Virtual Environment Model of Glucose Homeostasis for Diabetes Patients

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***Abstract*—A medical device is designed to meet the patient specific requirements. The required biological behaviour of the medical device is driven by mostly the operating environment. Most of the time, a medical device fails due to lack of understanding of the system requirements, including the functional and non-functional requirements. For example, the U.S. Food and Drug Administration (FDA) has reported a large number of serious illnesses and deaths related to IIP. Our approach is to trigger hidden requirements at an early stage of the system development. In order to achieve our goal, this paper proposes an abstract development of virtual environment model of the glucose homeostasis for diabetes patients to analyze the patient specific medical devices, such as an Insulin Infusion Pump (IIP). The main objective of this environment model is to assist in the construction, clarification, and validation of the system requirements by developing and designing the closed-loop model of medical devices.**

***Index Terms*—Homeostasis, Diabetes, Formal methods, Environment modelling.**

I. Introduction

Since software plays a vital role for better controllability, operability and safety in medical domains, the device manufacturers are required to validate any software used in their devices, and test rigorously the functional behaviour of the device for detecting critical flaws and security vulnerabilities. To address the critical flaws and security vulnerabilities including device development process, the regulators provide guidelines to develop a safe and dependable critical medical systems. These guidelines play a major role to comply with certification standards. Due to increasing system complexities, regulatory agencies are always looking for new methods and tools for improving the engineering-based review strategy that could provide the system assurance.

The *Insulin Infusion Pump* (IIP) is a complex medical device that is used by millions of people to regulate normal levels of glucose for controlling diabetes. This device is used to deliver insulin doses in a controled manner in order to maintain an appropriate level of glucose. Over the past few years, IIPs have been used successfully to treat diabetes. However, the failure rate of the IIPs have increased tremendously. These failures cause several deaths and serious illnesses. The U.S. Food and Drug Administration (FDA) reported 17,000 adverse-events from 2006 to 2009 including 47 deaths due to IIP's malfunctions [1]. The root causes of these device failures are considered as product design and engineering flaws, which are identified by the FDA officials during investigation of the reported deaths and illnesses related to the IIPs.

The medical device manufacturers use an artificial environment model for simulating and testing the functionalities and effectiveness of medical devices. Such type of environment models are very expensive and critical to use for testing and validating the medical devices. These models are based on complex mathematical equations, that require high computation and large memory for simulating the environment. However, these models are not able to simulate and to check the overall functionalities of a device. It is important to know that, these models are also not applicable to use at the early phases of the development life-cycle for testing or verifying the requirements. Our experience and knowledge show that an environment model can be used for validating the system requirements at an early stage of the system development. This approach has some other benefits, such as finding missing requirements, validating assumptions and strengthening the existing requirements. To apply this approach, we need to develop the closed-loop model by using an abstract model of the virtual environment. The designed abstract model should capture all the essential features. The closed-loop model is a combined model of the medical device model and the environment model, where both models interact to each other using sensors and actuators. Medical device model uses actuators and sensors to respond according to the functional activities of the virtual environment. If sensors sense abnormal activities then the device must actuate for delivering medicine or any other activities. If sensors sense normal behaviours then the device should not do anything. By observing the virtual behaviour of the environment, we can ensure that the medical device behaves correctly under the required conditions. This approach has potential benefits of giving a confidence in the product development that the behaviour of medical device is safe within the biological virtual environment.

