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# Method for automatic adjustment of an insulin bolus calculator: In silico robustness evaluation under intra-day variability

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ABSTRACT

*Background and objective:* Insulin bolus calculators are simple decision support software tools incorporated in most commercially available insulin pumps and some capillary blood glucose meters. Although their clinical benefit has been demonstrated, their utilisation has not been widespread and their performance remains suboptimal, mainly because of their lack of flexibility and adaptability. One of the difficulties that people with diabetes, clinicians and carers face when using bolus calculators is having to set parameters and adjust them on a regular basis according to changes in insulin requirements. In this work, we propose a novel method that aims to automatically adjust the parameters of a bolus calculator. Periodic usage of a continuous glucose monitoring device is required for this purpose.

*Methods:* To test the proposed method, an in silico evaluation under real-life conditions was carried out using the FDA-accepted Type 1 diabetes mellitus (T1DM) UVa/Padova simulator. Since the T1DM simulator does not incorporate intra-subject variability and uncertainty, a set of modifications were introduced to emulate them. Ten adult and ten adolescent virtual subjects were assessed over a 3-month scenario with realistic meal variability. The glycaemic metrics: mean blood glucose; percentage time in target; percentage time in hypoglycaemia; risk index, low blood glucose index; and blood glucose standard deviation, were employed for evaluation purposes. A *t*-test statistical analysis was carried out to evaluate the benefit of the presented algorithm against a bolus calculator without automatic adjustment.

*Results:* The proposed method statistically improved ($p < 0.05$) all glycemic metrics evaluating hypoglycaemia on both virtual cohorts: percentage time in hypoglycaemia (i.e. BG < 70 mg/dl) (adults: 2.7 ± 4.0 vs. 0.4 ± 0.7, $p = 0.03$; adolescents: 7.1 ± 7.4 vs. 1.3 ± 2.4, $p = 0.02$) and low blood glucose index (LBGI) (adults: 1.1 ± 1.3 vs. 0.3 ± 0.2, $p = 0.002$; adolescents: 2.0 ± 2.19 vs. 0.7 ± 1.4, $p = 0.05$). A statistically significant improvement was also observed on the blood glucose standard deviation (BG SD mg/dL) (adults: 33.5 ± 13.7 vs. 29.2 ± 8.3, $p = 0.01$; adolescents: 63.7 ± 22.7 vs. 44.9 ± 23.9, $p = 0.01$). Apart from a small increase in mean blood glucose

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on the adult cohort (129.9 ± 11.9 vs. 133.9 ± 11.6, $p = 0.03$), the rest of the evaluated metrics, despite showing an improvement trend, did not experience a statistically significant change.
*Conclusions:* A novel method for automatically adjusting the parameters of a bolus calculator has the potential to improve glycemic control in T1DM diabetes management.


## 1. Introduction

### 1.1. *Type 1 diabetes mellitus*

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disease characterised by an autoimmune destruction of the insulin-secreting beta-cells of the endocrine pancreas. The resulting absolute insulin deficiency results in hyperglycaemia (i.e. high blood glucose). At present, the majority of people with T1DM control their blood glucose levels by drawing blood from the fingertips and measuring glucose concentration with an electronic glucose metre (i.e. self-monitoring of blood glucose) [1], and by administering insulin through multiple daily injections (i.e. basal-bolus therapy) in order to mimic the natural insulin secretion of the pancreatic beta-cells. An alternative therapy to multiple daily injections is provided by continuous subcutaneous insulin infusion (insulin pump therapy), which allows variable basal rates of insulin and avoids uncomfortable injections.

Large intervention trials [2] have shown how tight glycaemic control, avoiding hyperglycaemia, can prevent long term microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (coronary heart disease, stroke and peripheral vascular disease) complications. Such complications place a heavy burden on health services [3]. These trials also reported the associated risk of induced hypoglycaemia that highlights the crucial need for accurate and timely insulin dosage.

In practice, simple rules, mainly based upon empirical experience, are often used by people with T1DM to estimate the necessary amount of insulin. However, these rules fall short in optimising insulin therapy due to the complexity of glucose metabolism.

Insulin bolus calculators [4,5] are simple software tools incorporated in most of the commercially available insulin pumps [6], some blood glucose meters [7], personal digital assistants [8] and smartphones [9], aiming to provide decision support with calculation of insulin boluses. Gross et al [10] demonstrated the clinical benefit of using bolus calculators by reducing the number of correction boluses for elevated glucose levels as well as decreasing the amount of carbohydrates needed to recover from hypoglycaemic episodes. In a paediatric population using insulin pumps, Shashaj et al. [11] demonstrated that the bolus insulin dose calculated using a bolus calculator was more effective in improving pre- and postprandial glycaemic control with fewer correction boluses, without differences in the prandial insulin requirements and without restriction in the carbohydrate content of meals. In a study by Garg et al. [8], an insulin guidance software (ACCU-CHEK(r) Advisor, Roche, Indianapolis, IN) was tested in a crossover study of 12-month duration. The mean HbA1c was significantly lower from 3 to 12 months in the experimental group ($p < 0.02$) and an HbA1c reduction of 0.6% was maintained at 12 months in the experimental group. In a study by Lepore et al. [12], a bolus calculator was demonstrated to improve long-term metabolic control and reduce glucose variability in pump-treated subjects with T1DM. Finally, Barnard and colleagues [13] reported a reduced fear of hypoglycaemia and improved confidence in dosage accuracy in people with T1DM when using bolus calculators.

Although insulin bolus calculators have been proven to be clinically effective, they are still far from being widely used and achieving optimal glycaemic control. Different attempts have been carried out to improve the performance of such calculators [14–17], but thee have had varying success [18]. This is in part due to barriers such as requiring too many capillary blood glucose measurements or not contemplating realistic intra-subject variability. One of the main difficulties that people with diabetes, clinicians and carers face when using bolus calculators is having to set its parameters and adjust them on a regular basis according to changes in insulin requirements.

In this paper we present a novel approach to automatically adjust the parameters of a bolus calculator without requiring any initial tuning. Periodic usage of a continuous glucose monitoring (CGM) [19] device is required for this purpose.

## 2. Methods

### 2.1. *Insulin bolus calculator*

The most standard insulin bolus calculator consist of a relatively simple formula that uses subject-specific metabolic parameters to calculate an insulin dose [5]. This is described as

$$B = \frac{CHO}{ICR} + \frac{G_c - G_{sp}}{ISF} - IOB, \tag{1}$$

where $B$ is the recommended dose of insulin (IU); $CHO$ is the total amount of carbohydrate in the meal (g); $ICR$ is the insulin-to-carbohydrate ratio (g/IU), which describes how many grams correspond to one unit of fast acting insulin; $G_c$ is the current capillary blood glucose level (mg/dL); $G_{sp}$ is the blood glucose set-point (mg/dL); $ISF$ is the insulin sensitivity factor (mg/dL/IU), which is a personal relation describing how large a drop in blood glucose one unit of insulin gives rise to; and $IOB$ is the insulin-on-board, which describes the amount of active insulin remaining from previous injections. Various formulas