Automatic Control of Physiological State and Function

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# Recent Trends in Blood Glucose Control Studies

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**Abstract**

Diabetes mellitus is a disease of the endocrine system in which blood glucose levels are constantly above the normal range. Since insulin-dependent diabetic patients require insulin administration to maintain blood glucose levels within the normal range, automatic blood glucose control methods to reduce the burden of such open-loop insulin therapy have been studied. In this review, we first introduce some important mathematical models of glucose-insulin metabolism, followed by some representative blood glucose control systems, where most of them use model predictive control as control algorithm, developed to date and discuss their implications in the near future.

**Keywords:** Diabetes mellitus; Hypoglycemic effect; Endocrine system; Insulin; Blood glucose level

## Introduction

Diabetes mellitus is a disease of the endocrine system in which blood glucose levels are constantly above the normal range due to absence of insulin secretion caused by pancreatic β-cell apotosis or a defect in endogenous insulin action. According to the International Diabetes Federation (IDF) the number of diabetic patients in the world is 371 million as of 2012 and is estimated to be more than 550 million in 2030 [1].

Hyperglycemia causes several chronic and life-threatening complications including microvascular and macrovascular diseases such as retinopathy, nephropathy, ischemic heart disease, stroke and neuropathy. To decrease the risks of such complications, diabetics regulate their blood glucose level by insulin administration, if needed. In particular, type 1 diabetic (T1D) patients, whose endogenous insulin production becomes blunted due to β-cell self-destruction by the immune system, require exogenous insulin therapy for life, which consists of blood glucose measurement by finger pricking and subcutaneous insulin administration previous to every single meal intake, in addition to a basal insulin dose to maintain normoglycemia during no-food intake periods. However, it is not easy to estimate the necessary insulin dose accurately for a given meal, which leads to not only hyperglycemia but also hypoglycemia, where the latter is considered more dangerous especially during bedtime due to unawareness of hypoglycemic symptoms.

Many studies on automatic blood glucose control systems have been done to solve the above problems [2]. Recently, most of the control systems utilize model-based control methods such as model predictive control (MPC), where a mathematical model plays a crucial role since its accuracy determines the performance of the control algorithm. In this article, we present some up-to-date studies on mathematical models of glucose-insulin metabolism and blood glucose control methods.

## Mathematical Models of Glucose-Insulin Metabolism

Glucose-insulin metabolism is a very complex system that includes glucose production and utilization, direct and indirect effect of insulin on glucose uptake, insulin sensitivity and renal glucose excretion. For blood glucose control, it is important to estimate blood glucose response to insulin as accurately as possible. Mathematical models of glucose-insulin metabolism have been developed [3] since 1960s starting with Bolie [4]. Recent trends of studies are towards 1) models for patients in a specific state, and 2) models of blood glucose excursion after a meal including not only carbohydrates but also fat and/or protein. Here, we briefly introduce several representative and recently developed models.

The Bergman minimal model [5] is one of the most representative models that also serves as the base of many mathematical models utilized in recent studies. Bergman model was obtained from results of intravenous glucose tolerance tests (IVGTT), which consists of measurement of blood glucose profile after an intravenous glucose bolus; and constructed focusing on responses of blood glucose and insulin in a remote compartment, which has a direct effect on decreasing blood glucose. The minimal model has a small number of parameters to represent predominant properties of glucose-insulin metabolism.

However, it was based on data from non-diabetics and one of its main drawback is that some results obtained by the model are not realistic, i.e., blood glucose level may not converge to an equilibrium and remote insulin concentration is not bounded, which led to the development of many enhanced minimal models [6-8]. For instance, De Gaetano and Arino [6] developed a modified minimal model that is globally asymptotically stable and has bounded solutions. Furthermore, modified models for fitting a specified state of patients have also been developed. Van Herpe et al. [9] developed an ICU minimal model considering features typical of ICU patients such as variability of insulin resistance and recovering activity of the pancreas. Hovorka et al. also proposed detailed models of glucose-insulin metabolism for critically ill [10] and T1D patients [11].

