iGLU 1.1: Towards a Glucose-Insulin Model based Closed Loop IoMT Framework for Automatic Insulin Control of Diabetic Patients

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Abstract—The diet schedule and food intake effect on body glucose is the key problem of the diabetic patient. For type 1 diabetic patients, it is necessary to optimize the diet schedule and insulin regimen to control the body glucose level in the postprandial state. Hence, a closed-loop system containing insulin delivery and diet schedule is required for type 1 diabetic patients. In the current paper, a mathematical model of glucose-insulin is proposed to investigate the glucose profile along with plasma insulin level for type 1 diabetic patients. Four different and most common cases have been considered with the scheduled plan of diet and insulin regimen to simulate the glucose profile along with plasma insulin level. The glucose-insulin model was simulated using MATLAB to investigate the artificial pancreas system. The analysis includes glucose absorption parameters and net hepatic glucose balance (NHGB). The results represent that the proposed mathematical model may be useful to predict the glycaemic status of diabetic patients and personalise it as per their historical data.

Index Terms—Glycemic control, Type 1 diabetes, Glucose-insulin modeling, Closed loop control system, Artificial pancreas system, Continuous glucose measurement, Insulin secretion

I. INTRODUCTION

When the human body has a problem to maintain the amount of blood glucose then, the condition refers to Diabetes. It has exponentially increased in the past decades over the world [1]. The unhealthy lifestyle is the prominent factor in magnifying the chance of being a diabetic patient. The unbalanced diet is one of the main factors for the occurrence of diabetes Mellitus [2]. Therefore, diagnosis and treatment of diabetes Mellitus are attracting points of research in smart healthcare. Nowadays, a traditional process has been followed to control the diabetes mellitus of a person located at a remote location. This traditional process depicts the supervision of diabetologist for insulin secretion along with continuous glucose monitoring (CGM) [3]. Time to time, the glucose values have been monitored by a diabetologist and insulin secretion has been recommended accordingly. The framework of a blood glucose control system has been shown in Fig. 1. An investigation of artificial pancreas (AP) model with variations of glucose consumption has been done with different cases of diabetic patients [4]. Mathematical modelling has been explored to balance the body glucose level. During investigations of multiple cases, various parameters have also
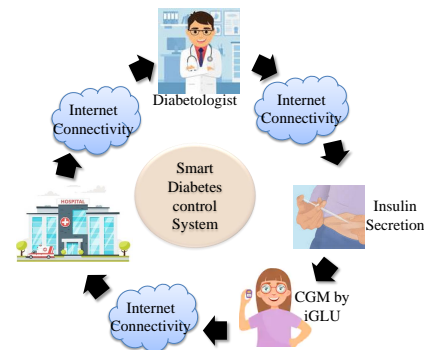

Fig. 1: Framework of a diabetes control system

been analyzed which represent the variations in glucose level with or without consumption of insulin. The mathematical modelling for artificial pancreas relates the plasma insulin level with body glucose and consumption level. The proposed model is investigated by the real-time data of diabetic patients for validation of the mathematical model.

The rest of the paper is organized as follows. Automatic glucose monitoring and control in IoMT have been discussed in Section II. The novel contribution of has been summarized in Section III. The related works are discussed in Section IV. The glucose-insulin closed-loop system with modelling is described in Section V. The model has been validated through standard cases of medication is presented in Section VI. Section VII presents conclusions and future directions.

II. OUR VISION OF AUTOMATIC GLUCOSE MONITORING AND CONTROL IN IoMT FRAMEWORK - iGLU 1.1

The diabetes control system requires a diabetologist at the remote location for the recommendation of insulin secretion according to measured glucose values. In this process, presence of diabetologist is necessary to provide the insulin doses when patient send data of blood glucose, plasma insulin and other glucose consumption parameters to provide precise treatment and scheduled dosage for remote located patients.

