Petri Nets in Modeling Glucose Regulating Processes in the Liver

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Abstract

Diabetes is a chronic condition, considered one of the civilization diseases, that is characterized by sustained high blood sugar levels. There is no doubt that more and more people is going to suffer from diabetes, hence it is crucial to understand better its biological foundations. The essential processes related to the control of glucose levels in the blood are: glycolysis (process of breaking down of glucose) and glucose synthesis, both taking place in the liver. The glycolysis occurs during feeding and it is stimulated by insulin. On the other hand, the glucose synthesis happens during fasting and it is stimulated by glucagon. In the paper we present a Petri net model of glycolysis and glucose synthesis in the liver. The model is created based on medical literature. Standard Petri nets' techniques were used to analyse the properties of the model: traps, reachability graphs, tokens dynamics, deadlocks analysis. The results are described in the paper. Our analysis shows that the model captures the interactions between different enzymes and substances, which is consistent with the biological processes occurring during fasting and feeding. The model constitutes the first element of our long-time goal to create the whole body model of the glucose regulation in a healthy human and a person with diabetes.

Keywords

diabetes, glycolysis, glycogenesis, bioinformatics, Petri nets, modelling

1. Introduction

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood glucose) or when the body cannot effectively use the insulin it produces. Diabetes is considered one of the civilization diseases. According to International Diabetes Federation data for 2021 [28] and IDF Diabetes Atlas [27], one in ten people in the world, that is, approximately, 537 million adults (20-79 years), are living with diabetes. The total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045. It is estimated that 6.7 million adults died from diabetes or its complications in 2021, which means 1 death every 5 seconds. Diabetes was responsible for at least \$966 billion in health expenditure in 2021, which is 9% of the global total spent on healthcare.

It is therefore not surprising, that in many fields of science intensive work has been undertaken not only to cure the disease, but also, and perhaps above all, to prevent or delay its future health complications (such as heart disease, chronic kidney disease, nerve damage, and other problems with feet, oral health, vision, hearing, and mental health) or improving the quality of life of patients and their families.

More and more advanced systems are being developed to continuously measure blood glucose levels without the need to puncture the skin (CGM - continuous glucose monitoring [8, 2]), the insulin pump industry has been developing rapidly. Closed loop systems (so called artificial pancreas), enabling automatic insulin delivery by the pump, were also created and operate successfully, both as a commercial solution (a.o. MiniMed 780G System [30], Tandem Tslim Control IQ [31], CamAPS FX [26]), or developed on a DIY basis (a.o. AAPS [25], Loop [29]). Countless applications are being developed for diabetics and their families, as well as health care professionals, such as bolus calculators, applications for counting food nutritional value, diabetes management, statistics and many others. Intensive work is also underway on the use of artificial intelligence in this field [12, 11, 7]. However, we have noticed that most non-medical solutions focus on solving a particular problem without offering a broader view of

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diabetes. On the other hand, medical papers usually focus on one single element of the whole process of glucose regulation for healthy and diabetic people. Therefore, there exists a great need for a more holistic approach, which recently became more and more popular.

Our long-term goal is to create a simple and intuitive mathematical model representing the changes occurring in the body of a healthy person and a person with diabetes. This model should be easily analysable and clear, but at the same time capable of representing complex processes consisting of interactions between many components. In our opinion, Petri nets (PNs) constitute a perfect tool for this purpose. Due to PNs intuitive graphical representation and mathematical properties, the model would be useful for people with and without medical background. This could allow for a better understanding of the processes occurring in a human body, predicting new therapeutic targets and designing drug therapies. We are aware, that our goal (modelling the entire process) is ambitious and would not be reached at once. Hence, our first step, presented below, is to model the glycolysis process in the liver. The medical basis of our model is taken from [20].

