

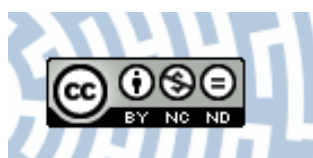


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Citation style: Deja Rafał, Froelich Wojciech, Deja Grażyna. (2021). Rule-based Medical Treatment Graph for the Modeling of Hypo- and Hyperglycemia at Onset. „Procedia Computer Science” (Vol. 192, 2021, s. 1393-1400), DOI: 10.1016/j.procs.2021.08.142



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25rd International Conference on Knowledge-Based and Intelligent Information & Engineering Systems

Rule-based Medical Treatment Graph for the Modeling of Hypo- and Hyperglycemia at Onset

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Abstract

This paper proposes a rule-based medical treatment graph (RB-MTG), a decision support tool that assists physicians in establishing insulin therapy. The RB-MTG models clinical pathways, i.e. the sequences of blood glucose measurements and insulin injections. It provides visualization of alternative clinical pathways, especially those that lead to dangerous states of the patient's health. By interpreting the RB-MTG, the physician assesses the patient's condition and plans their insulin therapy. At each phase of the treatment, the RB-MTG suggests the insulin dosage that leads to normoglycemia - the blood glucose level that is the norm for a healthy person. This way, it is possible to avoid the course of the disease that leads to hypo- or hyperglycemia. Physicians have verified the usefulness of our approach.

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Peer-review under responsibility of the scientific committee of KES International.

Keywords: decision support systems; modeling clinical pathways; diabetes mellitus

1. Introduction

The main goal of diabetic therapy is to keep the patient's blood glucose level (BGL) in a range called normoglycemia. Too low BGL (hypoglycemia) may result in loss of consciousness, seizures, or even death. On the contrary, too high BGL (hyperglycemia) usually leads to various severe complications like kidney damage, neurological damage, cardiovascular damage, and many others. Therefore, maintaining normoglycemia is a crucial feature of human health.

From the very beginning of diabetic therapy, it is vital to avoid hypo- or hyperglycemia. As the BGL of diabetic patients may substantially vary, the stabilization of BGL during the short period of patient stay at a hospital is challenging. The stabilization of the BGL can be achieved by different means, the most important one being the injection

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of insulin. However, the human body's reaction to insulin substantially depends on many factors and differs for diverse patients [1]. Therefore, for each patient, the administered insulin doses have to be continuously verified. This is done by measuring the BGL several times a day, usually before each meal, two hours after the meal, and during the night.

The insulin-glucose interaction in the human body has to be analyzed and adjusted if necessary. We support this task by modeling the course of the therapy (clinical pathway) for each patient individually and groups of them.

Modeling clinical pathways is a problem that has already been investigated in the literature.

Some diabetic models rely on mathematical equations containing variables reflecting the patient's clinical state [3]. The medical interpretation of that model is not always easy for physicians. Because of its mathematical form.

Modeling diabetes can be achieved using ontologies. These models' challenge is a proper definition of the constituent ontological terms and their mapping to medical data. One of the solutions for this inconvenience is using the fuzzy set approach [9]. The other model of that type is based on fuzzy cognitive maps (FCMs)[2].

Though the Bayesian networks (BN) are known for their efficiency in modeling uncertainties, it turns out that they do not present the clinical pathways well enough. Also, the Markov Decision Process (MDP) [7] was used to model the course of diabetes. In that case, an appropriate reward function has to be defined, enabling an evaluation of the undertaken decision. The specification of that function is not a trivial problem.

This paper proposes a new method of modeling diabetic clinical pathways, specifically those that lead to hypo- or hyperglycemia. The model we present here is an enhancement of the Medical Treatment Graph (MTG) we proposed previously [4]. Using the MTG, it is possible to plan and adapt the insulin therapy. However, avoiding unwanted hypo- and hyperglycemia is still cumbersome. Those clinical pathways that lead to hypo- or hyperglycemia need to be clearly distinguished from one another. For that reason, in this paper, we propose a Rule-Based Medical Treatment Graph (RB-MTG). The RB-MTG is a further step toward meeting the expectations of the physicians.