To provide a better solution for evaluation of insulin doses, our vision of diabetes control environment has been illustrated

in Fig. 2. We presented a near infrared based glucometer called iGLU for noninvasive blood glucose monitoring [5], [6]. *The current paper extends the iGLU with insulin control mechanism and hence called iGLU 1.1*. The proposed work summarizes the glucose-insulin model to estimate the glucose consumption parameters with the integration of IoMT framework for a consultancy from diabetologist.
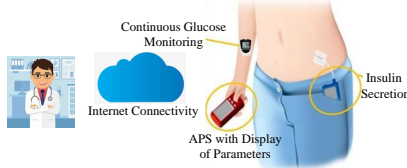

Fig. 2: System overview of diabetes control environment

This proposed model can create an environment, in which different cases of diabetes can be analyzed in terms of controlling of net glucose level, plasma insulin level and glucose excretion. In this proposed system, glucose-insulin based APS system determines the various parameters of glucose consumptions along with plasma insulin and glucose level for precise treatment of remote located diabetic patients. The data is stored on the cloud to analyze at the end of a diabetologist. After viewing these reports, prescribed treatment is recommended for diabetic patients. The required treatment is provided to the patient through telemedicine. Using this process, diabetic patient is treated with proper diagnosis at a remote location.

This facility of automation makes the system easier for smart healthcare in terms of diabetes control. The overall data of prescribed meal and insulin secretion plan along with glucose and plasma insulin concentration values are also stored on the cloud which will be accessible through patients and doctors for future reference. This overall system also facilitates to both the patient and doctor for instant diagnosis and corresponding treatment with previous data of the patient.

III. NOVEL CONTRIBUTIONS OF THE CURRENT PAPER

- A novel glucose-insulin model is proposed which represents an artificial pancreas system (APS) with continuous glucose monitoring.
- Four different cases have been considered to validate the proposed glucose-insulin model. In this modelling, glucose consumption parameters have also been determined which are responsible for body glucose level regulation.
- Proposed model has also been analyzed in terms of blood glucose and plasma insulin variations with respect to scheduled diet and insulin secretion plan followed by medical protocols.
- Proposed model (APS) are integrated with IoMT framework for remote located diabetic patients to provide prescribed diet and insulin plan and diagnosis with the help of diabetologist.

IV. RELATED PRIOR RESEARCH WORK

The first glucose-insulin mathematical model has been explored to estimate the coefficients of normal blood regulation [7]. Bergman developed the model which estimates the insulin sensitivity index for type 2 diabetic patients [8]. To overcome some gaps, De Gaetano represented the dynamical model of non linear differential equation for delay model using healthy subjects [9]. An FDA approved Uva/Padova Simulator was represented for the clinical trials. The parameter distributions developed to construct the profiles of type 1 diabetic patients (virtual patients) [10]. The Hovorka maximal model represents an intravenous glucose tolerance test of healthy subjects [11]. The model has been enlightened to describe the collected data of 12 type 1 diabetic patients with 20 hours monitoring [12]. A mathematical model is developed to represent the postprandial blood glucose of 10 type 1 diabetes patients [13]. A long-term glucose-insulin model is introduced with the clinical data for two days [14]. A meal detection algorithm has been developed with type 1 diabetic patient data which is based on continuous glucose measurement. This work also represents the glucose-insulin model with bolus meal calculation [15]. 30 subjects have also been considered to develop a variable state dimension algorithm. Meal detection has also been done in the absence of meal declaration [16]. In the way of diabetes regulation, an intelligent PID controller (iPID) has been introduced for type 1 diabetic patients [17].

A lot of models have been presented with different parameters in terms of meal detection and glucose-insulin concentration measurement. Various parameters such as glucose absorption rate, net hepatic glucose balance, peripheral glucose utilization and renal excretion rate are required to determine the glucose consumption in the body. These parameters are necessary to determine the blood glucose level regulation with scheduled diet and necessary insulin secretion plan. Hence, in the current paper; a glucose-insulin mathematical model is proposed to control the blood glucose level of type 1 diabetic patients with prescribed diet and insulin secretion plan.

