A data driven approach to evaluate and improve the protocol for strict glucose control in the Intensive Care Unit

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A data driven approach to evaluate and improve the protocol for strict glucose control in the Intensive Care Unit

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Preface

This thesis is the result of my graduation project that was written as a fulfilment of one of the requirements for the degree of Master of Science for the curriculum of Operations Management & Logistics at the Eindhoven University of Technology (TU/e). The project was performed in cooperation with the Department of Intensive Care Medicine of the Maastricht University Medical Centre (MUMC+). The supervisors from both organisations provided me with valuable insights and support to complete this project. A graduation project requires significantly more effort compared to course work and projects during the study curriculum. It is, therefore, very important to have people around you to discuss the difficulties along the road. I am grateful for the support and motivation I received from both the supervisors, as well as from my family and friends.

Firstly, I would like to thank my supervisors from the Eindhoven University of Technology, Anna Wilbik and Irene Vanderfeesten. Whenever I had a question, Anna was always more than willing to help me and she provided me with different research directions. Furthermore, she understood the difficulties I was facing and was always interested in my personal situation. I would also like to thank Irene, who has provided me with valuable feedback and helped to give direction to the research. I think that insights from both Anna and Irene were complementary to each other and enhanced this research to a higher level.

Secondly, I would like to thank all the people from the MUMC+, who have contributed to this thesis in one way or another. The case study at your organization provided the implications of the performed methods in practice. I would specifically like to thank Dennis Bergmans, Walther van Mook and Serge Heines. Your insights especially in the medical side of this work were crucial to my understanding of the project. I would also like to thank you that you for always be more than willing to make time to provide me with insights and feedback, despite your busy schedules. Without your contributions, this research would have not been possible. Furthermore, I would like to thank Jerry Townsend (ICT application specialist) for extracting the relevant data from the operational systems.

Thirdly, I would like to thank my family, my girlfriend Eline, and my friends, who have all shown interest in my project and provided support, motivation and distraction when needed.

Lastly, I would like to thank my parents, for always being supportive during my studies.

Ivo Kuiper

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Executive summary

Introduction

The healthcare sector has been challenged with rapidly soaring expenditures. Healthcare facilities are, therefore, put under pressure to increase their efficiency without compromising quality. Today's healthcare industry generates large amounts of complex data regarding patients and hospital resources. Process mining and data mining provide valuable tools and techniques to discover hidden patterns in the data and can provide healthcare professionals with additional source of knowledge that can be used for clinical protocol evaluation.

Research objective

To maximize the benefits for both stakeholders of the research, the research has a practical goal as well as a scientific goal. The practical goal of the research is to provide the Intensive Care Unit (ICU) department of the MUMC+ with valuable insights regarding their strict glucose control protocol. The focus lies on the differences between the wards, the compliance to the protocol on each ward, and patterns in deviations from the protocol. The scientific goal is to discover whether a combination of process mining and data mining techniques creates added value to clinical protocol analysis. The research consists out of a literature study, interviews, a survey, and data analysis. Both goals are translated into the following main research question:

"What is the compliance to the strict glucose control protocol in the Intensive Care Unit of the MUMC+?"

Relevance

In the field of clinical data mining there is more effort needed to obtain a wider acceptance from healthcare professionals and for generalization of knowledge and reproductibility of its extraction process (Lavindrasana et al., 2009). Following this logic, this particular research forms a valuable contribution to the scientific world. Furthermore, this research provides new methods to perform clinical protocol evaluation. For example, a new method has been developed to put this protocol compliance in a broader perspective (fuzzy compliance). The research also provides new applications of data mining techniques, decision tree and fuzzy inference system rule extraction, for clinical protocol extraction (or process discovery as it is referred to in the process mining domain). In essence, the case study aims to demonstrate that data mining and process mining on clinical data can be seen as complementary techniques that can be used for clinical protocol evaluation and improvement.

Case description

The organization involved is the Maastricht University Medical Centre+ (MUMC+). The study is performed in the Department of Intensive Care Medicine. This department consists of the following wards: D3, E3, and F3. Wards D3 and E3 mainly treat mixed medical/surgical patients, where most patients (90%) are acute patients (requiring

immediate assessment or treatment). Ward F3 mainly treats patients who have undergone cardiothoracic surgery, where most patients (90%) are elective (requiring less urgent treatment and whose surgery can be scheduled for a future date). Patient and process data from 2014 and 2015 were extracted from ICIP IC, the patient data management system.

Compliance analysis

According to the interviews and survey, the same protocol is implemented on ward D3 and E3. However, this protocol is different from the protocol on ward F3. Although both protocols have a similar structure, there are some small differences such as a different target blood glucose level, different insulin boluses, different hypoglycemia policy, and different rules for duration to the next measurement.

The interviews showed that on wards D3 and F3, regulating the blood glucose level is less of a protocol act, but more about own insight of the nurses. However, according to the survey, the awareness of the protocol is higher on ward F3 (90%) compared to ward D3 (57.14%). In contrast to wards D3 and F3, the protocol is used for regulating the blood glucose level on ward E3. On this ward all the employees are aware of the protocol. According to the survey the threshold (of glucose concentration in mmol/L) to start insulin therapy according to the employees, equals 9.29, 8.13 and 9.05 for wards D3, E3 and F3 respectively.

Protocol compliance is defined as the percentage of glucose measurements that resulted in a correct change in medication settings (according to the protocol). An overview of the compliance measures can be found in the table below. In contrast to the interviews and the survey findings, the highest compliance to the protocol was revealed on ward D3 compared to ward E3 and F3. The compliances to the other protocol were also calculated. The compliance to the protocol of F3 when applied to ward D3 equals 25.53%. The compliance to the protocol of F3 when applied to ward E3 equals 22.17%. The compliance to the protocol of D3/E3 when applied to ward F3 equals 32%.

Ward	**D3**	**E3**	**F3**
Overall compliance (%)	37.67	33.01	22.78
Compliance hypoglycemic instances (%)	33.33	42.86	11.11
Compliance to other protocol (%)	25.53	22.17	32.07
Fuzzy compliance (%)	78.80	78.47	55.59

According to the MUMC+ supervisors, the compliance of the protocol can be more broadly interpreted. Therefore, fuzzy protocol compliance was developed and used to calculate compliance while allowing deviations from the protocol. The fuzzy compliances on ward D3, E3 and F3 were 78.80%, 78.47% and 55.59% respectively.

Rules on how the different wards regulate the blood glucose level were extracted from the data set. The extracted rules were compared to the protocol in order to identify the deviations from the protocol.

Practical (MUMC+ specific) conclusions

The strict protocol compliance is too low. The nursing staff has to decide either to comply to the medical protocol, to update the protocol and comply to the protocol, or to dismiss the protocol. Comparing the number of hypoglycemic events at the MUMC+ with the literature, confirms the room for improvement, as the number of patients with instances of severe hypoglycemic events is too high on all wards. Regardless the ever ongoing discussion on which target blood glucose level is best in a clinical setting, the percentage of patients with a hypoglycemic event can be reduced by better monitoring and reacting to low blood glucose levels. Moreover, multiple staff members made it known that the introduction of an improved protocol would bring back motivation among the nursing staff to work once more with the protocol. It is therefore recommended to introduce an updated version of the protocol. An updated version could serve all wards.

Scientific conclusions

The case study in this thesis shows that a combination of process mining and data mining techniques creates added value to clinical protocol analysis. Furthermore, both data mining techniques, decision trees as well as fuzzy inference systems, are useful for clinical rule extraction. These clinical rules can provide insight into how a medical team determines its actions. These insights can be used to locate the deviations from the protocol. The fuzzy inference rules are easier to read compared to the decision tree rules. However the decision trees are preferred, as they provide more specific rules compared to the fuzzy inference systems. These techniques were also very useful in locating the deviations from the protocol. Furthermore, this study was successful in providing insights into the strict glucose control protocol in the ICU wards D3, E3 and F3 of the MUMC+.

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1. Introduction

The healthcare sector is facing a major challenge. Healthcare expenditure in the Netherlands is soaring rapidly. By 2040, without intervention, we will be utilizing roughly one quarter of our Gross Domestic Product and one quarter of our working population to ensure provision of curative healthcare and long-term healthcare (van Rooijen, Goedvolk, & Houwert, 2013). The primary causes on the demand side are: an increase in chronic diseases and those related to Western lifestyles, the right to (claim) the best healthcare, and the ageing population. The primary causes on the supply side are: expensive new treatment technologies and treatment methods, volume incentives for healthcare providers and sluggish growth in productivity.

Preventing the above described scenario from becoming reality, requires changes in the current way of practice in existing health care services. Today's healthcare industry generates large amounts of complex data regarding patients and hospital resources. A combination of process mining and data mining techniques enables knowledge extraction that can result in cost-savings and improved decision making. In healthcare, the re-use of data is not exploited to the same extent as in industry (Mans, 2013). Data mining comprises a set of tool and techniques that can be applied on this processed data to discover hidden patterns, providing healthcare professionals an additional source of knowledge for making decisions. Process mining aims for discovering process knowledge. Performing process analysis in healthcare is particularly difficult because its processes are highly dynamic, highly complex, increasingly multi-disciplinary, and ad-hoc (Rebuge & Ferreira, 2012). Process mining can be seen as the bridge between data mining as a business intelligence approach and business process management (Van der Aalst).

Clinical protocols are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances (Field, 1992). A clinical protocol is aimed at reducing errors and unjustified variations in clinical practise in order to improve the quality of care based on the best practice as well as to contain the costs. A clinical protocol can also act as focus for quality control. It allows for checking whether the treatment of a patient was performed correctly.

This research is aimed at creating added value to clinical protocol analysis using both techniques described above. Clinical processes are often complex and therefore there can be many reasons for a deviation from the existing protocol. This research also provides insight into the current practice of glucose regulation, serving as a starting point for protocol improvements. The main focus is therefore on protocol compliance and improvement. Protocol compliance can be evaluated by comparing the actual process execution with the initial defined protocol. Comparing the current situation to the protocol gives insight into clues for unsatisfactory process performance and can provide directions for improvement.

1.1 Data mining

Data mining is the analytic process used for exploring (large amounts) of data. Data mining techniques search for patterns and/or systematic relationships between

variables and validate the findings by applying the detected patterns to new subsets of data. Business organizations use these techniques in order to gain a better understanding of their customers, their operations and to solve complex business problems. In healthcare, main applications of data mining techniques are medical image classification and the prediction of medical events.

1.2 Process mining

Process mining techniques allow for extracting information from event logs. The information obtained from the event logs is used to gain understanding in the current behavior of a process. In a healthcare context, process mining can be used to provide insights into how healthcare processes are really executed (Mans, 2013). However the techniques can also be used for improving healthcare processes. Process mining is, therefore, beneficial for both hospitals as well as patients.

There are three types of process mining: discovery, conformance and enhancement (Van Der Aalst, 2011). A discovery technique builds a process model from an event log without using any a-priori information. An enhancement technique extends an existing process model using information about the actual process recorded in the event log. A conformance technique compares an existing process model with an event log of the same process and checks whether the reality (as recorded in the log), conforms to the process model. As noted above, this research focuses on protocol compliance and improvement. It has, therefore, several overlaps to the different types of process mining.

There is a subtle difference in terminology between compliance and conformance. Conformance is mostly used in a process mining environment. In the business or financial domain the term compliance is used (e.g. Sarbanes-Oxley act). In this thesis, the term compliance is used as it better fits the language of the medical world.

1.3 Challenges related to process and data mining techniques in healthcare

Process mining in healthcare is very complex. Healthcare organizations are customer focused and many processes are client-specific. Processes in healthcare are overly complex and often referred to as 'spaghetti models' (Van Der Aalst, 2011) (Kaymak, 2012). A further challenge is that a single patient trace is not per definition a single case. A patient might suffer from multiple diseases, and therefore it is hard to distinguish the different treatment plans. These process-related challenges induce a higher level of uncertainty for process analysis. A further process mining challenge is the data storage in a hospital information system. Information systems in healthcare are not generally aimed at monitoring processes and removing inefficiencies, which makes the data extraction challenging.

Hospitals have multiple types of data sources: administrative systems, clinical support systems, healthcare logistics systems and medical devices. Previous research performed process mining on data obtained from administrative systems. These types of systems register services that have been delivered to patients (mainly for billing purposes) (Mans, 2013). When performing analysis on data from an administrative system, the

challenge that a single patient trace is not per definition a single case, is very difficult to deal with.

For medical data mining the main challenges are that the entered data are often incomplete or polluted. Furthermore, the high volume of data and the number of variables can be a challenge due to computational complexity. Another main challenge is that there can be inconsistencies due to the data representation if more than one model for expressing a specific meaning exist (Hosseinkhah et.al., 2009). The poor integration of healthcare data poses challenges on the confidence that can be placed in the results.

Process mining and data mining are seen as two different research fields. Both fields face specific challenges described above. Moreover, the scientific world is challenged to better integrate process and data mining techniques.

In this research, these challenges are addressed by focusing on one specific process at one department, based on data obtained from a clinical support system, rather than focusing on patient flows through the entire hospital, based on data from an administrative support system. The research uses regular data mining techniques applied in the field of process mining.

1.4 Research objective

The research project has two stakeholders, Eindhoven University of Technology and Maastricht UMC+. To maximize the benefits for both stakeholders, the student is required to reach different goals. Therefore, the research is aimed at two goals, namely a scientific goal and a practical goal.

Practical goal

During the first meetings, it became clear that the extent to which the Intensive Care Unit (ICU) of the MUMC+ complies to the strict glucose control protocol is unknown. This research should provide the ICU department with valuable insights regarding their strict glucose control protocol. The practical goal is formulated as follows:

"This research should provide insights regarding the strict glucose control protocol in *the ICU department of MUMC+, especially in the differences between the wards, the compliances to the protocol, deviations from the protocol, and patterns in the deviations."*

Scientific goal

This research project is also a master thesis project. It is, therefore, important that the findings provide a relevant contribution to the scientific world. Both process mining studies, as well as data mining studies are not new to the healthcare domain. However, these studies are usually performed on data obtained from an administrative system. Recently a study in the field of administrational process mining was performed (Mans, Schoneberg & Song, 2008). This research applied process mining techniques to discover typical paths followed by particular groups of patients.

As stated above, performing business process analysis in healthcare is particularly difficult because its processes are highly dynamic, highly complex, increasingly multi-disciplinary, and ad-hoc (Rebuge & Ferreira, 2012). It might, therefore, be better to start with simple processes with a shorter duration, single location, a single team, and a single perspective, such as the strict glucose control process in the ICU.

Furthermore, the data regarding glucose control in the ICU are stored in a clinical support system. These systems support processes of specialized departments such as an intensive care unit. Previously in the MUMC+, research has been performed on performing process mining techniques on medical data stored in a Clinical Support System (CSS) (Boere, 2013) (Lips, 2015). Other research focused on process and data mining data from a clinical support system individually. However, these techniques were never combined in one case study. This research is, therefore, aimed at creating added value to clinical protocol analysis by combining both process and data mining techniques on data from a clinical support system. The scientific goal is formulated as follows:

"This research, by performing a case study, should discover whether a combination of process mining and data mining techniques creates added value to clinical protocol analysis."

Research question

Both goals were translated into one main research question. This main research question is formulated as follows:

"What is the compliance to the strict glucose control protocol in the Intensive Care Unit of the MUMC+?"

Throughout the project, emphasis was placed on both delivering useful insights for the MUMC+ and on contributing to the literature by developing new applications of existing techniques for protocol evaluation (section 1.6). Although the main research question might imply solely an analysis, emphasis was put on designing and implementing new tools for performing the analysis. The main research question can therefore be considered as an overarching question. The corresponding sub-research questions are explained in the research methodology (chapter 3).

1.5 Case study

The organization involved is Maastricht University Medical Centre (MUMC+). The study is performed in the Department of Intensive Care Medicine. The MUMC+ is the result from a merger between the Faculty of Health, Medicine and Life Sciences (FHML) and the Academic Hospital Maastricht. The MUMC+ is the perfect partner for health recovery, health preservation and health promotion. The mission of MUMC+ is to provide the best possible care and improve health in the region through the integration of patient care, research, and education.

In 2014 the MUMC+ had 715 beds, 26 operating rooms and 27,207 admissions. The Department of Intensive Care Medicine consists out of the following wards: D3, E3, and

F3. Wards D3 and E3 are mixed ICU's, with mainly acute admissions, as opposed to ward F3, with mainly planned admissions and cardiothoracic surgery patients. These wards combined have 27 IC beds. Wards D3 and E3 mainly treat mixed medical/surgical patients, where most patients (90%) are acute patients (requiring immediate assessment or treatment). Ward F3 mainly treats patients who have undergone cardiothoracic surgery, where most patients (90%) are elective (requiring less urgent treatment and whose surgery can be scheduled for a future date).

1.6 Scientific relevance

In the field of clinical data mining there is more effort needed to obtain a wider acceptance from healthcare professionals and for generalization of the knowledge and reproducibility of its extraction process (Lavindrasana, Cohen, Depeursinge, Müller, Meyer, & Geissbuhler, 2009). Firstly, this research is a contribution to the scientific literature, as it enhances the acceptance of data and process mining techniques by healthcare professionals. Furthermore, it provides new methods to perform clinical protocol evaluation. For example, this study uses data mining techniques for determining protocol compliance and a new method was developed to put this protocol compliance in a broader perspective (fuzzy compliance). The research also provides new applications of data mining techniques for clinical protocol extraction (decision tree and fuzzy inference system rule extraction), or protocol discovery, as it is called in the process mining domain.

In essence, the case study aims to demonstrate that data mining and process mining (data obtained from clinical databases) can be seen as complementary techniques that can be used for clinical protocol evaluation and improvement. The combination of data and process mining techniques provides a natural link between processes and data on the one hand and performance and compliance on the other hand.

1.7 Thesis outline

Firstly, two major data mining techniques which are relevant for this research project are described in chapter 2. Thereafter, the research method of the project is described in chapter 3. In the following chapters the findings from the research are presented. The medical scientific background of glucose management is given in chapter 4. An overview of the version of protocols that were implemented at the different wards is presented in chapter 5. Chapter 6 describes the protocol compliance in the different wards based upon insights obtained in the interviews and from data analysis. Chapter 7 describes two methods for protocol discovery, or automatic protocol extraction. Rules regarding the regulation of the blood glucose level are extracted using decision trees and fuzzy inference systems. In chapter 8 the actual protocol is compared with the extracted rules that were presented in the previous chapter and the deviations to the strict glucose control protocol are described. Finally, chapter 9 provides the answer to the main research question, the general conclusions which can be distilled from this research, its limitations, and is finalized with suggestions for further research.

2. Background

This chapter provides the background for the main data and process mining elements used in this research. The first section is devoted to the process mining background of this thesis. The following sections describe the two data mining techniques that were used, decision trees and fuzzy logic and fuzzy inference systems. The last section provides general performance measures in datamining.

2.1 Protocol compliance and discovery in process mining

As stated in the introduction, there are three types of process mining: discovery, conformance and enhancement (Van Der Aalst, 2011). In the medical world, the term compliance is preferred over conformance; therefore compliance is used in this research. As noted above, this research focuses on protocol compliance and improvement. A compliance technique in process mining compares an existing process model with an event log of the same process and checks whether the reality (as recorded in the log), conforms to the process model.

Protocol discovery can be performed to obtain insight into the reality of glucose control. Comparing this reality to the protocol provides insight into where deviations from the protocol take place. Datamining techniques can be used for protocol discovery, i.e. classification algorithms have been used to discover decision rules at decision points in a process model based on the data attributes in the event log (Rozinat, 2010). The following two subsections describe the techniques used in this thesis.

2.2 Decision trees

In general, the goal of a decision tree is to predict the value of a target variable based on several input variables. Decision trees are therefore widely used for classification purposes. Moreover, decision trees can be used to extract patterns and rules from the data. The ability to break down a complex decision making process into a collection of simpler decisions, is an important feature of decision trees. An example of a decision tree can be seen in figure 1 below.

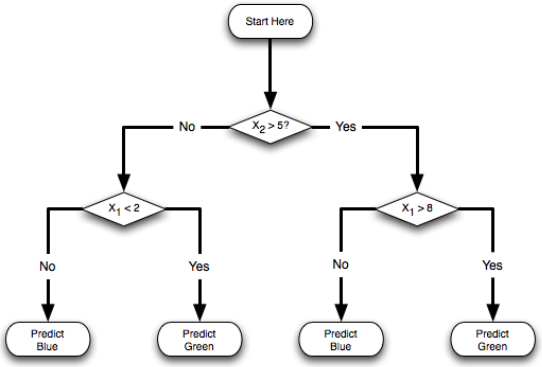


Figure 1: Example decision tree

A decision tree is constructed in a top-down recursive divide-and-conquer manner. The main components of a decision tree are the attributes, the branches, internal nodes, and

the leaf nodes. The attributes are the input variables, at the beginning all training examples are at the root. The internal nodes represent attribute value tests which are used to split the source set, or the attributes, into subsets. Each test compares a numeric attribute against a threshold value or a nominal attribute against a set of possible values (Kotsiantis, 2013). A heuristic or statistical measure is used for selecting the test attributes. Branches denote the outcomes of the attribute value tests. The leaf nodes denote the final class choice for a pattern. The partitioning process is recursively repeated until al examples from the training set belong to the same class, or if there are no remaining attributes for further partitioning. Ultimately, a complete discriminating tree is obtained.

For decision trees, it is very important to know how to split a training data set, i.e. how to select an attribute test that determines the distribution of training objects into subsets upon which subtrees are built consequently. The C4.5 algorithm uses two splitting criteria based upon information theory: gain criterion and gain ratio criterion. Using these criterions, an attribute that adds the most information regarding the decision upon a training set, is selected first, the next one is the most informative from the remaining attributes etc. How the splitting criteria can be obtained is explained in Appendix 1.

Decision trees are easy to understand and known for their accuracy. However, when decision trees become large, their interpretability decreases. It is possible to create a rule-based classifier by extracting IF-THEN rules from a decision tree (Han, Kamber, & Pei, 2006). For humans IF-THEN rules may be easier to understand compared to a large decision tree. The next section explains the process of extracting rules from the decision tree

Rule extraction from a decision tree

A decision tree is converted into a set of rules by creating one rule for each path from the root to a leaf node. A logical AND operator is used for each splitting criterion along a given path. The leaf node forms the rule consequent ("THEN"), since the leaf node in a decision tree holds the class prediction. The rules are extracted directly from the decision tree and they are mutually exclusive and exhaustive. Mutually exclusive in the sense that there cannot be rule conflicts, no two rules will be triggered for the same tuple (or path). The decision tree is exhaustive in the sense that there is one rule for every possible attribute-value combination. Therefore, the order of the rules does not matter (Han, Kamber, & Pei, 2006). Extracting rules from a decision tree is not difficult; from the decision tree in Figure 1, the following rules can be extracted:

IF $x_2 > 5$ AND $x_1 > 8$ THEN Predict Green
IF $x_2 > 5$ AND $x_1 < 8$ THEN Predict Blue
IF $x_2 < 5$ AND $x_1 > 2$ THEN Predict Green
IF $x_2 < 5$ AND $x_1 < 2$ THEN Predict Blue

Decision tree pruning

However, when all rules are extracted, there are also sections that provide little classification power. The default decision tree often overfits the data. Overfitting implies

that the tree classifies the original training set well, but the structure of the tree is particularly sensitive to this training set, and the performance on new unseen data is likely to be worse. Overfitting the model can be prevented by pruning the decision tree. Pruning implies reducing the size of the decision tree by removing sections of the tree that provide little classification power. Pruning also reduces the complexity of the final classifier. The default decision tree built on all the data is likely to be large and difficult to read. To extract an understandable decision tree that covers all important medical rules, it is important to prune the tree correctly. The pruned tree is likely to perform better on unseen test data. There are multiple pruning algorithms; reduced error pruning and cost complexity pruning are the most popular algorithms. See appendix 2 for more explanation on these algorithms.