The contribution of this paper is three-fold.

1. We propose a Rule-Based Medical Treatment Graph to model clinical pathways.
2. We offer a data mining algorithm to infer the RB-MTG from medical health electronic data.
3. We explain how the RB-MTG can be used to avoid hypo- and hyperglycemia.

The rest of this paper is organized in the following way. In Section 2, we provide an explanation of the medical data we use later for the construction of the RB-MTG. In Section 3, we present the contribution of this paper. In particular, we provide an algorithm we use later for the construction of the RB-MTG. Then in Section 4, we illustrate how the RB-MTG supports the physicians in their clinical practice. Section 5 concludes the paper.

2. Preprocessing medical data

We assume that at the time of admission to the hospital, the patient's health is described by the following variables: age - the age of the patient at the onset, sex - 0 (female) or 1 (male), weight - the patient's weight, C-peptide - insulin secretion, CRP Certificate of inflammation - 1 (high) or 0 (in norm range), PH - ACID based balance. Physicians have given the minimum and maximum for each variable. Using the normalized data, we group patients into clusters. For that purpose, we use the fuzzy c-means method with Euclidean measure ([5]). For each of those clusters, we build later a separate RB-MTG.

After the admission of a juvenile patient to a hospital, the sequence of glycemia measurements and insulin injection starts. An exemplary sequence is presented in Table 1. Note that the meal size and the insulin dose depend on each other; therefore, the so-called insulin ratio is calculated as the number of insulin units per 100 kcal. The insulin pre-meal ratio should be related to the patient's weight. Therefore the insulin ratio is calculated with respect to 100 kcal of a meal and 100kg of body weight. The obtained value is rounded. The value of glycemia is discretized dependent on the actual meal and it is given in Table 2.

From the formal point of view, we treat the considered data as the sequences of medical events. A medical event $u \in U$ is a pair: $u = \langle V_i = v, \tau \rangle$, where $V_i \in V$ is a variable and v denotes the value, V_i assumes at time τ . An event u occurs at time τ , when the variable V_i obtains certain value v from its domain $dom(V_i)$ at a particular time τ . The set U is the universe of all possible events.

Table 1. An example of raw clinical data

Time	Description	Value
7:55	<i>G</i> - glycemia measurement	139 mg/dl
8:00	<i>I</i> - insulin injection	3.5 units
8:05	Breakfast	240 kcal
10:55	<i>G</i> - glycemia measurement	189 mg/dl
11:00	<i>I</i> - insulin injection	2 units
11:05	Second breakfast	170 kcal
13:55	<i>G</i> - glycemia measurement	65 mg/dl
14:00	<i>I</i> - insulin injection	4 units
14:05	Lunch	380 kcal
16:55	<i>G</i> - glycemia measurement	71 mg/dl
17:00	<i>I</i> - insulin injection	4.5 units
17:05	Dinner	480 kcal
19:55	<i>G</i> - glycemia measurement	109 mg/dl
20:00	<i>I</i> - insulin injection	3 units
20:05	Supper	190 kcal
22:00	<i>G</i> - glycemia measurement	66 mg/dl

Table 2. Glycemic ranges and their clinical meaning

Glycemia [mg/dl]	Clinical meaning		
	before breakfast	before other meals	after meal
< 70	hypoglycemia	hypoglycemia	hypoglycemia
[70, 90]	normoglycemia	normoglycemia	normoglycemia
(90, 100]	mild-hyperglycemia	normoglycemia	normoglycemia
(100, 140)	mild-hyperglycemia	mild-hyperglycemia	normoglycemia
[140, 200]	mild-hyperglycemia	mild-hyperglycemia	mild-hyperglycemia
> 200	hyperglycemia	hyperglycemia	hyperglycemia

Let us consider now a pair $V = \{G, I\}$, where G refers to glycemia measurements and $dom(G) = \{1, 2, 3, 4\}$, and I is the insulin ratio. The domain of I is the set of positive integers.