V. DESCRIPTION OF GLUCOSE-INSULIN MODEL

To provide a better solution for evaluation of insulin doses, an advanced closed-loop automated insulin secretion diabetes control system with IoMT framework is presented which is shown in Fig. 3. Such computational model with the integration of IoMT framework can be implemented to diagnose and for the treatment of diabetic patients in terms of controlling their blood glucose level.

A. Glucose Insulin Control Closed Loop System

According to Fig. 4, the maximum time a normal person is in the blue area, which represents the normal condition of blood glucose concentration. If the additional glucose has been ingested in the form of meal, the person can move to the red-circled zone with high glucose value. Then, a signal has been sent to the pancreas, which results in the activation of β cells in form of insulin generation. This may bring the person back to the blue circled zone. Balancing of exercise and food
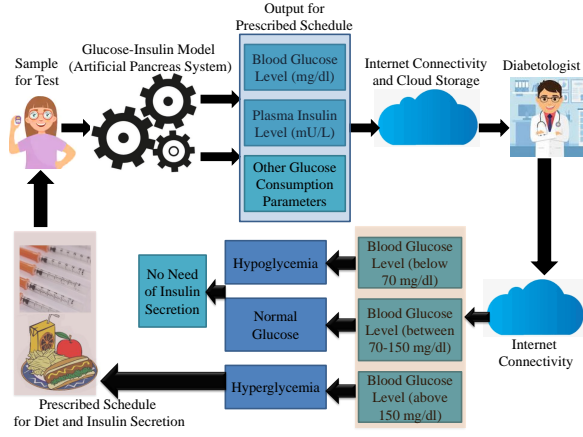
Fig. 3: Proposed APS model with IoMT framework.

Fig. 4: Closed loop system of glucose generation and consumption.

intake may keep the body into the blue circled zone. If insulin generation by β cells is not enough for glucose consumption, then the person may be in the red circled zone. Excess amount of food intake would result in the activation of α cells. Because of this, glucose is generated by the liver. Consistent high blood glucose concentration may be possible due to increased α cells compared to β cells. Because of this, enough insulin is not secreted in the body for glucose consumption. This condition refers to Diabetes Mellitus. The process has been represented in Fig. 4. A physiological closed-loop is presented for the glucose-insulin regulatory system. A normal person has blood glucose values in the range of 80-120 mg/dl in all fasting and prandial modes. The regulation of glucose and insulin according to each other helps to keep the body in this range for steady-state. If body glucose concentration is consistently high for a long time, then insulin secretion is required.

B. Proposed Model for Glucose and Insulin Relationship

The processing steps of the closed-loop system of glucose generation and consumption in the human body is in Fig. 4. The blood glucose values of an insulin-treated patient represent the glycaemic profile until a steady state. This glycemic profile is corresponding to the change in either insulin or diet. The objective of glucose-insulin modelling is to study glucose and plasma insulin responses independently. The model consists of a single glucose pool which represents cellular glucose (intestinal absorption and hepatic glucose balance). The glucose is removed by the insulin-free and dependent glucose utilization. Glucose excretion from cellular glucose exists above the renal threshold of glucose (RTG). Peripheral glucose exists as a function of plasma glucose and insulin levels. Although the liver produces and utilizes the glucose which depends on blood glucose and insulin levels. The system has been modelled in terms of the net hepatic glucose balance (NHGB) which is obtained as glycogenesis. This is derived from different blood glucose and insulin levels [18]. This hepatic glucose has been selected to remove the non-physiologically based mathematical function to represent handling of hepatic glucose.
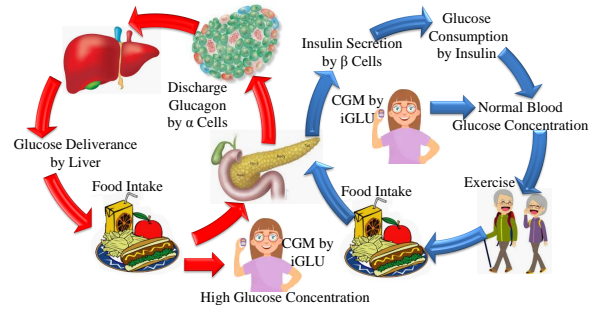
In the current model, it consists of a separate portion for plasma and active insulin. The presented differential equations along with secondary relations constitute the computing model. The variation in plasma insulin I_P is expressed by:

