Simulation and Comparison of Glucose-insulin Models for Type 1 Diabetes Virtual Patient

Geovanny Satama-Bermeo, Karol Quilachamín, Álvaro Torres, Malena Loza, and Alberto Sánchez
Universidad San Francisco de Quito USFQ, Colegio de Ciencias e Ingeniería, Quito, Ecuador
Email: {gsatama, kjquilachamin, atorresc, mloza, asanchez}@usfq.edu.ec

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***Abstract*—This paper presents the development of a simulation tool using MATLAB for the Bergman, Hovorka and Cobelli mathematical models for the glucose-insulin interaction with the aim to analyze their responses in managing Type 1 Diabetes Mellitus. PID controllers for each model were implemented to regulate normoglucemia levels using exogenous insulin. Each model was tested for different scenarios in terms of carbohydrates grams and patient weight. The tool implements a GUI which allows for analysis of the different responses of each model and their comparison.**

***keywords*—Diabetes, mathematical model, glucose, insulin, virtual patient.**

I. Introduction

Due to the increasing prevalence worldwide of diabetes, it has become a public health challenge. According to the Pan-American Health Organization, in 2040 there will be 109 million people worldwide suffering from diabetes. Diabetes term is used to describe chronic metabolic disorders characterized by hyperglycemia events as a result of a deficient insulin production by the pancreas [1]. This illness affects people of any age; however, in the last decades, there has been an increase in children and young people [2].

There are three types of diabetes: Type 1 Diabetes Mellitus (T1D), Type 2 Diabetes Mellitus (T2D), and Gestational Diabetes Mellitus (GD) [3]. T1D represents 10% of all diabetes cases. In this study, the focus is based on T1D [4]. T1D is an autoimmune disease due to the fact that the immune system destroys beta cells in the pancreas so that, it is not able to produce insulin. Therefore developing high levels of blood glucose. [5].

In terms of symptomatology, the most common are: blurry vision, heavy thirst, more hunger, numb or tingling feet, among others [3]. On the other hand, the fact to have a poorly control of diabetes can lead to long term complications such as retinopathy, nephropathy and cardiovascular pathologies [3].

As the main problem is the absence of insulin, the treatment is based on a meal planning and exogenous insulin dosing to control the glucose concentration. There are many insulin types such as: rapid-acting insulin which is used in continuous subcutaneous insulin infusion therapy through an insulin pump; intermediate-acting insulin which is absorbed slower and lasts longer in the body; and long acting insulin last almost all day [6].

Therefore, the aim of this research is to implement Bergman, Hovorka and Cobelli's mathematical models to perform simulation of glucose-insulin reaction in healthy and T1D patients. The amount of food taken can be introduced by a graphical interface and the insulin bolus is automatically calculated by PID controllers. Food and insulin are taken into consideration to examine the effect on the glucose concentration in the bloodstream.

This paper is organized in the following manner: section II presents the mathematical equations used to implement the glucose-insulin reaction for each model. In Section III simulation results are presented for a variety of scenarios with respect to meal disturbances and insulin intake. The overall findings are presented in the conclusions section.

II. Methodology

In this section, each model is explained based on its equations and compartments. All models are implemented using MATLAB software. Moreover, different test scenarios are introduced to test the models and results are presented using the developed interface.

A. Bergman's minimal Glucose/Insulin model

The Bergman's model is developed in 3 compartments as is shown in Fig. 1. The inputs of the model are exogenous insulin and food; and the output is plasma glucose [7]. This model is very useful due to its facility to understand the glucose/insulin behaviour and also its adaptability with different controllers [8]. The equations which represent the subsystems of this model and the constants used for code implementation of type 1 diabetes (T1D) virtual patient are presented in [9].

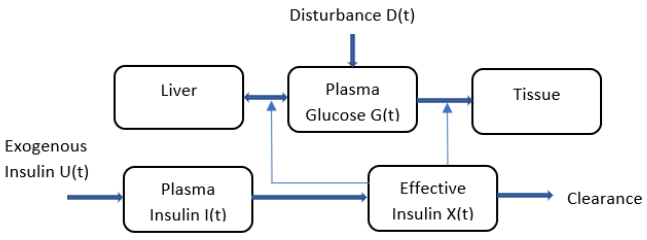

Fig. 1 Bergman's Diagram model

A PID controller is implemented in order to enter the correct amount of exogenous insulin to the system with the aim of stabilizing the glucose plasma concentration in the patient. The controller design implemented is based on [10]

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and was manually tuned. The PID gains found to obtain the best response are presented in Table I.