A clinical pathway is a sequence $s = \langle u_{\tau_1}, u_{\tau_2}, \dots, u_{\tau_n} \rangle$, where τ_i is the real-time at which an event occurs. The length of s depends on the period, the patient stays in the hospital. By S we denote the set of all those sequences.

Table 3. Periods of daily therapy

T	Description	Period	Event
t_1	before breakfast	[6:00 - 10:00]	<i>G</i>
t_2	breakfast	[6:00 - 10:00]	<i>I</i>
t_3	after breakfast	[9:00 - 12:00]	<i>G</i>
t_4	second breakfast	[9:00 - 12:00]	<i>I</i>
t_5	after second breakfast	[11:00 - 15:00]	<i>G</i>
t_6	lunch	[11:00 - 15:00]	<i>I</i>
t_7	after lunch	[14:00 - 17:00]	<i>G</i>
t_8	dinner	[14:00 - 17:00]	<i>I</i>
t_9	after dinner	[16:00 - 20:00]	<i>G</i>
t_{10}	supper	[16:00 - 20:00]	<i>I</i>
t_{11}	after supper	[19:00 - 23:00]	<i>G</i>

As suggested in [6], we sequence a single therapeutic day of a patient. Each period within the therapeutic day is a label $t_i \in T$, where $T = \{t_1, t_2, \dots, t_w\}$. The new, discrete time scale is given in Table 3. This is in accordance with the physicians' discrete time scale for the planning of daily insulin therapy. Note that some time intervals overlap what is happening in clinical practice.

To map medical events to the discrete time scale, we define a function $t : RT \rightarrow T$, where RT denotes the domain of real-time. It means that each u_τ that occurs in real-time τ is mapped to a new, discrete time scale as $u_{t(\tau)}$.

Thus, for each patient, we obtain a clinical pathway $S^p = \{s_1, \dots, s_{nw}\}$, where $s_i = \langle u_{t_1}, u_{t_2}, \dots, u_{t_w} \rangle$ and $nw = n/w$ is the number of days. $S = \{S^1, \dots, S^{np}\}$ is the set of all clinical pathways, np is the number of therapeutic days considered.

3. Rule-based Medical Treatment Graph

The set of medical sequences defined in the previous section serves now for the modeling of glucose-insulin interaction. Our approach consist of two steps:

1. Mining rules.
2. Constructing the RB-MTG.

3.1. Mining rules

For mining rules from the previously presented medical sequences, we apply rough set theory [8]. The medical data we consider form an information system $I = (D, U)$, where D is the set of therapeutic days and U is the set of attributes, which are here medical events, where $u \in U$ is a mapping $u : U \rightarrow V_u$ and the set V_u is the value set of u .

Let us create the set of information tables T_k such that $T_k = (D, U_k \cup \{d\})$, where $d = \langle G = v, t_{k+1} \rangle$ and is called the decision attribute, and $k \in \{2, 4, 6, 8, 10\}$, U_k is restricted to all events preceding the event d , i.e. $t(u \in U_k) < t(d)$. As already mentioned, we are interested only in rules leading to hyper or hypoglycemia so $v = \{1, 4\}$.