$$\frac{dI_P}{dT} = \left(\frac{I_{absorb}}{V_{oi}} \right) - P_{ie} \times I_P \quad (1)$$

In the above expression, P_{ie} is the rate constant of insulin elimination. I_{absorb} is insulin absorbance rate and V_{oi} is the insulin distribution volume. The rate of change of active insulin follows first order kinetics which is represented as:

$$\frac{dI_{Act}}{dt} = (P_1 \times I_P) - (P_2 \times I_{Act}), \quad (2)$$

where P_1 and P_2 are rate constants which represent the insulin action delay. The absorption rate of insulin is represented as,

$$I_{absorb}(t) = \left(\frac{I_{type} \times t \times T_{D50}^5 \times D}{t[T_{D50}^5 + t^5]^2} \right), \quad (3)$$

In the above expression, t is the time period from insulin injection. T_{D50} is the time at which 50% of the total dose D has been consumed and I_{type} is a specific parameter in terms of insulin absorption for different types of insulin (short, intermediate and long-acting). A linear equation can be formed for T_{D50} of dose D is:

$$T_{D50}^5 = p \times D + q, \quad (4)$$

where p and q are specific parameters which relate to the dose of insulin and time at which 50% insulin was absorbed. hence, $I_{absorb}(t)$ becomes,

$$I_{absorb}(t) = \left(\frac{I_{type} \times t(p \times D + q) \times D}{t[p \times D + q + t^5]^2} \right). \quad (5)$$

If insulin regimen contains more injections then, totally absorbed insulin I_{absorb} will be the sum of individual absorbed insulin from multiple injections. The steady-state insulin has been represented which is based on the superposition principle up to three days for steady-state:

$$I_{steady}(t) = I(t) + I(t+12) + I(t+24) + I(t+48) \quad (6)$$

From the above expression, it is concluded that this expression is not applicable for short-acting insulin. For steady-state absorbed insulin:

$$I_{Act,steady}(t) = I_{Act}(t) + I_{Act}(t+12) + .. + I_{Act}(t+48) \quad (7)$$

The equilibrium insulin level can be expressed in terms of steady-state active insulin:

$$I_{equil}(t) = P_2 \left(\frac{I_{Act,steady}(t)}{P_1} \right). \quad (8)$$

This is considered to compute net hepatic glucose balance (NHGB) and peripheral glucose uptake.

The insulin level is responsible for the periphery and hepatic control action. Now, the change in the glucose values with respect to the time which is represented by a differential equation. After replacing the value of $I_{Act,steady}$ from Eq. 7 in Eq. 8, we derive the following expression:

$$I_{equil}(t) = P_2 \left(\frac{I_{Act}(t) + I_{Act}(t+12) + .. + I_{Act}(t+48)}{P_1} \right) \quad (9)$$

The change in glucose values with respect to the time represented by the differential Eq. 10:

$$\frac{dG_{plasma}}{dt} = \frac{[NHGB(t) + G_{abgut}(t)]}{V_g} - \frac{[G_{aiu}(t) + G_{ren}(t)]}{V_g}, \quad (10)$$

where, $G_{abgut}(t) =$ Absorbed glucose from the gut, $G_{aiu}(t) =$ Consumption of peripheral and insulin independent glucose, $G_{ren}(t) =$ Renal glucose excretion, $V_g =$ glucose distribution volume, $\frac{[NHGB(t)+G_{abgut}(t)]}{V_g} =$ Total body glucose without consumption, and $\frac{[G_{aiu}(t)+G_{ren}(t)]}{V_g} =$ Consumed and renal excreted glucose. According to Michaelis-Menten relationship, total plasma glucose is related to the glucose consumption with reflection of different insulin concentration:

$$G_{aiu}(t) = \left(\frac{G_{plasma}[(c.S_p.I_{equil} + G_{ii})(k + G_{ref})]}{G_{ref}(k + G_{plasma})} \right), \quad (11)$$

where $c =$ Slope between peripheral glucose and insulin level, $G_{ii} =$ Insulin independent glucose utilization, $G_{ref} =$ Reference glucose for consumption, and $[S_p \times I_{equil}] =$ Effective insulin level.

The glucose concentration in gut contains the mean in the form of carbohydrates which is represented as the following:

$$\Delta G_{gut} = G_{Emp} - (K_{gabsorb} \times G_{gut}), \quad (12)$$

where $G_{gut} =$ The amount of glucose in gut, $G_{Emp} =$ Gestric emptying, and $K_{gabsorb} \times G_{gut} =$ Glucose consumption for systemic circulation. An advanced artificial pancreas system has been modeled. Eq. 11 represents the relationship between glucose consumption and steady-state active insulin concentration. This relationship defines the main function of the proposed artificial pancreas system. The description and specific values of modeling parameters are shown in Table I.

VI. Validation of with Multiple Cases and Results

To analyze the behaviour of this proposed system, 4 different cases have been taken with their physiological parameters, diabetes levels, diet schedule, frequent blood glucose readings and insulin secretion time. The body glucose has been monitored of the individual case as per decided plans of diet for diabetes control. The simulation results explored the functional parameters which are necessary to analyze and to monitor the diabetes level. This proposed glucose-insulin model is only proposed to investigate the different conditions for diabetes control.

Case 1: A woman wants to control her sugar level. Her weight is 70 Kg. and is taking three injections of intermediate and/or short-acting insulin every day. A woman desires to start her family but consistently has considerably high blood glucose levels after morning, despite the number of attempts to normalise her control in anticipation of becoming pregnant. Clearly, diet schedule for glucose regulation will not be good during pregnancy. According to this condition, the blood glucose is monitored frequently.

Case 2: A person aged 45 was confirmed as having diabetes at an early age. The weight of the person is 68 Kg. He is following the prescription for combined short and/or intermediate-acting insulin dose four times per day. According to his continuous glucose monitoring, he leads to higher glucose level during the night but he has a low glucose level in the morning. For this condition, the plasma insulin level is monitored frequently with diet and insulin secretion schedule.

Case 3: This overweighted patient aged 58 is insulin-dependent (type 1 patient) has the main problem of gaining weight. The weight is 98 Kg. She is sensitive to take insulin secretion, because the more insulin she will take, the more she has to eat. She smokes and is at higher risk of a heart attack. By adjusting her carbohydrates intake and insulin regimen accordingly may help her reduce weight without going 'hypo'. For this condition, the plasma insulin level is monitored frequently with diet and insulin secretion schedule.

Case 4: An eighteen years old insulin-dependent patient is weighted 70 Kg and has just shifted from his home first-time for University. He is also not a good cook. He appears pretty awful in mornings. He leads to the pretty low glucose level in the morning, at times being at risk of going 'hypo'. By altering his prescribed insulin dose, his glucose level may not be actually so low in the morning. According to this

TABLE I: Parameters of iGLU 1.1 System

iGLU 1.1 Parameters	Descriptions
P_{ie}= 5.4 l/hr	Rate constant of insulin elimination
P_1= 0.025 /hr	Rate constant of insulin delay action
k= 10 mmol/l	Michaelis constant
G_{ii}= 0.54 mmol/hr/kg	Insulin independent glucose utilization
G_{ref}= 5.3 mmol/l	Reference glucose for consumption
c= 0.015 mmol/hr/kg/mU*l	Slope b/w peripheral glucose and insulin
$k_{gabsorb}$= 1/hr	Constant for glucose absorption from gut
V_{oi}= 0.142 l/kg	Insulin distribution volume
V_g= 0.22 l/kg	Distribution volume of glucose