As far as we know, there is no environment model for IIP, which can be used for simulating and testing the system requirements at an early stage of the system development during design and development. This paper contributes by providing the development of virtual environment model of the glucose homeostasis for diabetes patients to analyze the patient specific medical devices like Insulin Infusion Pump (IIP). The prime use of this environment model is to assist in the construction,

clarification, and validation of the given system requirements by designing the closed-loop model using formal methods at an early stage of the development life-cycle. We use a simple logic for modelling the biological environment of an IIP. The environment model is based on continued monitoring of the glucose-insulin regulatory system [2]. The proposed virtual environment model describes normal and diabetic conditions, by using α-cells and β-cells, and rising or dropping plasma glucose level to model the pancreatic behaviour, and blood test levels for the diagnosis of diabetes/pre-diabetes. The key features of this model is to consider both normal and abnormal (hyperglycemia or hypoglycemia) behaviour that can be used to characterize a patient model. There are several benefits of our approach: 1) Development of simple and complex environment models using simple logic in several refinements; 2) Use of an environment model for identifying missing requirements and emerging behaviour; 3) Assist in meeting the criteria of certification standards; and 4) Validation of the system assumptions and behavioural requirements.

The structure of this paper is as follows. Section II presents the related work. Section III presents basic concepts of the virtual environment modeling. Section IV presents glucose homeostasis (GH) system, and the formal definition of the glucose homeostasis (GH) is presented in Section V. Section VI discusses the usability of the environment model. We conclude the paper and discuss the future work in Section VII.

II. Related Work

The human biological system is one of the complex, dynamic and infinite systems, that is not fully understood yet. The medical practitioners and engineers use physical and mathematical model to characterize the biological behaviour. Over the last decade, several models exist for describing the glucose homeostasis and diabetes. These models are either clinical or non-clinical. The clinical models are used for identifying and predicting the diagnostics, control, progression, complication, etc. of diabetes. The non-clinical models are used for modelling the insulin-glucose, hepatic glucose, glucagon, and insulin receptor dynamics, beta-cell insulin release, and brain glucose homeostasis. The first mathematical model based on differential equations to model the glucose and insulin concentration, illustrating the dynamics of insulin-glucose for diagnostic purpose and evaluating several parameters of the diabetic and pre-diabetic conditions proposed in [3]. The proposed model was very useful for describing the dynamics of insulin and glucose and their concentration level. An integrated insulin-glucose model for analyzing the diabetic condition using a bidirectional insulin-glucose feedback mechanism was presented in [4]. The theoretical treatment of the effect of external potassium on oscillations in the pancreatic β-cells was presented in [5]. This model was able to demonstrate that insulin infusion may be useful for mimicking pancreatic insulin secretion. There are several models produced by academia and industries that incorporate different physiological processes associated with insulin-glucose dynamics and different variations [6].

The literature suggests that existing models, with their mathematical constraints and higher order differential equations, are not easy to express in first order logic, and thus make it difficult to express the system requirements for verification purpose. Moreover the existing models have been developed for specific purposes that cannot support desired global behaviours. We want to describe the complete system by introducing the abstract notions of possible features that can be later extended for any particular use. The concept of environment modelling for GH system is motivated by our previous work on heart modelling [7] and GH modelling [8]. We have adopted the same methodology to design an efficient and optimum environment model for the GH system based on abstract notions of pancreatic behaviours. The model is defined through analyzing the glucose regulation mechanism. The virtual environment model is described abstractly using first-order logic considering various safety properties at each incremental step, and normal and abnormal behaviour (hyperglycemia, hypoglycemia or diabetic complications).

III. Methodology for Environment Modelling

To use an environment model for developing the medical systems, we need to focus on the expressiveness of the selected modelling language to describe the complex and realistic environment using various levels of abstraction. The modelling language should have well-defined syntax and semantics for the tools to analyze desired behaviour. The language should allow refinement based modelling including temporal, functional, reactive and non-deterministic behaviour for specifying the required components of environment. The Event-B modelling language fulfills the basic requirements as an environment modelling language. In fact, there is another benefit that we can also use the same modelling notations for designing the medical systems. The refinement approach allows to model both the medical system and the environment together to specify the required level of abstractions as well as concrete details. Environment modelling requires higher level of abstractions to describe non-deterministic behaviour compared to the system behaviour. Functional behaviour of both the environment and system models are described by the dynamical states, which show system interactions using sensors and actuators.

