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Nonlinear Insulin to Carbohydrate Rule for Treatment of Type 1 Diabetes

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Abstract: This paper develops a nonlinear insulin to carbohydrate rule for use by type 1-diabetes patients. The goal is to refine the commonly used Insulin to Carbohydrate Ratio (ICR) formula. The latter is a strictly linear rule relating carbohydrates consumed to insulin infusion. The new relationship presented in this paper is nonlinear and depends on the availability of a nonlinear dynamic model describing a patient's blood glucose response to food and insulin. Such a model can be obtained by use of nonlinear system identification tools applied to patient test data. The suggested procedure is of similar complexity to the existing standard ICR rule. Hence it has the potential to be of clinical importance especially in developing countries where sophisticated solutions such as an artificial pancreas are unlikely to be used due to excessive cost. Simulations are presented which show that there exists a significant difference between the suggested insulin provided by the rule developed here and that given by the standard ICR rule.

Keywords: diabetes; blood glucose regulation.

1. INTRODUCTION

Diabetes is a major chronic disease. It affects over 60 million people worldwide (Wild et al., 2004). Treatment is invasive and often leads to poor outcomes for patients. Indeed, diabetes is the sixth highest cause of death in the author's home country. For this reason there has been huge research emphasis on better understanding the disease and on developing better treatment options.

Recently, significant research effort has been directed at developing a, so-called, Artificial Pancreas (Bequette, 2005; Klonoff et al., 2009; Harvey et al., 2010; Soru et al., 2012). The goal is to provide a mechanism that enables closed loop control of blood glucose levels by interconnecting a continuous glucose sensor to an insulin infusion pump. Whilst significant progress has been made and preliminary patient trials have been reported, it is widely accepted that such a system is still some distance from being a realistic option for diabetes sufferers. Difficulties include cost, drift in the sensors and delays which inhibit the achievement of tight control. Indeed, the performance reported from current solutions of this type is only marginally better than the performance achieved by standard treatment options. The latter includes the commonly used Insulin to Carbohydrate Ratio (ICR) formula (Gillespie et al., 1998). The ICR formula is a simple *linear* relationship linking carbohydrate consumption to desired insulin infusion. On the other hand, it is widely accepted that the system linking food, insulin and blood glucose levels is inherently nonlinear (Bergman, 2005; Kanderian et al., 2009). This suggests that one should be able to improve upon the ICR rule.

With the above as background, in this paper we develop a nonlinear form of the ICR rule. Our rule depends upon the availability of a nonlinear dynamic model fitted to each individual patient. Such a model can be obtained, for example, by applying nonlinear system identification tools to test data obtained from simple metabolic tests (Schittkowski, 2002; Schön et al., 2011; Andrieu et al., 2004).

To use the formula developed here, patients will simply need to consult a look-up table linking grams of carbohydrates consumed to a suggested insulin bolus. This is no more difficult than using the current linear ICR. The scheme is thus inexpensive and easily adopted. In particular, this seems to be a desirable first step prior to going to more sophisticated solutions such as an artificial pancreas.

The layout of the remainder of the paper is as follows: in Section 2 we describe the usual ICR rule and the conceptual differences with the rule proposed in this paper. In Section 3 we introduce the dynamical model upon which our result is based. In Section 4 we introduce the notation to be used and derive two relationships between blood glucose concentration at different points in time. In Section 5 we derive the new nonlinear ICR rule. In Section 6 we illustrate the ideas via simulations. In Section 7 we describe suggested implementation procedures for real patients. Finally, in Section 8 we draw conclusions.

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2. THE STANDARD LINEAR ICR RULE

Type 1 diabetes is usually treated by injecting an insulin bolus with each meal. Patients typically estimate the carbohydrate content of the meal and then inject a suitable insulin bolus (Gillespie et al., 1998). Different methods exist on how the bolus should be calculated. For example, a starting insulin to carbohydrate ratio can be estimated with the 500 (or 450) rule:

- The 500 rule states you should divide 500 by the total daily dose of insulin, i.e. how many insulin units are consumed in a normal day on average. The result is the amount of carbohydrates that are covered by 1 unit of *fast-acting* insulin.
- The 450 rule is similar, but suggests you should divide 450 by the total daily dose of insulin. The result is the amount of carbohydrates that are covered by 1 unit of *regular* insulin.