TABLE I: PID parameters for Bergman's model

Parameter	Value
K_p	-2.7
T_i	200
T_d	15

B. Hovorka's Glucose/Insulin model

Hovorka is a glucoregulatory model which represents the input-output relationship between subcutaneous insulin intake and intravenous glucose concentration [11]. Another input for the model is food ingestion. This model has a compartmental approach based on the glucose kinetic and insulin action. As seen in Fig. 2 its structure is composed of three subsystems: glucose absorption subsystem, subcutaneous insulin absorption subsystem and insulin action subsystem which also can represent outputs of the system. Parameters and constants needed for Hovorka model code implementation are presented in [11].

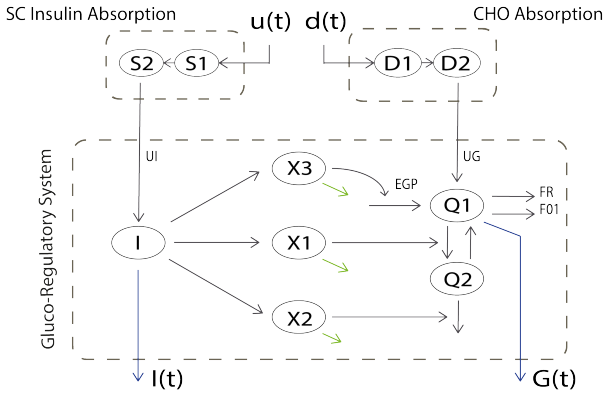

Fig. 2: Hovorka's model diagram.

1) Glucose absorption subsystem: This subsystem is composed of two compartments which describes carbohydrates absorption and glucose conversion [11]. The base of this process is the quantity of ingested carbohydrates in time which will determine the intestinal absorption rate of glucose. Equations that define this subsystem are presented in [11].

2) Subcutaneous insulin absorption subsystem: The insulin is administered subcutaneously to the patient. There are many methods [12] to know the insulin absorption rate. When the insulin enters the bloodstream, it becomes the plasma insulin whose concentration can be calculated. Equations that describe this subsystem can be found in [13].

3) Insulin action subsystem: In this subsystem, the relationship between insulin and glucose can be studied. The insulin absorption rate is the input of the subsystem. It involves three actions of insulin on glucose kinetics: transport and distribution, glucose disposal and endogenous production of glucose. Equations that represent all the characteristics of the subsystem are presented in [11].

A PID controller is implemented in this model using Dahling tuning method [14]. The value of PID parameters used in this work are shown in table II.

TABLE II: PID parameters for Hovorka's model

Parameter	Value
K_p	-0.807
T_i	266.571
T_d	67.433

C. Cobelli's Glucose-Insulin model

Cobelli et al. developed a simulation model of glucose-insulin system using data of two hundred four healthy people. The model has two main subsystems: glucose and insulin which are outlined by compartments [15]. The glucose-insulin dynamic in humans is described by six subsystems. Moreover there are 14 equations that describe the complete model [16]. This model represents a healthy patient; however, some modifications have been made in order to simulate T1D patients.

1) Healthy patient: The Cobelli's model for healthy patients will be described in the next. Parameters used for MATLAB code implementation are presented in [17].

2) Glucose subsystem: This subsystem describe glucose kinetics. It establishes how glucose is transported between muscle and adipose tissues. Moreover, glucose fluxes that represent inputs and outputs of other modules are considered i.e, glucose produced by the liver and intestinal absorption of carbohydrates. All this glucose processes are described by equations in [16].

3) Insulin subsystem: In this subsystem, the insulin transport between plasma and liver is described. Moreover, it is considered the insulin utilization in glucose metabolism process as well as the insulin secretion by pancreas beta cells. Degradation process that occurs in the liver and in the periphery are also considered. Equations that describes insulin kinetics are explained in [16].

The process of glucose and insulin will be explained in the following subsections

4) Endogenous glucose production: In this compartment, the liver is modelled with the aim of establishing the endogenous glucose flux based on the glucose and insulin quantity in plasma as shown in [16].