From the viewpoint of daily management of blood glucose levels, avoiding hyperglycemia and hypoglycemia after every meal is arguably the most important. Hence, mathematical models that represent glucose-insulin metabolism including meal digestion and absorption have also been developed [12,13] to realize an appropriate control for the postprandial state. Dalla Man et al. [12] developed a detailed simulation model (Figure 1a) of the glucose-insulin system

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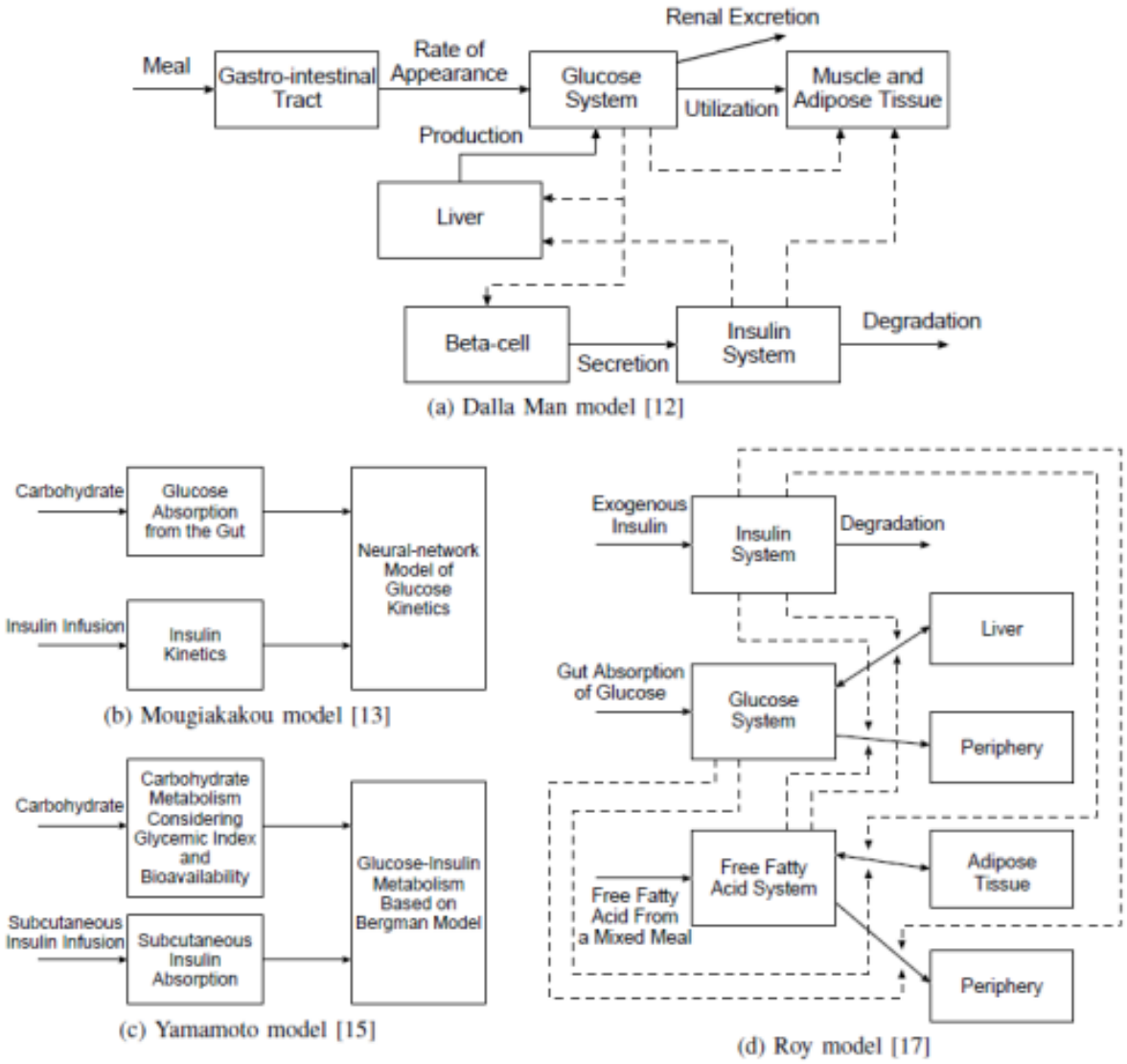