In the rough set theory, the rule-based classifier is based on decision relative reducts, i.e., a minimal subset of attributes (here events) $U' \subseteq U$, which determine the decision d . The reducts calculation is based on the indiscernibility relation $IND(U') = \{(x, y) \in D \times D : \forall u \in U'(u(x) = u(y))\}$, which determines the indiscernibility classes $[z]_{U'} = \{z \in D : \forall u \in U'(u(x) = u(z))\}$. Decision rules are defined by the so-called positive region $POS(U') = \{z \in D : [z]_{U'} = [z]_{\{d\}}\}$. Every object $z \in POS(U')$ determined a decision rule. The idea is to deduct minimal rules with respect to the number of attributes at the conditional part (this way, we consider only these events that are sufficient to reach the glycemia episode). Therefore, the indiscernibility classes are calculated separately for each individual row of a decision table with a decision equal to e.g., hypoglycemia. The other such rows are temporarily removed from the table. We consider only the reducts with a minimal number of attributes for the deduction of the rules for such a row.

For the rule r we define the support and confidence coefficient by $supp(r) = card(\|lh(r)\| \cap \|rh(r)\|) / card(U)$ and $conf(r) = card(\|lh(r)\| \cap \|rh(r)\|) / card(\|lh(r)\|)$, where $lh(r)$ denotes the conditional part of the rule and $rh(r)$ is the decision part. With $\|lh(r)\|_U$ we denote the set of all objects from decision table T that fit to the conditions defined by $lh(r)$.

It can be noticed that each rule is the subset of the given medical sequence. Let the rule be in the form $w_1 \wedge \dots \wedge w_l \rightarrow d_k$ then $w_1, \dots, w_l, d_k \subseteq s$ can be seen as the sub-sequence of one of the daily patient sequence; $s \in S$. Obviously w_l and d_k describe the events that happen in the defined time interval from T . With W we denote the set of all sub-sequences defined by the ruleset, and by $U^w \subseteq U$ the set of events existing in the ruleset.

3.2. Creating the RB-MTG

Based on the set of rules, we build the RB-MTG. Each rule gives partial information about the clinical pathways that end with hypo- or hyperglycemia in some time interval. Also, the rule could be non-deterministic. Therefore we are aggregating the set of rules to form a graph, RB-MTG, that will present the whole picture of one therapeutic day concerning the given glycemia episode (hyper- or hypo-glycemia).

The RB-MTG is defined as a 4-tuple: $RB - MTG = (N, E, \sigma, \omega)$, where $N \subseteq U^w$ is the set of nodes of the graph, $E \subseteq N \times N$ is the set of edges, $\sigma : N \rightarrow [0, 1]$ and $\omega : E \rightarrow [0, 1]$ are the corresponding node and edge weight functions.

Let U_t be the subset of events occurring in the time interval t , and $N_{ij} \subset U_t$ is restricted to the events of a particular variable G or I and its value. That is N_{ij} contains similar events, i.e., referring to the same variable and value of glycemia or insulin ratio. We assume that $N_{ij} \in N$ is the RB-MTG node, where indexes t and j are uniquely identifying the node; t refers to the time interval of the event and j to the pair of the considered variable and its value.

It is worth mentioning that the RB-MTG relies on the set of rules; however, its parameters σ and ω are calculated using the whole set of patients sequences. This allows us to evaluate how likely the given event or the event sequence happens during the therapy. Let $\sigma(N_{ij}) = \frac{card(N_{ij})}{card(U_t)}$ - it estimates how likely an event from N_{ij} occurs in the set of events from U_t .

The edge of RB-MTG is defined as an ordered pair of nodes: $E_{tjl} = \langle N_{tj}, N_{lk} \rangle$, where N_{tj}, N_{lk} represents the sets of events occurring at time t and l , respectively.

Let $S_{tl} \subset S$ be the set of the sequences of the pair of events u_t, u_l . Let us distinguish from S_{tl} those sequences S'_{tl} that match the given pair of nodes in RB-MTG. We define that set as $S'_{tl} = \{u_t, u_l | u_t \in N_{tj}, u_l \in N_{lk}\}$.

Let $\omega(E_{tjl}) = \frac{\text{card}(S'_{tl})}{\text{card}(S_{tl})}$ estimates the probability of the pair of events. The function ω is called the *strength* of the edge E_{tjl} .