The environment model provides essential information about environment components, basic characteristics of each component, and structural relationship between components. The structural relationship between two components shows a common interface channel or medium to exchange the information. All these components together form the overall environment that simulates the virtual operating environment for medical systems. Each component can have several instances of the environment, which can be specified non-deterministically for capturing the functional behaviours. The environment model can have numerous sensors and actuators including system components. The environment components are described formally, and a list of properties validates the expected functional behaviours of the components. Following,

we discuss further in detail various guidelines for modelling the virtual environment model for medical systems [9].

A. Modelling Components

To design an environment model, we need to include all the essential components to describe the required system behaviour. These essential components can be expressed in both abstract and concrete as per the granularity levels of the system component definition. For example, few components can be described abstractly to capture only desired behaviour and to avoid the complex computations. Note that the complex computation should not affect the required system behaviour. The development of the environment model can start from a very abstract model that can be further enriched by introducing new components or details of the components. Each refinement level contains more components or detailed functionalities. All the models from abstract to concrete levels can be used for simulation purpose that can satisfy the required behaviour of the system.

B. Components Composition

The environment components are linked to each other through physical or logical relationships. The relationship preserves architectural definition of the system components. The given relationships allow all the environment components to communicate or to exchange the information. Each component responses according to the current actual input that is sensed by sensors. A large system can consist of several small components, which can be specified by functions. Each system component uses different types of sensors that can be described as functions with different sensors types. These small components can be used further to design the virtual environment model.

C. Properties of Components

To design an environment model, only components definitions and relationships are not enough. These things only provide the skeleton of an environment model, but it cannot provide any guarantee that we have designed the correct environment model. To design a correct environment model, we need to provide a set of properties related to the functional behaviours. Model properties are indispensable to characterize the environment components to satisfy the required behaviours. It is important to include those properties that are necessary to check system requirements. These may include behaviour constraints of a component, required input attributes for components, and state invariants for each component with respect to the medical systems for verifying the desired behaviour.

D. System Modelling

To ensure the effectiveness of environment modelling, it is important to include the system model itself for analyzing the overall system behaviour. In fact, we need to model both the system model and the environment model together to understand the peculiar behaviour of the system. For instance, to analyze an Insulin Infusion Pump (IIP), we need to model both the IIP and GH model. However these two models connect to each other and form a closed-loop model. These models interface with each other as sensors and actuators. It is important to include the details of the system and environment model including sensors and actuators for interaction considering desired levels of detail, and required safety properties.

E. Model Simulation

The environment models developed using any methodology require simulation and dynamic execution for understanding the correctness of biological behaviour. The simulation allows to check the temporal behaviour, interactions between of system components, and new changes evolving over time. However, it must meet all the requirements for a real biological system. Simulation not only guarantees the correctness of system behaviours, but also helps domain experts to understand the designing environment.

IV. The Glucose Homeostasis System

Glucose is the major metabolic fuel of the human body. To maintain an appropriate level of glucose in the body and to provide normal functionality, we need a regular supply of glucose to the body. Failure of the glucose level causes several diseases such as diabetes mellitus, galactosemia and glycogen storage diseases [6].

Fig. 1 depicts the normal GH system[1], which presents the structural flow of the hormones and a functional behavioural pattern of the different organs. It is vital for the body to maintain an appropriate glucose concentration, so both low and high glucose levels are serious, life-threatening problems. The body regulates its glucose concentration using the pancreas and the liver. The pancreas produces two main hormones *insulin* and *glucagon* to control the GH system. The body cells use the available glucose whenever the body receives glucose from the infusion or hepatic function. There are two different types of cells that use the glucose. For instance, the brain and nervous system cells use glucose without insulin, while other types of cells like muscle and fat cells use glucose with the help of insulin. The glucose concentration level fluctuates in the body, and is maintained in the plasma through the pancreatic secretion of glucagon and insulin. In general, the body attempts to maintain an appropriate level of glucose in the body, but there are some natural stable oscillations that occur in the glucose and insulin concentrations [2].

