Blood glucose levels regulation in a healthy and in a diabetic person modelled with Petri Nets.

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Abstract

A healthy person's body automatically maintains normoglycemia, i.e. the proper level of sugar in the blood. Insulin and glucagon are pancreatic hormones of key importance for the regulation of energy metabolism and blood glucose concentration. They work in opposite ways - the role of insulin is to prevent hyperglycemia, while glucagon plays a different role - it prevents hypoglycemia. In a person with diabetes, the above process is impaired (or does not work at all). Therefore, external mechanisms for achieving the proper blood sugar level are necessary, for the most part, administering exogenous insulin. In the paper we present an elementary Petri net model of normoglycemia maintaining in a healthy person, and a basic model of the processes occurring in the body of a person suffering from diabetes. Comparison and analysis of both models allows for a better understanding of the mechanisms operating in the (healthy and sick) human body. Such an exploration also makes it possible to better adapt the treatment to a sick person and constitutes the initial step on the way to 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, normoglycemia, bioinformatics, Petri nets, modelling

1. Introduction

The body of a healthy person strives to maintain normoglycemia, i.e. the appropriate level of sugar in the blood. According to the World Health Organization [24] and the American Diabetes Association [26], the expected values for normal fasting blood glucose concentration are between $70mg/dL$ ($3.9mmol/L$) and $100mg/dL$ ($5.6mmol/L$), while two hours after eating the levels should be up to $140mg/dL$.

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. There are three main types of diabetes: type 1, type 2, and gestational diabetes (diabetes while pregnant). Type 1 diabetes is a condition in which the immune system destroys insulin-making cells (beta cells) in the human pancreas. That means that the body cannot produce either enough endogenous insulin, or none at all. Type 2 diabetes is a chronic condition that happens when high blood sugar levels (hyperglycemia) persist in a body. It happens when pancreas is not able to produce enough insulin, body does not use insulin properly, or both. For people with diabetes, blood sugar level targets are as follows [25]:

- before meals : 72 to $126mg/dL$ (4 to $7mmol/L$) for people with type 1 or type 2 diabetes
- after meals : under $162mg/dL$ ($9mmol/L$) for people with type 1 diabetes and under $153mg/dL$ ($8.5mmol/L$) for people with type 2 diabetes

In case of diabetes, the body's spontaneous pursuit of normoglycemia is very difficult or even impossible, and it must be moderated from the outside.

Diabetes is considered one of the civilization diseases. According to the International Diabetes Federation data for 2021 [20] and the IDF Diabetes Atlas [19], 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 one 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.

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It is therefore not surprising, that in many fields of science, intensive work has being 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* [6, 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 (MiniMed 780G System [22], Tandem Tslim Control IQ [23], CamAPS FX [18], a.o.), or developed on a DIY basis (AAPS [17], Loop [21], a.o.). 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, 10, 5]. However, we have noticed that most non-medical solutions focus on solving a particular problem without offering a broader view of 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 becomes more and more popular.

Our long-term goal is to create a simple and intuitive mathematical model representing the glucose regulation mechanisms 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 preliminary step, presented below, is to model processes of achieving normoglycemia in the case of a healthy or suffering from diabetes person.

In this paper, we present an elementary model of the glucose level regulating processes in a healthy body, as well as very basic model of processes taking place in the body of a sick person, aiming to achieve normoglycemia. We believe that the analysis of both models may be of great importance for understanding the processes taking place in a healthy body and disease of diabetes and shows how complicated the process of maintaining the appropriate sugar level may be. Such knowledge may allow for appropriate adjustment of therapy to a given person.

We use standard Petri net analysis tools, such as the reachability graph and t-invariants, to study out models. In the following section, we recall the basic concepts of Petri nets, and in subsequent parts of the paper we introduce and discuss Petri nets models of glucose levels regulating processes in a healthy and diabetic person. 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, 9, 13, 14].