With every edge, we associate a certainty coefficient, defined by $\text{cer}(E_{tjl}) = \frac{\omega(E_{tjl})}{\sigma(N_{tj})}$. Note that the certainty coefficient describes the distribution of events along the edges starting at the given node.

Let us assume $p = [p_1, p_2, \dots, p_n]$ is any path within the RB-MTG, where $p_i \in N$, $1 < n \leq 11$ is a given node. Here, the index i indicates the place of the node within the path. Note the p is a clinical pathway as described in Section 1.

We extend the ω coefficient to evaluate any pathway within the RB-MTG, i.e.,: $\omega(p) = \sigma(p_1) \cdot \prod_{i=1}^{n-1} \frac{\omega(p_i, p_{i+1})}{\sigma(p_i)} = \sigma(p_1) \cdot \text{cer}(p_1) \cdot \dots \cdot \text{cer}(p_n) = \sigma(p_1) \cdot \text{cer}([p_1 \dots p_n])$.

Similarly, the certainty coefficient for the pathway of any length is calculated as $\text{cer}(p) = \prod_{i=1}^{n-1} \text{cer}(p_i, p_{i+1})$.

Using functions $\omega(p)$ and $\text{cer}(p)$, the physicians can assess the credibility of any pathway within the RB-MTG. They also allow filtering from the RB-MTG those pathways that represent exceptional (rare) medical cases. Assuming ω_{\min} is a threshold given by the physicians, it is possible to produce a sub-graph: $MTG' = (N', E', \sigma, \omega)$ for which $\omega(p) > \omega_{\min}$ for any p .

3.3. Creating the RB-MTG

Below we present the algorithm for building the RB-MTG.

The RB-MTG consists of two collections: those related to nodes N and those for edges E . Both of them are initially empty. The main loop (starts at line 5) iterates through the sequence of events related to rules derived previously. The events in the sequences are indexed by i and are then referred to the time interval. The graph edge connects two consecutive events of the sequence occurring in time intervals referred by t and l respectively. In the RB-MTG, the dependency $l = t + 1$ is not always true.

Then, the algorithm searches through the collections N and E , checking out whether they contain a particular event (line 14) and edge (line 17) detected in the j^{th} sequence.

If the node or edge is not found within the graph, it is added to the corresponding collection, and the weight of the node and edge are respectively calculated using the separate functions *CalcNodeWeight* and *CalcEdgeWeight*. In the *CalcNodeWeight* function the number of events equal to the one passed as the function parameter in the given time interval and occurred in medical sequences are calculated straightforwardly. The same is done with the edges. Then the support of both coefficients is counted.

Let us note that the algorithm has a linear computational complexity concerning both the number of the patient's sequences and the number of events within the sequence.

4. Case study

At first, the patients' static data were normalized and partitioned using the fuzzy c-means clustering algorithm. Then, for each cluster, the data related to BGL and pre-meal insulin doses have been gathered in the form of decision tables. Let us follow the modeling clinical pathways that lead to hypoglycemia (see Table 2 for definition). The approach to model the clinical pathways of hyperglycemia is analogous. Below, we present the examples of the derived rules for hypoglycemia.

$\langle G = 3, t_1 \rangle \wedge \langle I = 3, t_2 \rangle \Rightarrow \langle G = 1, t_3 \rangle$ (Supp: 0.022, Conf: 0.14)

$\langle G = 3, t_1 \rangle \wedge \langle I = 4, t_2 \rangle \wedge \langle G = 3, t_3 \rangle \wedge \langle I = 4, t_4 \rangle \Rightarrow \langle G = 1, t_5 \rangle$ (Supp: 0.011, Conf: 0.5)