Glycolysis is the pathway of breakdown of glucose into pyruvate following glucose uptake by cells. It is an ancient metabolic pathway, meaning that it evolved long ago, and it is found in the great majority of organisms alive today[14]. The process is highly important in maintaining the homeostasis of glucose levels in the body of a healthy person, especially the glycolysis that occurs in the liver. For that reason we start modelling diabetes from this process. Our model allows to scrupulously follow the glycolysis process in a healthy person, as well as to analyse what happens in an organism in which insulin secretion is disturbed or completely absent. Insulin and glucagon are hormones produced and released by the pancreas to regulate blood sugar levels. Insulin is released by the beta cells of the pancreas and reduces blood sugar levels while glucagon is released by the alpha cells of the pancreas and increases blood sugar levels. The two hormones are responsible for maintaining homeostasis of blood glucose levels. An increase in blood glucose levels triggers the release of insulin which promotes glycolysis, while when glucose levels decrease, glucagon is released to stimulate the opposite process.

In this paper, we present a model of the glycosite and the opposite process in the liver designed using Petri nets. We also use standard Petri nets' analysis tools, such as the reachability graph, to study it. In the following section, we recall the basic concepts of Petri nets, and in subsequent parts of the paper we introduce created Petri net, modeling the processes occurring in the liver, and then conduct an analysis of it. The paper ends with a summary and future plans.

2. Preliminaries

In this section we recall the basic notions concerning Petri nets and its properties [4, 10, 15, 16, 9].

A finite labelled transition system with initial state is a tuple $TS = (S, \rightarrow, T, s_0)$ with nodes S (a finite set of states), edge labels T (a finite set of letters), edges $\rightarrow \subseteq (S \times T \times S)$, and an initial state $s_0 \in S$. A label t is enabled at $s \in S$, denoted by $s[t\rangle$, if $\exists s' \in S \colon (s, t, s') \in \rightarrow$. A state s' is reachable from s through the execution of $\sigma \in T^*$, denoted by $s[\sigma\rangle s'$, if there is a directed path from s to s' whose edges are labelled consecutively by σ . The set of states reachable from s is denoted by $[s\rangle$. A sequence $\sigma \in T^*$ is allowed, or firable, from a state s, denoted by $s[\sigma\rangle$, if there is some state s' such that $s[\sigma\rangle s'$.

An (initially marked) Petri net (PN) is denoted as $N = (P, T, F, M_0)$ where P is a finite set of places, T is a finite set of transitions, F is the flow function $F: ((P \times T) \cup (T \times P)) \to \mathbb{N}$ specifying the arc weights, and M_0 is the initial marking (where a marking is a mapping $M: P \to \mathbb{N}$, indicating the number of tokens in each place). A transition $t \in T$ is enabled at a marking M, denoted by $M[t\rangle$, if $\forall p \in P: M(p) \ge F(p, t)$. The firing of t leads from M to M', denoted by $M[t\rangle M'$, if $M[t\rangle$ and M'(p) = M(p) - F(p, t) + F(t, p). This can be extended, as usual, to $M[\sigma\rangle M'$ for sequences $\sigma \in T^*$, and $[M\rangle$ denotes the set of markings reachable from M. We call a marking M deadlock if it does not enable any transition, i.e. for every $t \in T$ we have $\exists p \in P: M(p) < F(p, t)$. The reachability graph RG(N) of a bounded (such that the number of tokens in each place does not exceed a certain finite number) Petri net N is the labelled transition system with the set of vertices $[M_0\rangle$, initial state M_0 , label set T, and set of edges $\{(M, t, M') \mid M, M' \in [M_0\rangle \land M[t\rangle M'\}$.



Figure 1: A Petri net and its reachability graph.

Let $x \in P \cup T$, $\bullet x = \{y \in (P \cup T) \mid (y, x) \in F\}$ and $x^{\bullet} = \{y \in (P \cup T) \mid (x, y) \in F\}$. We extend this notation to sets: for $S \subseteq P \cup T$, we have $\bullet S = \bigcup_{x \in S} \bullet x$ and $S^{\bullet} = \bigcup_{x \in S} x^{\bullet}$. Let S be a non-empty subset of places. We call $S \subseteq P$ a *trap* if $S^{\bullet} \subseteq \bullet S$. The following property follows directly from the definition: once a trap is marked under some marking, it is always marked at the subsequent markings reachable from this one.