Low and high glucose levels are the two main biological responses that the body uses to maintain an appropriate plasma glucose concentration. When the glucose level drops, then the α-cells in the pancreas produce glucagon, which is transformed into glucose with the help of the liver. This process helps to increase the glucose concentration in the body. Similarly, when the plasma glucose level goes higher than expected, then the β-cells in the pancreas are stimulated to lower the glucose concentration [6]. This stimulation process

[1]The 'normal GH system' is when the GH system functions as it should, i.e., there are no abnormal behaviours exhibited by the system.

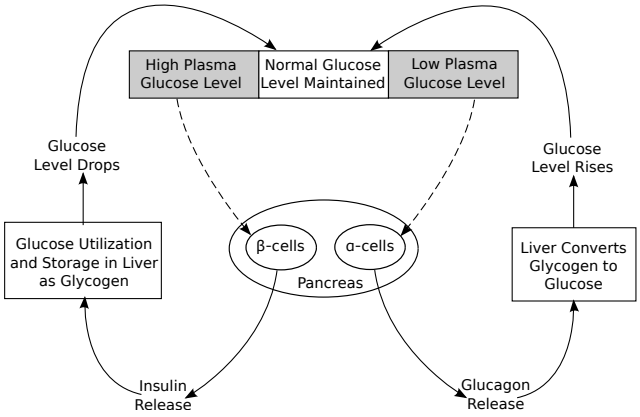

Fig. 1. The GH System (adopted from [6])

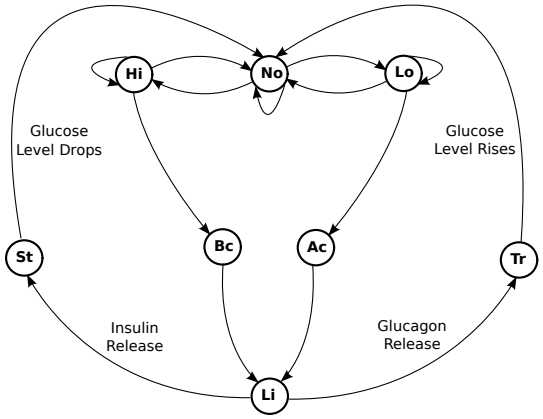

Fig. 2. The GH Automata

can be completed within 5 to 15 minutes, and during this period the insulin is produced by β-cells of the pancreas. The secreted insulin can be used by insulin dependent cells to utilize the available glucose, and to stop the natural hepatic glucose production for reducing the glucose concentration in the blood. The liver is the central organ for regulation of glucose and glycogen and behaves as a distributor of nutrients through blood to other tissues. The presence of insulin inhibits the transformation of glucagon to glucose.

V. Formal Definition of Glucose Homeostasis

The GH model is mainly based on the glucose regulation system of the body. This method uses advanced capabilities of the combined approach of formal verification and behaviour simulation, in order to achieve considerable advantages for GH system modelling. Fig. 1 shows the main components of the GH system. The system comprises different states of the glucose level in the blood and biological organs, in order to control the glucose level. To formalize the GH system, we consider eight significant landmark nodes (*Hi, No, Lo, Ac, Bc, Li, St, Tr*) in the homeostasis functional network as shown in Fig. 2, which can control the GH system. We have identified these landmarks through a literature survey [6], [2], [3], [4], and use them to express an abstract functionality of the system. We introduce the necessary elements to formally define the GH systems as follows:

Definition 1 (The GH System). *Given a set of nodes N, a transition T, is a pair (i, j), with i, j* $\in$ *N . A transition is denoted by i* $\rightsquigarrow$ *j. The GH system is a tuple GHS = (N, T,* N_0*) where:*