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 $F\colon ((P \times T) \cup (T \times P)) \to \mathbb{N}$ specifying the arc weights, and M_0 is the initial marking (where a marking is a mapping $M\colon P \to \mathbb{N}$, 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 $\forall p \in P\colon M(p) \geq F(p,t)$. 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 $\exists p \in P\colon M(p) < F(p,t)$. 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 $\{(M, t, M') \mid M, M' \in [M_0\rangle \wedge M[t\rangle M'\}$.

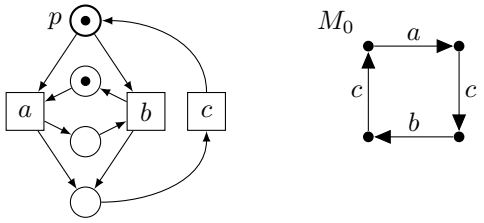

Figure 1: A Petri net and its reachability graph.

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 an exemplary Petri net, together with its reachability graph.

Let $x \in P \cup T$, ${}^\bullet x = \{y \in (P \cup T) \mid F(y,x) > 0\}$ and $x^\bullet = \{y \in (P \cup T) \mid F(x,y) > 0\}$. A Petri net $N = (P, T, F, M_0)$ can be represented in the form of matrices with integer coefficients: an *input matrix*, an *output matrix* and an *incidence matrix* [13]. Assume that $\#P = n$, $\#T = m$. The *input matrix* is a matrix $C^+ = (a_{i,j})_{n \times m}$, where $a_{i,j} = 1$ if $p_i \in a_j^\bullet$ or $a_{i,j} = 0$ if $p_i \notin a_j^\bullet$. The *output matrix* is a matrix $C^- = (a_{i,j})_{n \times m}$, where $a_{i,j} = 1$ if $p_i \in {}^\bullet a_j$ or $a_{i,j} = 0$ if $p_i \notin {}^\bullet a_j$. The *incidence matrix* is a matrix $C = (a_{i,j})_{n \times m}$ where $C = C^+ - C^-$. *T-invariant* is a vector $x \in \mathbb{N}_m$ satisfying $C * x = 0$. The t-invariant contains transitions of the PN and firing all transitions from one t-invariant will reproduce a given marking before firing of transitions. This property follows directly from the definition.

An inhibitor net is a quintuple $\mathrm{S} = (P, T, F, I, M_0)$, where: (P, T, F, M_0) is a Petri net, as defined above; $I \subseteq P \times T$ is the set of inhibitor arcs (depicted by edges ended with a small empty circle). The set of *inhibitor entries* to a is denoted by ${}^\circ a = \{p \in P \mid (p,a) \in I\}$. A transition $a \in T$ (of an inhibitor net) is enabled in a marking M whenever ${}^\bullet a \leq M$ (all its entries are marked) and $(\forall p \in {}^\circ a)\ M(p) = 0$, i.e. all inhibitor entries to a are empty. The execution of a leads to the same marking as in the ordinary Petri nets case.

3. Models

3.1. Healthy

Figure 2 presents a model of glucose regulation in a healthy organism. The model is quite small and basic but it preserves the key interactions in the process of maintaining normoglycemia and allows to have an insight in the whole phenomenon. The model is consistent with the medical literature about diabetes (see: [8, 3] a.o.).

The model contains 8 places and 8 transitions. Places *H*, *N* and *L* represent the levels of glucose (respectively): elevated (high), normal and low. Those levels correspond to the blood glucose concentration mentioned in the Introduction. By normal level we mean (in accordance with appropriate guidelines) the level of glucose concentration between $70mg/dL$ to $100mg/dL$ in case of fasting, and $140mg/dL$

two hours after eating. A token located in one of places *H*, *N*, *L* informs that the concentration of glucose is in the corresponding level. That level can be affected in a couple of ways.

