Formalizing the Glucose Homeostasis Mechanism

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Abstract. The failure of hardware or software in the medical domain can lead to injuries and loss of life. Design errors are a major source of the defects that are introduced during the system development process. Traditional validation and verification techniques such as simulation and testing are effective methods for detecting these defects, but are seriously limited in that they cannot guarantee to find all existing defects. Formal methods provide a complementary alternative to testing and simulation, and, although we do not yet have a 'theory of coverage' when combining formal validation and verification techniques with testing and simulation, the combination provides better coverage than any one of them on its own. The insulin infusion pump (IIP) is a critical system that is used by millions of people around the world. IIP failures are responsible for a large number of serious illnesses and deaths. This paper presents the formalization of the glucose homeostasis mechanism that provides an environmental model for the IIP. We can then use this model to validate the appropriateness and correctness of system behaviours at an early stage of development.

Keywords: Homeostasis, Diabetes, Event-B, Formal methods, Proof-based development, Refinement.

1 Introduction

Glucose is the main source of energy for humans, and the glucose-insulin regulatory system maintains an appropriate blood plasma glucose concentration level within the body. The *glucose homeostasis* (GH) system has to maintain a very narrow range of plasma glucose concentration in the blood. The normal range of glucose concentration for most humans after fasting is 70-100 mg/dL. Levels lower than 70 mg/dL are likely to cause a state of hypoglycemia, which is life threatening. Levels higher than 100 mg/dL cause hyperglycemia, and chronic elevated hyperglycemia would normally be diagnosed as *diabetes*. Several diabetic diseases occur when the GH system is not able to maintain the glucose concentration in the blood within the normal range [1–3].

The *Insulin Infusion Pump* (IIP) is an advanced medical device that is designed to maintain normal levels of glucose for people diagnosed with diabetes or some other failure of the GH system. The IIP is a small computerized system that delivers insulin in order to maintain an appropriate level of glucose. Over the past few years, IIPs have been used more and more to control diabetes. However, over these years, the failure rate of the IIP due to malfunctions also has increased tremendously. The failure of the IIP

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is responsible for a large number of serious illnesses and deaths. For instance, during 2006-2009, 17,000 adverse-events were reported by the U.S. Food and Drug Administration (FDA), including 41 deaths due to malfunctioning of an IIP [4]. FDA officials have found that many deaths and illnesses related to the devices are caused by product design and engineering flaws, and these are considered to be firmware (software) problems [5, 6].

Since software plays such an important role in the medical domain, certification standards and regulators like the FDA, need to make sure that the developed health care systems or related devices are safe and reliable [7, 6, 8]. Regulatory agencies have been striving for a rigorous engineering-based review strategy that could provide this assurance. Many people believe that formal techniques have the potential to provide us with the assurance we need in developing and certifying safe and dependable medical systems. Formal techniques have been successfully used in several applications of health systems and medical devices [9–11, 8]. However, we caution that formal techniques need to be much better targeted at practical software development and certification than they seem to be at present [12].

1.1 Motivation

Biological environment modelling, used for simulating/testing the functional behaviour of devices or drugs, is an extremely challenging problem. There are several clinical models [3] based on complex mathematical equations, that require high computation and a large memory to simulate the expected behaviour. There is a lack of simulation of biological environment, which can be used at an early stage of the system development during system design and development. For example, an IIP requires an interactive glucose homeostasis environment to verify the correctness of system behaviour (see Fig. 1). Medical devices are tightly coupled with the biological environment in which they are designed to work. They use actuators and sensors to respond to abnormal behaviours in the biological environment, and we can observe the resulting behaviour in the biological environment (by observing the behaviour of the model) to ensure that the system behaves correctly under the required conditions.This approach is clearly dependent on the fidelity of the model of the biological environment. If the model is accurate, this approach can help to provide us with assurance that the behaviour of the device is safe within that environment, and will effectively achieve its purpose.