2.3 Fuzzy Logic and Fuzzy Inference Systems

> *"If you remove sand grains from a sand dune one by one, when does the sand dune turn into sand hill, when into a sand pile?" ~ Sorites paradox*

Sorites paradox, sometimes translated as the paradox of the heap is a paradox that arises from vague predicates (Fisher, 2000). Assuming that by removing a single or a few grains of sand, a sand dune does not turn into a sand pile. But if the process were to be repeated often, is a single remaining grain still a sand dune? If not, when did the sand dune turn into a pile of sand?

Fuzzy sets were originally developed to account for numerous concepts used in human reasoning which are imprecise and vague, i.e. large, slow, etc. (Dubois & Prade, 2012) The original idea was to use fuzzy sets to represent gradualness. Gradualness refers to the idea that many categories in natural language are a matter of degree, including truth. Sorites paradox, as described above, serves as an example for gradualness. Fuzzy sets are also very convenient for representing some form of epistemic uncertainty, or the idea of representing partial or incomplete information by sets, in other words. Fuzzy logic can also represent bipolarity, or the idea that information can be described by distinguishing between positive and negative sides, possibly handled separately, as it seems to occur in the human brain. Overall fuzzy logic deals with approximate reasoning instead of precise reasoning; this is contrary to the foundation of conventional computer logic.

Degree of membership

The basic idea behind the fuzzy set is that an element belongs to a fuzzy set with a certain degree of membership. The fuzzy set has fuzzy boundaries. A proposition is neither true nor false, but may be partly true or partly false to any degree. This degree is usually taken as a real number in the interval [0,1]. The fuzzy set is used for representing some precise gradual entity consisting of a collection of items (sets). The mathematical notion of a fuzzy set F on a finite universe U is unambiguously defined by the membership function $\mu_f: U \rightarrow [0,1]$. The mathematical object representing the fuzzy set is the membership function $\mu_f(x)$ indicating the grade of membership of element $x \in U$ in F. An example can be seen in Figure 2. In this figure, the gradual distinction in price level between low, good and high, for an oil barrel, is represented by a fuzzy set.

An oil price level of $20.00 represents a membership value of 0.15 with 'Good' and a membership value of 0.85 with 'High'. The term 'membership value' denotes the degree to which a case can be seen as 'part of the concept'. Some people would argue that a price of 20$ per oil barrel is a good price where others argue it is a high price. Fuzzy set theory accepts that an oil barrel price can be either, 'not', 'partly' or 'fully' a member of the concept 'high price'.

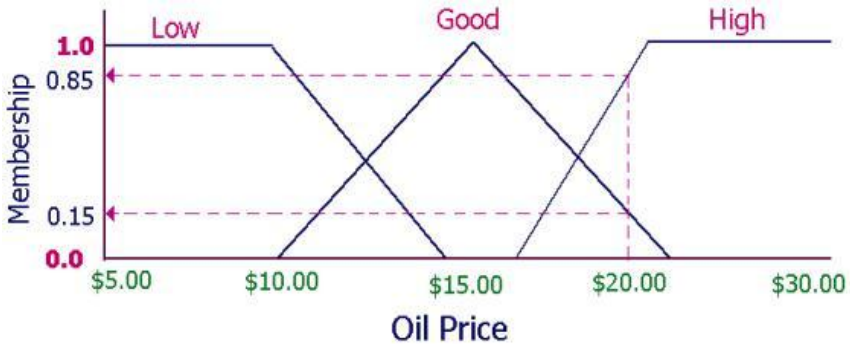


Figure 2: Example fuzzy set

Membership functions

The membership value is defined by the membership function (MF) expressed on a continuous scale from 0 to 1. There are many different membership functions such as the triangular MF, trapezoidal MF, Gaussian MF, generalized bell MF, etc. In this thesis only the trapezoidal and the Gaussian membership functions are used. The trapezoidal MF consists of straight lines and has the form of a trapezium. It has the advantage of simplicity. An example of the trapezoidal MF can be seen at the left hand side of Figure 3**.** An example of the Gaussian MF can be seen at the right hand side of Figure 3**.**

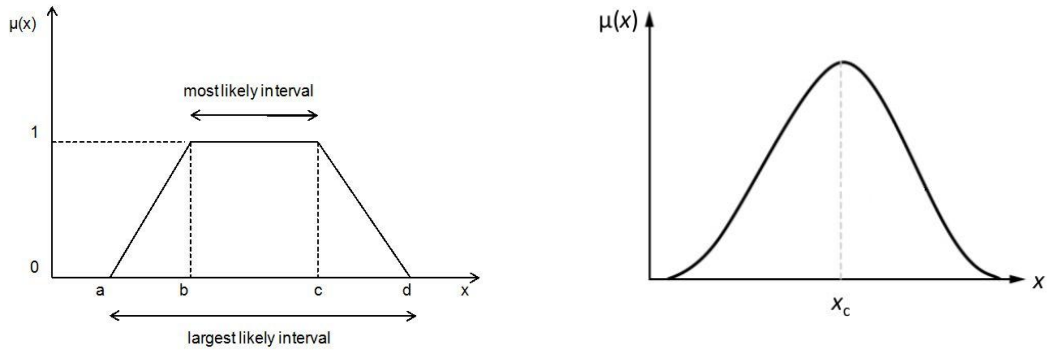


Figure 3: Trapezoidal and Gaussian membership functions

The X-axis denotes the range of possible values for the input variable. The Y-axis denotes the corresponding membership value (in range [0,1]). For the trapezoidal MF, the letters (a,b,c,d) denote the corners of the trapezium which defines the degree of membership, either no membership, partial membership or full membership. The area between b and c represents all values that are a full member, so for all values in this interval the membership value equals 1. Values in the intervals [a,b] and [c,d] denote partial membership. The membership value in these intervals depends on how close the

x-value is to b or c. For example, a value in the interval [a,b], has a high membership value if it is close to b and a low membership value if it is close to a. The trapezoidal MF can take on several forms, for more information see appendix 3. The membership in a trapezoidal MF is defined as follows:

$$f(x; a, b, c, d) = max\left(min\left(\frac{x-a}{b-a}, 1, \frac{d-x}{d-c}\right), 0\right),$$

where x denotes the value for which the membership value is calculated.

The membership in a Gaussian MF is defined as follows:

$$f(x; \sigma, c) = e^{\frac{-(x-c)^2}{2\sigma^2}},$$

where parameter c locates the distance from the origin, σ indicates the width of the curve and x denotes the value for which the membership value is calculated.

Fuzzy Inference System

A fuzzy inference system is an expert system where the knowledge is represented in the form of fuzzy rules. Compared to a set of crisp rules, fuzzy systems reduce the number of rules by at least 90 per cent (Negnevitsky, 2004). Fuzzy inference is the process of formulating the mapping between a given set of inputs and an output using fuzzy logic. The process involves three main components: membership functions, logical operators, and fuzzy IF-THEN rules (Turban, 2010). In a fuzzy inference system, the values of a variable are represented by membership functions instead of crisp values, i.e. the value "long" of variable duration to next glucose measurement, can be represented with a trapezoidal or Gaussion MF with specific parameters. The rules are expressed using fuzzy variable values, i.e. IF blood glucose level is *high* and increase in delta blood glucose level is *large*, THEN time to next blood glucose measurement is *short*. The logical operators combine and consolidate the fuzzy variables to reach the most accurate conclusion. The most used fuzzy inference techniques are the so-called Mamdani method and the Sugeno method. These methods are comparable and are explained under Appendix 4.

2.4 Performance measures

Performance measures are used to compare the performance of the different models. Models can be assessed on their *predictive accuracy* (the ability to correctly predict the class label of new or previously unseen data), their *speed* (calculation time), *robustness* (whether the model is able to make reasonable accurate predictions with missing and erroneous values), their *scalability* (ability to construct a prediction model with large amounts of data) and their *interpretability* (the level of understanding and insight provided by the model). This section is devoted to accuracy performance measures for classification decision trees.

The accuracy gives an indication of how good a model can predict new cases and allows for comparing different models. Many accuracy measures for classification models can be obtained from the confusion matrix. A confusion matrix for a binary classification problem (with only 2 classes) can be seen in Figure 4.

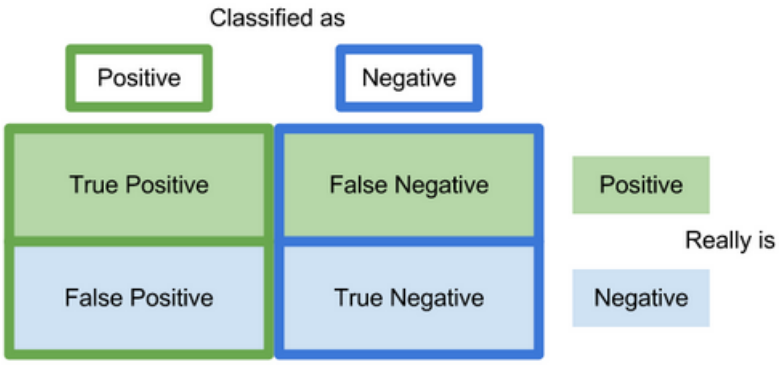


Figure 4: Confusion matrix for binary classification problems

True Positive (TP) and True Negative (TN) are correctly predicted. False Positive (FP) and False Negative (FN) are incorrectly predicted. Multiple accuracy metrics, such as accuracy, sensitivity or recall, specificity or true negative rate, false positive rate and precision can be calculated from the confusion matrix.

In case of a multi-class classification problem the confusion matrix would have as many rows and columns as there are classes. However, in this case, accuracy metrics that can be obtained from the confusion matrix become limited to per class accuracy rates and the overall classifier accuracy. In this thesis, only multi-class classification problems are faced, therefore, only the overall classifier accuracy is relevant. For completeness, the other performance measures based on the confusion matrix are explained in Appendix 5.

Accuracy: denotes overall model performance and is calculated by the ratio of correctly classified instances divided by the total number of instances.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

Resubstitution error: equals the difference between the actual dependent variable in the training data and the predictions the tree makes for the dependent variable based on the input training data. The resubstitution error can be calculated as follows:

$$Resubstitution\ Error = \frac{\sum_{i=1}^{n}(False\ Classification)_i}{Total\ Number\ of\ Cases}$$

A high resubstitution error means that the predictions of the model are not very accurate. However a low resubstitution does not always mean high prediction accuracy for new data. The resubstitution error is often overly optimistic for predictive accuracy. The generated tree often over fits the training set. Overfitting implies that the model classifies the original training set well, but the structure of the model is particularly sensitive to this training set and the performance on new unseen data is likely to be worse. To obtain a more representative insight into the performance of a model, it is better to look at the K-fold cross validation error. In case the model is a decision tree, it is often possible to find a simpler (pruned) tree that performs better than a more complex tree on new data.

K-fold cross validation error: is used in order to get a better sense of the predictive accuracy of the decision tree on new data. K-fold cross validation randomly splits the training data in k parts. K trees are trained, each one on nine remaining parts of the data. Then for each of the trained trees the predictive accuracy is determined, based on the data not included in training that tree. This method gives a better estimate of the predictive accuracy than the resubstitution error, since it tests the tree on new data. The cross validation error is calculated by averaging the k individual accuracy measures and can be expressed as follows.

$$Cross\ validation\ error = \frac{1}{k}\sum_{i=1}^{k} A_i$$

Mean Absolute Error: is simply the average of all absolute differences between the predicted and actual values. This performance measure can be used on numerical data.

$$MAE = \frac{1}{n}\sum_{j=1}^{n}\left|actual\ output_j - prediction_j\right|$$

3. Methodology

This chapter provides insight into the methods that were used to perform this project. Firstly, the research questions are described. Thereafter, the chapter continues with explaining the strategy for answering the research question.

3.1 Research questions

To maximize the benefits for both stakeholders of the research, the research has a practical goal as well as a scientific goal. The practical goal and the scientific goal of this research, as described under section 1.4, were respectively set to be:

> *"This research should provide insights regarding the strict glucose control protocol* in *the ICU department of MUMC+, especially in the differences between the wards, the compliances to the protocol, deviations from the protocol, and patterns in the deviations."*

And:

> *"This research, by performing a case study, should discover whether a combination of process mining and data mining techniques creates added value to clinical protocol analysis."*

These goals were summarized in the following main research question:

> *"What is the compliance to the strict glucose control protocol in the Intensive Care Unit of the MUMC+?"*

Before the main research question can be answered, several preparatory research has to be completed. The following sub-research questions are addressed in this preparatory phase. The sub-research questions provide guidance to each subsection. The sub questions are explained below, accompanied by an explanation of the subsection.

1) *What is glucose control?*
   This section aims at acquiring domain specific knowledge in the field of glucose management in general.

2) *What strict glucose control protocols are available* in *the ICU department and what are the differences between the wards?*
   In the ICU department of the MUMC+, there are multiple versions of the strict glucose control protocol available. This section aims to create an overview of which glucose control protocol is used on which ward and an overview of the differences between these protocols.

3) *To what extent are the strict glucose control protocols used in the ICU?*
   a. *According to the interviews*
   b. *According to the data analysis*
   The MUMC+ is interested the degree of compliance to the different versions of the strict glucose control protocol found at sub question 2 in the ICUs. This question will be addressed in two ways: by interviewing the ICU staff (a) and by

checking the compliance as performed in the process mining domain (b). The findings from the interviews form the basis for the subsequent survey.

4) *If the strict glucose protocol is not followed (completely), are there any unwritten rules for glucose control?*

   This section aims to find out whether it is possible to automatically extract rules for a clinical protocol, in this case the strict glucose control protocol, from historical data. This question corresponds to protocol discovery in the process mining domain, however, the techniques involved stem from the field of data mining. In order to answer this research question, decision trees and fuzzy inference systems will be used. All calculations and modelling are performed in Matlab, a platform that is optimized for solving engineering and scientific problems.

5) *Are there any deviations from the protocol in the extracted rules?*
   a. *If yes, where are the deviations (according to the data)?*
   b. *Can we find patterns in the deviations?*
   c. *Why do the deviations occur according to the* MUMC+ supervisors *(interviews)?*

   Should the glucose control protocol not always be followed in practice, it will be interesting to know where and why deviations take place and if we can find any patterns in the deviations. We wish to look for a common factor that could explain the deviation from the protocol, therefore the deviations from the protocols will be discussed with the MUMC+ supervisors.

3.2 Research Design

The main research question (*What is the compliance to the strict glucose control protocol in the Intensive Care Unit of the MUMC+?)* and the sub questions will guide this research project. This section provides the methods that will be used to answer the sub questions and how this will eventually lead to an answer to the main research question.

To enhance the structure and academic validity, the research will be conducted according to an adapted version of the regulative cycle from van Strien (1997). The original regulative cycle is a research method developed for problem-solving projects. The original regulative cycle consists of multiple steps: problem definition, diagnosis, plan or (re)design, intervention, and evaluation and can be seen in Figure 5.

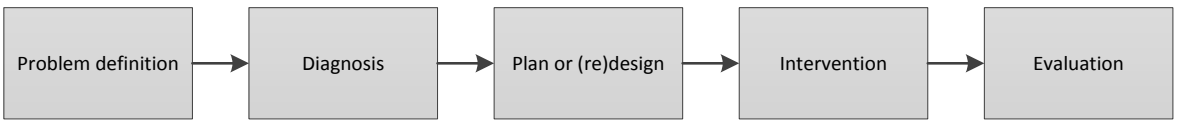


Figure 5: Original regulative cycle

In this research project only the first three steps are performed. The third step involves the use of datamining techniques which proceed according to the CRISP-DM reference model (Figure 6). In the original regulative cycle, the last step (Evaluation) is used for evaluating the results of the intervention. Since with this problem the intervention step does not occur, the evaluation step consists of evaluating the project.

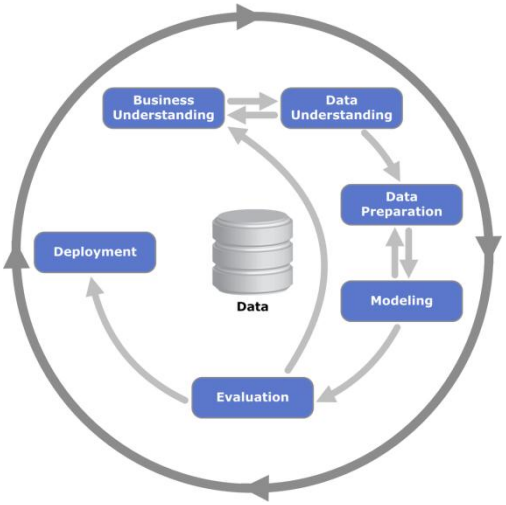


Figure 6: CRISP-DM

In the CRISP-DM cycle, the first phase (business understanding) is meant to reach a detailed understanding of the objectives and requirements. The second phase, or data understanding phase, is aimed at collecting the first data and to develop a general understanding of the data. The third phase is the data preparation phase, in which the data is prepared in such a way that the data can serve as input for the next phase, which is the modelling phase. Activities vary from data cleaning to data selection. In the modelling phase, various modelling techniques are applied to the data and models are constructed. Depending on the technique, it is sometimes necessary to go back and forth to the data preparation phase to adapt the data set. In the evaluation phase, the results from the previous phase are summarized and the created models are evaluated. The deployment is usually the phase in which the models are applied and put into practice. However, this phase will be skipped in this research project. An overview of the research method used for this project, based on a combination of the regulative cycle and the CRISP-DM reference model, can be seen in Figure 7.

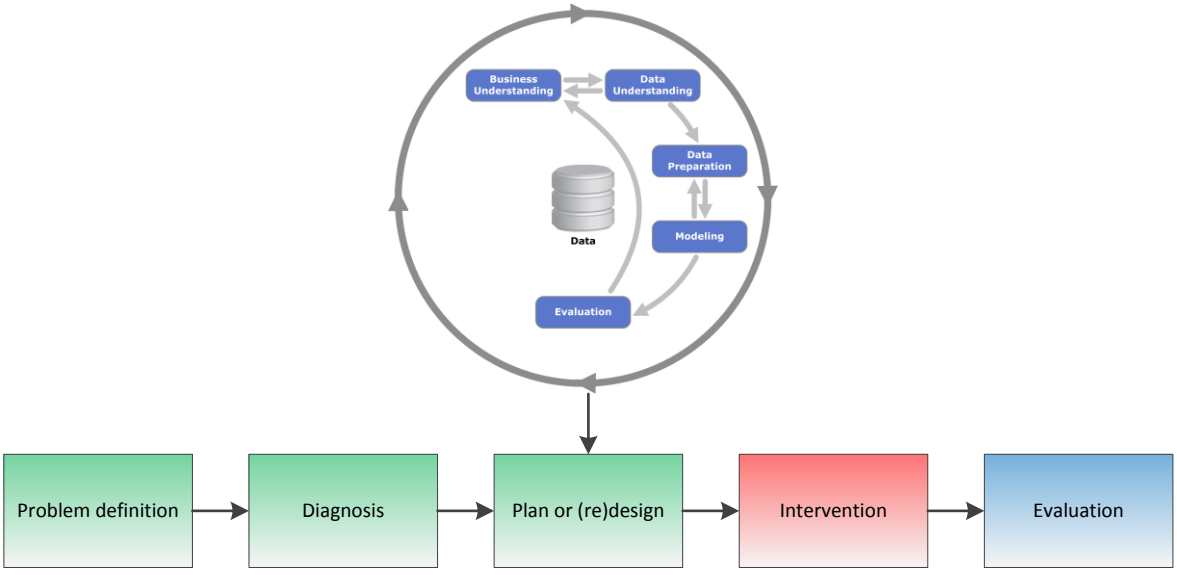


Figure 7: Adapted regulative cycle extended with CRISP-DM

Problem Definition: the lack of insight into the strict glucose control protocol in the ICU of MUMC+ motivates this research project. The research proposal and the research methodology (chapter 3) form the problem definition stage.

Diagnosis: in this phase the problem situation will be investigated. This phase produces specific knowledge on the context and the nature of the problem. Sub-questions 1, 2 and 3 belong to the diagnosis phase. After this phase the student has a clear insight into what glucose management is, which versions of the protocol are used at which department and in the compliance on the different wards to the strict glucose control protocol.

Plan or (re)design: in this phase, sub questions 4 and 5 are tackled. Datamining techniques are used for protocol discovery. The possibilities for automatically extracting rules according to which the glucose level can be regulated are explored (sub question 4). Since for this sub question datamining techniques are used, the CRISP-DM model is used here. Sub question 5 investigates the deviations from the protocol and potential patterns in the deviations.

Intervention or implementation: the results from the (re)design phase are not implemented. However findings obtained in this research can guide an intervention if required (i.e. the implementation of a new strict glucose control protocol).

Evaluation: in this phase, recommendations and conclusions are given. For the conclusions section, a distinction was made between case-specific (practical conclusions) and a more general section (scientific conclusions). Furthermore, this phase includes a reflection on the research containing limitations and suggestions for future research.

4. Glucose management

The reason behind this chapter is to become familiar with glucose control. Sub-research question one will be answered, which was defined as follows:

"What is glucose control?"

Glucose control is aimed at maintaining a stable blood glucose level in critically ill patients in order to prevent adverse outcomes. Glucose measurements are expressed in mmol/L. Hyperglycemia is a condition in which an excessive amount of glucose circulates in the blood plasma. This is generally a blood glucose level of more than 11.1 mmol/L. Hyperglycemia is common in critically ill patients, both with and without diabetes. Insulin is the preferred agent for glucose control in hospitalized patients. Regular insulin is used for continuous insulin infusion and an insulin bolus of rapid-acting insulin is used for correctional doses. Insulin has minimal side-effects except for hypoglycemia. Hypoglycemia denotes low glucose levels of less than 2.2 mmol/L. If the blood glucose level is too low, the medical staff can administer additional glucose in order to increase it. Glucose control is performed with a glucose control protocol.

The chapter starts with an introduction explaining the reasons behind glucose control. Then the Leuven studies will be discussed; these had a substantial influence on the development of tighter blood glucose control protocols. Thereafter, opposing findings from other studies will be presented. Then the reader receives insight into potential cost savings by implementing a tighter blood glucose control protocol. Hereupon the future of glucose control in the ICU will be discussed. The chapter ends with a conclusion.

4.1 Introduction

At the end of the last century, research was performed to evaluate the hospital care rendered to hyperglycemic individuals who did not have a diagnosis of diabetes before admission (Levetan, Passara, Jablonski, Kass, & Ratner, 1998). This research found that 33% and 37.5% of the surgical and medical patients respectively showed instances of hyperglycemia. Of these patients, 66% had at least two blood glucose measurements higher than 11.1 mmol/L. The average glucose peak was 16.5 mmol/L. Another study at the medical, cardiothoracic surgery, cardiac, general surgical, and neurosurgical Intensive Care Units found on admission hyperglycemia in 27.4% of the patients (Whitcom, Pradhan, Pittas, Roghmann, & Perencevich, 2005). Especially among the surgical and the cardiothoracic patients, hyperglycemia proved to occur frequently (36.1% and 31.2% respectively).

For critically ill patients the glucose level is dysregulated resulting in the development of hyperglycemia, irrespective of previously diagnosed diabetes. Peripheral insulin resistance develops in these patients, which is reflected by the combined picture of higher levels of insulin, elevated hepatic glucose production, and impaired peripheral glucose uptake (Vanhorebeek, Langouche, & Van den Berghe, 2007). This condition is also known as 'stress diabetes' or 'diabetes of injury'. Hyperglycemia has been clearly associated with a higher risk of morbidity and mortality of critically ill patients (Krinsley, 2003), both adults and children (Faustino & Apkon, 2005). Newly discovered

hyperglycemia was associated with higher in-hospital mortality rate compared to those patients with a history of diabetes and patients with normoglycemia (Umpierrez, Isaacs, Bazargan, You, Thaler, & Kitabchi, 2002). In severe illness, hyperglycemia and insulin resistance are thus common, but moreover they are also associated with adverse outcomes.