- *N = { Hi, No, Lo, Ac, Bc, Li, St, Tr } is a finite set of landmark nodes in the GH network;*
- $T \subseteq N \times N$ *= {No* $\mapsto$ *Hi, Hi* $\mapsto$ *No, No* $\mapsto$ *Lo, Lo* $\mapsto$ *No, Hi* $\mapsto$ *Hi, No* $\mapsto$ *No, Lo* $\mapsto$ *Lo, Hi* $\mapsto$ *Bc, Lo* $\mapsto$ *Ac, Bc* $\mapsto$ *Li, Ac* $\mapsto$ *Li, Li* $\mapsto$ *St, Li* $\mapsto$ *Tr, St* $\mapsto$ *No, Tr* $\mapsto$ *No, St* $\mapsto$ *Hi, Tr* $\mapsto$ *Lo, Tr* $\mapsto$ *Hi, is a set of transitions to present data flow between two landmark nodes. It should be noted that the last three transitions are possible when we consider the case of failure of the GH system;*
- N_0 *= No is the initial landmark node (normal glucose level);*

The automata shows the flow of the GH system, where by default the GH system is considered to be in its normal state (No). The normal state indicates that there is an appropriate glucose level in the blood. Whenever the glucose level fluctuates in the blood, resulting in a high or low glucose level, the GH system controls the fluctuated glucose level with the help of the pancreas and liver. The high and low states are presented by Hi and Lo nodes (see Fig. 2). The pancreas has two type of cells: α-cells and β-cells, which are indicated by the Ac and Bc nodes, respectively. The liver is denoted by the Li node that is used to convert the glycogen to glucose using glucagon, and to store the glucose as glycogen in the liver with the help of insulin. If the liver is well behaved, then the glucose level either rises or drops according to whether there is a low or high glucose level in the blood, respectively. Eventually, the glucose level returns to an appropriate level.

A. Diabetes or Abnormal Homeostasis System

Fig. 3 presents abnormal behaviour of the GH system. The liver plays a central and crucial role for regulating the glucose level in the blood. The main task of the liver is the continual supply of required glucose energy sources to the body. Failure of the GH system causes several diseases, and in particular, diabetes. There are two type of diabetes: *insulin-dependent diabetes* (also know as *type 1 diabetes*) and *non insulin-dependent diabetes* (also know as *type 2 diabetes*). Insulin-dependent diabetes may be caused by insufficient or no insulin secreted due to β-cells defects. In non insulin-dependent diabetes, insulin is produced, but the insulin receptors in the target cells do not work due to insulin resistance in the cells, so the insulin has no effect. In both cases there can be a very high glucose level in the blood. Low glucose level can be caused by α-cell defects or abnormal glucagon release, which can be further classified as insufficient or no glucagon secretion, excess insulin, and excess glucagon secretion. Excess glucagon secretion and defects in β-cells may also indicate a persistent high glucose level, which can be classified as hyperglycemia-induced diabetes complications [6].

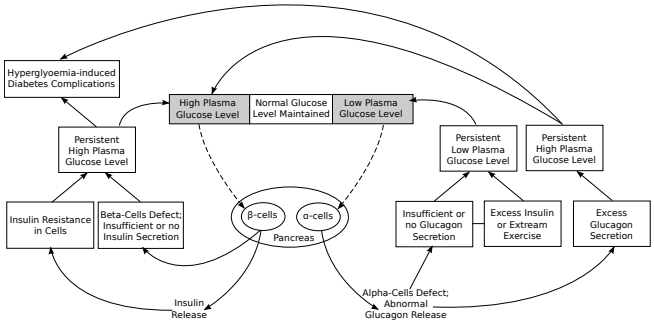

Fig. 3. Abnormal GH System (adopted from [6])