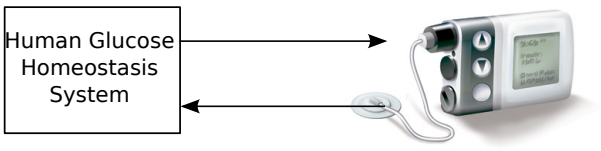

Fig. 1. Interaction between IIP and Human Glucose Homeostasis System

To model a biological environment (the GH) for an IIP, we propose a method for modelling a mathematical GH model based on simple logic. This environment model is based on continued monitoring of the glucose-insulin regulatory system [1]. We believe that for our purpose, we can model the GH system under normal and diabetic conditions, by using α-cells and β-cells, and rising or dropping plasma glucose level to model pancreatic behaviour, and blood test levels for diagnosis of diabetes/prediabetes. This model is developed through an incremental refinement, which helps to introduce several properties in an incremental way and to verify the correctness of the glucose homeostasis model. The key feature of this model is that it exhibits all possible normal or abnormal (hyperglycemia or hypoglycemia) conditions, which characterize a patient model. The environment model also demonstrates the failure of the GH system. There are several motivations behind this approach, which are given as follows:

1. The use of simple logic to understand the complex behaviour of the GH system.
2. Formalization of the GH system to provide a biological environment for verification and validation.
3. Verification and validation of the required behaviour of an IIP under a patient model using closed-loop modelling.
4. To analyze the interaction between the biological homeostasis model and an IIP, and use this to obtain the necessary certification for the IIP.

The mathematical GH model based on standard logic is verified through the Rodin [13] proof tool and model checker ProB [14].

2 Related Work

Clinical models are used for identifying and predicting the various stages of diseases like diagnostics, control, progression, complication etc. Bolie et al. [2] presented 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. Silber et al. [15] proposed an integrated insulin-glucose model for analyzing the diabetic condition using a bidirectional insulin-glucose feedback mechanism. Chay et al. [16] proposed the theoretical treatment of the effect of external potassium on oscillations in the pancreatic β-cells, which can be used to demonstrate that insulin infusion may be useful for mimicking pancreatic insulin secretion. Several other models have been developed that incorporate different physiological processes associated with insulin-glucose dynamics and different variations [3, 17–19].

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. However, we were motivated and encouraged by our previous work on heart modelling [10] that presents an abstract notion of complex heart behaviours. We have adopted the same methodology to design an efficient and optimum environment model for the GH system using formal techniques. To our knowledge, there does not exist any environment

model for homeostasis system based on formal methods that can be used for validation/verification at the early stage of system development. Our approach is based on formal techniques for modelling the GH system through analysis of the glucose regulation mechanism. In this article, we propose a methodology to develop an environment model for the GH system, based on *logico-mathematical* theory enabling the validation/verification of system requirements [10]. The model is developed using an incremental refinement approach that helps to introduce several properties in a progressive way, and to verify the correctness of the GH model under normal and abnormal behaviours (hyperglycemia, hypoglycemia or diabetic complications).

3 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 [3].

Fig. 2 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 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 type of cells that use the glucose. For instance, the brain and nervous system cells use glucose without insulin, while other type of cells like muscle and fat 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 [1].

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 [3]. This stimulation process 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.

[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.

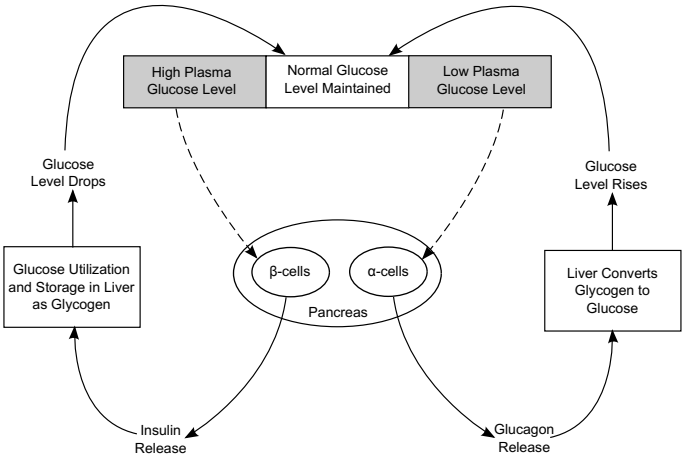

Fig. 2. The GH System (adopted from [3])

