exercise
V_{max}	μU/ml min	150	Maximum insulin clearance rate