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Personalized mechanistic models for exercise, meal and insulin interventions in children and adolescents with type 1 diabetes

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HIGHLIGHTS

- Personalized mechanistic models are developed for young type 1 diabetic patients.
- Exercise, meal and insulin interventions are incorporated in the model.
- Rate of perceived exertion (RPE) is used as a marker of exercise intensity.
- Blood glucose predictions of the personalized models are closer to clinical data.
- Personalized parameter estimates are precise and within the physiological ranges.

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ABSTRACT

Personalized mechanistic models involving exercise, meal and insulin interventions for type 1 diabetic children and adolescents are not commonly seen in the literature. Patient specific variations in blood glucose homeostasis and adverse effects of exercise-induced hypoglycemia emphasize the need for personalized models. Hence, a modified mechanistic model for exercise, meal and insulin interventions is proposed and tailored as personalized models for 34 type 1 diabetic children and adolescents. This is achieved via a 3-stage methodology comprising of modification, *a priori* identifiability analysis, and personalized parameter estimation and validation using the clinical data. Rate of perceived exertion is introduced as a marker quantifying exercise intensity. Six out of 16 parameters in the modified model are identified to be estimable and are estimated for each subject as personalized parameters. The R^2 values for both fitness and validation vary between 0.7 and 0.96 in 97% of the patients, indicating the goodness of the proposed model in explaining the glucose dynamics. For most of the estimated parameters, values of personalized point estimates and their confidence intervals are found to be within physiological ranges reported in the modeling literature. Personalized values of appearance rate of exercise effect on glucose uptake in 34 subjects are 54–250% higher than the nominal values of adults. This is expected for children and adolescents as the literature shows that they exhibit higher fat and exogenous carbohydrate oxidation rates during exercise when compared to adults.

1. Introduction

Blood glucose (G) management in type 1 diabetic patients is influenced by three major exogenous interventions – exercise, meal and insulin. The effects of these interventions on G dynamics vary from patient to patient and do not follow a one-size-fits-all dynamics. Development of personalized mechanistic models which can capture the patient specific variations will be helpful in many ways like, (i) understanding the personalized mechanism of glucose–insulin dynamics for various levels and types of interventions; (ii) prior prediction of adverse events like exercise-induced hypoglycemia (especially in type 1 diabetic children and adolescents), and (iii) development of safe and efficient treatment protocols that can control the G levels within the normal ranges. The recent developments in sensor technology, especially the advent of frequently sampling G measurement sensors, and the arrival of various classes of G prediction models since early 1960s (Balakrishnan et al., 2011), made the development of personalized models practically possible.

Most of the available mechanistic models on type 1 diabetic subjects (Balakrishnan et al., 2011) do not include exercise effects in them and they were validated for adults alone. There are few

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mechanistic models developed and/or validated for type 1 diabetic children and adolescents. The virtual patients of UVa simulator (Kovatchev et al., 2009) were validated for type 1 diabetic children and adolescents. Chen et al. (2010) modified the existing delay differential equation model in the literature (Sturis et al., 1991; Tolic et al., 2000) and fitted it to the type 1 diabetic children. However, these two mechanistic models (Chen et al., 2010; Kovatchev et al., 2009) did not explain exercise effect on G dynamics. There are a few mechanistic models that explain the exercise effects on G dynamics of adults (Kim et al., 2007; Lenart and Parker, 2002; Roy and Parker, 2007), among which some models (Kim et al., 2007; Lenart and Parker, 2002) are too complex to be tailored as a clinically preferred personalized patient model. Further, these two models were validated using the data of healthy adult cohorts only. Roy and Parker (2007) developed a simple exercise model and validated it using adult cohorts of healthy and type 1 diabetic subjects. In spite of the fact that type 1 diabetes is usually diagnosed in children and adolescents, the above-mentioned mechanistic models with exercise effects were not validated using children and adolescents cohorts. The exercise effect models (Kim et al., 2007; Lenart and Parker, 2002; Roy and Parker, 2007) on type 1 diabetic patients quantified exercise intensity using percentage of maximum oxygen consumption during exercise (PVO_2^{max}), whose measurement requires sophisticated devices which constraints their practical applicability in the routine life of patients. A few mechanistic models used heart rate (HR) as a measure to quantify exercise but they were not validated using the clinical data (Dalla Man et al., 2009). Measurement of HR in the routine life is possible with sensors and monitors, but the accuracy of them depends on the cost. Apart from these two markers, there is also a diabetes modeling study which measured 8 activity and stress related variables using an armband type of sensor (Rollins et al., 2010).