In the past, the general blood glucose policy was to tolerate blood glucose levels up to 12.2 mmol/L (220 mg/dL) in fed critical patients (Boord, Graber, Christman, & Powers, 2001). Only excessive hyperglycemia, defined as glucose levels exceeding 12.2 mmol/L, was treated. The main reasoning behind this policy stems from the classic dogma that moderate hyperglycemia in critically ill patients is beneficial for organs that largely rely on glucose for energy supply but do not require insulin for glucose uptake, such as the brain and blood cells. The fear for hypoglycemia and subsequent brain injury also supported this policy (Vanhorebeek, et al., 2007).

4.2 The Leuven studies

In 2001 the Leuven study, a randomized, controlled study in a surgical intensive care unit (ICU), found that strict control of blood glucose levels (between 4.4 - 6.1 mmol/L) with insulin reduced morbidity and mortality (Van den Berghe, Wouters, & Weekers, 2001). This strict control of blood glucose levels is called 'Intensive Insulin Therapy' (IIT). The Leuven studies were very important to glucose control in the ICU. Therefore the terminology used in these studies (strict glucose control and IIT), was also used for this research.

In the IIT insulin infusion was started when the blood glucose level exceeded 6.1 mmol/L, and was adjusted to maintain normoglycemia: 4.4 to 6.1 mmol/L. According to this research strict blood glucose control resulted in a significant reduction in in-hospital mortality from 11 to 7 percent in the entire study population. However, in the subgroup of patients who stayed in the ICU for three or more days the benefit was more explicit: a reduction of mortality from 21 to 14 percent for patients that were treated for at least three days, and a reduction of mortality from 26 to 17 percent for patients that were treated for at least five days. The reason for the decrease in morbidity and mortality among the patients is that complications such as infections and organ failure were reduced. However, the number of hypoglycemic events increased from 0.8% to 5%. Furthermore, it remained unclear whether IIT also improves the prognosis of patients in a medical ICU, who are often more severely ill than patients in a surgical ICU, and therefore, have a higher risk of death.

As the 2001 Leuven study received criticism on performing the research limited to a surgical ICU, the experiment was repeated in 2006 in a medical ICU setting (Van den Berghe, et al., 2006). It was a randomized, controlled study of patients in a medical ICU, targeting on patients who require intensive care for at least three days. Adult patients who were admitted to the ICU and expected to require at least a third day of intensive care, were eligible for inclusion. Patients were randomly assigned to two treatment arms, either to receive IIT or to receive conventional insulin treatment.

- Conventional insulin treatment: continuous insulin infusion (50 IU of Actrapid HM in 50 ml of 0.9 percent sodium chloride) with the use of a pump, was started only when the blood glucose level exceeded 12 mmol/L (215 mg per decilitre) and was adjusted to maintain a blood glucose level between 10 and 11 mmol/L (180 and 200 mg per decilitre). The insulin infusion would be reduced when the blood glucose level fell below 10 mmol/L and eventually be stopped.

- Intensive insulin treatment: insulin infusion was started when the blood glucose level exceeded 6.1 mmol/L (110 mg per decilitre), and was adjusted to maintain normoglycemia: 4.4 to 6.1 mmol/L (80-110 mg per decilitre). The maximum continuous intravenous insulin infusion was arbitrarily set at 50 IU per hour. At the patient's discharge from IC a conventional approach was adopted (maintenance of blood glucose level at 11 mmol/L or less).

Van den Berghe (2006) provided many insights. First of all, hypoglycemia occurred more often in the intensive-treatment group. Most patients who had hypoglycemia had only one episode. The severity of the hypoglycemia was similar in both groups. No hemodynamic deterioration, convulsions, or other adverse side effects were noted in association with any hypoglycemic event.

There was a difference in the intention-to-treat analysis (the intention-to-treat group consists of all patients that are randomized in the trial independent of the length of stay (LOS)) and the patients with three or more days LOS in the ICU. This study concluded that the IIT led to a reduction in morbidity for all patients. Only for patients with three or more days length of stay (LOS) in the ICU, the IIT led to a reduction in mortality and morbidity. The difference in effect between the intention-to-treat population and the patients staying in the ICU for at least three days can be explained assuming that the benefit from intensive insulin therapy requires time to be realized. The intervention is not focused on curing disease; it is focused on preventing complications that occur during intensive care. Prevention probably does not occur when the patient has a high risk of death from the disease causing admission to the ICU and when the intervention is administered for a relatively short time. For patients admitted to the ICU with less likelihood of dying, the intensive insulin therapy might prevent complications. This could explain the difference between the two groups.

4.3 Contradicting literature

Since the Leuven studies were undeniably single centre studies, and hampered by several flaws in study design, other researchers attempted to replicate these studies' findings in other centres, using somewhat different study designs. These are consecutively discussed in the sections below.

4.3.1 Glucontrol study

The Glucontrol (Preiser, et al., 2009) study aimed to compare the effect of IIT to the effect of an intermediate glucose control for 3500 patients treated in medico-surgical ICU's. The target blood glucose values for the IIT group were set according to the Leuven studies (4.4 - 6.1 mmol/L). The target blood glucose values of the intermediate

glucose control group (7.8 - 10.0 mmol/L) were selected to prevent the adverse effects of hyperglycemia, whilst reducing the risk of hypoglycemia. Unfortunately, the trial was stopped early because of a high number of unintended protocol violations. Nevertheless 1101 admissions were analysed. Both groups were similar in type of patients. Average overall blood glucose levels were 6.5 mmol/L for the IIT group and 8.0 mmol/L for the intermediate glucose control group. Average morning blood glucose levels were 6.1 mmol/L for the IIT control group and 7.7 mmol/L for the intermediate glucose control group. The percentage of patients treated with glucose amounted to 96.3% and 66.2% respectively. Proportion of time spent in the target blood glucose value was similar for both groups. The rate of hypoglycemia was higher for the patients receiving IIT (8.7%) than for patients receiving an intermediate glucose control therapy (2.7%). The ICU mortality rate was similar for both groups (17.2% and 17.2%). The Glucontrol researchers stated that for confirmation of the 3 to 4% mortality reduction due to IIT implementation, as concluded in the Leuven studies, a multicentre research setting is needed with a sample size of at least 5000-6000 patients. The only ongoing clinical trial, meeting the requirements at that moment, was the NICE-SUGAR study.

4.3.2 NICE-SUGAR study

Within 24 hours after admission to the ICU, the NICE-SUGAR trial assigned 6104 patients expected to stay for 3 or more consecutive days in the ICU, randomly to undergo either intensive glucose control (4.5 – 6 mmol/L) or conventional glucose control (<10 mmol/L) (NICE-SUGAR Investigators, 2009). The main interest of the study was to compare the 90-days mortality, ICU LOS, the number of days on mechanical ventilation, and the number of hypoglycemia instances, for both groups. Average overall blood glucose levels were 6.4 mmol/L for the IIT group and 8.0 mmol/L for the conventional glucose control group. The mortality rate in the intensive control group (27.5%) was higher than the mortality rate in the conventional control group (24.9%). The treatment effect was similar for both surgical and medical ICU patients. Hypoglycemia was more often reported in the intensive control group (6.8%) than in the conventional control group (0.5%). There was no significant difference between both groups in the ICU LOS, hospital LOS and the number of days of mechanical ventilation.

4.3.3 Meta-Analysis

Friedrich et al. (2010) performed a reanalysis of meta-analytic data from two previous studies. The study was performed in order clarify the effect of IIT on morbidity and mortality, by combining a larger pool of data obtained from previous studies. Both reviews analyzed in this research were grouped randomized controlled trials by type of intensive care unit. The more recent review concluded that IIT reduced mortality in patients admitted to surgical ICU's, but not in patients admitted to medical ICUs, mixed medical-surgical ICUs, or in all patients combined. Meta-analytic results are sensitive to methodologic decisions. Especially grouping patients by type of ICU rather than by type of patient, may not be intuitive for clinicians. For example, the type of ICU in which a patient is treated depends on the hospital. Friedrich et al. (2010) combined the data of two other systematic reviews to revaluate the effect of IIT in critically ill surgical and medical critically ill patients, regardless of the type of ICU they were admitted to. The

authors concluded that IIT does not reduce mortality in critically ill surgical patients or medical patients.

4.4 Resource utilization: conventional and intensive insulin therapy

As discussed in the introduction, healthcare costs are soaring rapidly. In order to decrease the costs of healthcare, it is important to look the costs of a treatment. A certain treatment recommendation might be advised in the medical literature; however it is also important to know the economic consequences of a treatment. The costs of the IIT were compared with the costs of conventional insulin treatment (Van den Berghe et al., 2006). Costs were calculated based on length of stay and the frequency of crucial cost generating morbid events occurring in both groups. Costs were determined for the following healthcare resources: days in the ICU, days on general ward, duration of medical ventilation, days on hemodialysis/hemofiltration, duration of therapy with certain drugs, blood transfusions, insulin administration, and blood glucose monitoring. These specific total costs are calculated by multiplying the frequency of resource usage with its corresponding cost.

The IIT requires slightly more resources (e.g. more insulin, and more administration and monitoring costs). However, the benefits easily outweigh these costs. The average treatment cost for a patient in the conventional group was 10,596 Euro. The per-patient treatment cost for a patient receiving IIT was 7931 Euro. Per patient the intensive insulin protocol saves 2638 Euro. This cost saving can mainly be addressed to a reduction in the length of stay in the ICU and to a reduction of several morbid events such as renal failure, sepsis, blood transfusions, and mechanical ventilation dependency. The cost savings realized by the IIT due to a shorter stay at ICU were not offset by extra costs due to a longer length of stay on a normal ward. Days spent on a regular ward were equal for both patient groups.

Krinsley & Jones (2006) performed a similar study to assess the effect of IIT on the cost of care. However, this research was performed in a mixed medical-surgical adult ICU of a university-affiliated community teaching hospital. Actual data from a 1600 patient study by Krinsley (2004) was used. In this study, 800 patients under the conventional treatment were compared to 800 patients under IIT. The target glucose range in this study was set at 4.4 – 7.8 mmol/L (Krinsley, 2003). In their analysis costs associated with days at ICU, days at non-ICU, ventilator periods, laboratory, pharmacy and radiology services, and post-ICU hospital days were included. Krinsley & Jones (2006) calculated cost savings of 1580 Dollars per patient under intensive insulin therapy.

Krinsley measured length of stay in the ICU in hours, arguing this avoids inaccuracies in calendar-day measurements. When measuring the LOS in calendar days, the intensive therapy leads to a reduction in ICU days of 13.9%. When measuring LOS in number of hours, the intensive therapy leads to a reduction in ICU days of 17.2%. However, the method to measure length of stay in hours is not consistently applied. For example, the duration of hospitalization after ICU discharge, is only given in days. It could be that the additional reduction in hours by calculating the ICU LOS in hours

instead of days, are spent on a regular ward in the hospital. This could mean that the final cost saving estimate is overstated. A critical note, however, is that both studies presented in this section, were completed before the Glucontrol and the NICE-SUGAR studies.

The actual savings are not equally distributed among the different types of patients. For example, the largest net savings can be ascribed to surgical, cardiac, and gastrointestinal patients. The costs for septic shock, miscellaneous medical and respiratory patients increased. The largest increase in costs can be ascribed to a small group of patients with septic shock. These additional costs are assumed to occur because of the large decrease in mortality rate resulting in "expensive survivors".

4.5 Future of Glucose Management

Until recently, intermittent measurements of blood glucose have been the only means of monitoring blood glucose levels (Wernerman, et al., 2014). Due to the development of several continuous glucose monitoring (CGM) systems, interest has grown in the possible beneficial effects of continuous monitoring over intermittent monitoring. Ideally CGM systems will be used as input for insulin algorithms. An algorithm can be defined as 'a formalized sequence of instructions for solving a complex problem in finite processing steps' (Khalil, et al., 2014). An optimal system should be accurate, safe, efficacious, simple to use, reliable, flexible for different patient populations, assessable in real-time, fit into workflow, require a low number of glucose measurements (if not based on CGM), and take into account inter- and intrapatient variability and carbohydrate intake (Wernerman, et al., 2014). Most algorithms for glycemic control are based on intermittent glucose measurements. When CGM will be more widely adopted, new algorithms, which use the CGM system as input, need to be designed.

4.6 Conclusions

Regulation of blood glucose levels in the ICU is of great concern from both scientific and medical perspective and to the patients. Over the years studies conducted in this field have shown conflicting results. The support to the IIT is mainly built on the findings from the Leuven studies which point out that the IIT decreases morbidity and mortality caused by hyperglycemia. The Glucontrol study showed similar mortality rates for both the intensive and the conventional insulin therapy, however in the intensive group the number of hypoglycemic events was significantly higher. The NICE-SUGAR study found a higher mortality rate in the intensive control group (27.5%) compared to the mortality rate in the conventional control group (24.9%). Also the meta-analysis by Friedrich et al. concluded that IIT does not reduce mortality in critically ill surgical patients or medical patients. The controversy on how to optimally treat hyperglycemia in the ICU is continuing (Van den Berghe, 2013). Initially, many hospitals implemented insulin protocols based on the IIT. In 2010, tight glycaemic control was practised in nearly half of the ICUs in the Netherlands (Schultz, Binnekade, & Harmsen, 2010). Local guidelines for blood glucose regulation have changed in the Netherlands after the publication of the NICE-SUGAR trial. However, trends in metrics for blood glucose control show that tight glycaemic control is only modestly adopted in the Netherlands

(van Hooijdonk, et al., 2015). The implementation of these protocols, however, leads to a substantial cost saving per patient. In the future the glucose protocols should be based on algorithms using real-time data from the continuous glucose monitoring system (CGM) as input, instead of intermittent glucose measurements.

5. Overview of glucose control protocols on different ICU wards of MUMC+

Glucose control can be performed using a glucose control protocol. The ideal glucose control protocol will help reach the glucose target range timely, effectively treat all degrees of hyperglycemia, minimize glycemic variation and the risk of hypoglycemia, and is easy for nurses to carry out in a timely fashion (Wilson, Weinreb, & Hoo, 2007). Multiple glucose control protocols exist in the ICU department of MUMC+.

This chapter focuses on gaining insight in the different versions of the strict glucose control protocol as used in the different intensive care units of the MUMC+. Sub-research question two will be answered, which was defined as follows:

"What strict glucose control protocols are available in the ICU department and what are the differences between the wards?"

The semi-structured interviews provided insight into the different versions of the protocol that were implemented at the different ICU wards. The different versions of the protocol can be found in Appendix 6.

5.1 Protocol implemented on each ward

On wards, D3 and E3, the protocol shown in appendix 6.1 was implemented. On ward F3, the protocol shown in appendix 6.2 was implemented. Both protocols have a similar structure. The protocol implemented on D3 and E3 consists of four sections: 'startup medication dosing scheme', 'blood glucose level decreased by less than 30% or increased', 'blood glucose level decreased by more than 30%', and 'hypoglycemia policy'. In this research, the last three sections, are referred to with the term 'continuation schedule'. The protocol implemented on F3 consists of three sections, on this protocol the 'hypoglycemia policy' is merged with the other sections. The interpretation of both protocols is similar. When the glucose level falls below the maximum target level, insulin therapy is started according to the startup medication dosing scheme. For each subsequent glucose measurement the medication settings are changed depending on the change in the blood glucose level and the current blood glucose level. The differences in both protocols are described in the following section.

5.2 Differences between the protocol implemented on D3/E3 and the protocol implemented on F3

The main difference between the protocols is that they each aim for a slightly different blood glucose target level. The protocol on ward D3/E3 has a blood glucose target level between 4.5 and 7.0 mmol/L, where the protocol on ward F3 has a target level between 4.5 and 6.5 mmol/L. In each of the following subsections, the protocol differences are described per protocol section.

5.2.1 Differences in section 'startup medication dosing scheme'

Table 1 and table 2 denote the 'startup medication dosing scheme' section for the protocols of wards D3/E3 and F3 respectively. Comparing these sections for both protocols, it is noticed that:

- The blood glucose reference level is different for the first two rows.
- The Perfusor Novorapid settings are equal, despite the different reference levels.
- The insulin boluses are higher in the protocol of ward F3.

Opstartschema		
Bloedglucose (mmol/l)	Perfusor Novorapid (50^{E}/50ml NaCl 0.9%)	Bolus
< 7,0	-	
7,0 - 8,0	1 E/u	
8,0 - 10	2 E/u	
10 - 15	4 E/u	4 E Novorapid
15 - 20	6 E/u	6 E Novorapid
> 20	6 E/u	8 E Novorapid

Table 1: 'startup medication dosing scheme' protocol D3/E3

Opstartschema		
Bloedglucose (mmol/l)	**Perfusor Novorapid (50^{E}/50ml NaCl 0.9%)**	**Bolus**
< 6,5	-	
6,5-8	1	
8-10	2	
10-15	4	6 E Novorapid
15-20	6	8 E Novorapid
>20	6	10 E Novorapid

Table 2: 'startup medication dosing scheme' protocol F3

5.2.2 Differences in section 'blood glucose level decreased by less than 30% or increased'

Table 3 and table 5 denote the 'blood glucose level decreased by less than 30% or increased' section for wards D3/E3 and F3 respectively. Since the protocol for F3 describes hypoglycemic events in this subsection, it was chosen to add the subsection 'hypoglycemia policy' for D3/E3 here (table 4). Comparing these sections for both protocols, it is observed that:

- The blood glucose reference levels are different.
- Insulin boluses are higher in the protocol of ward F3.
- The protocol on D3/E3 provides more rules for hypoglycemia and the amount and start of a glucose bolus is different.
    - For D3/E3 a 50 ml glucose 50% bolus is administered when the blood glucose level is below 3.5. If the blood glucose level, as a result of the first glucose bolus, increases to more than 4.5, the Novorapid perfusor can be restarted on the previous setting minus 1. If the blood glucose level remains below 4.5, another 30 ml glucose 50% bolus is administered. If the blood glucose level, as a result of the second glucose bolus, increases to more than 4.5, the Novorapid perfusor can be restarted on the previous

setting minus 2. If the blood glucose level remains lower than 4.5, another 50 ml glucose 50% bolus is administered and the situation is discussed with the doctor.

- For F3 a 20 ml glucose 50% bolus is administered when the blood glucose level is between 2.5 and 4.5. A 30 ml glucose 50% bolus is administered when the blood glucose level is below 2.5.

Bloedglucose < 30% gedaald, óf bloedglucose gestegen		
Bloedglucose (mmol/l)	**Perfusor Novorapid** (50^{E}/50ml NaCl 0.9%)	**Actie**
< 3.5	Stoppen	Handel conform hypobeleid
3,5 - 4,5	- 1.0 E/u	Na 30 min glucose controle
4,5 tot 7,0	Ongewijzigd	
7,0 - 8,0	+ 0.5 E/u	
8,0 - 9,0	+ 1.0 E/u	
9,0 - 10	+ 1.5 E/u	
10 - 15	+ 2.0 E/u	2E Novorapid iv als bolus
> 15	+ 3.0 E/u	4E Novorapid iv als bolus

Table 3: 'blood glucose level decreased by less than 30% or increased' protocol D3/E3

Hypobeleid		
Bloedglucose (mmol/l)	**Perfusor Novorapid** (50^{E}/50ml NaCl 0.9%)	**Actie**
< 3,5	Stoppen	50 ml glucose 50% in 10 minuten en glucose controle na toediening
Indien > 4,5	Herstarten -1 E/u	Glucose controle na 30 minuten en handel conform vervolgbeleid
Blijft glucose < 4,5	Perfusor gestopt laten	30 ml glucose 50% in 10 minuten en glucose controle na toediening
Na 2^{e} dosis glucose 50%, indien > 4,5	Herstarten -2 E/u	Glucose controle na 30 minuten en handel conform vervolgbeleid
Na 2^{e} dosis glucose 50% nog steeds < 4,5	Perfusor gestopt laten	50 ml glucose 50% in 10 minuten en overleggen met arts

Table 4: 'hypoglycemia policy' protocol D3/E3

Bloedglucose <30% gedaald óf bloedglucose gestegen		
Bloedglucose (mmol/l)	**Perfusor Novorapid (50^{E}/50ml NaCl 0.9%)**	**Bolus**
< 2,5	stoppen	30 ml glucose 50%
2,5-4.5	stoppen	20 ml glucose 50 %
3,5-4,5	stoppen	
4,5 tot 6,5	ongewijzigd	
6,5-7,5	+1 E/h	
7,5-8,5	+2 E/h	
8,5-10	+2 E/h	2E Novorapid iv
10-15	+2 E/h	4E Novorapid iv
>15	+ 3 E/h	6E Novorapid iv

Table 5: 'blood glucose level decreased by less than 30% or increased' protocol F3

5.2.3 Differences in section 'blood glucose level decreased by more than 30%'

Table 6 and table 7 denote the 'blood glucose level decreased by more than 30%' section for wards D3/E3 and F3 respectively. Comparing these sections for both protocols, it is observed that:

- The blood glucose reference levels are slightly different.
- The glucose bolus is higher on ward D3/E3. For D3/E3 the hypoglycemia policy is followed when the blood glucose level is below 3.5. In practice this results in a 50 ml glucose 50% bolus. For F3 a 30 ml glucose 50% bolus is administered when the blood glucose level is below 3.5.

Bloedglucose > 30% gedaald		
Bloedglucose (mmol/l)	**Perfusor Novorapid** (50^{E}/50ml NaCl 0.9%)	**Actie**
< 3,5	Stoppen	Handel conform hypobeleid
3,5 - 4,5	Stoppen, indien waarde > 5mmol/l is herstarten met de helft van de laatste dosering	Om de 15 min glucose controle tot glucose > 5mmol/l is
4,5 tot 7	Halveren	
7 - 10	-1 E/u	
> 10	Ongewijzigd	

Table 6: 'blood glucose level decreased by more than 30%' protocol D3/E3

Bloedglucose > 30% gedaald		
Bloedglucose (mmol/l)	**Perfusor Novorapid (50^{E}/50ml NaCl 0.9%)**	**Bolus**
< 3,5	stoppen	30 ml glucose 50%
3,5-4,5	Stoppen	
4,5 tot6.5	halveren	
6.5-10	-1 E/h	
>10	ongewijzigd	

Table 7: 'blood glucose level decreased by more than 30%' protocol F3

5.2.4 Timing of glucose measurements

The protocol on D3/E3 only prescribes when to measure the next blood glucose, in case of hypoglycemia. If the blood glucose level is between 3.5 and 4.5 the blood glucose level should be checked every 15 minutes until the level is higher than 5.0. In case a glucose bolus is administered, the blood glucose level should be checked immediately. If as a result of the first glucose bolus, the blood glucose level exceeds 4.5, then the blood glucose level can be checked after 30 minutes. If a second glucose bolus is required, the blood glucose level should be checked every 10 minutes. If, as a result of the second glucose bolus, the blood glucose level exceeds 4.5 the blood glucose level can be checked after 30 minutes. If the blood glucose level remains below 4.5, the patient should receive another glucose bolus, and the blood glucose level should be measured after 10 minutes.

The protocol on ward F3 prescribes to measure a blood glucose level once every hour until a stable setting is reached. Once the blood glucose level is stable, measuring the blood glucose level once every two hours is sufficient. If a blood glucose level is below 3.5, the next glucose measurement should be within 15 minutes.

5.3 Conclusions

According to the interviews, two different protocols are currently available in the ICU department. Wards D3 and E3 have the same protocol. Ward F3 has a different protocol. Although both protocols have a similar structure, there are some small differences, e.g. different target blood glucose levels, different insulin boluses, a different hypoglycaemia treatment policy and different rules for duration to the next measurement.

6. Protocol compliance at different wards

This chapter focuses on the compliance of the strict glucose control protocol at the different ICU wards. Sub-research question three will be answered, which was defined as follows:

> *"To what extent are the strict glucose control protocols used in the ICU?*
>
> *a. According to the interviews*
>
> *b. According to the data analysis"*

To obtain these insights, a combination of semi-structured interviews, a survey and data analysis was performed. On each ward two interviews took place, one with the care-coordinator, and one with a regular nurse. Transcriptions of the interviews can be found in Appendix 7. An overview of the survey questions can be found in Appendix 12. In the interviews, two types of glucose measurements were discussed: point of care glucose measurements and arterial blood gas glucose measurements. The difference between these measurement methods is explained in the first subsection of this chapter. Thereafter, the chapter is divided into two more sections: protocol compliance according to the interviews and protocol compliance according to the data analysis.