4 Proposed Idea

Our proposed method describes a GH model based on logico-mathematics to help the formal community verify the correctness of IIP models. The GH model is mainly based on the glucose regulation system of the body. This method uses advance capabilities of the combined approach of formal verification and behavior simulation, in order to achieve considerable advantages for GH system modelling. Fig. 2 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. 3, which can control the GH system. We have identified these landmarks through a literature survey [3, 1, 2, 15], 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;*

• $T \subseteq N \times N = \{$*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

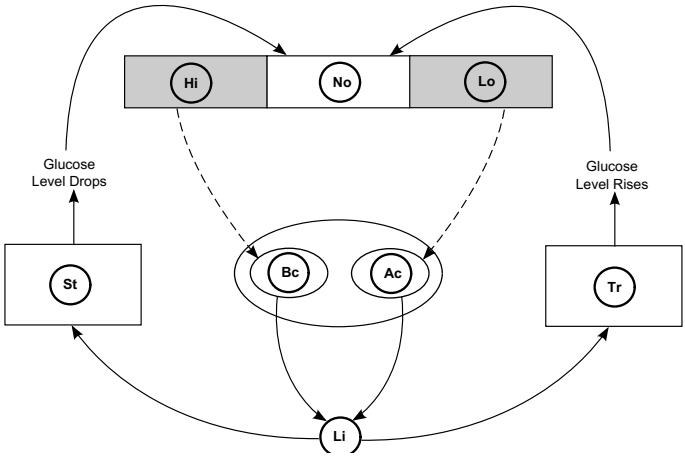

Fig. 3. The GH Automata

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. 3). 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.

4.1 Diabetes or Abnormal Homeostasis System

Fig. 4 presents abnormal behaviours 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 [3].

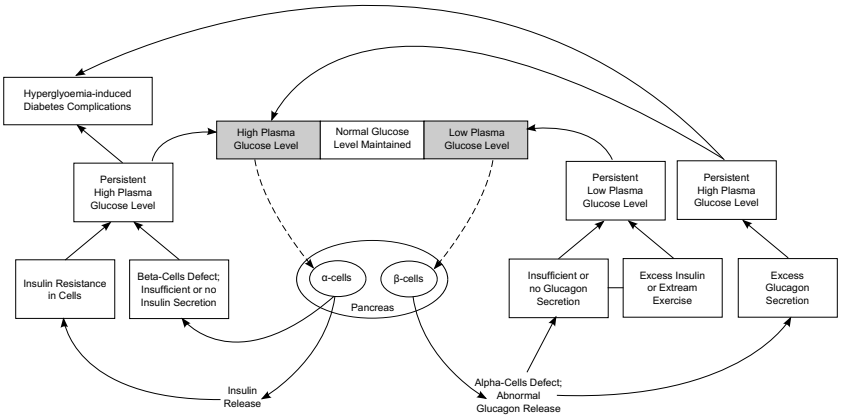

Fig. 4. Abnormal GH System (adopted from [3])

4.2 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) [20]. The FPG test is used to detect diabetes and prediabetes. 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, prediabetes, 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 [20]. 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 (Blood Glucose Level). *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 prediabetes to be the range where* $FPG \in 100\,..\,125$ *or* $OGTT \in 140\,..\,199$*.*

5 Formalization of the GH System

To develop a biological environment of the GH system based on formal techniques, we use the Event-B modelling language [21] that supports an incremental refinement to design a complete system in several layers, from an abstract to a concrete specification. Firstly, the initial model captures the basic behaviour and biological requirements of the GH system in an abstract way. Then subsequent refinements are used to formalize the concrete behaviour for the resulting GH biological environment that covers normal and abnormal behaviours (hyperglycemia, hypoglycemia or diabetic complications).