**Figure 1:** Structure of glucose-insulin metabolism models.

for healthy and type 2 diabetics considering meal rate of appearance, endogenous glucose production, glucose utilization and in-sulin secretion. Mougiakakou et al. [13] developed a model (Figure 1b) for type 1 diabetics including meal intake that consists of compartmental models of insulin kinetics and glucose absorption, and neural networks representing glucose kinetics. Recently, it has been understood that not only the carbohydrate amount in a particular meal but also glucose absorption rate influence blood glucose excursion. Thus, mathematical models considering glycemic index (GI) of foods, which is an index that represents the impact of carbohydrates from a meal on blood glucose levels, have been developed [14,15]. Wolever et al. [14] gave a mathematical function representing the glycemic impact of carbohydrates, while Yamamoto et al. [15] proposed a mathematical model (Figure 1c) including a carbohydrate metabolism subsystem that provides a time-dependent carbohydrate absorption as glucose-equivalent depending on the amount ingested and parameters related to the glycemic index and carbohydrate bioavailability [16] of foods.

Moreover, other macronutrients, i.e. protein and fat, may have some effect on blood glucose levels as well. Hence, estimation methods of the necessary insulin and mathematical models considering impact of all three macronutrients on blood glucose have also been developed [17-20]. Roy and Parker [17] developed an extended Bergman minimal model (Figure 1d) including a meal disturbance input corresponding to the absorption of carbohydrate, protein and free fatty acid from the gut. Holt et al. [18] proposed an insulin index of foods that represents insulin demand of foods for 1000 kJ including of carbohydrate, protein and fat; and Bao et al. [19] later demonstrated its superiority to the conventional carbohydrate counting method. Alternatively, Pankowska et al. [20] developed a fat-protein counting method to have a better estimation of the prandial insulin amount. However, there is no established mathematical model of fat and/or protein metabolism to date, and therefore, more accurate models of glucose-insulin metabolism during postprandial state can be expected in order to develop a desirable 24-hour blood glucose control.

As forementioned, mathematical models of glucose-insulin metabolism have become more complex. In spite —or because— of this, some simplified models have also been developed for blood glucose control. For instance, Lombarte et al. [21] proposed a