6.1 Glucose measurements

In general, all wards have two ways of measuring the blood glucose level in patients: Arterial Blood Gas measurements (ABG) and Point-of-Care measurements (POC). The difference between these measurement types is explained here, as it is relevant for the data extraction and analysis, to know the distinction between the two measurements.

6.1.1 Arterial Blood Gas glucose measurements

The first and most performed measurement is the arterial measurement. Critically ill patients often have a thin catheter inserted into an artery in order to monitor the blood pressure in real time. This catheter can also be used to obtain samples for arterial blood gas (ABG) measurements. An arterial blood gas is a blood test performed using blood from an artery. An ABG test is mainly focused on measuring the arterial oxygen tension (PaO_2), carbon dioxide tension ($PaCO_2$), and acidity (pH). Standard blood tests such as a glucose measurement can also be performed on arterial blood. Therefore, nurses often request inclusion of a glucose measurement, when they wish to perform an ABG test.

When an arterial blood gas measurement is performed, the nurse first takes a blood sample from the arterial catheter. Thereafter, the nurse sends the blood sample together with a form that indicates the required tests, to the laboratory. The laboratory confirms receipt of the sample. When the laboratory starts performing the required tests, the tests are entered into the system. To communicate that the lab is working on the tests, the measurements are tagged with the status 'Lab volgt', meaning that the laboratory is determining the outcomes from the measurements. Glucose measurements have a high priority, thus, in general the laboratory tries to process them immediately. Once the measurements are finished, the laboratory enters the outcomes into the system, and the label 'Lab volgt', is replaced by a value. The downside of an ABG glucose measurement

is that there can be a delay between the moment a blood sample was taken and the moment the result is entered into the system, depending on the workload of the laboratory. An overview of the process can be seen in Figure 8.

Figure 8: Arterial glucose measurement

6.1.2 Point-of-Care glucose measurements

Instances of hyper- or hypoglycemia require immediate treatment. The duration of an ABG glucose measurement is, therefore, not suitable in such situations. For these situations, there is an alternative way to determine the blood glucose level. If hyper- or hypoglycemia is suspected, the nurse performs a Point-of-Care (POC) measurement. Point-of-Care testing is defined as medical testing at the site of patient care and is often accomplished through the use of a portable handheld instrument. When a POC glucose measurement is performed, the nurse first uses the handheld to scan the barcode of the patient. This action ensures that a blood glucose measurement will be saved in the system under the right patient. A small blood sample from the patient's finger is taken, a so called capillary measurement. This blood sample is collected on a test strip and entered into the POC handheld. The POC handheld determines the blood glucose value of the blood. After determination of the blood glucose value, the nurse places the handheld back into the docking station. Once this action is performed, the docking station communicates the results to the laboratory, where the results will be verified. Once verified by the laboratory, the results will also be visible in the ICIP IC system. The benefit from POC glucose measurements is that the nurse can determine the blood glucose level almost immediately, which enables a quick response. An overview of the process can be seen in Figure 9.

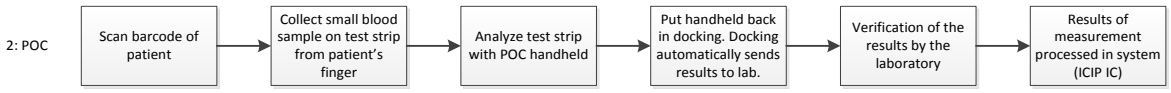


Figure 9: POC glucose measurement

6.2 Protocol compliance according to the interviews and survey

6.2.1 Ward D3

Interviews:

Both the care coordinator and a nurse from ward D3 confirmed that the protocol under appendix 6.1 was implemented. The care coordinator estimated that the protocol was implemented six years ago. After implementation, the protocol was used for six months. Both the care coordinator and the nurse know how to find the protocol on Odin (the MUMC+' Online, Document and Information Navigation system). Hospital-wide documents such as policies, agreements and protocols are saved in Odin. According to the care coordinator, the protocol has not been used for years. Controlling the blood

glucose level is done based on the experience and insight of nurses. The nurse believes that everyone is roughly aware of the protocol, but stated that it is less of a protocol act, but more about own insight. The nurse stated using the protocol in daily practice, without checking the paper version of the protocol. For stable patients on ward D3, the glucose levels are usually checked together with the Arterial Blood Gas measurements. This measurement is performed at least once every shift. However, if a high glucose level, i.e. >20, was measured, then the nurse wants to know the blood glucose level after one hour, in order to see the results of the medication. POC measurements are convenient for patients without an arterial line, or when a glucose measurement is required between two ABG measurements. On ward D3 there is no fixed schedule to which ABG measures are performed. Tests are performed according to the state of a patient. Depending on the blood sugar level, the amount of insulin is adapted. Insulin therapy is started with a dosage of one unit per hour. Administering a bolus is more or less a guess, however, on the ICU, there is room for adjustments. Overall the aim is to achieve a stable blood sugar level of 7.

Furthermore, the nurse stated that insight into the compliance of the strict glucose control protocol would be very relevant in initiating a refresher training. In practice the Novorapid perfusor is started when the glucose level is around 10, although it should be started when the glucose level is higher than 7. Moreover, the nurse stated that it was not really known why the protocol was implemented in the first place.

Survey:
The survey was completed by 7 of the 45 employees on ward D3. The average amount of work experience of the respondents equalled 8.7 years. Of the respondents, 57.14% was aware of the protocol and 28.57% stated that the protocol is still available on the ward. On the question: 'To what extent is the strict glucose control protocol followed, on a scale from 1 to 5?' responded 42.85% with 1 and the median was 2. These findings are in line with the findings obtained in the interviews. The average lower and upper target glucose level equal 3.71 and 8.21 respectively. The average glucose level for which insulin therapy is started equals 9.29. The additional comments on ward D3 were:

- "Before starting the Novorapid Perfusor, attention is paid to the specific case (reason for admission, diabetic history, feeding and medication). This is the reason nurses often act based on their own insight rather than the protocol."
- "Introducing a new protocol, would bring back motivation among the nursing staff to work again with the protocol. It would be beneficial if the doctors inserted a new guideline in ICIP."
- "Adherence to the protocol results in more hypoglycemic instances."

6.2.2 Ward E3

The care coordinator from ward E3 confirmed that the protocol under appendix 6.1 was implemented as a reaction to the Leuven studies. According to the care coordinator, the protocol is still used for regulating the blood glucose in patients. The protocol can be found in Odin; however, there is also a physical version of the protocol available behind the desk. Every patient on E3 receives a blood glucose measurement at their intake.

Thereafter, the blood glucose is measured on regular intervals. The patient's blood glucose level is checked at least once every shift (8 hours). However, if not stable, a blood glucose level is measured every 2 to 3 hours. Most blood glucose measurements on E3 are POC measurements. The only fixed measurement is every morning between 05:15 and 05:30, when multiple daily checks are performed including a blood glucose measurement. The Novorapid perfusor is started when the blood glucose level is above 7 mmol/L, and the Novorapid perfusor setting is adjusted according to the protocol. There is one exception for patients not really in need of intensive care, but who are placed on ward E3 for capacity reasons. If those patients do not have adequate oral intake, their blood glucose level can be high. According the protocol, insulin should be given. However, for these patients, is often decided to wait with insulin, for when these patients start to eat again, their blood glucose level returns to normal. Over the years the staff on E3 gathered a lot of experience working with the protocol. According to the care-coordinator, everyone works with the protocol and it does not give any problems. In case of difficulties, a doctor is consulted.

Survey:
The survey was completed by 12 of the 37 employees on ward E3. The average amount of work experience of the respondents equalled 18.67 years. All the respondents were aware of the protocol and everyone declared that the protocol is still available on the ward. On the question: 'To what extent is the strict glucose control protocol followed, on a scale from 1-5?' responded 58.33% with 4 and the median was 4. The average lower and upper target glucose level equal 4.29 and 7.46 respectively. The average glucose level for which insulin therapy is started equals 8.13. The survey results confirm that on ward E3, the strict glucose control protocol is still being adhered to. However, slightly less than the care coordinator believes. The additional comments on ward E3 were:

- "You have to look at the individual patient, some patients react really strongly to changes. You don't want to get a yoyo-effect.".
- "Nowadays, the protocol is slightly more widely interpreted. New insights advise that a glucose level below 10 can be pursued. I also take feeding and diabetes into consideration."
- "A high glucose level can be awaited in first instance, because the glucose level often decreases after a while, especially for non-diabetic patients."

6.2.3 Ward F3

Both the care coordinator and the nurse on F3 confirmed that the protocol under Appendix 6.2 was implemented about six years ago. Both know where the protocol is stored in Odin. The care coordinator mentioned the protocol was implemented because it would lead to a reduction in the amount of complications. After implementation of the protocol, the target glucose range was set higher due to too many hypoglycemic events. The target range is between 4.5 and 8. Furthermore, on ward F3, the strict glucose control protocol is no longer followed. The nurse is aware of the protocol, with the required time between measurements according to the protocol, and the required changes in the insulin dose. Insulin therapy is started when a blood glucose measurement returns a blood glucose level above 8. However, the measurements are not

performed according to the protocol. The main reason is that on F3 there is a fixed schedule for Arterial Blood Gas measurements. This schedule is as follows: once a patient enters the ward, a measurement is performed. The second measurement is performed 2 hours after the first measurement, the third measurement is performed 4 hours after the first measurement, the fourth measurement is performed 8 hours after the first measurement, and the fifth measurement is the morning after arrival on the ward. In general, patients are measured 5 times after arrival. Any further measurement depends on the glucose level and the fluctuation. Regulating blood glucose levels is done according to insight and experience of the medical staff. When insulin therapy is started, usually the perfusor is set to 1 unit per hour and decreased or increased by 1 additional unit depending on the glucose level. An insulin bolus is an exception, and is determined by the doctor.

Survey:

The survey was completed by 10 of the 37 employees on ward F3. The average amount of work experience of the respondents equalled 12.87 years. Of the respondents, 90% was aware of the protocol and 40% stated that the protocol is still available on the ward. On the question: 'To what extent is the strict glucose control protocol followed, on a scale from 1-5?' responded 50% with 3 and the median was 3. The average lower and upper target glucose level equal 4.10 and 8.40 respectively. The average glucose level for which insulin therapy is started equals 9.05.

	D3	**E3**	**F3**
Target level protocol	4,5 – 7,0 mmol/l	4,5 – 7,0 mmol/l	4,5 – 6,5 mmol/l
Target level staff interview	4,5 – 7,0 mmol/l	4,5 – 7,0 mmol/l	4,5 – 8,0 mmol/l
Target level survey	3.71 – 8.21 mmol/l	4.29 – 7.46 mmol/l	4.10 – 8.40 mmol/l
Threshold to start insulin therapy protocol	7,0 mmol/l	7,0 mmol/l	6,5 mmol/l
Threshold to start insulin therapy staff interview	10 mmol/l	7,0 mmol/l	8 mmol/l
Threshold to start insulin therapy survey	9.29 mmol/l	8.13 mmol/l	9.05 mmol/l
Duration to next measurement according to the protocol	• stable patient: - • unstable patient: - • hypoglycemia: Once every 10,15 or 30 minutes	• stable patient: - • unstable patient: - • hypoglycemia: Once every 10,15 or 30 minutes	• Stable patient: Once per 2 hours • Unstable patient: Once per hour • hypoglycemia: Once per 15 minutes
Duration to next measurement according to the staff	• Stable patient: Once per shift • Unstable patient: Once per hour	• Stable patient: Once every shift (8 hours) • Unstable patient: Once every 2-3 hours • hypoglycemia: Once every 10,15 or 30 minutes	• Stable patient: Fixed schedule for ABG measurements • Unstable patient: Fixed schedule ABG + additional measurements according to insight of the staff

Table 8: Protocol compared with interview and survey findings

6.3 Protocol compliance according to the data analysis

A method for finding compliance to the strict glucose control protocol is to apply the protocol to each glucose measurement and compare the result with the medication actually administered. Manual inspection is mainly done retrospectively by medical experts and is time consuming. The deployment of automatic or semi-automatic methods for systematic follow-up of compliance, based on the availability of proper data resources, would therefore be a great improvement in the field (Peleg, Keren, & Denekamp, 2007). This section focuses on a semi-automatic method for determining the compliance.

6.3.1 Data collection

This section describes where the data is stored and how it was retrieved. The study performed was a retrospective study on historical data. In the MUMC, several information systems are available for processes. The leading system within the MUMC is the SAP system. However, the SAP system is not able to store large amounts of patient specific medical information generated in the ICU's. Therefore, the ICU has its own Patient Data Management System (PDMS). The PDMS can be seen as a Clinical Support System (CSS) that provides assistance with clinical decision-making tasks. The PDMS helps to represent and store the medical data of the patients. More or less all the electronic devices that are connected to the patient generate data, which is stored at the PDMS. The PDMS can, therefore, be compared with a data warehouse containing all the treatment information of the patients. In the ICU department of MUMC+, the system currently in use is the Intellispace Critical Care and Anesthesia (ICCA) system by Philips. This system is known as ICIP IC as it is installed with this name. Each bed on the ICU is connected to the ICCA system. Therefore, all data generated on the patients can easily be saved and visualized on the monitor next to the bed. The data were extracted from the ICIP IC by the authorized IT specialist.

Since medical data are sensitive to privacy issues, the data set was anonymous. Instead of names, an anonymized patient ID was used.

For performing the analysis, data regarding the glucose measurements (arterial and point-of-care), and the medication settings (Novorapid perfusor, insulin bolus and glucose bolus) are required. Initially, the data was provided in multiple files per type of intervention, per ward, per year. Appendix 8.1 denotes a graphical representation of the data structure as provided.

6.3.2 Data pre-processing

Data pre-processing is an important step in the data mining process. This section describes the processing performed on the raw data to prepare it for analysis. The pre-processing phase includes removing out-of-range values, impossible data combinations, missing values and duplications. Also variable names were standardized over the multiple files.

The initial large data sets concerning both types of glucose measurements were merged into new files 'glucose measurements' per ward per year. POCT glucose measurements

were not merged, since these glucose measurements occur in the operating rooms. The initial large data sets concerning the different medication settings were merged into new files 'medication' per ward per year.

Thereafter, these datasets were split into hospitalization number specific datasets for glucose measurements and medication settings. After this transformation, new files were created for hospitalization numbers where both glucose measurement data and relevant medication settings were available. All data sets containing one or more observations of a glucose level higher than 30, were checked manually for the presence of diabetic ketoacidosis. Patients with diabetic ketoacidosis and hyperosmolar non-ketoacidotic hyperglycemic patients were excluded. Appendix 8.2 denotes a graphical representation of the data structure after pre-processing. For 2014, this resulted in 157, 138 and 499 cases on ward D3, E3 and F3 respectively. For 2015, this resulted in 157, 150 and 425 cases on ward D3, E3 and F3 respectively.

Each glucose measurement was coupled to a medication setting. This coupling process occurred as follows. For each glucose measurement the corresponding time is selected. Thereafter, the first medication setting is searched that was logged in ICIP IC in the interval starting at the moment the glucose measurement occurred up to one hour after the measurement, as this medication setting should reflect the reaction of the nurses to a glucose measurement. If there was no medication setting available in this time interval, the medication setting remained equal to the last known medication setting. Note, that boluses occurring in the last medication settings were set to zero in case there was no new medication setting available in the interval.

6.3.3 Descriptive statistics

Descriptive statistics were performed on the data. These statistics can be found in the statistics overview (Table 11). The blood glucose level range denoting the minimum and the maximum blood glucose level are similar in all wards. It is remarkable to see that glucose levels of around 30 are occurring. Potential reasons include stress, the administering of corticosteroids, or a history in diabetes type 2 which is not addressed appropriately. Comparing the statistics of ward D3, E3, F3 it can be concluded that over both years, ward D3 has the lowest mean glucose level (7.87). However, the mean glucose level was only slightly higher on ward D3 (7.90) and ward E3 (7.91). The standard deviation of the glucose level was the lowest on ward F3 (2.52), compared to ward D3 (2.81) and ward E3 (2.65). A potential reason could be that on ward F3 blood measurements are performed more often, on average once every 269 minutes. On ward D3 there is a glucose measurement once every 342 minutes on average and on ward E3 once every 312 minutes on average. Furthermore, the standard deviation of the duration between measurements is lower on ward F3 (222) compared to ward D3 (295) and ward E3 (343). The smaller standard deviation of the duration between measurements denotes a more constant duration between measurements. Since blood glucose levels on ward F3 are measured more often and constantly, the nursing staff is better able to reduce the number of hyperglycemic instances. Ward F3 has the lowest percentage of hyperglycemic instances (8.20%), compared to ward D3 (10.40%) and ward E3 (9.22%).

However, there is also a slightly higher percentage of hypoglycemic instances (0.21%) compared to ward D3 (0.18%) and ward E3 (0.15%).

In the NICE-SUGAR study, the conventional control group had a mean glucose level of 7.99. The intensive control group had a mean glucose level of 6.38. The ICU wards performed similarly to the conventional control group in the NICE-SUGAR study, with mean glucose levels of 7.87, 7.90 and 7.91 for wards D3, E3 and F3. The NICE-SUGAR study found severe hypoglycemia (< 2.2 mmol/L) in 6.8% of the patients in the intensive-control group and in 0.5% of the patients in the conventional-control group. Ward D3 and E3 have a high percentage of patients in which severe hypoglycemia was found, respectively 5.29 and 5.96%. Ward F3 performs better, 2.92%.

Defining glycemic variability as the standard deviation of the mean of all blood glucose measurements has fallen out of favor, as strongly different glycemic patterns can generate identical mean glucose and standard deviations (Clain, Ramar, & Surani, 2015). In other words, solely looking at the standard deviation, does not provide enough information. Therefore, other measures for glycemic variability were searched. In literature, there is no golden standard for glycemic variability. In consultation with the MUMC+ supervisors, the following measures were chosen: mean absolute glucose change and the variability index. The variability index denotes the mean of absolute difference of sequential blood glucose levels divided by the difference in blood glucose level measurement time (in hours). Ward F3 obtains the lowest variability index (0.68) compared to ward D3 (0.91) and ward E3 (0.75). I.e. on average, the absolute blood glucose level of a patient on ward D3 changes with 0.68 every hour. The mean absolute glucose change is similar in all wards.

6.3.4 Protocol compliance according to the data analysis

In order to process a comparison between the dataset and the protocols, the protocols were manually converted to a computer processable format. The rules of the protocol were applied to the dataset using Matlab queries. For each glucose measurement, Matlab automatically determined the required change in medication setting. In this protocol compliance analysis, there was focused on whether the medication settings were changed according to the protocol. The prescriptions on the required time to the next measurement are not taken into consideration.

In general, the protocols exist out of three different parts: the 'startup medication dosing scheme', 'regular dosing scheme', and the 'hypoglucose policy'. The protocol on ward D3/E3 (appendix 1.1) for example prescribes that the startup medication dosing scheme should start when the blood glucose level is higher than 7.0 and the medication settings in the startup medication dosing scheme are only based on the current blood glucose value. The first glucose measurement in every (patient-specific) data set is checked for compliance to the startup medication dosing scheme. The following glucose measurements are checked according to the regular dosing scheme. The regular dosing scheme determines first whether the glucose measurement has decreased by more than 30%, or whether the glucose measurement has decreased by less than 30% or has increased, compared to the previous glucose measurement. Thereafter, the new

medication settings are determined based upon the current glucose level. Furthermore, the protocol prescribes that the hypoglucose policy should start whenever the glucose measure is below 3.5.

As described in the data pre-processing section, each row in the data set refers to a glucose measurement and its consequences in the medication settings. Protocol compliance was calculated in Matlab and was performed as follows: both protocols, for D3 and E3 and for F3 were expressed by conditional constructs. The protocols were transformed into sets of IF-THEN-ELSE statements. For each glucose measurement the corresponding set of IF-THEN-ELSE statements determined the required medication settings conform protocol. The required medication settings were then compared to the actual medication settings for each case. If all the medication settings (Novorapid perfusor, glucose boluses and insulin boluses) matched, there was compliance to the protocol. The variable ComplianceCheckTotal is set to one in order to denote compliance and to zero for non-compliance. In general protocol compliance is defined as the percentage of glucose measurements for which the actual medication settings equal the medication settings prescribed by the protocol, or the percentage of rows for which the variable ComplianceCheckTotal equals 1.

An overview of the compliance to the protocol according to the data analysis is presented in Table 9. The highest compliance to the protocol was on ward D3, compared to ward E3. Furthermore, on ward E3 there was the highest compliance to the protocol in hypoglycemic instances. In addition, the protocol compliance to the protocol from ward D3/E3 was also calculated on the data from ward F3 and vice versa. The compliance to the protocol of F3 on ward D3 equals 25.53%. The compliance to the protocol of F3 on ward E3 equals 22.17%. The compliance to the protocol of D3/E3 on ward F3 equals 32.07%.

Ward	**D3**	**E3**	**F3**
Overall compliance (%)	37.67	33.01	22.78
Compliance hypoglycemic instances (%)	33.33	42.86	11.11
Compliance to other protocol (%)	25.53	22.17	32.07
Fuzzy compliance (%)	78.80	78.47	55.59

Table 9: Compliance according to the data analysis

6.3.5 Fuzzy protocol compliance according to the data analysis

As described in the background chapter, fuzzy logic uses fuzzy sets to represent gradualness. Fuzzy logic can, therefore, represent bipolarity. Is the distinction between compliance and non-compliance really black or white? To answer this question, membership functions have been created for the compliance of the Novorapid perfusor, insulin bolus and glucose bolus settings. According to the MUMC+ supervisors, compliance to the protocol can be broadly interpreted. The difference between accepted deviation and non-accepted deviation is gradual, and can, therefore, be represented by membership functions (MF). Table 10 presents an overview of the boundaries for accepted and non-accepted deviation. These boundaries are used for creating the membership functions (figure 10).

Medication	Fully Accepted Deviation	Fully not Accepted Deviation
Novorapid perfusor	1 unit/hour	2 units/hour
Insulin bolus	2 units	3 units
Glucose bolus	10 mL	15 mL

Table 10: Accepted and not accepted deviation from the protocol in changes to medication settings

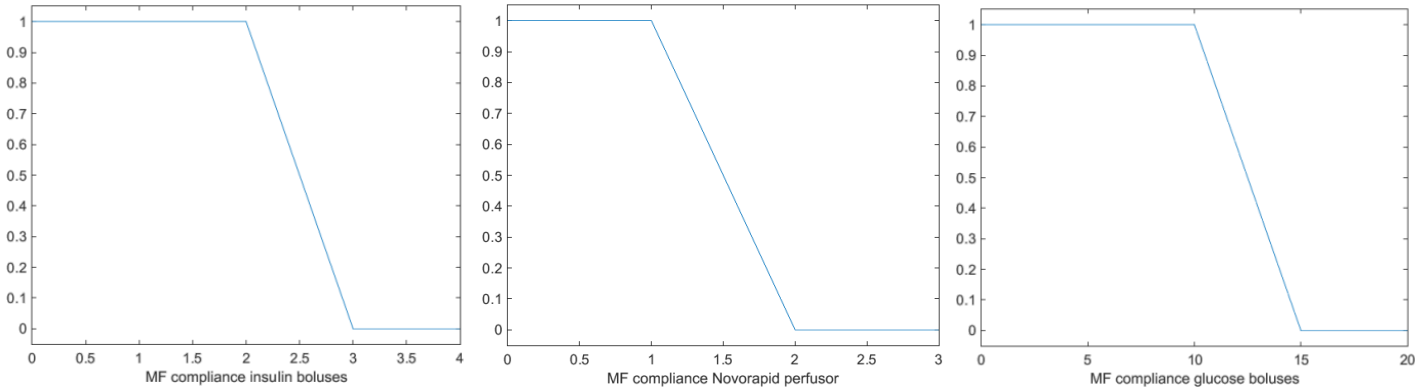


Figure 10: Membership functions Novorapid perfusor, insulin boluses, glucose boluses

The membership functions provide a broader interpretation of compliance. For every glucose measurement, the membership was calculated to the protocol. A membership of 1 denotes full compliance; a membership of 0 denotes non-compliance. The absolute deviations from the change in the settings of the Novorapid perfusor, insulin boluses and glucose boluses, determine the membership to protocol compliance. For instance, for the membership function of the Novorapid perfusor, an absolute deviation of 1 unit/hour is fully accepted, the membership is therefore 1. An absolute deviation of more than 2 units/hour is not accepted, the membership is therefore 0. An absolute deviation between 1 and 2 units/hour is partially accepted, the membership is expressed by the membership function. I.e. if according to the protocol, a change in the Novorapid perfusor of +2 was required, and the actual change was +0.5, the deviation then is 1.5, which is corresponding to a membership of 0.5. The overall membership to protocol compliance for each glucose measurement was calculated as the product of the three membership functions. The mean of the fuzzy compliance for all glucose measurements denotes the fuzzy compliance per ward. Over 2014 and 2015, the fuzzy compliances on ward D3, E3 and F3 were 78.80%, 78.47 and 55.59% respectively.