5.1 The Context and Abstract Model

To model a biological environment for diabetes, we choose the standard GH mechanism. An abstract behaviour of the GH system is depicted in Fig 5. This figure shows an automata that models the changing state of the glucose in the body. When the glucose level is normal then it can either stay in the same state or can switch to any other state (high or low). If the glucose level is in either the high or low state, it will stay in the same state or it will switch back to the normal state. To model the GH system, we identify necessary biological behaviour under various glucose levels. In the context of the initial model, we define two enumerated sets *Glucose_level* to indicate the different type of glucose levels in the body using *Normal*, *High* and *Low*, and *GHS* to indicate the glucose level status using *OK* and *KO*. *OK* presents the normal glucose level, while *KO* presents an abnormal level of the glucose in the body.

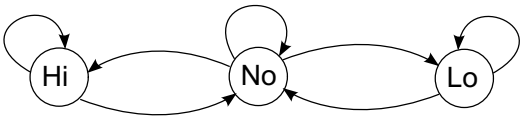

Fig. 5. Automata of an Abstract Model

$axm1 : Glucose\_level, \{Normal\}, \{High\}, \{Low\})$
$axm2 : partition(GHS, \{OK\}, \{KO\})$

An abstract model is used to indicate the normal or abnormal condition through observing the glucose level in the body. The machine model formalizes the dynamic behavior of the GH system. To define the dynamic properties, we introduce two variables *Current_Glucose_Level* and *Diabetic_Condition*. The variable *Current_Glucose_Level* represents the current state of the glucose level in the body, and the other variable *Diabetic_Condition* represents diabetic conditions *OK* or *KO*. A list of interesting safety properties is given in invariants ($inv3$-$inv4$). Invariant ($inv3$) expresses that the current glucose level is either high or low if and only if the diabetic condition is KO. The last safety property states that the current glucose level is normal if and only if the diabetic condition is OK.

$inv1 : Current\_Glucose_Level \in Glucose\_level$
$inv2 : Diabetic\_Condition \in GHS$
$inv3 : Diabetic\_Condition = KO \Leftrightarrow$
$\quad Current\_Glucose\_Level = High \vee Current\_Glucose\_Level = Low$
$inv4 : Current\_Glucose\_Level = Normal \Leftrightarrow Diabetic\_Condition = OK$

In this abstract model, we introduce three events *Normal_Glucose* to present a normal state of the GH system, *High_Glucose* to indicate a high glucose level, and *Low_Glucose* to show a low glucose level.

The event *Normal_Glucose* specifies a set of required conditions for the GH system to be in the normal state. The guard of this event shows that the current glucose level can be in any state (Normal, High or Low). The action of this event assigns the current GH state to Normal, and the diabetic condition is set to OK.

EVENT Normal_Glucose
WHEN
grd1 : $Current\_Glucose\_Level = Normal \vee$
$\quad Current\_Glucose\_Level = Low \vee$
$\quad Current\_Glucose\_Level = High$
THEN
act1 : $Current\_Glucose\_Level := Normal$
act2 : $Diabetic\_Condition := OK$
END

The next event *High_Glucose* is used to set the current glucose level to High, and the diabetic condition to KO, when the current glucose level is normal or high. Similarly, the last event *Low_Glucose* is also used to set the current glucose level to Low, and the diabetic condition to KO, when the current glucose level is normal or low. All these events behave similar to the given abstract level automata (see Fig. 5).

EVENT High_Glucose
WHEN
grd1 : $Current\_Glucose\_Level = Normal \vee$
$\quad Current\_Glucose\_Level = High$
THEN
act1 : $Current\_Glucose\_Level := High$
act2 : $Diabetic\_Condition := KO$
END

EVENT Low_Glucose
WHEN
grd1 : $Current\_Glucose\_Level = Normal \vee$
$\quad Current\_Glucose\_Level = Low$
THEN
act1 : $Current\_Glucose\_Level := Low$
act2 : $Diabetic\_Condition := KO$
END

Due to limited space, we present here only summary information about each refinement of the homeostasis mechanism, and omit detailed formalization and proof details. The following outline is given about every refinement level to understand the basic formal notion of the GH model.