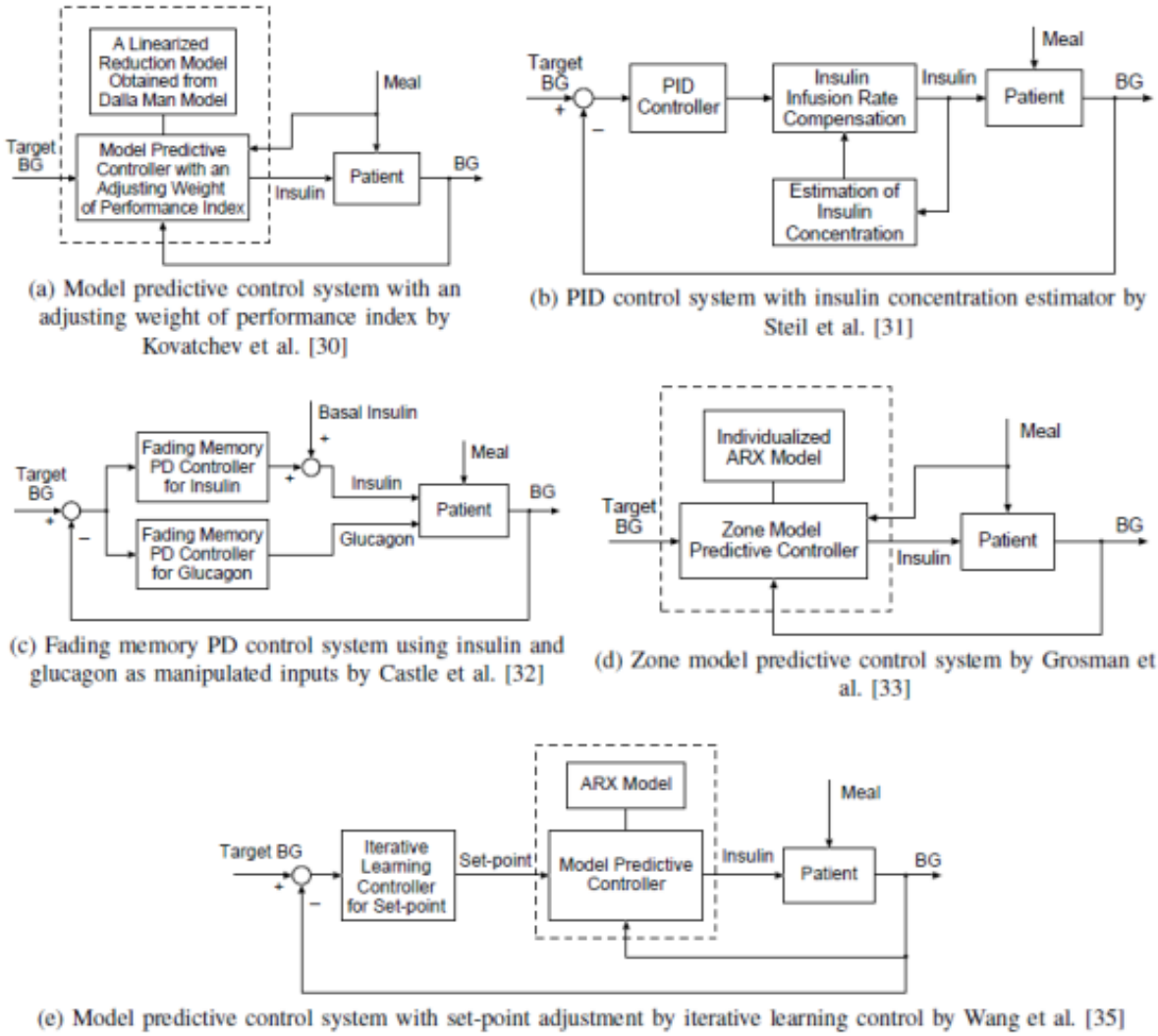
mathematical model given by third-order differential equations with eight identifiable parameters representing inter- and intra-individual properties of glucose-insulin metabolism. For blood glucose control purposes, fairly simplified models that represent the most significant processes of glucose-insulin metabolism are most preferred, and thus more studies in this area are expected in the upcoming years.

## Blood Glucose Control Systems

Blood glucose control systems have been studied since 1970s [11,22-26], and some of them were clinically applied or commercially supplied. However, no system has sufficient performance for blood glucose management of diabetics. The Biostator (Miles Laboratories, USA) and STG-22 (Nikkiso, Japan) are well-known blood glucose control systems. In particular, STG-22 adjusts insulin infusion rate based on "basal insulin plus additional insulin calculated by proportional and differential (PD) control" strategy to mimic insulin secretion of non-diabetics, and achieves fairly acceptable blood glucose control when basal insulin and PD parameters are set appropriately. Nevertheless, it uses an invasive blood glucose measurement by continuous blood sample of 2 mL/h, and it cannot be used for daily blood glucose control due to its non-portability. In the following, we introduce recent works on blood glucose control including open-loop, semi-closed-loop, and closed-loop strategies.

Recently, there has been some focus on portable blood glucose control systems. Intensive insulin therapy [27] is currently achieved with continuous subcutaneous insulin infusion (CSII) [28], which maintains normal blood glucose levels by automatically administering continuous basal insulin under the skin preprogrammed from patient-specific daily blood glucose profile. However, since CSII systems administer only basal insulin, patients must inject bolus insulin before each meal. To avoid the risk of hypoglycemia under intensive insulin therapy, an insulin pump with low-glucose suspension (LGS) that stops basal insulin infusion when blood glucose levels drop below a specific threshold was developed. Clinical application in Europe since 2009 showed that the pump with LGS function can effectively reduce the frequency of hypoglycemia [29].