6.4 Conclusions and discussion

The interviews pointed out that on wards D3 and F3, regulating the blood glucose level is less of a protocol act, but more about personal and professional insight of the individual nurses. The main reason is that the nursing staff prefers to pay attention to the specific case. Also the fear of hypoglycemic instances led to the abandonment of the protocol on wards D3 and F3. However, according to the survey, the awareness of the protocol is higher on ward F3 (90%) compared to ward D3 (57.14%). In contrast to wards

D3 and F3, the protocol is used for regulating the blood glucose level on ward E3. On this ward all the employees (100%) are aware of the protocol. Some of the employees on ward E3 interpret the protocol slightly wider, taking also the individual patient into account. According to the survey, the threshold to start insulin therapy according to the employees, equals 9.29, 8.13 and 9.05 for wards D3, E3 and F3 respectively, while the protocol prescribes a threshold of 7.0 mmol/L for wards D3/E3 and 6.5 mmol/L for ward F3. The threshold is the lowest on ward E3. This confirms that the staff of ward E3 is more aware of the protocol and starts insulin therapy more timely. However, the higher awareness of the protocol does not result into a lower mean blood glucose level. The mean blood glucose levels are more or less equal on all wards.

In contrast to the interviews and the survey findings, the highest compliance to the protocol (according the data analysis) was on ward D3 (37.67%), compared to ward E3 (33.01%) and F3 (22.78%). However, on ward E3 there was the highest compliance to the protocol in hypoglycemic instances (42.86%), compared to ward D3 (33.33%) and ward F3 (11.11%). The strict protocol compliance is too low. The nursing staff has to decide either to comply to the medical protocol, to update the protocol and comply to the protocol, or to dismiss the protocol.

The compliances to the other version of the protocol (implemented on another ward) were also calculated. The compliance to the protocol of F3 on ward D3 equals 25.53%. The compliance to the protocol of F3 on ward E3 equals 22.17%. The compliance to the protocol of D3/E3 on ward F3 equals 32%. Because the compliances are so similar on each ward, a future version of the protocol can be used on all wards.

According to the MUMC+ supervisors, the compliance of the protocol can be more broadly interpreted. Therefore, fuzzy protocol compliance was developed and used to calculate compliance while allowing deviations from the protocol. The fuzzy compliances on ward D3, E3 and F3 were 78.80%, 78.47% and 55.59% respectively. Considering the fuzzy compliances, glucose control is performed reasonably well, with room for improvement.

Comparing the number of hypoglycemic events at the MUMC+ with the literature, confirms the room for improvement The NICE-SUGAR study found severe hypoglycemia (< 2.2 mmol/L) in 6.8% of the patients in the intensive-control group and in 0.5% of the patients in the conventional-control group. Ward D3 and E3 have a high percentage of patients in which severe hypoglycemia was found, respectively 5.29 and 5.96%. Ward F3 performs better, 2.92%. In comparison to the conventional control-control group (blood glucose <10 mmol/L) of the NICE-SUGAR study, the number of patients with instances of severe hypoglycemic events is too high on all wards. This leaves room for improvement.

The next chapters are aimed on extracting rules for glucose regulation automatically. The deviating rules from the protocol will provide insight into where the deviations take place. These insights should contribute to the improvement of glucose control in the ICU wards of MUMC+.

		D3			E3			F3		
Statistics	*Year* # *Files* # *Glucose measurements*	*2014* 153 5983	*2015* 149 7005	*Both* 302 12988	*2014* 136 7335	*2015* 149 6870	*Both* 285 14205	*2014* 499 9285	*2015* 425 8049	*Both* 924 17344
Range glucose level (mmol/L)		0.6 – 30.1	1.1 – 29.9	0.6 – 30.1	0.6 – 27.9	0.6 – 29.9	0.6 – 29.9	1.2 – 29.7	0.8 – 31.1	0.8 – 31.1
Median glucose level (mmol/L)		7.4	7.2	7.3	7.4	7.5	7.5	7.5	7.5	7.5
Inter quartile range glucose level (mmol/L)		2.6	2.6	2.6	2.5	2.7	2.6	2.4	2.4	2.4
Mean glucose level (mmol/L)		7.8171	7.9137	7.8692	7.8248	7.9706	7.8953	7.8879	7.9315	7.9082
Standard deviation glucose level (mmol/L)		2.6325	2.9454	2.8059	2.5992	2.6929	2.6459	2.4840	2.5569	2.5181
Mean duration between measurements (hours)		5.5951	5.7810	5.6953	5.3065	5.0983	5.2058	4.4689	4.4947	4.4809
Standard deviation duration between measurements (hours)		4.5141	5.2614	4.9319	6.5221	4.6990	5.7143	3.0198	4.3616	3.6982
Number of hypoglycemic instances (<2.2 mmol/L)		19	5	24	7	14	21	16	20	36
Percentage hypoglycemic instances (%)		0.32	0.07	0.18	0.10	0.20	0.15	0.17	0.25	0.21

Number of hyperglycemic instances (>11 mmol/L)	557	794	1351	633	676	1309	725	697	1422
Percentage hyperglycemic instances (%)	9.31	11.33	10.40	8.63	9.22	9.22	7.81	8.66	8.20
# patients with hypoglycemic instance	12	4	16	7	10	17	12	15	27
Percentage patients with hypoglycemic instance (%)	7.84	2.68	5.29	5.15	6.71	5.96	2.40	3.53	2.92
Compliance to protocol (%)	35.82	39.14	37.67	33.51	32.61	33.01	23.09	22.36	22.78
Compliance to protocol in hypoglycemic instances (<2.2 mmol/L) (%)	31.58	40.00	33.33	42.86	42.86	42.86	12.50	10.00	11.11
Variability Index* $\frac{(mmol/liter)}{h} * N^{-1}$	0.9602	0.8599	0.9106	0.6866	0.8173	0.7546	0.5858	0.6944	0.6829
Mean absolute glucose change (mmol/L)	1.33	1.34	1.33	1.34	1.29	1.32	1.41	1.37	1.39
Compliance to other protocol (%)	23.23	27.49	25.53	23.16	21.11	22.17	32.53	31.54	32.07
Fuzzy compliance to protocol (%)	80.07	77.59	78.80	78.94	78.18	78.47	56.60	54.41	55.59

Table 11: Statistics overview

* Variability index ($\sum \frac{|X_{n+1}-X_n|}{|T_{n+1}-T_n|} * N^{-1}$)

7. Automatic protocol extraction

The previous chapter concluded that there is room for improvement regarding the strict glucose control protocol in the ICU wards. It is very interesting to discover patterns in the actions of nurses regarding glucose control. Without looking at the protocol, can we define rules according to which the glucose level is regulated according to the data? This chapter provides an answer to sub-research question 4, which was defined as follows:

"If the strict glucose protocol is not followed (completely), are there any unwritten rules for glucose control?"

In this chapter two types of rules are extracted: rules for determining the time between the current and the next blood glucose measurement and rules for determining the amount of medication, regarding the Novorapid perfusor and glucose boluses. Rules for determining the amount of insulin bolus are omitted, as data regarding insulin boluses was missing. The aim of this chapter is to provide insight of the process of obtaining the rules and to give an overview of the extracted rules. The extracted rules are used in the next chapter to locate deviations from the protocol.

For the rule extraction two methods are used: rule extraction from a decision tree and rule extraction from a fuzzy inference system. The chapter is, therefore, divided into two sections, one for each method. These sections are divided into subsections per ward. The first decision tree or fuzzy inference system on ward D3 is an example of how the process of obtaining rules for glucose control from the data works in both methods. They are, therefore, explained more extensively. For the remaining decision trees or fuzzy inference systems only the results are shown. The results will be discussed per rule extraction method in the concluding sections (7.1.4 and 7.2.4). Rules are only extracted for the 'continuation schedule' of the glucose control protocol, excluding the 'startup medication dosing scheme'.

Decision trees in Matlab

The decision trees and fuzzy inference systems were created with Matlab. In a decision tree in Matlab, a node with the function of a splitting criterion is represented by a triangle (Δ) and a leaf node is represented by a dot. For creating a classification tree the function fitctree is used. Fitctree in Matlab is based on techniques from the book Classification & Regression trees (Breiman, Friedman, Stone, & Olshen, 1984) and uses cost-complexity pruning as pruning method.

7.1 Decision tree rule extraction

7.1.1 Decision tree rule extraction D3

Decision tree rule extraction for determining the required duration until the next blood glucose measurement (D3)

The decision tree classifies the required time until the next blood glucose measurement using the current measurement and the change in the glucose level compared to the previous blood glucose measurement. The tree provides insight into how the medical

team of ward D3 determines the accepted duration until the next measurement. Since this is the first decision tree, the process of obtaining it is explained in detail.

The dependent variable, in this case the time to next measurement variable, was transformed into a categorical variable (0 – 30 minutes: 1, 30 – 60 minutes: 2, etc.). This categorical variable was merged with the two independent variables into a new data set. The default decision tree is created on all data for ward D3 in 2014 and 2015. Since the aim is on the continuation schedule, the first glucose measurement (or row) was excluded for every unique hospitalization number. The process of turning this data set into valuable insights is explained below and is visualized in Figure 11.

Firstly, the data set is being split using stratified holdout sampling. Stratified holdout sampling is used to guarantee that each class of the dependent variable is equally represented in both the test set as well as the train set. The class representation from the original data set is maintained. Thereafter, the training set needs to be balanced. The main motivation for the data balancing is that classifiers are typically more sensitive to detect the majority class. Building a decision tree on an imbalanced data set would result in a model that tends too much to the largest class. Classes that are less represented in the dataset are likely to be omitted in the pruned decision tree, meaning that there are no rules for these classes. Without data balancing, rules regarding exceptions, such as hypoglycemic events are not taken into consideration. Undersampling was used for balancing the data sample. This technique randomly selects observations from each class. The number of observations is constrained by a predefined maximum or the number of observations available in a class. Table 11 provides an overview of the class frequencies in the train set. The predefined maximum number of observations per class was set to 200 in discussion with a professional in the field of data mining. In the balanced train set, all the classes contained out of 200 observations except for class 2. The default decision tree, trained on the balanced train set, can be seen in figure 12.

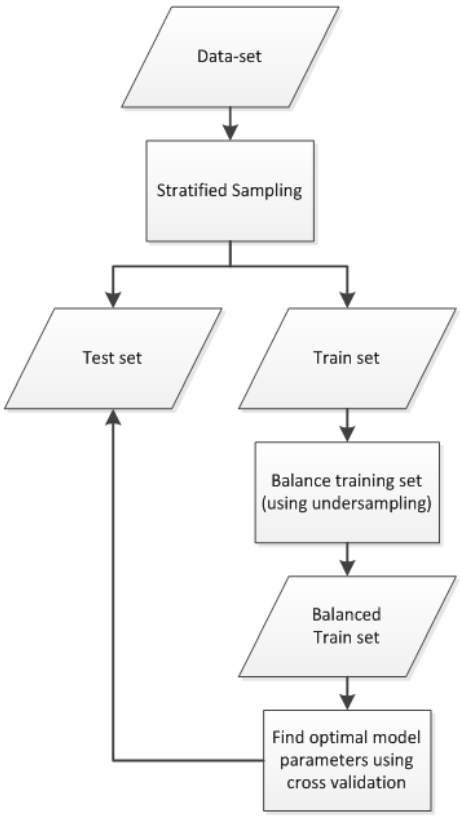


Figure 11: Model extraction process

Class	1	2	3	4	5	6	7	8	9
Time interval	0-30	30-60	60-90	90-120	120-150	150-180	180-210	210-240	>240
# instances	319	141	269	427	528	539	575	654	6699

Table 12: Classes and frequencies time to next measurement (D3)

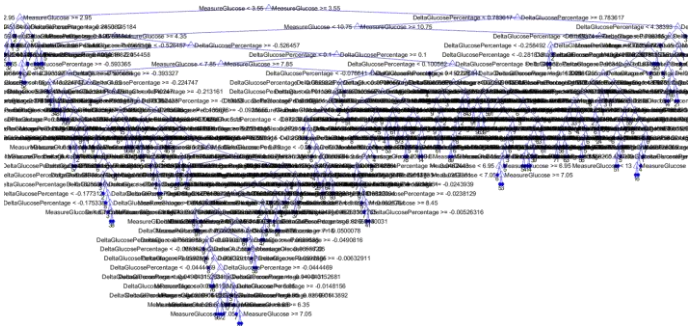


Figure 12: Default decision tree time to next measurement (D3)

Controlling the depth of the tree

As described in the background chapter, a deep tree with many leaves is usually highly accurate on the training data. However, the same level of accuracy is often not reached on the independent test set. A tree with many leaves tends to overfit the training data. By making the three shallower it can become more robust. Furthermore, the default decision tree, results in many unclear rules. Pruning the tree increases its interpretability. Cross validation was used to determine the optimal pruning level.

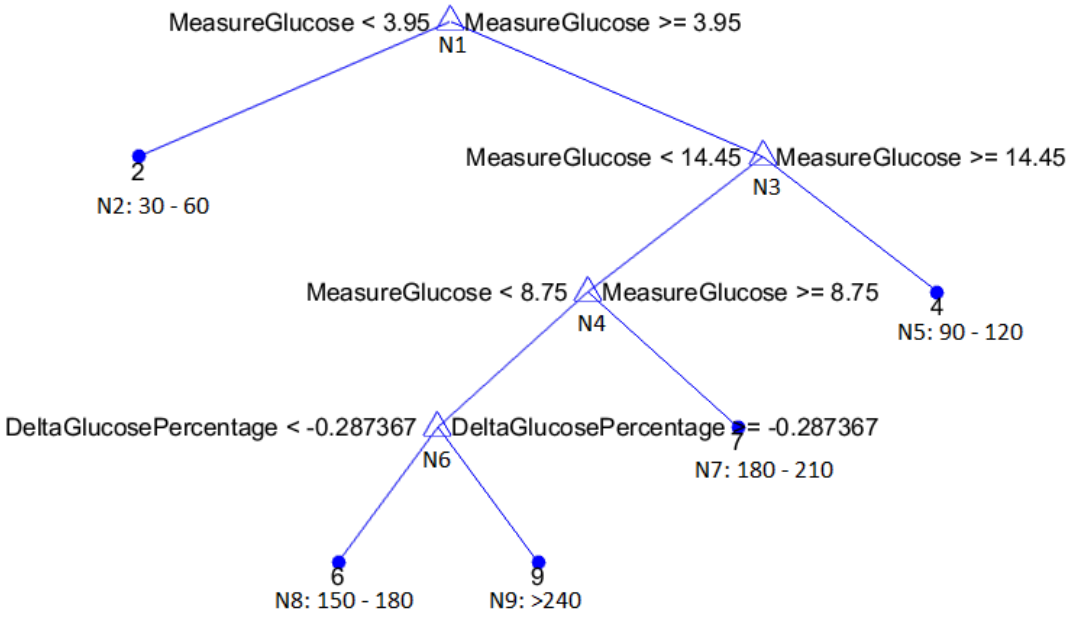


Figure 13: Decision tree duration to next measurement (D3)

The pruned decision tree is a graphical representation from the most important decision rules. In Figure 13, the numbers of the nodes are depicted by the N-numbers. Matlab assigns these numbers always in the same order, top-down and for each row from left to right.

The decision tree is converted into a set of rules by creating one rule for each path from the root to a leaf node. A logical AND operator is used for each splitting criterion along a given path. The leaf node forms the rule consequent ("THEN"), since the leaf node in a decision tree holds the class prediction. For leaf nodes, the final classes are written behind the node number, i.e. node 2 receives the class 30 – 60 minutes. These final

classes correspond to the classes created during the classification of the dependent variable. Table 13 provides an overview of the rules that were extracted. Interpretation of the delta percentage glucose becomes clear after the following example:

< -28.7 The glucose level decreased by more than 28.7% (since delta percentage glucose is smaller than -28.7)

> -28.7 The glucose level decreased by less than 28.7% or increased (since delta percentage glucose is smaller than -28.7)

Rules					Balanced train set			Test set		
								Accuracy: 49.90		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
N2	2	<3.95		30 – 60	4.31	32.00	23.90	2.76	11.43	10.05
N5	4	>14.45		90 – 120	6.55	21.93	10.44	2.92	12.16	7.98
N7	7	[8.75-14.45]		180 -210	26.94	14.93	3.44	21.96	6.46	0.79
N8	6	[3.95-8.75]	<-28.7	150 – 180	4.88	21.18	9.69	4.73	2.50	-2.78
N9	9	[3.95-8.75]	>-28.7	> 240	57.32	15.43	3.94	67.64	70.51	4.49

Table 13: Extracted rules for duration to next glucose measurement (D3)

In general, the *support* for a particular decision tree rule refers to the proportion of records in the data that rest in that particular terminal leaf node (Larose, 2005). The *confidence* of the rule refers to the proportion of records in the leaf node for which the decision rule is true (Larose, 2005). These performance measures are usually calculated on the train set only. In this research, both performance measures were calculated for both the train set as well as the test set. The interpretation however is slightly different and is therefore explained first.

Performance measures for balanced train set

For the balanced train set, the support was obtained from the Node probability table (Table 14). The node probability function in Matlab returns for every node the proportion of observations from the original data set satisfying the conditions for the node. Due to the pruning of the tree, the final nodes consist of cases from multiple classes. For example, the support for node 2 equals 4.31%. This means that 4.31% of the entire balanced train set conforms to the antecedent of the rule corresponding to node 2.

	1	2	3	4	5	6	7	8	9
1	1.0000	0.0431	0.9569	0.8914	0.0655	0.6221	0.2694	0.0488	0.5732

Table 14: Node probability

The confidence in a rule in the balanced train set can be obtained from the class probability matrix (Table 15). The rows represent a specific node in the decision tree and the columns denote the multiple classes. The class probability matrix gives for every

node the estimated class probabilities for each class. For example, if an observation satisfies the conditions of node 2, there is a 32.00% probability that the observations belong to class 2. To determine which rules are better not used, the column confidence difference was added for both the train set as well as the test. Confidence difference in the balanced train set equals the difference between the confidence of the rule and the prior proportion of the predicted class in the balanced train set.

	1	2	3	4	5	6	7	8	9
1	0.1149	0.0810	0.1149	0.1149	0.1149	0.1149	0.1149	0.1149	0.1149
2	0.1867	0.3200	0.2000	0.1200	0.0667	0.0400	0.0267	0.0267	0.0133
3	0.1116	0.0702	0.1110	0.1146	0.1170	0.1182	0.1188	0.1188	0.1194
4	0.1115	0.0644	0.1076	0.1070	0.1153	0.1205	0.1231	0.1231	0.1276
5	0.1140	0.1491	0.1579	0.2193	0.1404	0.0877	0.0614	0.0614	0.0088
6	0.1043	0.0720	0.1016	0.1062	0.1173	0.1136	0.1117	0.1256	0.1477
7	0.1279	0.0469	0.1215	0.1087	0.1109	0.1365	0.1493	0.1173	0.0810
8	0.1294	0.1176	0.1412	0.0824	0.1176	0.2118	0.0706	0.0588	0.0706
9	0.1022	0.0681	0.0982	0.1082	0.1172	0.1052	0.1152	0.1313	0.1543

Table 15: Class probability

Performance measures for test set

The support of a rule applied in the test set is the proportion of the test set that was classified by a particular rule: it is a representation of how often a rule is applied in the test set. The confidence of a rule applied in the test denotes the percentage of observations that were classified correctly using a particular rule.

A rule with a confidence of 64% might seem valid at first sight. However, one needs to take into account the prior proportion of the predicted class. Applying a rule for which the prior proportion is higher than the confidence of the rule, reduces the probability of randomly selecting the correct predicted class. In this case, randomly selecting a class provides a better prediction than applying the decision rule. The confidence difference equals the difference between the confidence of the rule and the prior proportion of the predicted class in the test set. Rules are only valid if the confidence difference is positive. The fourth rule has a negative confidence difference in the test set and can therefore be ignored. The overall model performance is denoted by the accuracy. The accuracy of the model is the percentage of observations in the test set that were correctly classified with the pruned decision tree. This first decision tree obtains an accuracy of 49.90%.

Decision tree rule extraction for determining the required change in the Novorapid perfusor setting (D3)

This decision tree classifies the change in the setting of the Novorapid perfusor using the current glucose measurement and the change in the glucose level compared to the previous blood glucose measurement. The extracted rules provide insight into how the medical team of ward D3 determines the change in the Novorapid perfusor setting. The

process of obtaining the rules is similar to the decision tree for determining the required time until the next glucose measurement. For this reason, only the extracted rules are shown for this and the remaining decision trees. For every set of rules, the process of obtaining it, can be found under Appendix 10. The extracted rules for changing the Novorapid perfusor setting are in Table 16.

Rules					Balanced train set			Test set		
								Accuracy: 47.27%		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then Novorapid perfusor**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
5	1	<8.15	>-10.6	Keep current	25.22	24.94	12.23	45.38	93.55	11.14
7	12	>12.55		+2	9.78	17.53	4.82	5.14	14.62	13.03
8	2	<3.25	<-10.6	Stop perfusor	1.65	65.38	54.2	0.91	26.09	24.39
9	7	[3.25-8.15]	<-10.6	-1	27.76	23.34	11.14	20.40	3.88	1.94
11	10	[9.65-12.55]		+1	17.47	28.73	16.02	11.30	14.69	9.55
12	10	[8.15-9.65]	<-10.9	+1	3.68	34.48	21.77	2.73	14.49	9.35
13	9	[8.15-9.65]	>-10.9	+.5	14.42	37.44	24.73	14.15	6.98	4.14

Table 16: Extracted rules for Novorapid perfusor setting (D3)

Decision tree rule extraction for determining the next glucose bolus (D3)

This decision tree classifies whether or not a glucose bolus should be administered using the current glucose measurement and the change in the glucose level comparing to the previous blood glucose measurement. The extracted rules (Table 17) provide insight into how the medical team of ward D3 administers glucose boluses.

Rules					Balanced train set			Test set		
								Accuracy: 90.38		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then glucose bolus (ml)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
3	1	>5.25		0	50	63.33	30	90.30	99.87	0.0046
4	11	<2.65		50	15	88.89	55.56	.43	27.27	26.92
5	5	[2.65-5.25]		20	35	57.14	33.81	9.26	0.85	0.73

Table 17: Extracted rules for glucose bolus (D3)

Decision tree rule extraction for determining the next insulin bolus

Unfortunately, as is to be seen in Table 18, the number of insulin boluses that were captured in the ICIP IC system is very low. The reason for this is that insulin boluses are often saved as a remark under the current medication task in ICIP IC. This data was not delivered, and therefore insulin boluses could not be considered in this research.