Note that the reachability graph of a bounded Petri net captures the exact information about the reachable markings of the net, and therefore reflects the entire behaviour of a given net. Figure 2 depicts a Petri net, together with its reachability graph. Reachability graphs of real biological systems are usually quite large and therefore difficult to analyse. To deal with this inconvenience, we use reduced reachability graphs, called *stubborn reduced reachability graphs*, created on the basis of partial order reduction techniques, where not all interleaving sequences of concurrent behaviour are considered. As a result of the reduction only a subset of the complete reachability graph is constructed, nevertheless it still allows the discussion of certain properties, in particular: it preserves all deadlock states and the whole cyclic behaviour.

The reduction of a reachability graph to a stubborn reduced reachability graph proceeds as follows:

- 1. For a given marking, determine a set of "independent" transitions (called *stubborn set*), such that their behaviour cannot be influenced by any transitions from the complement of this set (i.e. *excluded* transitions). Additionally, the following conditions must hold: any sequence of excluded transitions cannot enable or disable an included transition (hence their firing can be postponed) and the set contains at least one enabled transition.
- 2. Compute a *stubborn reduced reachability graph*, using a variation of a standard algorithm: at each marking (node), instead of firing all enabled transitions, only transitions of a stubborn set are fired.

The notion of stubborn sets capture the lack of interaction between transitions, and such excluded transitions may not be interesting from our point of view (for instance in case of biological systems). Executions of transitions from outside a stubborn set could be postponed because it does not affect the merits of the system's behaviour¹.

3. Model

Our Petri net model, presented in Figure 2, represents the process of glycolysis and the opposite activity in a liver described in [20]. It contains 17 places and 13 transitions.

Homeostasis is the state of steady chemical conditions maintained by organism. In our paper we focuse on the glucose homeostasis. There are three basic organs of the human body that control the level of glucose: the pancreas, the liver and the fat tissue. The goal of our PN model is to represent the processes occurring in the liver that control the level of glucose. Two basic processes are present, namely: glycolysis and synthesis of glucose.

¹Due to lack of space, we do not provide detailed definitions and properties here, interested readers are referred to the literature (a.o. [17], [18], [6], [21]).

The glycolysis in the liver is stimulated by the presence of insulin and glucose, which physiologically is associated with feeding. Those substances, in the PN model, are represented by places: Insulin and *Glucose* respectively. The presence of insulin activates various protein phosphatases (place *PP*). It results in an increase in the expression of glucokinase (place GK) and leads to increasing the kinase activity of complex 6PFK2/FBPase2 (place Kin) and to decreasing the phosphatase activity of 6PFK2/FBPase2 (place Pho). As a result of kinase activity of 6PFK2/FBPase2, the level of fructose-2,6-bisphosphate (F2,6P2) is increasing (place F26P2), leading to an elevation of 6-phosphofructo-1-kinase (6PFK1) activity (place *a6PFK1*) and a reduction of fructose-1,6-bisphosphatase (FBPase) activity (place *nFBPase*). All those changes cause an increase in glycolysis rates. The glycolysis is represented by the part of the net (places and transitions) leading from place *Glucose*, through place *F6P* to place *Pyruvate*, which represents the final product of the glycolysis. Long after the feeding, during the fasting time, the levels of glucose and insulin in the blood are very low. It provokes a production of glucagon by the pancreas. The presence of this enzyme is represented by place *Glucagon*. By the signal cascade, (places *cAMP* and *PKA*), glucagon alters the level of glucokinase and of phosphorylation of complex 6PFK2/FBPase2. It results in an increase of the phosphatase activity of 6PFK2/FBPase2 (place Pho) and a decrease of the kinase activity of 6PFK2/FBPase2 (place Kin). The phosphatase activity of 6PFK2/FBPase2 causes a decrease of F2,6P2 level (place *mF26P2*). It leads to a reduction of 6PFK1 activity (place *n6PFK1*) and an elevation of FBPase activity (place *aFBPase*). Those enzymes inhibit the glycolysis process and stimulates the synthesis of glucose from pyruvate.



Figure 2: The PN model representing the process of maintaining a glucose homeostasis by the liver. During feeding, when the levels of glucose and insulin are high, and glucagon is not present, the glycolysis occurs. During fasting, when the level of glucagon is high, the synthesis of glucose occurs.