B. Blood Sugar Concentration

The blood sugar concentration or blood glucose level is an amount of glucose (sugar) present in the blood of the body. The body naturally regulates blood glucose levels as a part of metabolic homeostasis. The glucose level fluctuates many times in a day. In general, the glucose level is always low in the morning, and it can rise for about an hour after having a meal. There are two types of tests used to detect abnormal behaviours: FPG (Fasting Plasma Glucose) Test and the OGTT (Oral Glucose Tolerance Test) [10]. The FPG test is used to detect diabetes and pre-diabetes. The FPG test measures blood glucose in a person who has fasted for at least 8 hours and is most reliable when given in the morning. The OGTT can be used to diagnose diabetes, pre-diabetes, and gestational diabetes. This test is applied when a person has fasted for at least 8 hours and 2 hours after the person drinks a liquid containing 75 grams of glucose dissolved in water. The normal glucose level should be within the range of 70 mg/dL to 99 mg/dL for a non-diabetic person using the FPG test, while the glucose level should be within the range of 70 mg/dL to 139 mg/dL for a non-diabetic person using the OGTT [10]. In the case of low glucose level, for both FPG and OGTT tests the glucose level should be within the range of 0 mg/dL to 70 mg/dL. Similarly, for a high glucose level, readings should be greater than 126 mg/dL in the FPG test, and greater than 140 mg/dL using the OGTT. A blood sugar level outside of the normal range indicates an abnormal glucose concentration. A high level of glucose is referred to as hyperglycemia and a low level of glucose is referred to as hypoglycemia.

Property 1 (Glucose level in blood). *The blood glucose level defines different stages, such as hyperglycemia, hypoglycemia and normal. We say that the glucose level is low (hypoglycemia) if* $FPG \in 0..69$ *or* $OGTT \in 0..69$*, and the glucose level is high (hyperglycemia) if* $FPG \geq 126$ *or* $OGTT \geq 200$*, and the glucose level is normal if* $FPG \in 70 \,..\, 99$ *or* $OGTT \in 70 \,..\, 139$*. We classify pre-diabetes to be the range where* $FPG \in 100 \,..\, 125$ *or* $OGTT \in 140 \,..\, 199$*.*

C. Formalization of the GH System

To develop a virtual biological environment of GH based on formal techniques, we use the Event-B modelling language [11] that supports an incremental refinement to design a complete system in several layers, from an abstract to a concrete specification. Initial model captures the basic behaviour and biological requirements of the GH system in an abstract way. The subsequent refinements are used to introduce α-cells and β-cells of the pancreas, functional behaviour of liver to convert and to store the glucose, abnormal conditions of the pancreas, diabetic conditions, and diabetes complications, and blood sugar concentration for assessing diabetes. The developed system results the dynamic behaviours of virtual GH biological environment that covers the both normal and abnormal behaviours (hyperglycemia, hypoglycemia or diabetic complications). A list of safety properties are defined at each incremental level to guarantee the correctness of designed virtual biological environment model for GH. A detail formalization process of the virtual biological environment model is available in [8].

VI. Usability of Environment Model

This section presents usability of environment modelling for developing an IIP as follows:

A. Verifying patient safety in closed-loop

The closed-loop system allows to monitor according to the system requirements as per the physiological needs. Each patient has specific needs according to the diabetic symptoms, which can be diagnosed by using an IIP. In fact, an IIP has configuration parameters that allow to configure the device for each patient by doctors by analyzing the chronicle conditions. To verify at an early stage of the system development, the environment model can be used by developing a close-loop system. Environment models describe normal and abnormal conditions of patients that can be helpful to analyze the IIP requirements and to check consistencies for finding missing requirements. The integration of the environment modelling and IIP allows to evaluate whether the IIP provides an appropriate therapy for diabetes as per the patient needs without delivering excessive insulin.