Description	Class	#	%
0 unit bolus	1	10133	99.82
1 unit bolus	2	1	0.01
2 unit bolus	3	0	0.00
3 unit bolus	4	4	0.04
4 unit bolus	5	0	0.00
5 unit bolus	6	0	0.00
6 unit bolus	7	1	0.01

Table 18: Classes and frequencies insulin bolus

7.1.2 Decision tree rule extraction E3

This section provides an overview of the extracted rules for glucose control on ward E3. Again, a similar rule extraction process was used. An overview of the extracted rules for determining the required duration to the next measurement (Table 19) is presented first, followed by the extracted rules for determining the Novorapid perfusor setting (Table 20) and the glucose boluses (Table 21). Due to data constraints, no rules overview is available for determining the insulin boluses.

Rules					Balanced train set			Test set		
								Accuracy: 46.52		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
2	2	<2.95		30 – 60	1.86	44.90	36.22	0.57	37.50	35.49
5	4	>9.95		90 – 120	19.14	15.11	3.69	14.83	8.47	2.19
6	3	[2.95-5.35]		60 – 90	12.52	18.84	7.42	10.81	5.32	1.65
7	9	[5.35-9.95]		> 240	66.48	14.31	2.89	73.78	60.27	5.60

Table 19: Extracted rules for duration to next glucose measurement (E3)

Rules					Balanced train set			Test set		
								Accuracy: 33.14%		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then Novorapid perfusor**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
4	2	<4.45		Stop perfusor	7.42	52.42	40.45	4.41	18.03	15.86
7	12	>10.35 -		+2	20.41	39.30	27.33	13.34	10.57	8.51
8	7	[4.45 7.95]	<-15.8	-1	20.71	28.90	16.93	11.42	10.76	8.23
10	9	[7.95 9.25]		+0.5	15.98	27.72	15.75	18.36	4.53	2.25
11	10	[9.25 10.35]		+1	11.25	34.04	22.07	8.64	15.90	11.06
12	8	[4.45 5.95]	>-15.8	-0.5	7.90	31.06	20.53	9.94	3.27	1.72
14	1	[5.95 7.95]	[-15.8 17.8]	Maintain	12.27	40.49	28.52	28.19	95.51	13.58
15	2	[5.95 7.95]	>17.8	Stop perfusor	4.07	23.53	11.56	5.71	4.43	2.26

Table 20: Extracted rules for Novorapid perfusor setting (E3)

Rules					Balanced train set			Test set		
								Accuracy: 96.41		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then glucose bolus (ml)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
3	1	>4.35		0	39.13	74.07	45.08	96.37	99.89	0.50
4	11	<2.95		50	40.58	57.14	28.15	0.61	11.76	11.51
5	5	[2.95-4.35]		20	20.29	78.57	49.58	3.02	2.38	2.13

Table 21: Extracted rules for glucose bolus (E3)

7.1.3 Decision tree rule extraction F3

This section provides an overview of the extracted rules for glucose control on ward F3. Again, a similar rule extraction process was used. An overview of the extracted rules for determining the required duration to the next measurement (Table 22) is presented first, followed by the extracted rules for determining the Novorapid perfusor setting (Table 23) and the glucose boluses (Table 24). Due to data constraints, no rules overview is available for determining the insulin boluses.

Rules					Balanced train set			Test set		
								Accuracy: 40.15		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
2	2	<3.55		30 – 60	1.72	31.82	25.53	1.31	9.30	8.08
6	9	[3.55-8.15]		> 240	55.45	14.86	2.97	61.29	61.28	4.41
8	3	> 9.65	< 27.7%	60 – 90	14.76	16.67	4.96	11.05	4.63	1.56
9	1	> 9.65	> 27.7%	0 – 30	6.17	20.25	8.54	4.78	10.83	4.74
10	6	[8.15-9.65]	< 25.2%	150 – 180	18.08	17.49	5.78	17.67	6.55	0.34
11	4	[8.15-9.65]	> 25.2%	90 – 120	3.83	21.43	9.72	3.78	7.26	0.25

Table 22: Extracted rules for duration to next glucose measurement (F3)

Rules					Balanced train set			Test set		
								Accuracy: 38.49%		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then Novorapid perfusor**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
6	9	[8.05 9.45]		+0.5	21.18	30.00	18.85	20.45	6.28	3.68
8	2	<4.25	<18.1	Stop perfusor	2.51	17.34	6.19	1.53	44.00	39.54
9	7	[4.25 8.05]	<18.1	-1	22.30	19.75	8.6	11.34	12.40	9.46
10	2	<5.15	>18.1	Stop perfusor	2.68	45.83	34.68	3.21	7.62	3.16
12	12	[9.45 15.75]		+2	21.63	32.73	21.58	16.91	9.04	6.57
13	14	>15.75		+3 or more	2.23	47.50	43.93	1.59	13.46	12.97
14	8	[5.15 8.05]	[-18.1 -9.2]	-0.5	10.09	30.94	19.79	8.87	5.52	3.41
15	1	[5.15 8.05]	>-9.2	Maintain	17.39	30.13	18.98	36.11	90.43	16.48

Table 23: Extracted rules for Novorapid perfusor setting (F3)

Rules					Balanced train set			Test set		
								Accuracy: 84.31		
Node	**Class**	**If glucose level (mmol/L)**	**and delta percentage glucose level (%)**	**then glucose bolus (ml)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**	**Support (%)**	**Confidence (%)**	**Confidence difference (%)**
3	1	>5.9		0	40.40	70.00	39.70	84.28	99.86	0.43
5	11	[5.15 5.90]		50	9.09	77.78	47.48	8.29	0	-0.24
6	11	<5.15	<-23.0	50	23.23	43.48	13.18	3.14	0.97	0.73
7	5	<5.15	>-23.0	20	27.27	51.85	28.62	4.29	2.84	2.68

Table 24: Extracted rules for glucose bolus (F3)

7.1.4 Conclusions decision tree rule extraction

Many insights can be obtained from the above extracted decision tree rules. This section explains how the different wards react to low blood glucose levels, normal blood glucose levels, and high blood glucose levels.

Regarding low blood glucose levels, ward D3 has a lower threshold to stop the Novorapid perfusor. The perfusor is stopped when the glucose level decreases below 3.25. On wards E3 and F3, the perfusor is stopped when de glucose level decreases below 4.45 and 4.25 respectively. Against the expectations, this does not result in the highest percentage of patients with hypoglycemic events for ward D3 (table 11). Furthermore, the staff of ward F3 gives mostly 50 ml glucose boluses, whereas the staff of ward D3 and E3 give a 20 ml glucose bolus as treatment for a blood glucose level in the intervals [2.65 – 5.25] and [2.95 – 4.35] respectively and a 50 ml glucose bolus for a blood glucose level below the interval. In case of low blood glucose levels, all wards perform the next blood glucose measurement within 30 to 60 minutes. This duration is too long. In case of hypoglycemia, the duration to the next blood glucose measurement should be less than 15 minutes.

Regarding normal blood glucose levels, the duration to the next blood glucose measurement is the longest on wards D3 and E3 (more than 240 minutes). On ward F3 the duration to the next measurement varies from 90 to 180 minutes, depending on the delta glucose percentage. The shorter duration to the next measurement on ward F3 can be explained by their fixed schedule for measurements. For all wards, the Novorapid perfusor is changed with -1, -0.5, 0, +0.5, or +1, depending on the delta glucose percentage. None of the wards administers a glucose bolus for normal blood glucose levels.

Regarding high blood glucose levels, the Novorapid perfusor is increased with +2 on wards D3 and E3. On ward F3 the Novorapid perfusor can also be increased with +3 if the blood glucose level is very high. The duration to the next blood glucose measurement is in the interval [90 – 120] minutes on wards D3 and E3. On ward F3 the duration to the next blood glucose measurement is in the intervals [0 – 30] minutes or [60 – 90] minutes, depending on the delta glucose percentage. None of the wards administers a glucose bolus for high blood glucose levels.

Overall, clinical rule extraction using decision trees is clearly possible. For future research it would be interesting to develop a method that can also check the result of a rule. I.e. for a rule regarding the duration to the next blood glucose measurement: was the next blood glucose level in the target range?

7.2 Fuzzy Inference System (FIS) rule extraction

The concept behind Fuzzy Inference Systems (FIS) was explained in the background chapter under section 2.3. The Fuzzy Logic Toolbox in Matlab was used for extracting fuzzy inference systems. This Fuzzy Logic Toolbox provides functions for analyzing, designing, and simulating fuzzy systems based on fuzzy logic. Usually the toolbox is used for modelling complex systems using simple logic rules, and then to implement these rules in a fuzzy system. However, in this research the Toolbox was used to create fuzzy partitions (with membership functions) for the input and output variables automatically. These fuzzy partitions were created with the genfis1 function. Multiple parameter settings were tested, in search of the optimal model. Thereafter, fuzzy rules were induced from the data and the membership functions. The rule induction method is based on research from Wang & Mendel (1992).

Wang & Mendel (1992) aimed at combining numerical information, obtained from sensor measurements and linguistic information obtained from human experts, in order to model complex control systems. Wang & Mendel (1992) extracted fuzzy rules from sensor data by dividing the input and output spaces into fuzzy regions and then generating fuzzy rules from the given data pairs. An example of how this is performed is given in the following section.

7.2.1 Fuzzy Inference System (FIS) rule extraction (D3)

Fuzzy inference system rule extraction for determining the required duration until the next blood glucose measurement (D3)

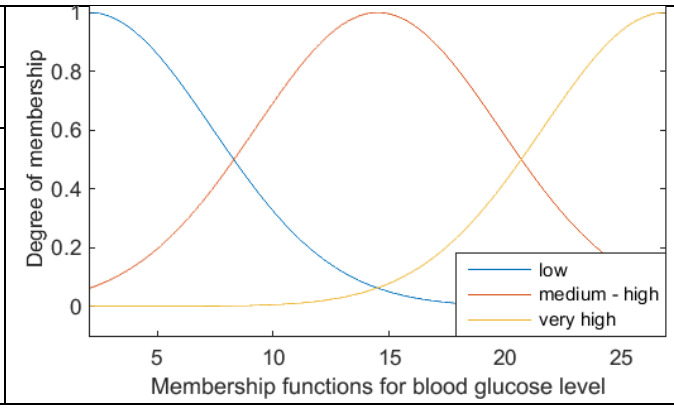
A fuzzy inference system was generated for extracting fuzzy rules on the required time until the next blood glucose measurement using the current measurement and the change in the glucose level compared to the previous blood glucose measurement. The set of fuzzy rules provides insight into how the medical team of ward D3 determines the accepted duration until the next measurement. Since this is the first fuzzy inference system, the process of obtaining it is explained in detail. For the remaining fuzzy inference systems, only the extracted rules and the mean absolute prediction error are presented. For the remaining fuzzy inference systems, the process of obtaining them can be found under Appendix 11.

The process of turning the data set into valuable insights is similar to the process in the previous section (Figure 11), with the main difference that a fuzzy inference system is built instead of a decision tree. Furthermore, a fuzzy inference system is built using continuous data for the dependent variable, instead of categorical data. However, still the continuous data was transformed into categorical data in order to balance the data set. After balancing, the corresponding continuous data was used to train the model.

The fuzzy inference system is trained on all data for ward D3 in 2014 and 2015. Since the aim is on the continuation schedule, the first glucose measurement (or row) was excluded for every unique hospitalization number. The process of turning this data set into valuable insights is explained below.

Firstly, a single-output Sugeno-type FIS structure was generated using the genfis1 function in Matlab. Genfis1 uses grid partitioning and it generates rules by enumerating all possible combinations of membership functions of all inputs. The grids in the grid partition are at the intersection of two membership functions. The created FIS structure provides the initial conditions of the membership function parameters. The initial conditions are fine-tuned using the anfis function. Anfis uses a hybrid learning algorithm to tune the parameters of a Sugeno-type fuzzy inference system. The membership functions are Gaussian membership functions. The first parameter denotes the standard deviation and the second parameter denotes the centre of the membership function. Labels were attached to each membership function based on the researcher's insight (Table 25).

Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
low	[5.264 2.1]	
medium - high	[5.26 14.4]	
very high	[5.272 26.9]	

Linguistic variable: delta glucose percentage (dgp)

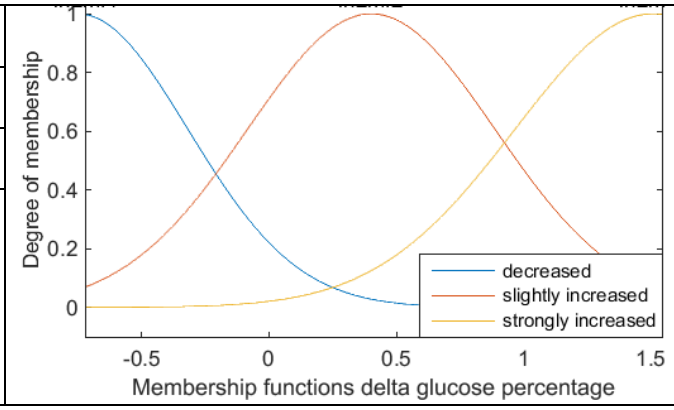
Linguistic value	Parameters	Membership functions
Decreased	[0.4307 -0.7482]	
Slightly increased	[0.4861 0.4018]	
Strongly increased	[0.5426 1.508]	

Table 25: Membership functions for independent variables

Genfis1 results in one rule for each subsection of the grid. However, in some parts of the grid, there are no, or a few data points. Rules obtained from such a part cannot make sense, due to the lack of data to support the rule. To eliminate these unsupported rules,

a scatterplot with the variable delta glucose percentage on the y-axis and the glucose level on the x-as. The grid was also plotted on this scatterplot (Figure 14). For each subsection, with no or, few data points, the consecutive rule was deleted. The extracted rules are listed in Table 26. The mean absolute prediction error on the test set using these rules was 1.1378 hour.

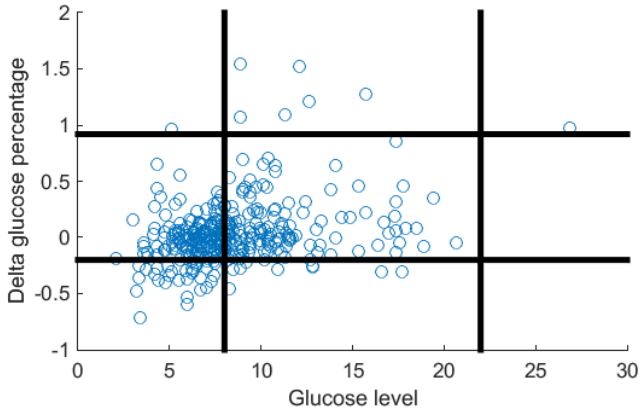


Figure 14: Scatterplot independent variables

If glucose measurement	**and delta glucose %**	**then perform next glucose measurement within (minutes)**
low	decreased	74
low	slightly increased	307
medium to high	decreased	265
medium to high	slightly increased	124
medium to high	strongly increased	223
MAE: 1.1378		

Table 26: Extracted rules for duration to next glucose measurement (D3)

Decision tree rule extraction for determining the required change in the Novorapid perfusor setting (D3)

The fuzzy inference system models the change in the setting of the Novorapid perfusor using the current glucose measurement and the change in the glucose level compared to the previous blood glucose measurement. The extracted rules provide insight into how the medical team of ward D3 determines the change in the Novorapid perfusor setting. The process of obtaining the rules is similar to the fuzzy inference system for determining the required time until the next glucose measurement. For this reason, only the extracted rules are shown for this and the remaining fuzzy inference systems. For every set of rules, the process of obtaining it, can be found under Appendix 11. The extracted rules for changing the Novorapid perfusor setting are in Table 27.

If glucose measurement	and delta percentage glucose level (%)	then Novorapid perfusor setting
low	decreased	-2.40
low	increased	-1.11
medium - high	decreased	2.45
medium - high	increased	1.44
medium - high	strongly increased	1.36
very high	increased	7.38
MAE: 0.6482		

Table 27: Extracted rules for Novorapid perfusor setting (F3)

Fuzzy Inference System rule extraction for determining the next glucose bolus (D3)

This fuzzy inference system models whether or not a glucose bolus should be administered using the current glucose measurement and the change in the glucose level comparing to the previous blood glucose measurement. The extracted rules (Table 28) provide insight into how the medical team of ward D3 administers glucose boluses.

If glucose measurement	and delta percentage glucose level (%)	then glucose bolus (ml)
very low	decreased	45.81
very low	slightly increased	6.96
medium	decreased	-11.34 -> 0
medium	slightly increased	0.06
MAE: 10.8696		

Table 28: Extracted rules for glucose bolus (D3)

Fuzzy Inference System rule extraction for determining the next glucose bolus (D3)

Unfortunately, as can be seen in Table 29, the number of insulin boluses that were captured in the ICIP IC system is very low. The reason for this is that insulin boluses are often saved as a remark under the current medication task in ICIP IC. This data was not delivered, therefore, insulin boluses could not be considered in this research.

Description	Class	#	%
0 unit bolus	1	10133	99.82
1 unit bolus	2	1	0.01
2 unit bolus	3	0	0.00
3 unit bolus	4	4	0.04
4 unit bolus	5	0	0.00
5 unit bolus	6	0	0.00
6 unit bolus	7	1	0.01

Table 29: Classes and frequencies insulin bolus

7.2.2 Fuzzy Inference System (FIS) rule extraction (E3)

This section provides an overview of the extracted rules for glucose control on ward E3. Again, a similar rule extraction process was used. An overview of the extracted rules for determining the required duration to the next measurement (Table 30) is presented first, followed by the extracted rules for determining the Novorapid perfusor setting (Table 31) and the glucose boluses (Table 32). Due to data constraints, no rules overview is available for determining the insulin boluses.

If glucose measurement	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**
low	decreased	46
low	increased	287
medium - high	decreased	125
medium - high	increased	155
MAE: 1.1606		

Table 30: Extracted rules for duration to next glucose measurement (E3)

If glucose measurement	**and delta percentage glucose level (%)**	**then Novorapid perfusor setting**
low	decreased	-2.75
low	increased	-1.26
medium - high	decreased	1.089
medium - high	increased	1.81
medium - high	strongly increased	1.47
very high	increased	2.49
MAE: 0.6409		

Table 31: Extracted rules for Novorapid perfusor setting (E3)

IF glucose measurement	**and delta percentage glucose level (%)**	**then glucose bolus (ml)**
very low	decreased	55.56
very low	increased	22.98
medium	increased	8.56
MAE: 11.0660		

Table 32: Extracted rules for glucose bolus (E3)

7.2.3 Fuzzy Inference System (FIS) rule extraction (F3)

This section provides an overview of the extracted rules for glucose control on ward F3. Again, a similar rule extraction process was used. An overview of the extracted rules for determining the required duration to the next measurement (Table 33) is presented first, followed by the extracted rules for determining the Novorapid perfusor setting (Table 34) and the glucose boluses (Table 35). Due to data constraints, no rules overview is available for determining the insulin boluses.

If glucose measurement	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**
low	decreased	0
low	increased	277
medium – high	increased	124
medium – high	strongly increased	163
very high	increased	86
MAE: 1.2223		

Table 33: Extracted rules for duration to next glucose measurement (F3)

If glucose measurement	**and delta percentage glucose level (%)**	**then Novorapid perfusor setting**
low	decreased	-2.69
low	increased	-2.04
medium - high	decreased	0.34
medium – high	increased	2.25
medium – high	strongly increased	1.41
very high	increased	3.46
MAE: 0.6686		

Table 34: Extracted rules for Novorapid perfusor setting (F3)

If glucose measurement	**and delta percentage glucose level (%)**	**then glucose bolus (ml)**
low	decreased	40.5
low	increased	32.5
medium	increased	17.82
high	increased	-1.43 → 0
MAE: 12.6006		

Table 35: Extracted rules for glucose bolus (F3)

7.2.4 Conclusions Fuzzy Inference System (FIS) rule extraction

Extracting clinical rules from a fuzzy inference system is possible. The benefit from FIS rules is that they are easy to interpret. Unfortunately, due to the different membership functions and labels, it was not possible to make a comparison between the rules of the wards. The next chapter describes where the extracted rules deviate from the protocol.

8. Deviations from the protocol

As the glucose control protocol is not always followed in practice, it will be interesting to know where and why deviations take place and if we can find any patterns in the deviations. We want to look for a common factor that could explain the deviation from the protocol. Information on frequently occurring non-compliance patterns may be useful for guideline authors and/or promotors. This chapter provides an answer to sub-research question 5.

> *"Are there any deviations from the protocol?*
>
> a. *If yes, where are the deviations (according to the data)?*
> b. *Can we find patterns in the deviations?*
> c. *Why do the deviations occur according to the* MUMC+ supervisors *(interviews)?"*

The aim is to detect the deviations from the protocol. Therefore, the extracted rules from the previous chapter are compared to the protocol. Compliant, non-compliant and neutral rules are selected. The chapter is divided per ward. Compliant means that both prerequisites of an extracted rule correspond to the protocol. Non-compliant means that at least one prerequisite is violated. Neutral rules, are extracted rules which either do not exist in the protocol, or rules for which there is a subtle violation in the rule consequent. In each sub-section the rules are evaluated. Only non-compliant rules are stated in this chapter. For each non-compliant rule, the violation is explained. A complete overview of the rating of the rules can be obtained in Appendix 12. The non-compliant rules were discussed with the MUMC+ supervisors in order to find reasons and patterns behind the deviations.

In the previous chapter distinction was made between new cases which should be treated according to the 'startup medication dosing scheme section and regular cases which should be treated according to the 'continuation schedule'. The startup medication dosing scheme from both protocols is not considered in this section as the rules that were extracted in the previous chapter are only applicable to the continuation schedule. In the conclusion (section 8.4) an overview of the practical insights for the MUMC+ is given.

8.1 Ward D3

For ward D3, 14 decision tree rules and 15 FIS rules were extracted. From the 14 decision tree rules, five were non-compliant to the protocol. From the 15 FIS rules, five rules were non-compliant to the protocol. An overview of the non-compliant rules can be found in the tables below. For each rule, the last column denotes the violation in the protocol.

If glucose level	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**	**Violation**
< 3.95	-	30 – 60	within 10 minutes required
low	decreased	74	within 10 minutes required
low	slightly increased	307	within 30 minutes required

Table 36: Non-compliant rules for duration to next glucose measurement (D3)

If glucose level	**and delta percentage glucose level (%)**	**then next Novorapid perfusor**	**Violation**
[3.25-8.15]	<-10.6	-1	wide glucose range
[8.15-9.65]	<-10.9	+1	delta glucose percentage
[8.15-9.65]	>-10.9	+.5	delta glucose percentage
medium - high	decreased	2.45	Either half dose or -1
very high	increased	7.38	max +3

Table 37: Non-compliant rules for Novorapid perfusor setting (D3)

If glucose level	and delta percentage glucose level (%)	then next glucose bolus (ml)	Violation
[2.65-5.25]	-	20	30 mL required
very low	slightly increased	6.96	30 mL required

Table 38: Non-compliant rules for glucose bolus (D3)

The non-compliant rules were discussed with MUMC+ supervisors. Most non-compliant rules are within an acceptable margin, and could be understood, except for the rules printed in red. The FIS rules for changing the Novorapid perfusor are strange. The changes in Novorapid perfusor according to these rules are not realistic as they are too large.

8.2 Ward E3

For ward E3, 15 decision tree rules and 13 FIS rules were extracted. From the 15 decision tree rules, five were non-compliant to the protocol. From the 13 FIS rules, five rules were non-compliant to the protocol. An overview of the non-compliant rules can be found in the tables below. For each rule, the last column denotes the violation in the protocol.

