COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 120 (2015) 123–134

journal homepage: www.intl.elsevierhealth.com/journals/cmpb


# Optimization of insulin pump therapy based on high order run-to-run control scheme

*Jianyong Tuo, Huiling Sun, Dong Shen, Hui Wang, Youqing Wang* *

*College of Information Science and Technology, Beijing University of Chemical Technology, Beijing 100029, PR China*

ARTICLE INFO

*Article history:*
Received 24 October 2014
Received in revised form
8 April 2015
Accepted 20 April 2015

*Keywords:*
Type 1 diabetes mellitus
Glucose regulation
High order run-to-run control

ABSTRACT

*Background and objectives:* Continuous subcutaneous insulin infusion (CSII) pump is widely considered a convenience and promising way for type 1 diabetes mellitus (T1DM) subjects, who need exogenous insulin infusion. In the standard insulin pump therapy, there are two modes for insulin infusion: basal and bolus insulin. The basal-bolus therapy should be individualized and optimized in order to keep one subject's blood glucose (BG) level within the normal range; however, the optimization procedure is troublesome and it perturb the patients a lot. Therefore, an automatic adjustment method is needed to reduce the burden of the patients, and run-to-run (R2R) control algorithm can be used to handle this significant task.

*Methods:* In this study, two kinds of high order R2R control methods are presented to adjust the basal and bolus insulin simultaneously. For clarity, a second order R2R control algorithm is first derived and studied. Furthermore, considering the differences between weekdays and weekends, a seventh order R2R control algorithm is also proposed and tested.

*Results:* In order to simulate real situation, the proposed method has been tested with uncertainties on measurement noise, drifts, meal size, meal time and snack. The proposed method can converge even when there are ±60 min random variations in meal timing or ±50% random variations in meal size.

*Conclusions:* According to the robustness analysis, one can see that the proposed high order R2R has excellent robustness and could be a promising candidate to optimize insulin pump therapy.



## 1. Introduction

In recent years, there is a clearly rising trend in the incidence of diabetes around the world, according to the statistic of IDF Atlas, there are about 387 million people living with diabetes in 2014 and it will increase to 592 million in 2035 [1]. Diabetes mellitus is a metabolic disease with hyperglycemia (high blood glucose level), and people with diabetes often feel thirsty, hungry, and excessive urination [2–6]. The chronic hyperglycemia increases the risk of complications, such as heart disease, stroke, blindness, renal failure, and so on [7–10]. There are three main types of diabetes (type 1, type 2, and gestational diabetes) and other specific type of diabetes [11]. This article focuses on type 1 diabetes which is characterized by absent or insufficient endogenous production of insulin. Consequently, people affected by type 1 diabetes have to completely rely on exogenous insulin infusion [12,13].

* *Corresponding author at*: Mail Box 4, 15# Beisanhuan East Road, Chaoyang District, Beijing 100029, China. Tel.: +86 10 64414261.
E-mail address: wang.youqing@ieee.org (Y. Wang).

http://dx.doi.org/10.1016/j.cmpb.2015.04.010

For type 1 diabetic patients, the only choice to reduce the blood glucose (BG) level is utilizing exogenous insulin. There are mainly two ways for exogenous insulin delivery: multiple daily injection (MDI) and continuous subcutaneous insulin infusion (CSII) pump. CSII shows superiority over MDI in keeping people with type 1 diabetes in higher percentage of time in euglycemia and therefore has an increased popularity over the years [14,15]. In the CSII pump therapy, insulin delivery rate is typically divided into two regimens: basal insulin and bolus insulin: the former one is used to keep the balance of intra-individual glucose secretion and the latter one is utilized to offset the glucose fluctuations induced by meals corresponding to three regulation times for breakfast, lunch and dinner, respectively. Due to intra- and inter-subject variability, the basal-bolus therapy should be individualized and optimized in order to keep one subject's blood glucose level within the normal range.

Due to its good learning ability, run-to-run (R2R) control has successfully been utilized to optimize CSII therapy by many scholars, e.g., Palerm et al. [16,17], Zisser et al. [18], Owens et al. [19], and Campos-Cornejo et al. [20,21]. Among these studies, only [17] adopts the R2R control strategy to adjust the basal insulin, and while other studies [16,18–23] use R2R to design the bolus insulin or parameter of the control algorithm. After analyzing and comparing these optimization methods, all of them use the first order R2R scheme, and to the author's best knowledge, there is no reported study using high order R2R for optimization of CSII pump therapy.