condition, the plasma insulin level is monitored frequently with diet and insulin secretion schedule. The functional parameters of glucose consumptions and plasma insulin levels are represented in Fig. 5. The transient response in blood glucose values has also been analyzed during a scheduled plan of diet and insulin secretions. In above Fig. 5, the diet plan has been scheduled as breakfast, before lunch (snacks), lunch, tea break and dinner meal in the form of carbohydrates for multiple cases. Short and long-acting insulin secretion has also been scheduled for different cases. The analysis has also been done after simulation of glucose-insulin model to control the glucose profiles for presented cases. The scheduled plans of doses and meals are recommended by medical representatives.

Glucose consumption parameters are estimated using MAT-LAB simulation with four possible cases of diabetic patients recommended by diabetologist. The comparison with previous work is represented in Table II. UVa/Padova is a known Type 1 Diabetes Simulator and it has database of emulated meal challenges of total 300 virtual subjects. The proposed model has considered real world subjects with clinical trials under observation of diabetologist with following the medical protocols. The proposed model would provide more realistic solution for glucose control in comparison to related works.

VII. CONCLUSIONS AND FUTURE RESEARCH

This paper presented an automated diabetes control system for diabetes control, in which continuous glucose monitoring has been performed to analyze the plasma insulin level. This advanced system iGLU 1.1 is overcomes the issues of the traditional diabetes control system. A model of glucose-insulin relationship is proposed for artificial pancreas system. In this work, glucose profiles are simulated with respect to the scheduled diet and insulin secretion for multiple cases. The variations in glucose and plasma insulin levels have also been analyzed to control diabetes Mellitus. The multiple cases have been selected to simulate the glucose-insulin model, in which meal plan and insulin regimen with secretion schedule have been decided as per the standards of medical protocols by a diabetologist. The selected cases are most probable which always requires treatment to control glucose level with the help of insulin secretion or food intake.

An unified system in the form of iGLU that combines serum accurate glucose detection [19] and automated insulin delivery is the ultimate goal of our on-going research. In our future, we intend to design a the complete iGLU for type 1 diabetic patient. The proposed system should have the functionality to balance the glucose and insulin level in the human body with a scheduled meal and bolus insulin secretion plan. The system is required to be the real-time wearable device with monitoring all glucose profiles of the human body.

ACKNOWLEDGMENT

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TABLE II: Comparison with Previous Works

Works	Parameters	Model-Simulator	Cases
Magdelaine, et al. [14]	Glucose and insulin dynamics	Uva/Padova Metabolic Simulator	Virtual data of type 1 diabetic patients
Turksoy, et al. [15]	Meal detection with CGM	Uva/Padova Metabolic Simulator	Virtual data of nine subjects
Xie, et al. [16]	Basal-bolus insulin sensitivity	Uva/Padova Metabolic Simulator	Virtual data of two subjects
MohammadRidha, et al. [17]	Meal detection using iPID model	Uva/Padova Metabolic Simulator	Virtual data of ten subjects
Proposed Work	Glucose Consumption parameters	MATLAB for model simulation (Easily accessible for system modeling)	Four possible cases of diabetic patients recommended by diabetologist

(a) Blood glucose and plasma insulin (case 1) (b) Functional paremeters of glucose (case 1) (c) Diet and insulin secretion (case 1)

(d) Blood glucose and plasma insulin (case 2) (e) Functional paremeters of glucose (case 2) (f) Diet and insulin secretion (case 2)

(g) Blood glucose and plasma insulin (case 3) (h) Functional paremeters of glucose (case 3) (i) Diet and insulin secretion (case 3)