The body tries to maintain the normal level of glucose. However, glucose is the main source of energy in the body, and every life process consumes it while occurring. It results in a decrease of the amount of glucose. The low concentration of glucose (place *L*) causes the hunger feeling and the desire to eat. After eating, which is represented by *eating* transition, the carbohydrates are available for the organism, what is pictured in place *Carb*. In such a situation, clearly, the level of glucose increases to the normal or high level (transitions *t3* and *t2*, respectively). However, the level of glucose is not only an effect of its delivery and consumption. The organism is not a passive observer of these processes, but actively participates in the glucose regulation, since the abnormal level of glucose is not desirable because it negatively affects the whole organism. The most important organ in the regulation process is the pancreas, represented by *Pancreas* place. Stimulated by the high level of glucose, the pancreas produces insulin, which is represented by transition *t1*. The presence of insulin is modelled by place *Insulin*. Insulin induces processes (transition *t4*) which result in reduction of the level of glucose and storage of it in various organs - place *Storage*, mostly liver and fat tissue.

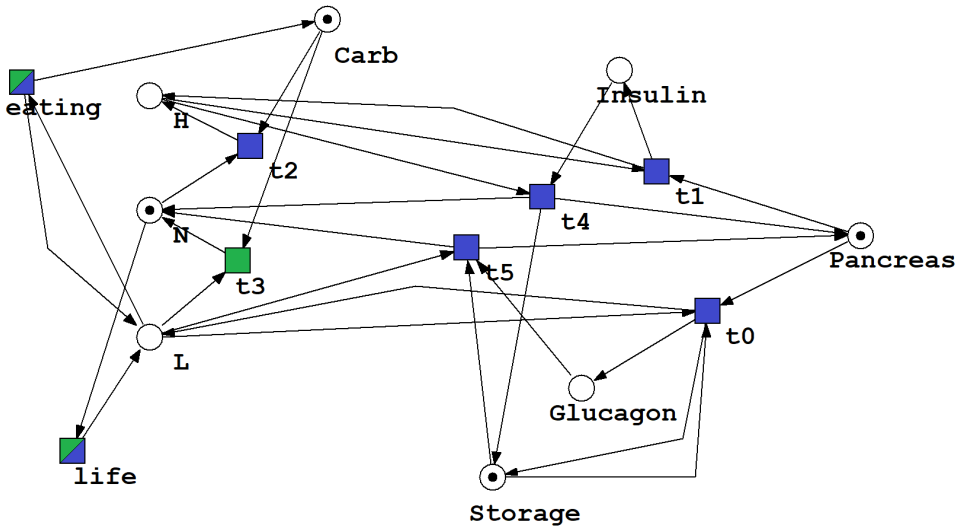

Figure 2: The elementary model of glucose regulation processes occurring in the healthy body. The transition color indicates the t-invariant in which the transition is included. There are two t-invariants: the first depicted in green, the second in blue. Transitions *eating* and *life* are included in both t-invariants. Created using [16].

On the other hand, when the level of glucose is low, the pancreas produces glucagon, which is represented by transition *t0* and place *Glucagon*, visualising the presence of that hormone. Opposite to insulin, glucagon stimulates processes (transition *t5*), aiming to release the stored substances from the liver and fat tissue (place *Storage*) and increase the level of glucose. Our PN model of processes taking place in the liver, related to storing and releasing of glucose in the presence of insulin and glucagon, is presented in [1].

To compute the reachability graph the PN needs to be bounded. The model presented in Figure 2 is not bounded, because when place *L* is marked transition *eating* can produce an unlimited number of tokens. However, such a situation is not possible in the real organism (infinitive eating and at the same time low level of glucose). In order to compute the reachability graph of the model, we removed the *eating* transition and assumed that only one instance of carbohydrates is available. It would correspond to the situation of the glucose regulation processes after one meal and before the next one. The initial marking used to compute the reachability graph is depicted in Figure 2. The obtained graph is presented in Figure 3.