B. Checking functional requirements

The closed-loop system exposes several conditions for normal and abnormal diabetic conditions, which are represented in (Fig. 3) using a range of situations that occur due to several types of malfunctions. The state of glucose homeostasis is presented as a boolean state to show normal and abnormal states. The insulin delivery mechanism is specified under various conditions. Some behaviour requirements are given as follows: 1) β-cells and α-cells defects cause high plasma glucose level. It is important that insulin must be released in an appropriate amount to stabilize the glucose level. 2) Insulin resistance in cells does not allow to reduce the high plasma glucose level, where an IIP requires to delivery insulin to control the glucose level. 3) Abnormal glucagon release also causes excessive glucagon secretion that maintains the high plasma glucose level. However, the IIP must deliver insulin as per the body requirements. We have discussed various abnormal behaviours of patients. These scenarios must be

covered in the environment model and the closed-loop model should provide evidence that the IIP delivers insulin doses whenever they are required by the patient. The insulin delivery process must be coordinated with GH model to ensure required amount of insulin for maintaining the normal glucose level.

C. Analyzing clinical requirements

Clinical requirements depend on the patient needs such as insulin resistance in cell, β-cells defect, α-cells defect, insufficient insulin secretion, insufficient glucagon secretion, excess insulin and excess glucagon secretion. These requirements are common critical conditions, which can vary for each patient because of different physiological needs.

The GH model is presented as abstract as possible to capture all possible scenarios of the natural glucose homeostasis system. Whenever, the functional behaviour of α-cells and β-cells change; or insulin and glucagon releasing behaviour change; or the functional behaviour of natural glucose homeostasis change, the glucose levels, which represents high plasma glucose level or low plasma glucose level will be affected. Moreover, we introduce other abnormal condition details, and blood sugar concentration using stepwise refinement. The present model is still abstract to cop with several major normal and abnormal conditions. For instance, we have not done any special treatment in our model to capture the required time duration to stabilise the normal glucose level after releasing insulin. The timing requirements can vary for each patients and it results in many symptoms, primarily those symptoms result from the delayed, non-physiologic timing of insulin release in relation to high glucose level. The normal and abnormal states of GH model are represented through the abstract behaviour, and α-cells and β-cells release functions requirements. In case of abnormal state of the glucose homeostasis, the IIP delivers the required amount of insulin to maintain the glucose level.

D. Finding essential safety properties

The closed-loop model provides higher assurance for safety and security. The environment based closed-loop modelling approach offers to find ambiguities and inconsistencies in the IIP specification. The abstract representation and set theory allow to software engineers to specify system requirements and desired safety properties. The generated proof obligations and discharging them show the correctness of system requirements according to the defined properties. Any inconsistencies between requirements are identified and fed back to main system requirements. This iterative process allow to find the correct requirements as per defined notions of the environment.

Another benefit of this approach is that the environment model can be reused with other systems, wherever a system requires environment modelling for verification and validation. This environment is always considered as a separate system, which can be further changed as per stakeholder demands for multiple purposes, such as simulation and testing. Each time this environment model can produce a different set of safety properties according to the integration of a new device specification.

VII. Conclusion and Future Challenges

There are several existing clinical models based differential equations and higher order polynomial equations that require significant computation and a large memory for implementation, which cannot be used at the early stage of the system development for developing the closed-loop model for verifying a IIP. In this paper, we have presented a methodology for modelling a biological environment of the GH using simple logical mathematics in an abstract way to simulate the desired behaviour to avoid the mathematical complexity. This is the first computational model based on logical concepts to simulate the GH behaviour in order to analyze the normal and diabetic conditions. The developed model highlights a different aspect of the problem, making different assumptions and establishing different properties concerning the variation in glucose levels, normal and diabetic conditions, and malfunction of biological organs like the liver and pancreas. This is a promising simulated biological environment model that can be used to develop a closed-loop model of the biological environment and IIP. As we know that the FDA has already reported several recalls related to IIP, so our approach may help to identify the possible bugs in early phase of the development life-cycle of IIP. Our most important contribution is that this formal model helps to obtain certification for the medical devices related to the homeostasis system, such as IIP. This environment model can also be used as a diagnostic tool to diagnose or understand patient requirements.

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