If glucose level	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**	**Violation**
<2.95	-	30 – 60	within 10 minutes
[2.95-5.35]	-	60 – 90	within 30 minutes
low	decreased	46	within 10 minutes
low	increased	287	within 30 minutes

Table 39: Non-compliant rules for duration to next glucose measurement (E3)

If glucose level	**and delta percentage glucose level (%)**	**then next Novorapid perfusor**	**Violation**
[4.45 7.95]	<-15.8	-1	half dose
[5.95 7.95]	>17.8	Stop perfusor	maintain current or +0.5
medium - high	decreased	1.089	maintain dose

Table 40: Non-compliant rules for Novorapid perfusor setting (E3)

If glucose level	**and delta percentage glucose level (%)**	**then next glucose bolus (ml)**	**Violation**
[2.95-4.35]	-	20	30 ml required
very low	increased	22.98	30 ml required
medium	increased	8.56	0 ml required

Table 41: Non-compliant rules for glucose bolus (E3)

The non-compliant rules were discussed with MUMC+ supervisors. Most non-compliant rules are within an acceptable margin, and could be understood, except for the rules printed in red. The rule that prescribes to stop the Novorapid perfusor when the blood glucose level is between the interval [5.95 – 7.95] and the delta blood glucose level is larger than 17.8%, is strange. According to the protocol, the Novorapid perfusor setting should have been maintained or increased with +0.5. A reason for this rule being extracted, might be that the Novorapid perfusor was stopped for other purposes (i.e. due to a change in medication or for further investigation of the patient).

8.3 Ward F3

For ward F3, 18 decision tree rules and 15 FIS rules were extracted. From the 18 decision tree rules, seven were non-compliant to the protocol. From the 15 FIS rules four rules were non-compliant to the protocol. An overview of the non-compliant rules can be found in the tables below. For each rule, the last column denotes the violation in the protocol.

If glucose level	**and delta percentage glucose level (%)**	**then perform next glucose measurement within (minutes)**	**Violation**
< 3.55	-	30 – 60	within 15 minutes
[3.55-8.15]	-	> 240	if stable, within 120 minutes
low	increased	4.62	within 30 minutes

Table 42: Non-compliant rules for duration to next glucose measurement (F3)

If glucose level	**and delta percentage glucose level (%)**	**then next Novorapid perfusor**	**Violation**
[8.05 9.45]	-	+0.5	delta % glucose level?
[4.25 8.05]	<18.1	-1	either maintain current or +0.5
<5.15	>18.1	Stop perfusor	either stop/-1/maintain current
[5.15 8.05]	[-18.1 -9.2]	-0.5	either maintain current or +0.5
medium – high	strongly increased	277	either +2 or +3

Table 43: Non-compliant rules for Novorapid perfusor setting (F3)

If glucose level	**and delta percentage glucose level (%)**	**then next glucose bolus (ml)**	**Violation**
[5.15 5.90]	-	50	0 mL required (probably due to a mix-up in ICIP IC with a treatment for hyperkalaemia)
low	decreased	40.5	50 mL required
medium	increased	17.82	0 mL required

Table 44: Non-compliant rules for glucose bolus (F3)

The non-compliant rules were discussed with MUMC+ supervisors. Most non-compliant rules are within an acceptable margin, and could be understood, except for the rules printed in red. The rule that prescribes to administer a 50 ml glucose bolus if the glucose level is in the interval [5.15 – 5.90], is strange because the blood glucose level is too high for giving a glucose bolus. A potential reason could be due to a mix-up in ICIP IC. The glucose bolus could be mixed with a glucose treatment for hyperkalaemia.

8.4 Conclusions

Discussion of the non-compliant rules with MUMC+ supervisors resulted in the following insights:

- All wards fail to perform the next glucose measurement within the required time in case of a hypoglycemic event.
- The administering of glucose in case of a hypoglycemic event is structurally too low on all wards.
- Most non-compliant rules are within an acceptable margin, except for the rules printed in red.
- A focus group interview can be performed to gain more insights in the deviations from the protocol.

9. Conclusions, limitations and future research

To maximize the benefits for both stakeholders, the student was required to reach two goals, namely a scientific goal and a practical goal. The practical goal was to provide insights regarding the strict glucose control protocol in the ICU department of the MUMC+, especially in the differences between the wards, the compliances to the protocol, deviations from the protocol and patterns in de deviations. The conclusions related to the practical goal are described in the first section. The scientific goal was to discover, by performing a case study, whether a combination of process mining and data mining techniques creates added value to clinical protocol analysis. The conclusions related to the scientific goal are described in the second section. Thereafter, the limitations of this particular study are described in the third section, followed by the directions for future research.

9.1 Practical (MUMC+ specific) conclusions

This study was successful in providing insights for the MUMC+ regarding the strict glucose control protocol in the ICU wards D3, E3 and F3. The interviews and the survey provided insight into which protocol was used at the different wards and insight into the compliance to the protocol at the different wards according to the nursing staff.

On wards D3 and F3, regulating the blood glucose level is less of a protocol act, but more about personal and professional insight of the individual nurses. On these wards, the fear of hypoglycemic instances led to the abandonment of the protocol. On ward E3, the protocol is used for regulating the blood glucose level. It is therefore notable that the mean blood glucose levels are more or less equal for all wards.

The descriptive statistics overview, based on general data analysis techniques, provides many interesting and relevant insights to the MUMC+. By transforming both protocols into computer-processable formats, the protocol compliance, according to the historical data, could be obtained quickly and accurately. In contrast to the interviews and the survey findings, the highest compliance to the protocol (according the data analysis) was on ward D3 (37.67%), compared to ward E3 (33.01%) and F3 (22.78%). The strict protocol compliance is too low. The nursing staff has to decide either to comply to the medical protocol, to update the protocol and comply to the protocol, or to dismiss the protocol.

Comparing the number of hypoglycemic events at the MUMC+ with the literature, confirms the room for improvement, as the number of patients with instances of severe hypoglycemic events is too high on all wards. Regardless the ever ongoing discussion on which target blood glucose level is best in a clinical setting, the percentage of patients with a hypoglycemic event can be reduced by better monitoring and reacting to low blood glucose levels. Moreover, multiple staff members made it known that the introduction of an improved protocol would bring back motivation among the nursing staff to work once more with the protocol. It is therefore recommended to introduce an updated version of the protocol.

The automatically extracted rules for glucose control provided insight in where deviations from the protocols take place and can be a starting point for protocol improvements. I.e. in case of low blood glucose levels, ward D3 has a lower threshold to stop the Novorapid perfusor compared to the others wards. The most important insights can be found in section 7.1.4. The decision on which approach in certain situations is the best, is left to the medical professionals. The descriptive statistics are too similar to be able to draw a conclusion.

9.2 Scientific conclusions

The case study in this thesis shows that a combination of process mining and data mining techniques creates added value to clinical protocol analysis. The insights obtained via the combination of techniques from the process mining and data mining domain, are useful for clinical protocol analysis. The fuzzy protocol compliance, a measure developed for this research, is very useful if the distinction between compliance and non-compliance is not really black or white. Furthermore, both data mining techniques, decision trees as well as fuzzy inference systems, are useful for clinical rule extraction. These clinical rules can provide insight into how a medical team determines its actions. These insights can be used to locate the deviations from the protocol. The fuzzy inference rules are easier to read compared to the decision tree rules. However the decision trees are preferred as they provide more specific rules compared to the fuzzy inference systems. Last but not least, this research project enhances the acceptance of data and process mining techniques by healthcare professionals.

9.3 Limitations

Although it is believed that this research is conducted in a systematic and reproductible way, there is always room for improvement. This section describes the potential weaknesses of this research.

The biggest limitation is the fact that this project only focused on one protocol. The calculation of the statistics is especially tailored to this specific protocol. The methods for rule extraction can very likely be used for other clinical protocol evaluations also. However, this cannot be proven based on the findings of this research project.

In data mining, the quality of the data is critical for the quality of the results. Data quality is affected by the way data is entered, stored and managed. This research faced challenges related to the accuracy, the reliability and completeness of the data. When entering a change in the medication settings in ICIP IC, the nurse can choose to simply select the nearest time window, or to log the actual time. Moreover a nurse can insert a change in medication settings up to 24 hours after the actual moment. The actual moment a medication setting was changed is therefore often difficult to determine. It would be beneficial for the hospital to automatically save changes in medication settings in ICIP IC directly. This improvement will make the data much more reliable, as there are fewer assumptions required to merge the data. An easier alternative would be to log all medication settings every 30 minutes to improve the accuracy of the data. Furthermore, the data were incomplete, i.e. data regarding insulin boluses were missing. This occurred due to the fact that insulin boluses are often not saved or saved

as a remark within the current medication. Insulin boluses are, therefore, kept outside the scope of the research.

9.4 Future research

Addressing the first limitation, future work could focus on implementing one of the rule extraction methods in multiple environments, in order to evaluate the generalisability of these methods. Furthermore, the research can be extended by performing other data mining techniques.

If it were decided to create a new glucose protocol based upon the findings of this research, there could be a follow up study to see whether the compliance to a new protocol would be higher and whether this would lead to a reduction in the percentage of patients who have a hypoglycemic event.

Should the quality of the data improve, by implementing continuous glucose monitoring (CGM) and real-time logging of changes in medication settings, datamining techniques could be used for determining the correct amount of medication. Ideally CGM systems will be used as input for insulin algorithms. In this case, a specific model for determining the medication settings will be trained and improved continuously for each individual patient.

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Appendix 1: Splitting criteria decision tree

The gain criterion can be obtained as follows (Podgorelec, Kokol, Stiglic, & Rozman, 2002): for any subset S of X, where X is the population, let $freq(j_i, S)$ be the number of objects in S which belong to class i. Then consider the "message" that a randomly selected object belongs to class j_i. The "message" has probability $freq(j_i, S)/|S|$, where $|S|$ is the total number of objects in subset S. The information from this message in bits is given by:

$$-log_2(freq(j_i, S)/|S|)$$

Summing over the classes gives the expected information (in bits) from such a message:

$$info(S) = -log_2\left(\frac{freq(C_j, S)}{|S|}\right)$$

When applied to a set of training objects, $info(T)$ gives the average amount of information needed to identify the object of a class in T. This amount is also known as the entropy of the set T. Entropy measures the extent of uncertainty or randomness in a data set. If all the data in a subset belong to just one class, there is no uncertainty or randomness in that dataset, so the entropy is zero. The aim of the algorithm is to build subtrees such that the entropy of each final subset is (close to) zero.

There is also a similar measure after T has been partitioned in accordance with the n outcomes of a test X. The expected information can be found as a weighted sum over the subset T_i:

$$info_X(T) = \sum_{i=1}^{n} \frac{|T_i|}{|T|} * info(T_i)$$

The information gained by partitioning T in accordance with the test X is given by:

$$gain(X) = info(T) - info_X(T)$$

The gain criterion selects a test to maximize the information gain. However the gain criterion is biased towards tests with many outcomes, therefore the gain ratio criteria was developed to overcome this bias. The gain ratio selects a test to maximize the gain ratio subject to the constraint that the information gain is large.

Appendix 2: Decision tree pruning algorithms

With reduced error pruning, each node is considered for pruning. Pruning means removing the subtree at that node, make it a leaf and assign the most common class at that node. A node is removed if the resulting tree does not perform worse that the original on the validation set. Nodes are removed iteratively, choosing the node whose removal most increases the decision tree accuracy. The process of pruning continues until further pruning is harmful. Reduced error pruning is very effective if there is a large amount of data available. However this measure always favors bigger trees. Reduced error pruning results in larger trees, which can be an issue for large datasets (Hall, Chawla, & Bowyer, 1998).

Breiman et al.'s cost-complexity pruning also involves replacing subtrees with leaves and occurs in two stages. First a sequence of increasingly smaller trees $T_1, T_2, \dots, T_k$ are built on the training data, where T_0 denotes the original tree before pruning and T_k denotes the root tree. In the second stage the tree that performs best in terms of classification accuracy on the pruning set is chosen as the pruned tree. The general idea is that not all pruned subtrees are considered but only those that are the best of their kind. The tree T_{i+1} can be obtained by replacing one or more of the sub-trees in the predecessor tree T_i with suitable leaves. The subtrees pruned first are those that obtain the lowest increase in apparent error rate per pruned leaf (Rokach & Maimon):

$$\alpha = \frac{\varepsilon(pruned(T,t),S) - \varepsilon(T,S)}{|leaves(T)| - |leaves(pruned(T,t))|}$$

Where $\varepsilon(T,S)$ denotes the error rate of tree T over the sample S, $|leaves(T)|$ denotes the number of leaves in T. $Pruned(T,t)$ denotes the tree obtained by replacing node t in T with a suitable leaf.

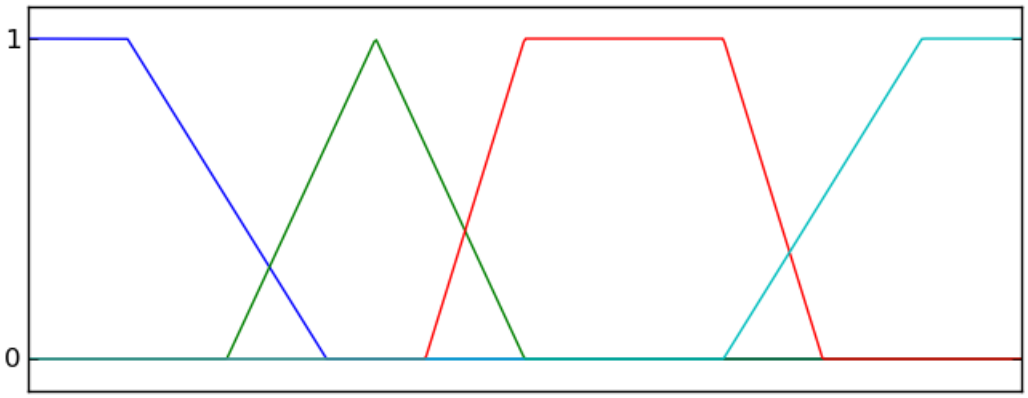
Repeating the process creates a series of trees T_0, T_1, T_2, T_3 ... of decreasing size. Pick the tree with the smallest error on the validation set or the smallest tree within one standard error of the minimum. If the given dataset is large enough, it should be split into a training set and a pruning set. The trees are then constructed using the training set and evaluated on the pruning set.

For determining the final rule set one should convert the tree after pruning into rules. Each rule antecedent can be removed if the error rate on the validation set does not decrease. At last the final rule set is sorted according accuracy.

Appendix 3: Different forms of trapezoidal MF

The trapezoidal membership function can take on different forms:

- The distance between a and b does not have to be the same as the distance between c and d. If the distances are unequal, this implies that the slopes will be different as well. This means that one side is more vague or fuzzy than the other side.
- Values can take on the same value, in such a way that the membership function has no longer a trapezoidal course.
    - If b and c are equal, the membership function looks like a triangle. In this case there is only one value with full membership (1). The green line in figure X is an example of this situation.
    - If a equals b, the membership function looks like the right half of a trapezium. In this case all values from a until c have full membership. The dark blue line in figure below is an example of this situation.
    - If c equals d, the membership function looks like the left half of a trapezium. In this case all values larger then b have full membership. The light blue line in figure below is an example of this situation.



Different forms of the trapezoidal membership function

Appendix 4: Mamdami method

Mamdani applied a set fuzzy rules delivered by experience human operators to the control the steam engine and boiler combination. The Mamdami-style fuzzy inference process exists out of the following four steps:

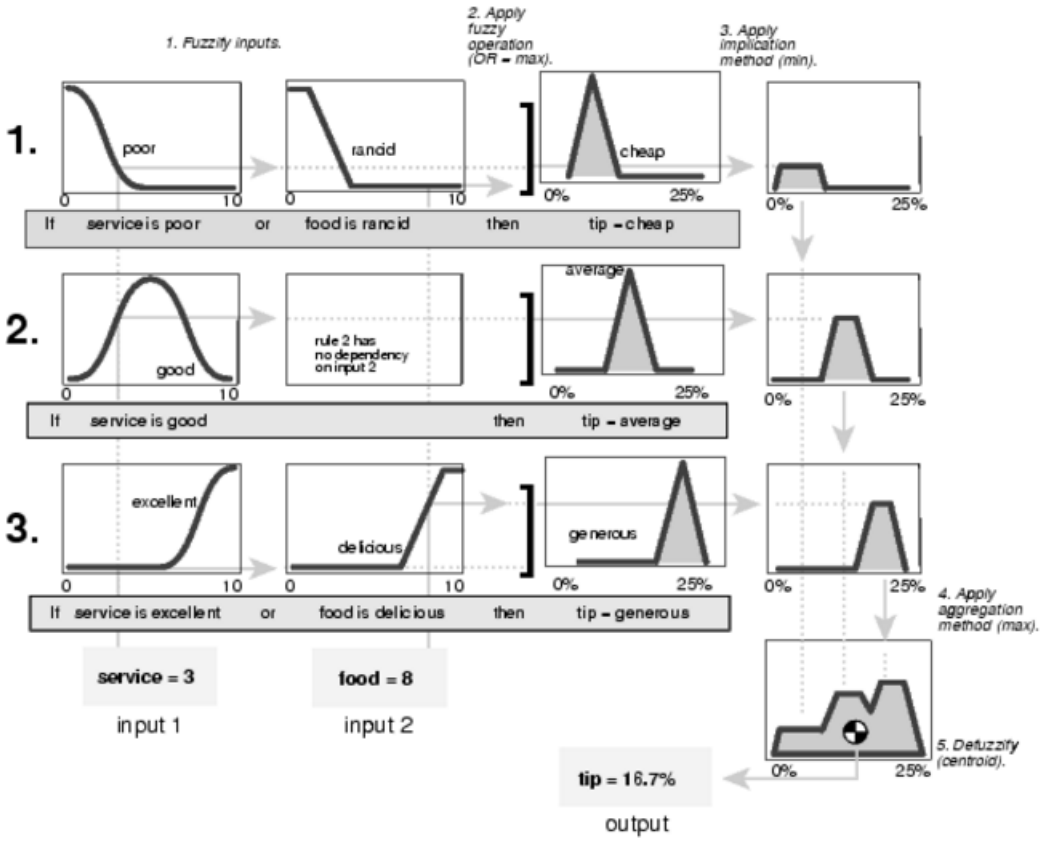
1) Fuzzification of the input variables: the crisp inputs provided by the user are converted into their fuzzy representations using their respective fuzzy membership functions. Some of the inputs can be measured directly (i.e. height, weight, etc.), some of them can be based only on expert estimates. There are different type of membership functions such as the triangular, trapezoidal, Gaussian and generalized bell membership function.

2) Rule evaluation: the fuzzified inputs are applied to the antecedents of the fuzzy rules. If a fuzzy rule has multiple antecedents, the fuzzy operator (AND or OR) is used to obtain a single number that represents the result of the antecedent evaluation. This number, which is called the truth value, is then applied to the consequent membership function (behind the THEN statement). A common way to do this is called clipping. Clipping means cutting the consequent membership function at the level of the antecedent truth.

3) Aggregation of the rule outputs: the outcomes of the rules are combined. The membership functions of all rule consequents previously clipped are combined into a single fuzzy set.

4) Defuzzification: Fuzziness helps us with evaluating rules, but the final output of the system has to be a crisp number again. In the defuzzification, the fuzzy output is converted back into a crisp value. The most popular defuzzification technique is the centroid technique. The centroid technique finds the point where a vertical line would slice the aggregate set into two equal masses. The centre of gravity (COG) can be described in mathematical form as follows:

$$COG = \frac{\int_a^b \mu_A(x) x dx}{\int_a^b \mu_A(x) dx}$$



Example of Mamdani type Fuzzy Inference System

An example of a Fuzzy Inference System can be seen in figure above. The example addresses a basic tipping problem. What should the tip be, given two numbers between 0 and 10 (where 10 is excellent) representing the quality of service and the quality of food at a restaurant. The following fuzzy rules are defined:

IF $service = poor$ AND $food = rancid$ THEN $tip = cheap$
IF $service = good$ THEN $tip = average$
IF $service = excellent$ OR $food = delicious$ THEN $tip = generous$

1) Fuzzification of the input variables: the crisp inputs as provided by the user are 3 for service and 8 for food. For rule 1 (IF $service = poor$ AND $food = rancid$ THEN $tip = cheap$), the crisp input of 3 for service is converted into a fuzzy membership of 0.2 with "poor" and the crisp input of 8 for food has no membership with "rancid". For rule 2 (IF $service = good$ THEN $tip = average$), the crisp input of 3 for service is converted into a fuzzy membership of 0.6 with "good". For rule 3 (IF $service = excellent$ OR $food = delicious$ THEN $tip = generous$), the crisp input of 3 for service has no membership with "excellent" and the crisp input of 8 for food is converted into a fuzzy membership of 0.7 with "delicious".

2) Rule evaluation: the fuzzified inputs are applied to the antecedents of the fuzzy rules. Rule 1 has an OR operator which is used to merge both antecedents of the rule. The OR operator takes the maximum of both membership functions. Rule 2 has only one antecedent. Rule 3 has also an OR operator, so the maximum of both

membership functions is taken. In case of an AND membership function the minimum of both membership functions would be taken. The number obtained by the combining the antecedents, or truth value, is applied to the consequent membership function. This process is called clipping, which means cutting the consequent membership function at the level of the antecedent truth.

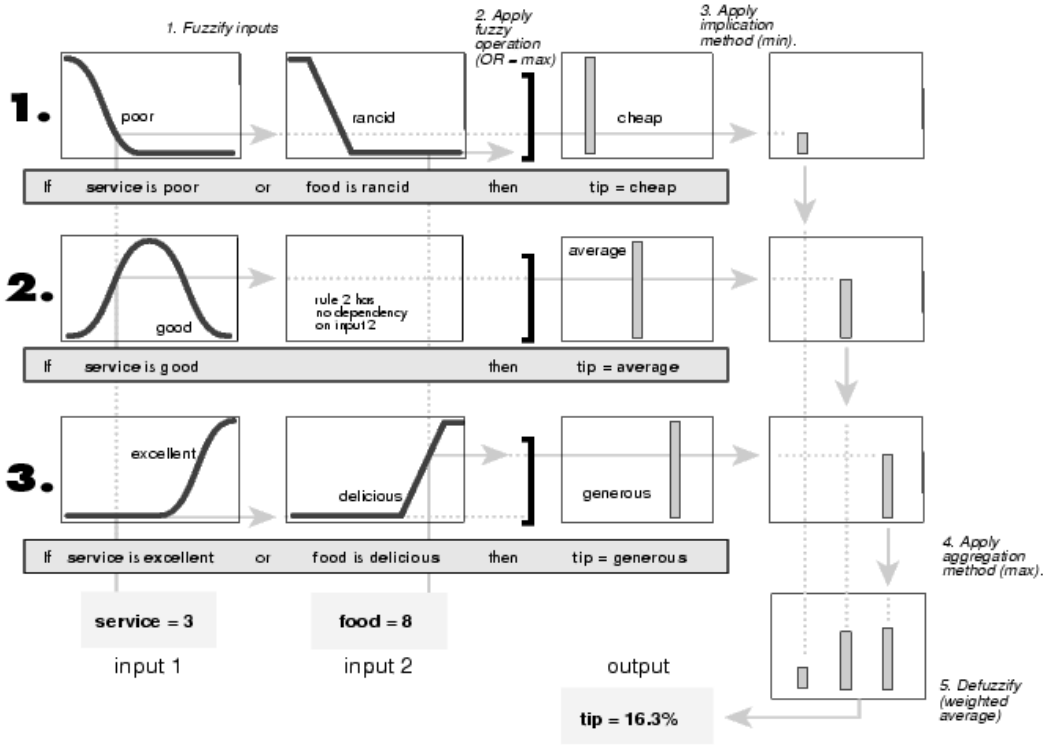
3) Aggregation of the rule outputs: the outcomes of the rules are combined. The membership functions of all rule consequents previously clipped are combined into a single fuzzy set.

4) Defuzzification: the centroid technique is used as defuzzification technique. The centroid technique finds the point where a vertical line would slice the aggregate set into two equal masses. For the tipping example the aggregate set can be sliced into two equal masses at a tip of 16.7%.

Another similar fuzzy inference method is the so-called Sugeno method. This method is similar to the Mamdani method in multiple aspects. The first two parts of the fuzzy inference process, fuzzifying the inputs and applying of the fuzzy operator are the same. The main difference is that Sugeno output membership functions are either linear or constant. A typical rule in a Sugeno fuzzy model has the form:

$$IF\ Input\ 1\ =\ x\ and\ Input\ 2\ =\ y, then\ Output\ is\ z\ =\ ax\ +\ by\ +\ c$$

The final output of a Sugeno fuzzy inference system is the weighted average of all rule outputs.