While analysing the reachability graph of the PN model one can notice that the model tends to the state with place *N* marked. From the initial state, the state *N|Pancreas|Storage* can be reached by three different paths of transitions executions. From that state (and by two side paths) executions of

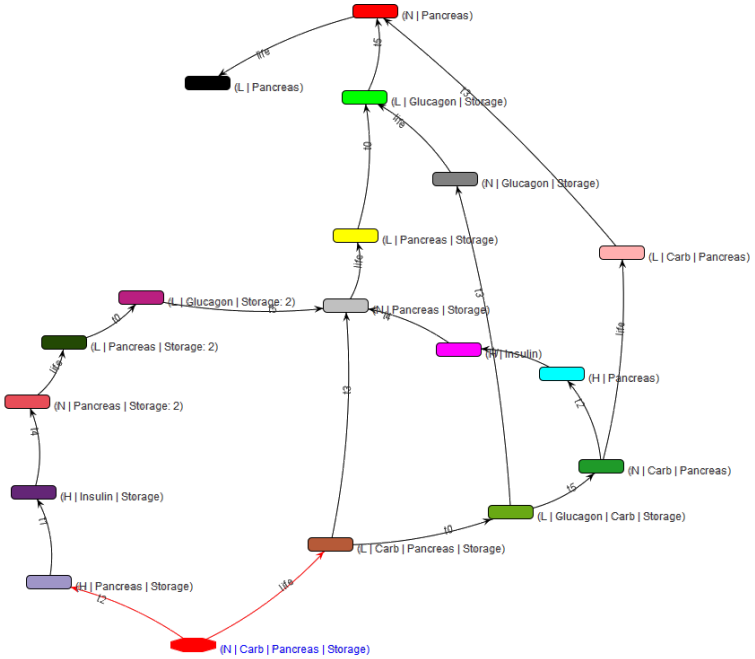

Figure 3: The reachability graph of the PN model presented in Figure 2, but with removed transition *eating*. The initial marking is located at the bottom and marked red. Created using [15].

transitions lead to state *N|Pancreas*. Notice that all those paths are related to maintaining the normal level of glucose (token in place *N*) by using available glucose sources, like carbohydrates (place *Carb*) and substances stored by the body (place *Storage*). After state *N|Pancreas* the deadlock marking *L|Pancreas* is reached, which corresponds to the situation where all available sources of glucose are used and the next meal is necessary.

The dynamic of the model is nicely captured by t-invariants present in the model. The PN model has only two t-invariants. The first contains transitions: *eating*, *life*, *t3* and is depicted green in Figure 3. The second contains transitions: *eating*, *life*, *t0*, *t1*, *t2*, *t4*, *t5* and is depicted blue in Figure 3. It is obvious that the PN model is covered by t-invariants. The first t-invariant corresponds to the process of glucose regulation related only to processes of glucose consumption and providing. Like it was mentioned above, the organism is not a passive observer of these processes, but actively participates in the glucose regulation. Those regulation mechanisms are represented by transitions included in the second t-invariant. By the definition of t-invariant, when the model starts with place *N* marked like in the initial marking, the execution of all transitions from the t-invariant will lead to the same, initial marking. Hence, firing the transitions corresponding to the glucose level regulation mechanisms of the body, included in the second t-invariant, would result in maintaining the normal level of glucose (token back in place *N*).

3.2. Unhealthy

Now let us look at Figure 4, which depicts how the issue of the glucose level regulation looks like in a person suffering from diabetes. The model contains 13 places and 27 transitions. For clarity, we have decided to use inhibitor arcs in this model, which, however, could be eliminated (in accordance with [11]). Similarly to the previous model, places *H*, *N* and *L* represents the levels of glucose (respectively): elevated (high), normal and low, but this time we apply guidelines for sick people, i.e. before meals: 72 to $126 mg/dL$ (4 to $7 mmol/L$) for people with type 1 or type 2 diabetes, and after meals: under $162 mg/dL$ ($9 mmol/L$) for people with type 1 diabetes and under $153 mg/dL$ ($8.5 mmol/L$) for people with type 2 diabetes.