Fig. 3: Liver modeling.

5) Glucose intestinal absorption: This compartment represents the glucose transit through the gastrointestinal tract in function of the ingested carbohydrates in time. The output is the glucose rate of appearance as shown in Fig. 4. The

mathematical representation of this model can be found in [16].

Fig. 4: Gastrointestinal tract model [18].

6) Glucose utilization: This compartment takes into account the glucose consumed by muscles and adipose tissue as outlined in Fig. 5. It is represented by 2 components. The first one (insulin independent) in which glucose is consumed by brain and erythrocytes. And the second, insulin dependent, which is associated with glucose in tissues and insulin quantity that passes to interstitial liquid. Equations that describe the process are presented in [16].

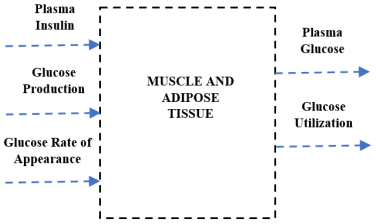

Fig. 5: Muscle and adipose tissue model.

7) Insulin secretion: This process is developed inside the pancreas. The compartment models beta cells which are responsible of insulin secretion according to the level of blood glucose concentration as shown in Fig.6. Thus, this compartment is different for healthy and T1D patients. Equations of this compartment are described in [16].

Fig. 6: Beta cell model.

8) Glucose renal excretion: Glucose renal excretion is produced when plasma glucose surpasses a certain threshold. This process can be modelled using a linear relationship with plasma glucose as shown in equations described in [16].

9) Model conditioning for T1D patients: Plasma glucose concentration changes due to carbohydrate intake in healthy patients. For T1D, the insulin secretion is null, so, it is necessary to provide exogenous insulin by injection or by continuing infusion using a pump. Therefore, the model needs some modifications. Equations and parameters are presented in [19] and [20] respectively.

- Subcutaneous insulin infusion model: The infusion is modelled by two compartments which take into account subcutaneous monomeric and no-monomeric insulin concentrations.
- Insulin subsystem modifications: It is needed to modify equations and initial conditions knowing that there is not insulin secretion. Initial condition now depends on the amount of exogenous insulin.
- Internal glucose production modification: Since internal synthesis of glucose depends on plasma insulin concentration, it is necessary to make changes in equations related to glucose production.

For T1D patients, a PID controller has been developed for this model. The parameters are presented in table III.

TABLE III: PID parameters for Cobelli's model

Parameter	Value
K_p	0.032
T_i	450
T_d	66

D. Tests scenarios

Some scenarios are developed for testing how each model works. The parameters as carbohydrates grams and patient weight are indicated in table IV. The stage for testing Bergman model includes one meal. In the other hand, Hovorka's model is simulated for three meals where the quantity of carbohydrates for breakfast is 40gr while for lunch is 60gr and for dinner it is 30gr. Cobelli's model simulates one meal for both healthy subjects as well as T1D patients.

TABLE IV: Tests scenarios

Model	CHO (gr)	Weight (Kg)
Bergman	60	86
Hovorka	40, 60, 30	70
Cobelli	78	78

E. Graphical User Interface

The system has its own built-in GUI which allows the user to examine the behaviour of each model. The interface for Cobelli's model (Fig.7) shows different charts that allow the user to analyze the results obtained. Similar graphical interfaces are designed for Bergman and Hovorka's model. Moreover, in order to have a complete meal simulation, a carbohydrates of food table were implemented (Fig. 8) so that, user can choose individual food and then start the simulation in each model.

III. Experimentation and Results

This section reports on the obtained results for each model with its PID control system and a comparison between all models under the different scenarios described in the previous section.

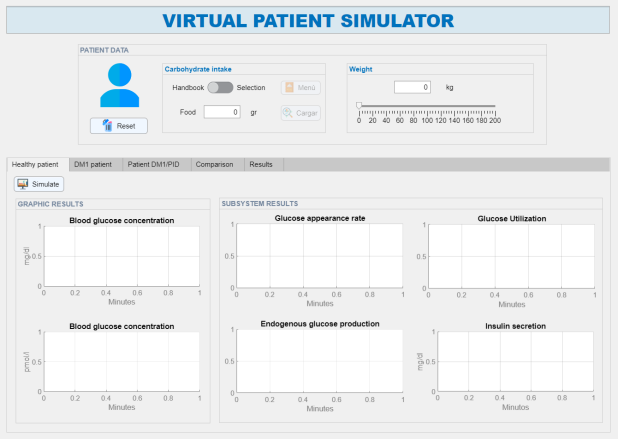

Fig. 7: Graphical User Interface.