$\langle G = 3, t_1 \rangle \wedge \langle I = 4, t_2 \rangle \wedge \langle G = 3, t_3 \rangle \wedge \langle I = 3, t_4 \rangle \Rightarrow \langle G = 1, t_5 \rangle$ (Supp: 0.011, Conf: 0.25)

$\langle G = 2, t_1 \rangle \wedge \langle I = 6, t_6 \rangle \Rightarrow \langle G = 1, t_7 \rangle$ (Supp: 0.011, Conf: 1)

$\langle I = 3, t_4 \rangle \wedge \langle G = 1, t_5 \rangle \Rightarrow \langle G = 1, t_7 \rangle$ (Supp: 0.011, Conf: 1)

$\langle I = 5, t_2 \rangle \wedge \langle I = 3, t_4 \rangle \wedge \langle I = 4, t_8 \rangle \Rightarrow \langle G = 1, t_9 \rangle$ (Supp: 0.011, Conf: 1)

Algorithm 1 Constructing the RB-MTG**Require:** W - the set of sequences from the set of rules.

```

1: Function GraphBuild( $W$ )
2:  $N = null$ ;  $NCount \leftarrow 0$ ; {a collection of nodes}
3:  $E = null$ ;  $ECount \leftarrow 0$ ; {a collection of edges}
4:  $l = 1$ ;
5: for  $j = 1$  to  $card(W)$  do {for each sequence}
6:   for  $i = 1$  to  $length(W[j])$  do {for each event}
7:      $t = t(\tau_i)$ ;
8:      $node = W[j][t]$ ; {create a node}
9:      $l = t(\tau_{i+1})$ ;
10:     $edge = \langle node, W[j][l] \rangle$ ; {create an edge}
11:     $N_{exists} = false$ ; {lacking node}
12:     $E_{exists} = false$ ; {lacking edge}
13:    for  $k = 1$  to  $l$  do {for the added nodes}
14:      if  $N[k][t] == node$  then {Is the node added?}
15:         $N_{exists} = true$ ; {a number of nodes}
16:      end if
17:      if  $E[k][t] == edge$  then {Is the edge added?}
18:         $E_{exists} = true$ ; {a number of edges}
19:      end if
20:    end for
21:    if not  $N_{exists}$  then
22:       $N[l][t] = node$ ;
23:       $CalcNodeWeight(N[l][t], l, t)$ ;
24:    end if
25:    if not  $E_{exists}$  then
26:       $E[l][t] = edge$ ;
27:       $CalcEdgeWeight(E[l][t], l, t)$ ;
28:    end if
29:  end for
30: end for
31:
32: return  $RB - MTG$ 

```

Algorithm 2 Calculating the node weight**Require:** S - the set of clinical sequences, N - a given node, l, t - the node index

```

1: Function CalcNodeWeight( $N, l, t$ )
2:  $NCount \leftarrow 0$ ;
3: for  $j = 1$  to  $card(S)$  do {for each subsequence}
4:   if  $S[j][t] == N$  then
5:      $NCount ++$ ;
6:   end if
7: end for
8:
9: return  $NCount / card(S)$ 

```

The first rule is interpreted as hypo-glycemia after the first breakfast, preceded by mild hyperglycemia in the morning (before the first breakfast). For the first breakfast, the insulin ratio of 3 was administered. However, the rule is only partly discriminating (confidence value 0.14). Other clinical pathways also started with mild hyperglycemia

Algorithm 3 Calculating the edge weight

Require: S - the set of clinical sequences, E - a given node, l, t - the node index

Function CalcEdgeWeight(E, l, t)