Eventually, all these exercise markers require sophisticated devices, or special sensors. There is another marker, namely, Rate of Perceived Exertion (RPE), which does not require any sophisticated devices or special sensors for its measurement and has been used in exercise settings since early 1980s (Borg, 1982). RPE explains the level of exertion an individual feels during exercise, and it can be self-measured via simple talk or pictorial tests based on one of the qualitative scales available in the literature (Borg, 1982; Robertson et al., 2000; Williams et al., 1994). The qualitative description of RPE scale could be ranging from “no exertion” to “maximal exertion” with steps of light, moderate, heavy exertions, etc. Each qualitative phrase in RPE scale is assigned with a number following a particular point system. The original RPE scale developed by Gunnar Borg (1982) rates exercise intensity between ranges of 6 (no physical exertion) and 20 (maximally hard exertion leading to exhaustion). Later on, a revised 11 point RPE scale varying between 0 and 10 was introduced. The cognitive ability of children and adolescents to interpret the actual meaning of the phrases corresponding to each Borg's scale was questioned, which led to formulation of non-pictorial Children's Effort Rating Table (CERT) of Williams et al.'s (1994), pictorial CERT (PCERT) of Yelling et al. (2002) and OMNI's pictorial walk/run scale for children (Robertson et al., 2000). The validity of PCERT and OMNI scales in children and adolescents is reported in literature (Roemmich et al., 2006; Utter et al., 2002). Despite RPE's recognition and simplicity involved in its measurement, it has not been used as variable quantifying exercise intensity in any of the above-mentioned exercise models related to type 1 diabetic subjects. Recently, in one of our works on personalized hybrid models (Balakrishnan et al., 2013a), RPE is employed as a marker and the models are validated using clinical data of type 1 diabetic children and adolescents.

In this work, a modified mechanistic model employing RPE as an exercise marker is proposed and validated using the clinical data of 34 type 1 diabetic children and adolescents retrieved from an exercise study of Diabetes Research in Children Network (DirecNet) public datasets (2005). First, the original Roy and Parker (2007) model is modified for exercise, meal and insulin interventions, followed by identification of estimable parameters using *a priori* identifiability analysis. Subsequently, the identified parameters are estimated for each patient as personalized estimates and their uncertainty is calculated using variance–covariance matrix. Finally, the personalized models with their point estimates are validated using new data.

The paper is organized as follows. Section 2 explains the nature of clinical data employed in this study; Section 3 elaborates the 3-stage methodology proposed for development and validation of personalized models; Section 4 summarizes the results of this study, and then discusses them. Finally, Section 5 provides the important conclusions of this study.

2. Nature of clinical data used

The clinical data of 34 type 1 diabetic children and adolescents are retrieved from one of the DirecNet (2005) exercise studies. Each subject visited the clinic in the noon (just before lunch) and stayed till dinner. Subjects were given with pre-lunch bolus insulin dose and lunch adhering to their routine values employed in the home settings, such as Insulin (Ins) to Carbohydrate (CHO) ratio, bolus dose amount (D_{bolus}), correction factor (C_F) and pre-lunch target G (T_{PM}). The basal insulin supply was maintained using insulin pumps; it was continued during exercise in 21 patients while it was stopped during exercise in 13 patients considered in this study. In the late afternoon, each subject underwent a 75 min treadmill walk exercise session, which comprised four phases and the RPE values corresponding to each phase were recorded. The G values during the clinical visit were measured with a sampling interval=5 min using Continuous Glucose Monitoring Sensors (CGMS). The distribution of the above mentioned measured data along with the subject's body weight (W) can be seen in Fig. 1. Details like the amount of infused basal dose are not directly provided in the DirecNet website. Hence, amount of basal insulin is calculated using the insulin replacement algorithms employed in clinical settings (see Appendix A).

3. Modeling methodology

A 3-stage methodology is proposed to acquire a personalized model for each type 1 diabetes child or adolescent (see Fig. 2). The model development in the first stage is based on the exercise model of Roy and Parker (2007), who proposed a nine-compartment exercise-effect model which can simulate glucose–insulin dynamics during short- and long-term exercise. They coupled the dynamics of exercise effect on hepatic glucose production (G_{gly}), glucose uptake (G_{up}), glycogenolysis (G_{gly}), and plasma insulin removal (I_e) with the three-compartment model of Bergman et al. (1979). The mathematical representation of 9 ordinary differential equations (ODEs) is as follows:

$$\frac{dG}{dt} = -p_1[G(t)-G_b]-X(t)G(t)+\frac{W}{V_G}[G_p(t)-G_{gly}(t)]-\frac{W}{V_G}G_{up}(t)+\frac{U_M(t)}{V_G} \quad (1)$$

$$\frac{dX}{dt} = -p_2X(t)+p_3[I(t)-I_b] \quad (2)$$

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