Many clinical trials have been run lately in an effort to develop closed-loop blood glucose control systems to maintain normal blood glucose levels throughout the day. Some research groups [26,30-32]




(a) Model predictive control system with an adjusting weight of performance index by Kovatchev et al. [30]

(b) PID control system with insulin concentration estimator by Steil et al. [31]

(c) Fading memory PD control system using insulin and glucagon as manipulated inputs by Castle et al. [32]

(d) Zone model predictive control system by Grosman et al. [33]

(e) Model predictive control system with set-point adjustment by iterative learning control by Wang et al. [35]

**Figure 2:** Structure of blood glucose (BG) control systems.

have developed feedback blood glucose control systems combining CSII and continuous glucose monitoring (CGM) that adjust subcutaneous insulin infusion rates based on blood glucose measurements obtained from a micro needle implanted subcutaneously. Most of the control methods utilized in these systems are model predictive control (MPC) and proportional, integral and differential (PID) control. Kovatchev et al. [30] applied a system (Figure 2a) to T1D patients that adjusts insulin infusion rate using MPC based on blood glucose measured by CGM, and showed that it can reduce the frequency of hypoglycemia and maintain blood glucose levels longer within a desirable range during the night. Steil et al. [31] constructed a modified PID control algorithm for T1D patients based on estimation of insulin concentration (Figure 2b), and showed that it improves blood glucose profiles before breakfast, which usually tends to be hyperglycemic. Castle et al. [32] developed a blood glucose control system (Figure 2c) using not only insulin but also glucagon, which is another important hormone for blood glucose regulation —especially to avoid hypoglycemia— and showed its effectiveness to reduce time of hypoglycemia, although its long-term effectiveness has not been examined.

As described above, feedback blood glucose control systems using CGM are currently being applied clinically and their effectiveness has been demonstrated. However, they cannot maintain blood glucose within a desirable range after a meal yet since blood glucose values measured with CGM have a dead time of more than 5 minutes. Therefore, patients must still determine the amount of additional insulin bolus by estimating the amount and component of their foods before each meal.

Several new control methods have been applied to blood glucose control in computer-simulated studies. Grosman et al. [33] applied a zone MPC [34] to blood glucose control of T1D patients (Figure 2d) that considers a performance index with penalty only if the output surpasses a specified range, and confirmed by simulation that blood glucose levels can be maintained more appropriately than by the existing open-loop blood glucose control methods, including the postprandial period. Wang et al. [35] constructed a blood glucose control system (Figure 2e) combining MPC and iterative learning of blood glucose responses after a meal, and verified by simulation of T1D patients that the system can achieve better control performance against variability of amount and time of meal than that with only an MPC controller.

As described above, several studies on blood glucose control have been made with promising results obtained by simulation in fairly realistic situations. However, none of them has been able to achieve blood glucose control performance comparable to that of non-diabetics. Adaptive control systems are an interesting challenge, while controller parameters for inter-individuality in T1D patients should be predetermined based on accurate identification of patient-specific blood glucose profile, except ICU patients.

## Conclusion

In this article we introduce recent studies on mathematical models of glucose-insulin metabolism and blood glucose control. Even though studies in this area have started more than three decades ago, no blood glucose system with performance similar to that of non-diabetics has been developed to date. This may be attributed to the measurement delay of current blood glucose sensors and the slow subcutaneous insulin absorption and hypoglycemic effect of rapid-acting insulin compared to endogenous insulin secretion. Ideally non-invasive sensors with shorter delay and insulin formulations with faster absorption would lead to better results than those achieved in recent studies. However, such technology is unlikely to be developed at least in the next years. For the time being, studies on blood glucose control can be extended to mathematical models with realistic macronutrient content, parameter tuning methods that include intra-individual variability, and control strategies for postprandial and post absorptive states that effectively maintain blood glucose levels within a safe range, among others.

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