$ECount \leftarrow 0$;

for $j = 1$ **to** $card(S)$ **do** {for each subsequence}

if $E[j][t] == E$ **then**

$ECount ++$;

end if

end for

return $ECount/card(S)$

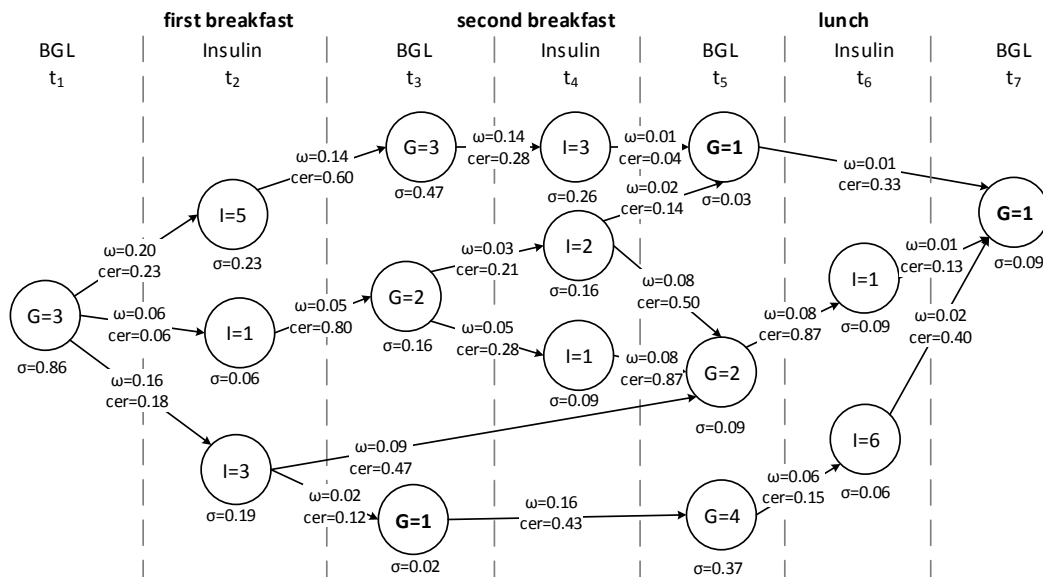


Fig. 1. Exemplary MTG

and insulin ratio 3 in the morning; however, the hypoglycemia after the first breakfast is not observed. The fourth rule shows that the hypoglycemia after lunch occurs when there is normoglycemia in the morning and the insulin ratio at lunch is equal to 6. However, there are also other ways to reach the hypoglycemia after lunch (support=0.11).

Based on the set of rules, we constructed the RB-MTG using the proposed Algorithm 1. Due to the space limitation, we can present in Figure 1 only a part of the obtained graph. Furthermore, we filtered out the clinical pathways that lead to hypoglycemia with low path certainty i.e., where $\omega_{min} < 0.0015$

The medical interpretation of the produces RB-MTG is the following: all pathways that lead to hypoglycemia starts with mild hyperglycemia before the first breakfast $\langle G = 3, t_1 \rangle$. 16% of such patients were administered 3 units of insulin per 100 kcal per 100 kg of body weight with the breakfast meal. Then, 2% of them had hypoglycemia after breakfast. The hypoglycemia after the second breakfast can be reached when observing mild hyperglycemia or normoglycemia in the previous measurement however, it is more likely to happen in the first case and when insulin ratios are higher (equal to 5 in the first breakfast and equal to 3 in the second breakfast). It is also likely ($cer = 0.33$) to obtain hypoglycemia after lunch if the hypoglycemia was observed after the second breakfast. In this example and two other cases on the graph (marked with a dotted edge) the clinical pathway is generalized.

5. Conclusions

The application of RB-MTG brings numerous advantages. First of all, it provides transparent visualization of clinical pathways leading to glycemic episodes. Using the rough set approach, we limit the medical events to be considered indispensable. With the certainty and strength coefficients assigned to each edge of the RB-MTG, it is possible to analyze the various possibly risky medical treatments quickly. The graph representation of alternative therapies is intuitive and thus easy to be used by physicians. Furthermore, by applying appropriate thresholding of the certainty coefficient, it is possible to interpret our RB-MTG at diverse approximation levels. This way, the decision-making task faced by the physician becomes easier.

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