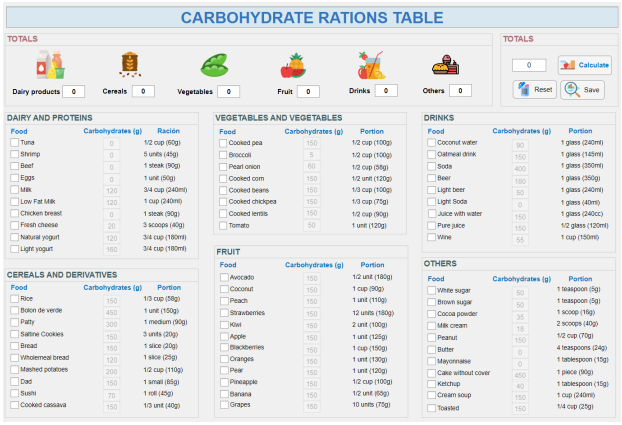

Fig. 8: Carbohydrates food table.

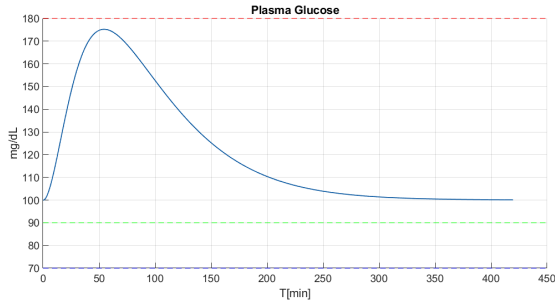

Fig. 9: Result of plasma glucose concentration of Bergamn's model

A. *Bergman's minimal Glucose/Insulin model*

For this model, one of the tests performed were under conditions described in table IV. The obtained results as can be seen in Fig. 9 (Glucose curve of Bergman's model with PID) are compared with results presented by [9]. Data taken for comparison was the peak of glucose, and 2 more 30 minute points after and before it.

Table V shows the relative error calculated over the three points described before. As can be seen, none of these present an error greater than 5%. The highest error corresponds to 30 minutes before the highest point. Even though, at that time

TABLE V: Data obtained from the reference model and Bergman's model with PID controller for glucose concentration

Reference (mg/dl)	Proposed (mg/dl)	Error (%)
175	178	1.71
173	167	3.47
143	139	2.79

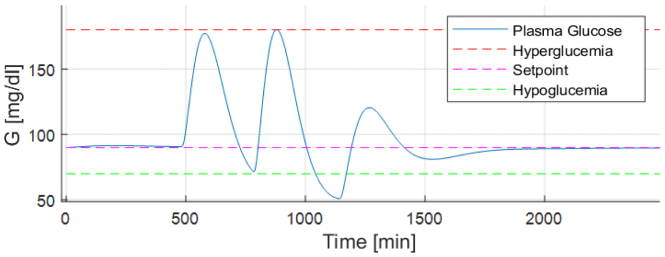

Fig. 10: Result of plasma glucose concentration of Hovorka model.

the glucose level is outside the normaglycemic band (70-140 mg/dl) [21], the patient is still in good condition because he has not spent two hours in hyperglycemia.

B. *Hovorka's Glucose/Insulin model*

Results of this model were obtained after performing the scenario presented in Table IV for a daily diet: breakfast (40gCHO), lunch (60gCHO) and dinner (30gCHO). Fig.10 presents glucose response of the model. Table VI shows the results of the model with the proposed PID and the results presented by [11]. Four points, three of them corresponds to a meal and the last one refers to hypoglycemia were considered for comparison.