First Refinement (Introduction of α-cells and β-cells of the Pancreas). The pancreas is a gland organ that is a part of the digestive system, which produces enzymes and hormones for food processing. The α-cells, and β-cells are generated by the pancreas. The α-cells produce glucose and the β-cells produce insulin that is secreted into the bloodstream in order to regulate the glucose or sugar level of the body. This refinement step introduces the α-cells and β-cells and their release functions to enrich the GH mechanism, and to identify the normal or diabetic conditions corresponding to the releasing functions of the α and β-cells. Moreover, this refinement level specifies the behaviour required to maintain the normal glucose level in order to release the required level of insulin by β-cells, and glucagon by α-cells in situations in which the glucose level is fluctuating, formalizing high and low glucose levels when the diabetic condition is abnormal, and the behaviour of the α-cells and β-cells is abnormal.

Second Refinement (To convert or to store glucose by the Liver). This refinement introduces the liver functionalities to regulate the glucose level in the body. The glucose is used by muscle and other cells, and an excessive amount of glucose is stored by liver as glycogen. Whenever the glucose level drops, the liver converts stored glycogen into glucose and releases it. The biological process of converting glucose into glycogen and converting it back from glycogen into glucose helps to maintain the appropriate glucose level. In this level of refinement, we formalize the liver functions for storing and converting glucose, including abnormal behaviour of the liver to address the variation in the glucose levels.

Third Refinement (Abnormal Condition of the Pancreas, Diabetic Conditions, and Diabetes Complications). This refinement formalizes the abnormal conditions of the pancreas, persistent low or high glucose level, and hyperglycemia-induced diabetes complications. All these abnormal conditions are captured to formalize required behaviour of the GH mechanism.

Fourth Refinement (Blood Sugar Concentration for Assessing Diabetes and Prediabetes). The final refinement introduces the process for assessing the blood sugar concentration or blood glucose level in the blood, thus determining the actual amount of glucose. The body naturally regulates blood glucose levels as part of the metabolic homeostasis. As we saw earlier, there are two types of tests: FPG and OGTT. To formalize the assessment of blood glucose concentration, we introduced the relevant mathematical properties (see Property 1). Assessment of glucose concentration using standard testing techniques FPG and OGTT is included in the formalization process for modelling the GH system.

5.2 Model Validation and Analysis

This section presents validation of the developed model through animation, using a model checker tool ProB [14], and the generated proof obligations. Validation, in this context, is a process that shows consistency between formal models and requirements. This tool enables us to validate the GH model according to the glucose fluctuation in the body. We have validated different kinds of scenarios of normal and abnormal glucose levels. In order to test the abnormal behaviour of the GH system, we have also validated the diabetics, prediabetics, and diabetics complication conditions.The ProB tool is not only used for animation, but it also verifies an absence of error, for example (no counter example exists) and no deadlocks at each level of developed model from abstraction to the final concrete model.

Table 1. Proof Statistics

Model	Total number of POs	Automatic Proof	Interactive Proof
Abstract Model	16	16(100%)	0(0%)
First Refinement	13	6(46%)	7(54%)
Second Refinement	7	6(86%)	1(14%)
Third Refinement	25	24(96%)	1(4%)
Fourth Refinement	62	60(97%)	2(3%)
Total	123	112(91%)	11(9%)

Table 1 shows the proof statistics of the development in the RODIN tool. In order to guarantee the correctness of the system behaviour, we established various invariants in the incremental refinements. This development results in 123(100%) proof obligations, in which 112(91%) are proved automatically, and the remaining 11(9%) are proved interactively using the Rodin prover. These proofs are quite simple, and can be achieved with the help of simplifying predicates. An incremental refinement of the GH system helps to achieve a high degree of automatic proof.

6 Conclusion and Future Challenges

There are several existing clinical models that are too complex to use for verification purpose. The existing models use differential equations and higher order polynomial equations, which require significant computation and a large memory to simulate the expected behaviour of the clinical models. However, in our approach, the GH model is presented in an abstract way to simulate the desired behaviour to avoid the mathematical complexity.

This paper presents a methodology for modelling a biological environment of the GH using simple logical mathematics. 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. Formalizing the GH system, we used the Event-B modelling language to develop the proof-based formal model in several layers of refinements. Incremental refinement based development allows us to achieve a high degree of automatic proof using the Rodin tool. Our incremental development reflect not only many facets of the problem, but also that there is a learning process involved in understanding the problem and its ultimate possible solutions.