Notice, that markings of places *Insulin*, *Glucose* and *Glucagon* have the greatest impact on the dynamics of the model. Markings of other places, associated with different enzymes and substances like 6PFK2/FBPase2 (places *Kin* and *Pho*), F26P2 (places *F26P2*, *nF26P2*), 6PFK1 (places *a6PFK1*, *n6PFK1*) and FBPase (places *aFBPase*, *nFBPase*), would be established according to the presence of insulin and glucose or glucagon. This could happen because those places are in-

cluded in different traps. There are eight traps in the model: $\{Kin, Pho\}, \{F26P21, mF26P2\}, \{a6PFK1, n6PFK1\}, \{aFBPase, nFBPase\}, \{n6PFK1, nFBPase\}, \{a6PFK1, aFBPase\}, \{a6PFK1, aFBPase\}, \{Pho, GK\}, \{Glucose, F6P, Pyruvate\}.$ It means that if at least one of the place from a trap is marked, the token would not leave the trap. Hence, if 6PFK1 is less active – we observe less tokens in place a6PFK1, and at the same time more tokens in place n6PFK1. This behaviour is consistent with the actual biological processes. The same holds for each trap. Transitions which transfer tokens among the places included in the traps are affected by markings of places *Insulin*, *Glucose* and *Glucagon*. Those markings in our analysis are fixed in the initial marking. Nevertheless, in the more extended model of glucose regulation (which is our final goal) markings of places *Insulin*, *Glucose* and *Glucagon* would arise from activity of particular parts of the model. Especially, in the case of diabetics, by endogenous (produced in the pancreas) and exogenous (provided from the outside) insulin supply. In the current state of the model those markings are set by hand.

The reachability graph of the net depicted in Figure 2 (created using [24]) contains 162 states with 702 arcs. The graph is presented in Figure 3, but due to its size it is too big to be depicted properly. Moreover, because of the size of the graph, it is difficult to grasp and observe the fundamental dynamic processes present the model, which is our goal in this phase of the analysis.





For that reason, from now on, to study the behaviour of our model, we use reachability graphs obtained according to stubborn reduction (described in Preliminaries), computed by [21]. Note, that such graphs' properties are sufficient for the analysis of our model, making it easier and more transparent.

As mentioned above, the PN model represents the two basic processes of glucose homeostasis in the liver: glycolysis and synthesis of glucose. Those processes in a human body occur alternately, one after the other. Hence, two kinds of initial markings of the PN model are possible. The first – associated with the feeding state, and the second – with the fasting. We may start our analysis from any of those two. Let us begin with the model in the feeding phase. This results in the presence of glucose and insulin, and consequently, in the initial marking, places associated with those substances are marked. In a human body, in such a situation, the level of glucagon is very low (in comparison to glucose and insuline) and in the model it is simply omitted. As mentioned above, markings of other places would be set according to the presence of glucose and insulin, we just have to make sure that at least one place of the each trap is marked.

The initial marking corresponding to the feeding phase is presented in Figure 2. For that marking, the stubborn reduced reachability graph is generated and depicted in Figure 4. One can easily notice, that every sequence of transitions executions ends up in the (black) deadlock marking. Hence, we always start with tokens present in places representing glucose and insulin, and eventually, those places are emptying, and the place representing pyruvate becomes marked. It indicates that glycolysis happened. Obviously, someone might notice, that the presence of one or two tokens is not representative for the modelling of biological processes. Usually, in biological models, the number or value of tokens existing in a place, corresponds to the level of the substance associated to the given place. The marking depicted in Figure 2 is chosen only for the illustration and to obtain a relatively small reachability graph. We have performed also analysis with higher numbers of tokens in initial markings. The behaviour of the model is very similar to the case of the marking in Figure 2 – each execution results in a deadlock marking, where places Insulin and Glucose are empty and place Pyruvate contains the same number of tokens as place *Glucose* in the initial marking. It indicates that the process of glycolysis has been accomplished. Since the reachability graphs for Petri nets with significantly larger initial markings are too large to be shown and analysed here, we present the plot depicting the changes of the markings of the crucial places - Figure 5.