In a healthy organism the body produces the suitable amount of insulin in the suitable time. In contrast to that, in a diabetic case, insulin is administrated from the outside and a diabetic person does not know their exact level of insulin. Because of that, three possible levels of insulin are present in the model: low (place *LI*), normal (place *NI* - in a healthy body it is the only one possible) and high (place *HI*). Only the level of glucose can be checked and based on that, in the ideal case, the suitable amount of insulin is administrated. Moreover, in a diabetic organism the internal mechanisms of glucose regulation do not work correctly, and even when the person is doing everything correctly by calculating the amount of eaten carbohydrates and corresponding dose of insulin, low or high glucose levels are still possible ([8, 3]). Such ambiguity is caused by changes that occur in the body and of which the person is not aware (because they cannot be monitored on an ongoing basis) and depends, among others, on physical activity, the state of the hormonal and digestive systems, as well as technical issues such as the quality of the injection or insulin age. This uncertainty is represented in our diabetic PN model. Due to the fact that we cannot predict or (more importantly) monitor many of the causes of inappropriate blood glucose levels, in our model we focus on the amounts of eaten carbohydrates and administrated insulin, and interactions between them.

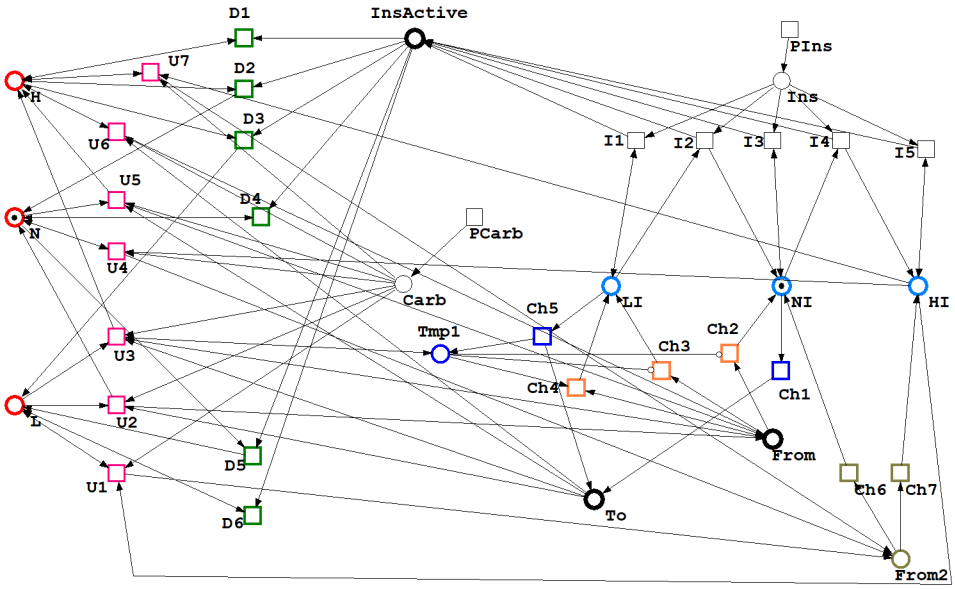

Figure 4: The model of interactions between level of glucose and insulin in diabetic case. Colors of elements are used to indicate groups of elements, which are described in the text. Created using [16].

Transition *PIns* corresponds to the administration of insulin, which is represented by place *Ins*. When insulin is provided, it may (or may not if the amount is not sufficient) affect the current level of insulin in the body. This is represented by transitions *I1* to *I5*. When insulin is provided (place *InsActive*), it can be used by the body to reduce (little or much) the level of glucose - transitions *D1* to *D6*. Still, the effect of insulin supply can be not sufficient and the level of glucose could not change. When carbohydrates are eaten (transition *PCarb* and place *Carb*), the level of glucose may rise or may not be changed, because of the presence of insulin in the blood. Insulin, during that process, is used by cells, hence its level may be reduced. Transitions from *U1* to *U7* represent the change of glucose level. Transitions from *Ch1* to *Ch5*, *To*, *From* and *From2* are responsible for managing the level of insulin.