(j) Blood glucose and plasma insulin (case 4) (k) Functional paremeters of glucose (case 4) (l) Diet and insulin secretion (case 4)
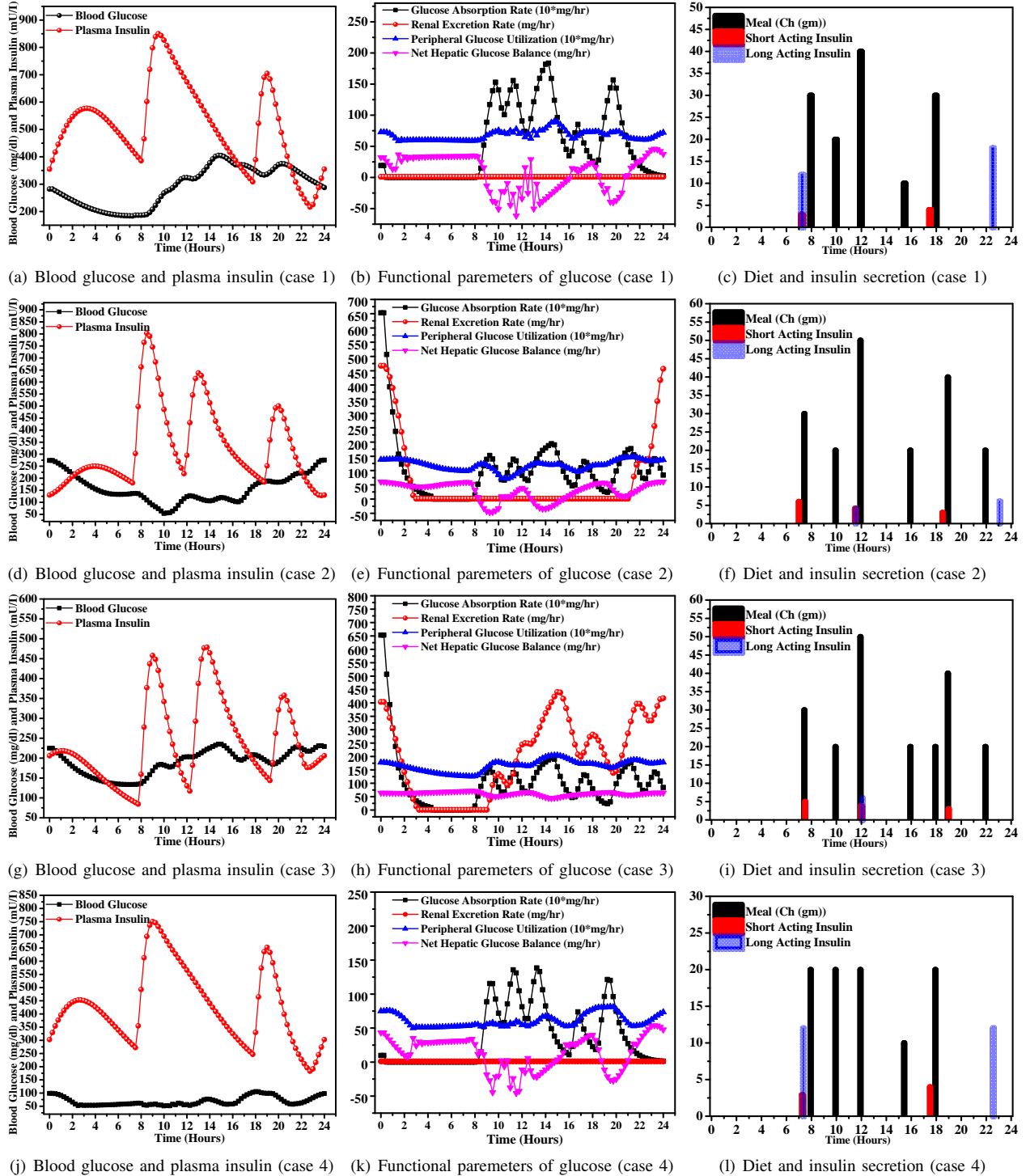
Fig. 5: Simulated functional parameters with glucose-insulin levels and schedules for All cases