For the first point, an error of 1.02% is observed, which indicates that the behavior of the graph at breakfast has a good response, managing a feasible glucose level. In the case of lunch, it is observed that the error increases, but does not exceed 10%, which shows that the development of plasma glucose is good and error is not considerable. For dinner, the error is less than 3%, this helps to maintain a level of confidence in the results since the progress of glucose allows to observe that the patient is at normoglycemic levels. In the last event, when the glucose exceeds hypoglycemia, there is an error of 10.25%, it is observed that the glucose level drops but does not exceed the time in which hypoglycemia is considered harmful. This error may be due to the high amount of carbohydrates ingested just before as can be seen in Fig. [19] since at lunch is when the patient ingests more carbohydrates.

TABLE VI: Data obtained from the reference model and Hovorka's model with PID controller for the glucose subsystem

Event	Reference (mg/dl)	Proposed (mg/dl)	Error (%)
Breakfast	176	177.8	1.02
Lunch	170	179.6	5.64
Dinner	120	123.4	2.83
Hypoglycemia	58.5	52.5	10.25

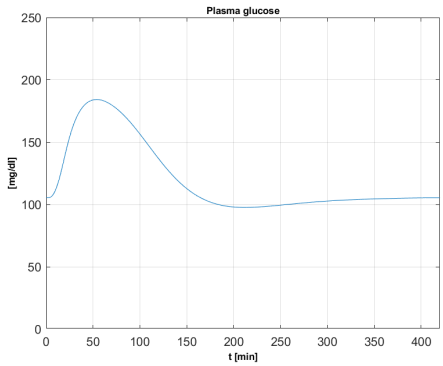

Fig. 11: Result of plasma glucose concentration for a healthy person.

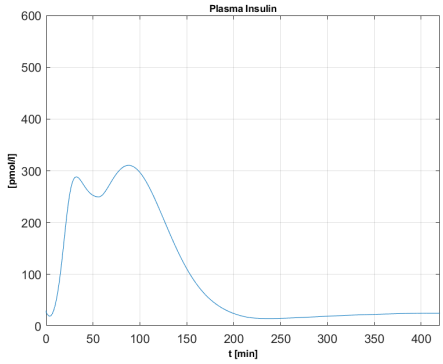

Fig. 12: Results of plasma insulin concentration for a healthy person.

C. Cobelli's Glucose/Insulin model

The Cobelli's model for a healthy patient allows the simulation of a person with a fully functional glucose-insulin metabolism. That is, glucose levels will be between 70 mg/dl and 200 mg/dl due to insulin action. This behaviour is evidenced in Fig.11 and Fig. 12.

To obtain a validation of the implemented model, a comparison is made with the results proposed by the author in [16]. A patient of 56 years and 78 kg of weight with a carbohydrate intake of 78 grams is considered for the analysis. Fig.13 shows the results obtained for the simulation of the glucose subsystem where it can be observed that, for a food intake, the glucose in the patient's plasma increases from 110 mg/dl to 180 mg/dl, due to an increase in blood sugar because of the metabolism of carbohydrates in the body.

After obtaining the simulation results, a comparison was done between the author's data presented in [16] and the data obtained in this simulation to calculate the error and observe how accurate the model implemented in this work is. According to the calculations, there is an average error of 5.35%, which indicates that the simulation provides data close to the model proposed by the author, which is reflected with the bounded curves in Figure 13.

After validation of the proposed model, a modification is made to parameters and insulin subsystem of the Cobelli's model. This allows to obtain a mathematical model of glucose-insulin regulation for T1D patient based on adding to the model an exogenous insulin compartment which represents the insulin injections through a pump. In Figure 14 shows how the insulin injection delivered by the PID pump affects the regulation of glucose in the blood and how insulin is present in blood plasma.

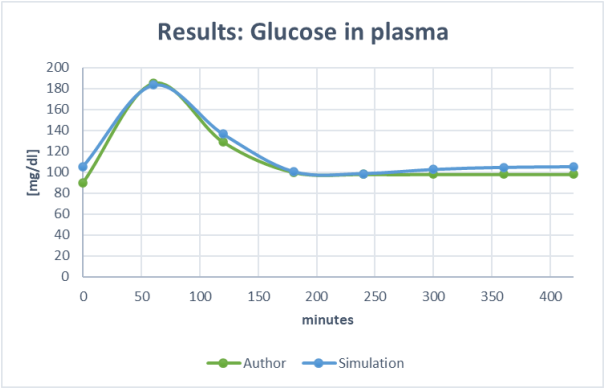

Fig. 13: Results of the glucose subsystem for the simulation of a healthy patient weighing 78 kg and a carbohydrate intake of 78 gr.