Figure 4: The reachability graph obtained for the PN model with the initial marking presented in Figure 2. The initial marking is located top left and depicted blue, while the final (deadlock) marking is on the right corner of the figure (depicted black). Created using [21].

After the feeding is finished, the fasting state starts, which means that the food from the environment is (temporarily) not more provided, and the level of glucose in the blood is declining. In that state of the organism, the pancreas is not producing insulin. When the level of glucose is low, the body is forced to use its own stored substances to ensure its suitable level in the blood. To obtain that goal, the pancreas starts to produce glucagon, and other organs, especially the liver, react to the presence of glucagon. This situation is represented in our PN model as the deadlock marking obtained after the feeding, with additional tokens added to place *Glucagon*. As the result, the initial marking of the PN model to represent the fasting phase would consist of: tokens in place *Glucagon* and tokens in place *Pyruvate*, empty place *Glucagon* and in the model it is omitted for simplification. Markings of other places are not that crucial as long as the each trap contains a token. Figure 6 depicts the reachability graph of the PN model presented in Figure 2, but with a different initial marking determined as follows: places are marked as in the deadlock marking from Figure 4 with two additional tokens in place *Glucagon*.



Figure 5: Changes in markings of places *Glucose* (red), *Pyruvate* (blue) and *Insulin* (green) in the feeding phase. In the initial marking places *Glucose* and *Insulin* contained each 100 tokens. At the end of model dynamic simulation place *Glucose* contains zero tokens, and *Pyruvate* contains 100 tokens. Created using [13, 22].



Figure 6: The reachability graph calculated for the PN model with the initial marking obtained from the deadlock marking, which is the final marking for the net in Figure 2 and two tokens added to place *Glucagon*. The initial marking is located top right and depicted orange, while the final (deadlock) marking is on the left bottom corner of the figure (depicted black). Created using [21].

Like in the previous case, each execution results in the deadlock marking. In the initial marking, places *Glucagon* and *Pyruvate* are marked, in the deadlock marking, places *Glucagon* and *Pyruvate* are empty and place *Glucose* contains the same number of tokens as *Pyruvate* in the initial marking. It corresponds to the process of glucose synthesis.

Like above, we have also analysed the dynamic of the PN model with larger number of tokens in initial markings. The changes of number of tokens in places *Glucose*, *Pyruvate* and *Glucagon* are depicted in

Figure 7. It is easy to observe that the number of tokens representing the level of glucose is increasing, while the number of tokens representing the level of pyruvate is deceasing. At the end of dynamics simulation, eventually there are as many tokens in *Glucose* as there were in *Pyruvate* in the initial state. The behaviour of the PN model with larger numbers of tokens is consistent with the behaviour of the model with the smaller one. The deadlock marking obtained after the fasting phase can be afterwards used as the initial marking for the simulation of the feeding and the next cycle of feeding and fasting can start.



Figure 7: Changes in markings of places *Glucose* (red), *Pyruvate* (blue) and *Glucagon* (green) in the fasting phase. In the initial marking places *Pyruvate* and *Glucagon* contained 100 tokens each. At the end of places dynamics simulation place *Pyruvate* contains zero tokens, and *Glucose* contains 100 tokens. Created using [22].

4. Conclusions and Future Work

The paper constitutes the first step towards designing a model representing the regulation of glucose levels in the body, which would aim to better understand the processes occurring in the body of a healthy person, as well as a person suffering from diabetes. As the first step, we model (with the use of Petri nets) glucose regulating processes in the liver. Two basic processes have been included in our model: glycolysis during the feeding phase and synthesis of glucose during the fasting phase. The model preserves the interactions between those processes, as shown in Section 3.

We are aware that we are setting an ambitious goal and that subsequent steps towards it may require the use of more advanced tools, such as extensions to Petri nets (for instance: stochastic Petri nets, continuous Petri nets, fuzzy Petri nets, see [1, 5, 3]). In the future, we also plan to verify our model (process modelling) and use it to find regularities and irregularities in the functioning of an unhealthy body. We hope that the consequence of our actions will be greater awareness of diabetes and improvement of the physical and mental condition of people suffering from it.

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