On the other hand, finger stick is widely used in previous years and it can only provide sparse glucose measurements for therapy optimization. While over the recent years, there are significant improvements on the continuous glucose monitoring system (CGMS), which has successfully been applied in clinical practice [24–27]. Correspondingly, blood glucose prediction is a hot topic in the related field [28,29]. In short, more data are available for therapy optimization.

In this study, a high order R2R control scheme is proposed to update both basal insulin and bolus insulin, and particularly a second order R2R and a seventh order R2R are chosen as two example. The seventh order R2R is a power tool to deal with differences of living habits between weekdays and weekends. Evaluated on 11 virtual subjects from the FDA-accepted UVa/Padova metabolism simulator [30,31], the proposed method not only make blood glucose converge to a safe range of 70–170 mg/dL in less than 10 days, but also has superior performance compared with the traditional first-order R2R control under the same condition, especially including meal amount variations, meal time variations, meal amount & time combined variations, or CGMS noise and drift. Hence, high order R2R control is more robust than the traditional first-order R2R control. Considering the inevitable uncertainties in real life, two kinds of uncertainties, meal timing and meal amount uncertainties, are both included to test the robustness of the proposed methodology. According to the simulation results, the proposed control algorithm can endure ±60 min random variations in meal timing, ±50% random variations in meal size, CGMS noise up to 10%, CGMS drift up to 18 mg/dL/h, or the added snack, while the traditional method diverges in such situation.

In sum, this study has the following contributions: First, the proposed algorithm can update the basal and bolus simultaneously and while the reported studies can only update one of them. Second, because CGMS is more and more popular and reliable, the CGMS readings are used to design the updating law and hence improved performance can be achieved. Furthermore, high order R2R (second order and seventh order) was first implemented to optimize the basal and bolus therapy, which can enhance the control performance.

The remainder of this paper is organized as follow: in Section 2, a high order R2R control scheme is proposed and applied to adjust the basal insulin and bolus insulin. In Section 3, simulation results are presented and analyzed, including comparing the control performance both second order formulation and seventh order formulation with the traditional first order method with respect to variations on meal time, meal amount, or CGMS noise and drift. At last, some conclusions are presented in Section 4.

## 2. High order R2R control scheme

### 2.1. High order R2R

Let us consider a single-input single-output process, of which the input–output relation is described as below:

$$y(k) = bu(k) + a(k) + \varepsilon(k) \tag{1}$$

where $k$ is the run index; $y(k)$ and $u(k)$ are the output and input of the process, respectively; parameter $b$ is the slope coefficient; $a$ is the drift coefficient; $\varepsilon(k)$ denotes disturbance [32].

Evidently, the optimal control action of $k$-th run is

$$u(k) = \frac{y^* - a(k)}{b} \tag{2}$$

where $y^*$ is the target value for the output. The above-mentioned expression can be easily extended to multi-input multi-output case. In this case, $b$ is a matrix and $a$ and $y^*$ are vectors, so Eq. (2) is changed as $u(k) = b^{-1}(y^* - a(k))$. It usually exploit exponentially weighted moving average (EWMA) formula to update the offset term, as shown below:

$$a(k+1) = \lambda[y(k) - bu(k)] + (1-\lambda)a(k) \tag{3}$$

Eq. (3) is a first order EWMA formula, and $\lambda$ is an adjusting parameter between (0, 1). Based on Eqs. (2) and (3), the traditional R2R control action can be described as

$$u(k+1) = u(k) + K[y^* - y(k)] \quad \left(K = \frac{\lambda}{b}\right) \tag{4}$$

Similarly to Eq. (3), the second order EWMA formula can be written as:

$$\begin{aligned} a(k+1) = {} & \theta\{\lambda[y(k) - bu(k)] + (1-\lambda)a(k)\} \\ & + (1-\theta)\{\lambda[y(k-1) - bu(k-1)] + (1-\lambda)a(k-1)\} \end{aligned} \tag{5}$$