In practice, Insulin to Carbohydrate Ratios computed in this fashion are only a starting point since, over time, patients adjust the policies according to their own specific needs. For example, it is common to have a different ICR for breakfast, lunch and dinner to account for perceived variations in insulin sensitivity during the day.

Fine tuning of the ratios is also made on a trial and error basis. It is common to make adjustments to the ICR based on finger prick measurements taken after 120 minutes of ingesting a meal. We will use this idea in the sequel for comparison.

A key point in the context of the current paper is that, in all cases, the insulin dose is simply made proportional to carbohydrates consumed. The only difference is the slope of the linear relationship. However, there are well known difficulties. For example, medical practitioners are aware that the standard ICR rule can overestimate the insulin requirements and hence lead to hypoglycaemia. We consider hypoglycaemia to occur when the blood glucose level falls below 70 $[mg/dl]$.

The new Insulin to Carbohydrate rule developed in the sequel is based on a standard nonlinear dynamic model of blood glucose concentration with respect to injected insulin, see (1)–(6). The new rule has the main advantage that, in addition to ensuring return to acceptable steady state blood glucose concentration levels, it also ensures blood glucose concentration will not fall below a pre-specific level, thus avoiding hypoglycaemia. Of course, there is a tradeoff associated with achieving this, which will be explained in Section 4.

The idea is to eliminate the initial guesswork in fine tuning a standard ICR rule by using extra information that, in any case, will be a minimal requirement if an artificial pancreas is to be contemplated. It can be considered, on the one hand, as a middle ground when considering the baseline information needed, and on the other hand, as a step forward from the linear extrapolation currently in standard clinical use.

	Minimum Value	Nominal	Maximum Value
τ_1	41	85	131
τ_2	10	40	70
τ_{SEN}	10	15	20
p_2	$9.5 \cdot 10^{-3}$	$1.6 \cdot 10^{-2}$	$2.33 \cdot 10^{-2}$
C_l	540	1250	2010
S_I	$9.64 \cdot 10^{-5}$	$9 \cdot 10^{-4}$	$1.73 \cdot 10^{-3}$
EGP	0.6	2	3.45
$GEZI$	10^{-8}	$3.19 \cdot 10^{-3}$	$6.39 \cdot 10^{-3}$
V_G	104	220	337
τ_m	21	126	231

Table 1. Range of parameter values

3. A NONLINEAR MODEL

In this section we describe a simple, yet realistic, model. The model was presented in Kanderian et al. (2009) and is based on Bergman's minimal model (Bergman, 2003, 2005). Typical parameters are available for a set of patients (see Table 1). The details of the model are:

3.1 Actuator:

$$\frac{dI_{SC}(t)}{dt} = -\frac{1}{\tau_1} \cdot I_{SC}(t) + \frac{1}{\tau_1} \cdot \frac{ID(t)}{C_l} \tag{1}$$

$$\frac{dI_p(t)}{dt} = -\frac{1}{\tau_2} \cdot I_p(t) + \frac{1}{\tau_2} \cdot I_{SC}(t) \tag{2}$$

where

- $I_{SC}(t)$: subcutaneous insulin concentration
- $I_p(t)$: plasma insulin concentration
- $ID(t)$ $[\mu U/min]$: subcutaneous insulin delivery (input)
- τ_1 $[min]$, τ_2 $[min]$: time constants
- C_l $[ml/min]$: insulin clearance

3.2 Patient:

$$\frac{dI_{EFF}(t)}{dt} = -p_2 \cdot I_{EFF}(t) + p_2 \cdot S_I \cdot I_p(t) \tag{3}$$

$$\frac{dG(t)}{dt} = -(GEZI + I_{\mathrm{EFF}}(t))G(t) + EGP + R_A(t) \tag{4}$$

where

- $I_{EFF}(t)$ $[min^{-1}]$: insulin effect on plasma glucose
- $G(t)$ $[mg/dl]$: plasma glucose
- $R_A(t)$ $[mg/dl/min]$: glucose rate of absorption from meals (disturbance)
- S_I $[ml/\mu U]$: insulin sensitivity.
- $GEZI$ $[min^{-1}]$: glucose effect to increase glucose uptake and lower endogenous glucose production at zero insulin.
- EGP $[mg/dl/min]$: endogenous glucose production.

3.3 Sensor

$$\frac{dG_{ISF}(t)}{dt} = -\frac{1}{\tau_{SEN}} \cdot G_{ISF}(t) + \frac{1}{\tau_{SEN}} \cdot G(t) \tag{5}$$

where