TABLE VII: Data obtained from the reference model and Cobelli's model for the glucose subsystem

Time (s)	Refer (mg/dl)	Simulation (mg/dl)	Error (%)
0	90	105.40	17.11
60	185	183.50	0.81
120	129	136.70	5.97
180	100	100.70	0.70
240	98	98.74	0.76
300	98	102.70	4.80
360	98	104.70	6.84
420	98	105.30	7.45
			5.35

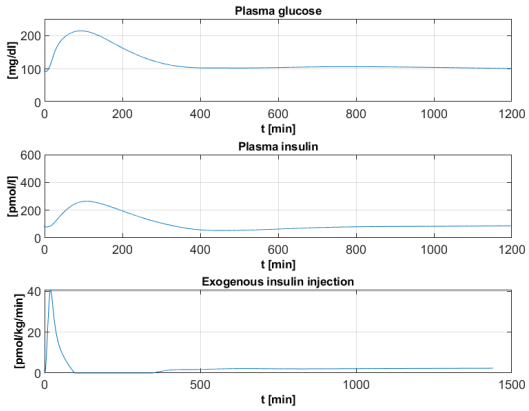

Fig. 14: Results obtained for a person with DM1 and automatic insulin infusion (Plasma glucose and insulin concentration).

D. Comparison of Glucose Results among the different virtual patients

Figure 15 presents glucose concentration curves as a result of a simulation of all models under the same conditions, that is 44 gr carbohydrates and 80 Kg of weight. As it can be

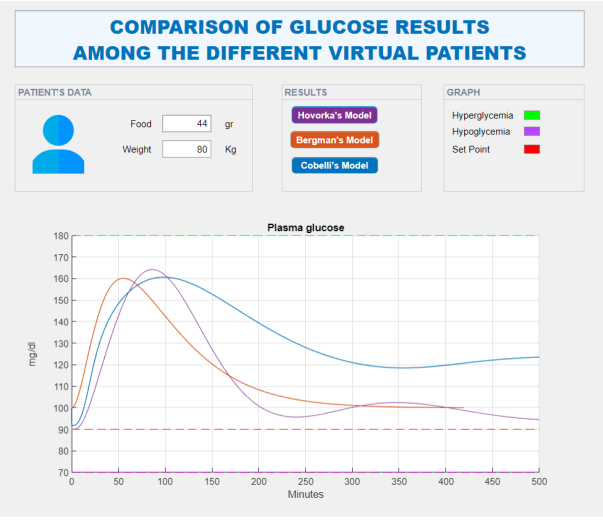

Fig. 15: Glucose curves of Bergman, Hovorka and Cobelli's model.

seen, after the food intake, the maximum peak of glucose for the three models is around 180 mg/dl. It is important to highlight that no model exceeds hypoglycemia level, which is very convenient. Moreover, the level of hyperglycemia has not been exceeded which is also evidence of the good behaviour of three models under these specific conditions.

IV. Conclusions

Simulation of a T1D virtual patient using Bergman, Hovorka and Cobelli's model and the control of glucose was the main objective of this work and was successfully accomplished by using a simple PID controller for each model. As a result, the blood glucose concentration has been analyzed related to the effect of meal disturbances and the amount of insulin dose determined by the controllers. Moreover, meal disturbances were introduced to the simulation through a carbohydrates food table. Results were visualized using a Graphical interface designed in App designer software.

Despite the simplicity of the Bergman's model compared to other models simulated in this work, the results presented were according to the reference work including the PID controller implemented. Also, for the experimental scenario, simulation yielded a glucose curve response that do not exceeds either the hyperglycemia nor hypoglycemia levels.

In the other hand, as the Hovorka model does include more compartments and physiological characteristics, it is able to simulate a daily diet. Results were also accurate with the reference work and the glucose curve were below hyperglycemia level but it was noted a peak that exceed hypoglycemia level in a short period of time.

Finally, Cobelli's model describes a healthy patient with features that make it closer to real case. Both healthy and T1D patient showed results in agreement with other literature. Moreover glucose response was in the expected levels.

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