One can easily notice, that the dynamic of the PN diabetic model is much less certain, and in contrast to the healthy model, it is not possible to predict the exact result of transitions executions. To calculate the reachability graph, similarly like for the healthy PN model, transitions *PIns* and *PCarb* were removed, and the initial marking was the one obtained after executions of those transitions once (place *Carb* and *Ins* marked with one token). It represents the situation after the meal and the administration of insulin. Places *NI* and *N*, like in Figure 4, were also marked with one token each. Moreover, inhibitor arcs were removed according to the procedure described in [11]. The obtained reachability graph is

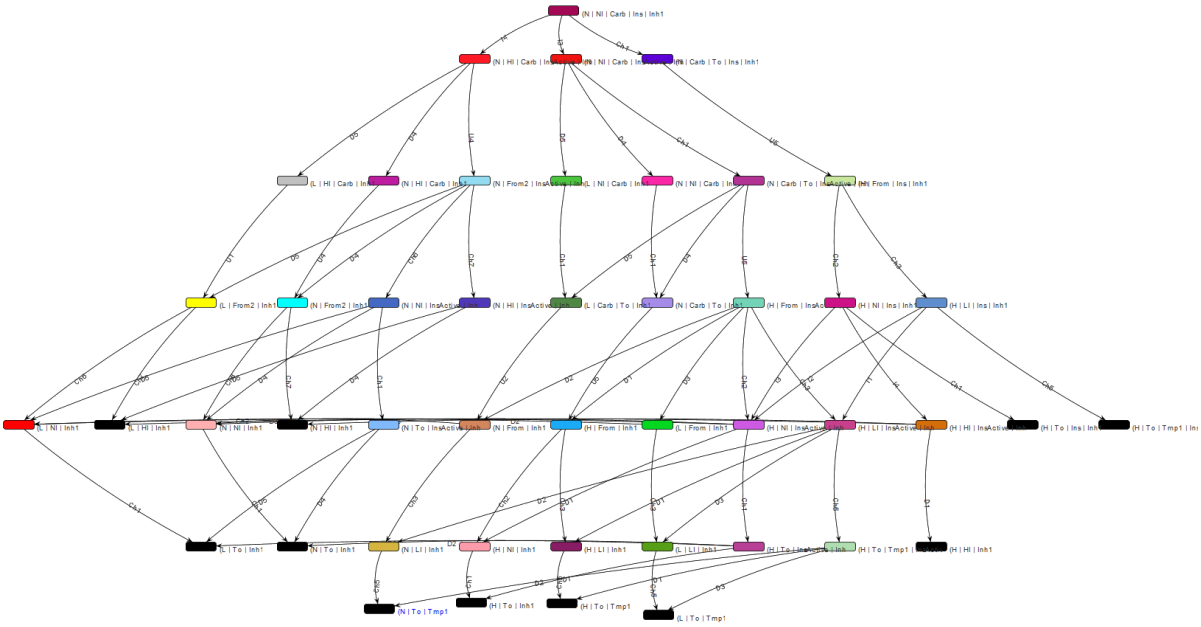

Figure 5: The reachability graph of the diabetic PN model. Created using [15].

presented in Figure 5. Even a cursory comparison of both models and graphs shows that in the case of a person with diabetes, the external mechanisms of glucose levels regulation do not necessarily produce the desired results. In the reachability graph it is difficult to see the desire to maintain normoglycemia, like in the healthy case. In general, it is difficult to observe the tendency towards any designated state. The graph is also much more complicated. From each state there are many possible paths of transitions executions, which lead to different intermediate and final states. The graph shows that the prediction of glucose level in the diabetic PN model, the same like for a diabetic person in real life, is much more uncertain and complex.

4. Conclusions and Future Work

In the paper we have presented the basic Petri net models of normoglycemia maintaining in a healthy person, and a person suffering from diabetes. We believe that the analysis and comparison of both models and their reachability graphs could facilitate the understanding of the entire process, which can be especially useful for a diabetic person. These models can also be used in diabetes education (for instance, with the use a Petri Net simulation displaying the token game), both for sick people and their families, as well as for people involved in medicine and health care.

The presented PN model of the healthy mechanism of glucose regulation seems to be very simple. However, its dynamic is very interesting and could be a source of basic knowledge about glucose regulation. Despite its simplicity, the analysis of the model shows the tendency to maintains normoglycemia. On the other hand, the diabetic PN model shows the much more complex dynamic and the difficulties in obtaining the desired normal level of glucose.

The paper constitutes a preliminary step towards designing a complete model visualizing 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.

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