Our most important goal 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. This has been the first attempt to our knowledge in GH modelling based on logico-mathematical theory. In the future, our goal will be to integrate IIP and the GH system to model the closed-loop system for verifying the desired behaviour under relevant safety properties, and guarantee the correctness of the functional behaviour of IIP.

References

1. Li, J., Kuang, Y., Mason, C.C.: Modeling the glucoseinsulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays. Journal of Theoretical Biology 242(3), 722–735 (2006)
2. Bolie, V.W.: Coefficients of normal blood glucose regulation. Journal of Applied Physiology 16(5), 783–788 (1961)

3. Ajmera, I., Swat, M., Laibe, C., Novère, N.L., Chelliah, V.: The impact of mathematical modeling on the understanding of diabetes and related complications. CPT: Pharmacometrics & Systems Pharmacology 2, e54 (2013)
4. Chen, Y., Lawford, M., Wang, H., Wassyng, A.: Insulin pump software certification. In: Gibbons, J., MacCaull, W. (eds.) FHIES 2013. LNCS, vol. 8315, pp. 87–106. Springer, Heidelberg (2014)
5. Center for Devices and Radiological Health: Safety of Marketed Med. Devices, FDA (2006)
6. A Reseach and Development Needs Report by NITRD: High-Confidence Medical Devices: Cyber-Physical Systems for 21st Century Health Care, http://www.nitrd.gov/About/MedDevice-FINAL1-web.pdf
7. Keatley, K.L.: A review of the fda draft guidance document for software validation: Guidance for industry. Qual. Assur. 7(1), 49–55 (1999)
8. Lee, I., Pappas, G.J., Cleaveland, R., Hatcliff, J., Krogh, B.H., Lee, P., Rubin, H., Sha, L.: High-confidence medical device software and systems. Computer 39(4), 33–38 (2006)
9. Bowen, J., Stavridou, V.: Safety-critical systems, formal methods and standards. Software Engineering Journal 8(4), 189–209 (1993)
10. Singh, N.K.: Using Event-B for Critical Device Software Systems. Springer, Heidelberg (2013)
11. Méry, D., Singh, N.K.: Real-time animation for formal specification. In: Aiguier, M., Bretaudeau, F., Krob, D. (eds.) Complex Systems Design & Management, pp. 49–60. Springer, Heidelberg (2010)
12. Wassyng, A.: Though this be madness, yet there is method in it? In: Proc. FormaliSE, pp. 1–7. IEEE (2013)
13. Project RODIN: Rigorous open development environment for complex systems (2004), http://rodin-b-sharp.sourceforge.net/
14. Leuschel, M., Butler, M.: ProB: A Model Checker for B. In: Araki, K., Gnesi, S., Mandrioli, D. (eds.) FME 2003. LNCS, vol. 2805, pp. 855–874. Springer, Heidelberg (2003)
15. Silber, H.E., Jauslin, P.M., Frey, N., Gieschke, R., Simonsson, U.S.H., Karlsson, M.O.: An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocations. The Journal of Clinical Pharmacology 47(9), 1159–1171 (2007)
16. Chay, T.R., Keizer, J.: Theory of the effect of extracellular potassium on oscillations in the pancreatic beta-cell. Biophysical Journal 48(5), 815 (1985)
17. Han, K., Kang, H., Kim, J., Choi, M.: Mathematical models for insulin secretion in pancreatic β-cells. ISLETS 4, 94–107 (2012)
18. De Gaetano, A., Arino, O.: Mathematical modelling of the intravenous glucose tolerance test. Journal of Mathematical Biology 40(2), 136–168 (2000)
19. Drozdov, A., Khanina, H.: A model for ultradian oscillations of insulin and glucose. Mathematical and Computer Modelling 22(2), 23 (1995)
20. Siperstein, M.D.: The glucose tolerance test: A pitfall in the diagnosis of diabetes mellitus. Adv. Intern. Med. 20, 297–323 (1975)
21. Abrial, J.R.: Modeling in Event-B: System and Software Engineering (2010)