Appendix 5: Additional performance measures

Sensitivity, recall or true positive rate: measures the proportion of positives that are correctly identified as such. Sensitivity quantifies the avoiding of false negatives. The sensitivity or recall is calculated by the ratio of correctly classified positives divided by the sum of correctly classified positives and incorrectly classified negatives.

$$Sensitivity = \frac{TP}{TP + FN}$$

Specificity or true negative rate: measures the proportion of negatives that are correctly identified as such. Sensitivity quantifies the avoiding of false positives.

$$Specificity = \frac{TN}{TN + FP}$$

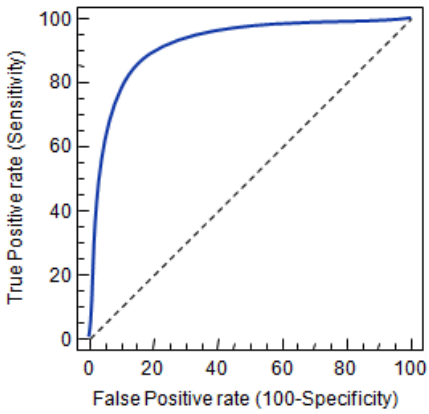
False positive rate: refers to the expectancy of the false positive ratio and can be calculated as follows:

$$False\ positive\ rate = \frac{FP}{FP + TN}$$

Precision: denotes the instances that are relevant and is calculated by the ratio of correctly classified positives divided by the sum of correctly classified positives and incorrectly classified positives.

$$Precision = \frac{TP}{TP + FP}$$

Area under the ROC curve: is graphical assessment technique where the true positive rate is plotted on the Y-axis and the false positive rate is plotted on the X-axis. An example of a ROC curve can be seen in the figure below. The area under the ROC curve denotes the accuracy of a classifier. A value of 50 means the classifier does not perform any better than random chance. A value of 1 indicates a perfect classifier.



Example ROC curve

Appendix 6: Different versions of protocol

6.1 Richtlijn voor intraveneuze toediening van kortwerkende insuline (implemented on D3 and E3)

Richtlijn voor intraveneuze toediening van kortwerkende insuline op de ICU.

Patiëntenpopulatie:
Elke IC patiënt tot orale voeding mogelijk is.

Regulatie van bloedglucose
Streefwaarden bloedglucose tussen **4,5 tot 7,0 mmol/l**.

Opstartschema		
Bloedglucose (mmol/l)	**Perfusor Novorapid** (50^E/50ml NaCl 0.9%)	**Bolus**
< 7,0	-	
7,0 - 8,0	1 E/u	
8,0 - 10	2 E/u	
10 - 15	4 E/u	4 E Novorapid
15 - 20	6 E/u	6 E Novorapid
> 20	6 E/u	8 E Novorapid

Bloedglucose < 30% gedaald, óf bloedglucose gestegen		
Bloedglucose (mmol/l)	**Perfusor Novorapid** (50^E/50ml NaCl 0.9%)	**Actie**
< 3.5	Stoppen	Handel conform hypobeleid
3,5 - 4,5	- 1.0 E/u	Na 30 min glucose controle
4,5 tot 7,0	Ongewijzigd	
7,0 - 8,0	+ 0.5 E/u	
8,0 - 9,0	+ 1.0 E/u	
9,0 - 10	+ 1.5 E/u	
10 - 15	+ 2.0 E/u	2E Novorapid iv als bolus
> 15	+ 3.0 E/u	4E Novorapid iv als bolus

Bloedglucose > 30% gedaald		
Bloedglucose (mmol/l)	**Perfusor Novorapid** (50^E/50ml NaCl 0.9%)	**Actie**
< 3,5	Stoppen	Handel conform hypobeleid
3,5 - 4,5	Stoppen, indien waarde > 5mmol/l is herstarten met de helft van de laatste dosering	Om de 15 min glucose controle tot glucose > 5mmol/l is
4,5 tot 7	Halveren	
7 - 10	-1 E/u	
> 10	Ongewijzigd	

Hypobeleid		
Bloedglucose (mmol/l)	**Perfusor Novorapid** (50^E/50ml NaCl 0.9%)	**Actie**
< 3,5	Stoppen	50 ml glucose 50% in 10 minuten en glucose controle na toediening
Indien > 4,5	Herstarten -1 E/u	Glucose controle na 30 minuten en handel conform vervolgbeleid
Blijft glucose < 4,5	Perfusor gestopt laten	30 ml glucose 50% in 10 minuten en glucose controle na toediening
Na 2e dosis glucose 50%, indien > 4,5	Herstarten -2 E/u	Glucose controle na 30 minuten en handel conform vervolgbeleid
Na 2e dosis glucose 50% nog steeds < 4,5	Perfusor gestopt laten	50 ml glucose 50% in 10 minuten en overleggen met arts

1	Patientenetiket zonder onderste Barcode
2	Patientenetiket zonder onderste Barcode
3	Patientenetiket zonder onderste Barcode
4	Patientenetiket zonder onderste Barcode
5	Patientenetiket zonder onderste Barcode
6	Patientenetiket zonder onderste Barcode
7	Patientenetiket zonder onderste Barcode
8	Patientenetiket zonder onderste Barcode
9	Patientenetiket zonder onderste Barcode

Glucose regulatie volgens protocol dec 2005 aangepaste versie 2012 RVE-MIC / ICU

6.2 Richtlijn voor intraveneuze toediening van kortwerkende insuline op IC (D3, E3, F3) (implemented on F3)

Richtlijn voor intraveneuze toedieng van kortwerkende insuline op IC (D3, E3 en F3)

Achtergrond

Normale bloedglucosespiegel is extreem belangrijk voor de kritiek zieke patiënt.
Normalisatie van de bloedsuikerspiegel wordt verkregen door insuline intraveneus toe te dienen.
Naast insuline zijn intake van calorieën (25 kcal/kg), ernst van de ziekte, corticoid toediening en ernst van de infectie meebepalend voor de hoogte van de bloedglucose.

Patiëntenpopulatie:

Elke IC patiënt tot orale voeding mogelijk is.

Regulatie van bloedglucose

Streefwaarden bloedglucose tussen **4,5 tot 6,5 mmol/l**.
Overleg zo nodig met een arts. (wat is extreem afwijkende waarden, getal noemen)

Opstartschema

1. Bepaal bloedglucosewaarde conform voorschrift
2. Start glucose 10% aan 100 ml/h in afwachting van sondevoeding of TPN.
3. Start insuline volgens schema.
4. Indien pat. niet bekend is met D.M en glucose bij opname <6.5, nog eenmaal 2 uur na opname de bepaling herhalen.

Opstartschema		
Bloedglucose (mmol/l)	**Perfusor Novorapid (50^{E}/50ml NaCl 0.9%)**	**Bolus**
< 6,5	-	
6,5-8	1	
8-10	2	
10-15	4	6 E Novorapid
15-20	6	8 E Novorapid
>20	6	10 E Novorapid

5. Controleer het kalium, indien kleiner dan 3,5 mmol/l start kaliumsuppletie aan 60 mol/24h. Herbepaal kalium na 4-6 uur. Vervolgbeleid in overleg met arts.
6. Meet bloedsuikerwaarde na 1 uur.

Vervolgbeleid :

1. Meet de bloedglucosewaarde ieder uur tot een stabiele instelling bereikt is.
   Bij stabiele instelling volstaat elke 2 uur glucose controle.
   Stabiele bloedglucose instelling wil zeggen binnen de ideaalwaarden en geen dosiswijziging de laatste 2 uur.
   Bij waarden < 3.5 mmol/l elke 15 min controleren.
2. Vergelijk de gemeten waarde met de vorige meting.
3. Handel volgens het schema :

Bloedglucose <30% gedaald óf bloedglucose gestegen		
Bloedglucose (mmol/l)	**Perfusor Novorapid (50^E/50ml NaCl 0.9%)**	**Bolus**
< 2,5	stoppen	30 ml glucose 50%
2,5-4.5	stoppen	20 ml glucose 50 %
3,5-4,5	stoppen	
4,5 tot 6,5	ongewijzigd	
6,5-7,5	+1 E/h	
7,5-8,5	+2 E/h	
8,5-10	+2 E/h	2E Novorapid iv
10-15	+2 E/h	4E Novorapid iv
>15	+ 3 E/h	6E Novorapid iv

Bloedglucose > 30% gedaald		
Bloedglucose (mmol/l)	**Perfusor Novorapid (50^E/50ml NaCl 0.9%)**	**Bolus**
< 3,5	stoppen	30 ml glucose 50%
3,5-4,5	Stoppen	
4,5 tot6.5	halveren	
6.5-10	-1 E/h	
>10	ongewijzigd	

Aandachtspunten:

- De maximale insulinedosis wordt op 50^E/h gesteld.
- Vlak na opname hebben patiënten gemiddeld 6^E/h nodig, waarbij 10% van de patiënten meer dan 20^E/h nodig hebben (waarop is dit gebaseerd, vlg ons niet nodig te vermelden
- De insulinebehoefte neemt af als de algemene toestand van de patiënt verbetert
- Koorts en infectie gaan gepaard met verhoogde insulinebehoefte.
- Voldoende calorie-intake is essentieel.
  Verminder of stop de insuline proportioneel bij plotse wijzigingen in calorie-intake (transport, operatie,...)
- Glucoseoplossingen die niet in continu infuus worden toegediend, kunnen als volgt gebufferd worden:
  - Glucose 5% : 16E Novorapid / liter
  - Glucose 3.3% : 12E Novorapid / liter
  - Glucose 2,5% : 10E Novorapid / liter

Ontslag

Indien de patiënt niet bekend is met DM, en een stabiele instelling heeft met $< 2^E$ insuline/h, kan de perfusor gestopt worden.
Indien na een uur de controlewaarde < 9 mmol/l is, kan de patiënt zonder insuline worden overgeplaatst naar de verpleegafdeling.
Bij hogere waarden dient contact te worden opgenomen met de assistent interne.

Bij bekend met diabetes, dient steeds de **assistent interne en de diabetesverpleegkundige** gecontacteerd te worden zodat follow up op de verpleegafdeling gewaarborgd kan worden.

Appendix 7: Transcriptions of the interviews

7.1.1 Interview with care-coordinator on D3

Algemene vragen:
Q: Op welke afdeling werkt u?
A: D3

Q: Hoe lang werkt u al op deze afdeling?
A: Sinds 1991, ongeveer 24 jaar.

Q: Wat is uw functie? Wat zijn uw voornaamste taken?
A: Ik ben unit manager, en meewerkend leider

Ervaringen omtrent gebruik van het strict glucose control protocol:
Q: Bent u op de hoogte van het strict glucose control protocol?
A: Ik weet dat het er is, we hebben het een aantal jaren geleden ingevoerd gekregen. Ik ben ervan op de hoogte.

Q: Weet u waar het protocol terug te vinden is?
A: Op ODIN, de database voor medische protocollen. Het protocol is niet terug te vinden op de werkvloer.

Q: Welk protocol wordt/werd er gebruikt?
Q: Een van de onderstaande versies of wellicht een andere waar ik nog geen hoogte van heb.
A: Er is gekozen voor de versie van het strict glucose control protocol met als titel: Richtlijn voor intraveneuze toediening van kortwerkende insuline op de ICU.

Q: Protocollen worden regelmatig uitgewerkt in een process model. Is er een process model beschikbaar van het strict glucose control protocol?
A: Nee.

Q: Wanneer is het strict glucose control protocol in gebruik genomen?
A: Ik zou het eerlijk gezegd niet precies weten, als ik moet gokken dan denk ik een jaar of 6 geleden.

Q: Wordt het strict glucose protocol tot op heden gebruikt?
A: Nee, het heeft misschien een half jaar geduurd. Het protocol ging vrij snel van de baan af. Het wordt al jaren niet meer gebruikt. Bij mijn weten hebben we het protocol ook nergens meer liggen op de afdeling. Het wordt niet meer gebruikt, het gaat allemaal op eigen inzicht.

Q: Indien niet, tot wanneer is het strict glucose protocol gebruikt?
A: Tot een half jaar na invoering.

Q: Wat is de reden dat het protocol niet wordt gebruikt?
A: Omdat je vaak in het protocol ook geen rekening houdt met bijvoorbeeld voedingen die even stilstaan. Bijvoorbeeld, men wordt gevoed, en de voeding wordt stilgezet vanwege onderzoek wat gedaan moet worden, dan kan je verwachten dat de bloedglucose gaat dalen omdat de patiënt insuline blijft krijgen volgens het protocol. Met het protocol kun je dus niet anticiperen op bepaalde activiteiten die er gaan komen,

en dat kan het verpleegkundig personeel wel. Ook bleek toen we het protocol nog volgden dat we de hele tijd met schommelingen te maken hadden, daarom is toendertijd gezegd; we gebruiken het niet, we gaan het puur op inzicht doen. Ook heeft het natuurlijk te maken met medicijnen: wanneer je hydrocortison gaat geven, dan weet je dat suikerspiegel omhoog gaat, dan zouden we daar vervolgens het protocol weer op moeten reageren met insuline en dat is eigenlijk niet de bedoeling, omdat je weet dat die vervolgens weer gaat dalen. Dat soort zaken staat allemaal niet in het protocol verwerkt.

Q: Het zou dus belangrijk zijn bij het maken van een model medicijnen en voeding mee te nemen?
A: Ja dat zou zeker belangrijk zijn.

Indien wel, in welke mate wordt/werd het strict glucose protocol gebruikt?
Wat zijn uw ervaringen met het strict glucose protocol?

Vragen omtrent het protocol zelf:
Q: Op welke patiëntenpopulatie is het strict glucose protocol gericht?
Q: Hoe werkt het strict glucose protocol, kunnen we de stappen van het protocol samen doornemen?

Q: Hoe wordt de bloedglucosewaarde gemeten?
A: Er zijn in principe 3 manieren. Je kent het principe van de Arterie lijn? Wij meten een bloeddruk in de Arterie, dat is een katheter die erin gaat met aansluiting op en dan krijgen wij een mooie waarde op de monitor. Via dit systeem kunnen wij ook bloed afnemen, dan hoeven we de mensen niet iedere keer met een naald te prikken. Bloed suiker wordt gemeten via de Arterie, dat noemen wij de statstrip. Statstrip is eigenlijk het prikken van bloed voor een aantal bepalingen te kunnen doen, waaronder ook de glucose valt. Je kunt via het lab ook met een ander grijs buisje de bloedglucose laten meten. De derde methode is dat we met een naaldje een druppel bloed prikken uit een vingertop van de patiënt. Vervolgens doen we dit op een strip papier die getest wordt met de handheld.

Q: Hoe vaak wordt de bloedglucosewaarde gemeten? Hoe wordt de tijd tussen twee opeenvolgende metingen bepaald?
A: Mensen die stabiel zijn, die al een tijdje liggen, die langere tijd dezelfde voeding krijgen sondevoeding of zelf eten, die geen diabetes voorgeschiedenis hebben, die controleren we in principe 1 keer per dag. Suikerpatiënten meten we vanzelfsprekend vaker.

Vragen omtrent de opslag van de data:
Q: Hoe worden de gemeten bloedglucose waarden opgeslagen in het systeem?
A: Als het via het lab gaat, dan sturen we een buisje naar boven naar het lab, daar bepalen ze de bloedglucose en dan komt het automatisch in het ziekenhuis systeem met een link naar het systeem dat wij hebben op de IC. Je ziet eerst wanneer je het opstuurt VOLG staan, dat betekent dat ze het boven ontvangen hebben en dat ze het aan het bepalen zijn. Later verandert het woordje VOLG in een waarde. De tweede manier als je met de POC een glucose meting doet, met de handheld dus, wanneer je het apparaat terug zet op het docking station dan gaat de uitkomst alsnog naar het lab. Het lab autoriseert de uitkomst en dan komt het vervolgens ook in het systeem.

Q: Indien handmatig: worden de gemeten waarden direct ingevoerd in het systeem?

A: Via het LAB en via de POC wordt er een tijdsbepaling aan een meting gekoppeld.

Q: Komt het tijdstip van een meting zoals genoteerd in het systeem overeen met de werkelijkheid?

Q: Hoe wordt het toedienen van een insuline (Perfusor Novorapid) opgeslagen in het systeem?
A: Op het moment dat er insuline gegeven moet worden dan wordt dat met de arts overlegd. De arts maakt de afspraak aan in het medisch gedeelte. Dan komt er een vinkje/rood vlaggetje onder in beeld, daar klikken wij dan op om de afspraak te attenderen (te laten zien dat we de afspraak gezien hebben). Dan komt er een signaaltje bij ons in het systeem en dan starten we de insuline vanaf een bepaalde tijd die in het systeem komt te staan bijvoorbeeld 10 uur. En vanaf 10 uur geef ik een waarde bijvoorbeeld 0, 1, 2, eenheden gekoppeld aan een snelheid (per uur).

Q: Vanuit een eerste inzicht in de data bleek dat een Bolus vaak geregistreerd wordt op 2 manieren. Als opmerking of als nieuwe regel medicatie. Kunt u mij hier meer over vertellen?
A: Vaak als er mondeling gezegd, dat er een bolus toegediend moet worden, dan moet het toch ergens geregistreerd worden. En als de perfusor staat ingesteld tussen 10 en 11 uur op 1 eenheid per uur (1 ml/uur), dan kan ik er bijvoorbeeld 3 van maken, en dan zet ik er als opmerking bij plus 2 eenheden (bolus). Overigens wordt een bolus niet door alle medewerkers hetzelfde omschreven. Sommigen schrijven bijvoorbeeld Bolus +2, iemand anders schrijft 2 eenheden extra.
Ook kan de arts een hele nieuwe afspraak aanmaken, want bij het maken van een afspraak kan er worden aangegeven of het een continu infuus is of als bolus.

Q: Hoe wordt het toedienen van glucose in het geval van hypoglucose opgeslagen in het systeem?
Indien handmatig: worden de toegediende doses direct ingevoerd in het systeem?
A: Dit is weer een Bolus, en wordt als nieuwe opdracht opgeslagen in het systeem. 20 ml glucose (50%) komt dan te staan in het medicatie gedeelte. Deze bolussen worden meestal als eenmalige opdracht afgegeven. Dat zie je dan ook weer aan het rode vlaggetje wat aangevinkt moet worden, dan vinkt het de verpleegkundige het af, wordt de medicatie toegediend, en dan wordt het in het systeem opgeslagen.

Q: Uit uw antwoorden begrijp ik dat het strict glucose control protocol niet meer wordt gebruikt omdat te weinig rekening houdt met medicatie & voeding. Kunt u een aantal zaken benoemen die direct de bloedsuikerspiegel beïnvloeden?
A: Hydrocortison, wordt veel gebruikt een heeft een grote invloed op de bloedsuiker. Mensen krijgen TPV, Intraveneuze voeding, die zit vol met glucose. Stel een patiënt gaat weg voor onderzoek en de TPV stopt tijdelijk. Dat betekent dat je bloedglucose zal gaan schommelen. Dus dan zou je de Insuline ook weer moeten stoppen.

Q: Komt het tijdstip van toediening zoals genoteerd in het systeem overeen met de werkelijkheid?
Additionele vragen

Q: Heeft u nog andere op of aanmerkingen omtrent het strict glucose control protocol?
A: Ik snap dat we een hele hoop dingen willen afkaderen, zeker in de cultuur waarin we alles willen gaan vastleggen tegenwoordig. We zullen altijd wel een misser houden in de vorm van een hypo- of een hyper-glycemie. Maar toen we in het begin met het protocol

gingen werken zag, kwam het vaker voor. Nu hebben we ervaring en een stukje inzicht en is het niet meer nodig. Het protocol is goed dat het er is hoor. Maar het is meer een leidraad, je zult altijd per patiënt afhankelijk moeten kijken, iedereen reageert weer anders op medicatie. Ik ben er niet voor, voor wat betreft dit, om het zo vast te kaderen. In ieder geval niet volgens dit protocol. Als er een ander protocol is dat beter werkt, dan ben ik best bereid om het te proberen. Opzich functioneert het goed zoals het nu gaat.

Q: Welke patiënten zou ik moeten selecteren bij het verzamelen van de data?
A: Er komen wel eens mensen hier die liggen hier voor de thuisbeademing. Mensen die problemen met de longen hebben en daarom thuis ondersteuning krijgen van een beademingsmachine. Die patiënten komen hier eens in de zoveel tijd om de beademingsmachine in te stellen. De mensen hebben vaak ook hun voeding nog thuis. Bij deze patiënten gaat de bloedsuiker glucose echt nog wisselen. Deze patiënten hoef je eigenlijk niet meer te doen. Maar om nu te zeggen, die wel, die niet, is heel moeilijk te bepalen. Dit zou je dan moeten doen op basis van een opname diagnose waarschijnlijk. Maar goed, ook een thuis beademings-patiënt kan doodziek zijn.

Van de andere kant komen er ook natuurlijk mensen waarbij de lever of de alvleesklier helemaal overhoop ligt. Deze mensen hebben een grote kans op schommelingen. Deze patiënten zou je dus zeker moeten doen.

Q: Mochten er nog additionele vragen komen, zou ik hierover dan contact met u kunnen opnemen?
A: Vanzelfsprekend.

7.1.2 Interview with nurse on D3

Algemene vragen:
Q: Op welke afdeling werkt u?
A: D3

Q: Hoe lang werkt u al op deze afdeling?
A: Ik denk 6 jaar nu.

Q: Dan heeft u net de introductie van het protocol meegemaakt?
A: Nee toen was het protocol al ingevoerd.

Q: Wat is uw functie? Wat zijn uw voornaamste taken?
A: IC verpleegkundige.

Ervaringen omtrent gebruik van het strict glucose control protocol:
Q: Bent u op de hoogte van het strict glucose control protocol?
A: Ja. We gebruiken het protocol ook nog in de dagelijkse praktijk. Maar ik raadpleeg het protocol niet meer, als zijnde het papieren protocol. Ja goed, hoe ik het hier hanteer. De glucoses worden samen met de bloedgassen afgenomen, dus minimaal 1 keer per dienst. Aan de hand van de glucose waardes start je met insuline of stel je insuline bij. Het is ook belangrijk te weten of de patiënt iets van calorische intake heeft en daaraan gerelateerd is het streven natuurlijk om een bloedsuiker rond de 7 te krijgen. Dat is eigenlijk in notendop wat het protocol inhoudt.

Q: Weet u waar het protocol terug te vinden is?
A: Ja, op ODIN.

Q: Welk protocol wordt/werd er gebruikt? Een van de onderstaande versies of wellicht een andere waar ik nog geen hoogte van heb?
A: Er is gekozen voor de versie van het strict glucose control protocol met als titel: Richtlijn voor intraveneuze toediening van kortwerkende insuline op de ICU. Er werden ook stikkers op de patiënten gezet zodat we het ook meteen konden scannen met de POC, daarom kan ik dit protocol nog goed herinneren.

Q: Wanneer is het glucose protocol in gebruik genomen?
A: Nee dat weet ik eigenlijk niet, jaren geleden al.

Q: Wordt het strict glucose protocol tot op heden gebruikt?
A: Ik denk dat iedereen globaal op de hoogte is, maar dat het niet zozeer een protocollaire handeling is maar meer een handeling van 'mijn inzicht zegt mij dat dat ik nu moet starten of nog eventjes moet wachten'. Het is niet zo dat omdat het protocol bijvoorbeeld zegt wanneer de glucose 8.5 moet ik starten met 1 eenheid. De individuele verpleegkundige kan er ook voor kiezen om nog een prikbeurt af te wachten. Het gaat eigenlijk vooral op eigen inzicht en gevoel.

Q: Is het voor jullie relevant inzicht te verkrijgen in hoe de bloedsuikerwaarde word gereguleerd?
A: Ik denk dat een opfriscursus niet slecht zou zijn, want uiteindelijk zie je toch dat glucoses meer richting 10 gaan en dat er dan met de perfusor gestart wordt, dan dat het 7 is, zoals het eigenlijk zou moeten zijn. Er zullen wel redenen zijn waarom er later wordt gestart, zo ben ik nu met insuline bij een patiënt gestart, die ook sondevoeding

heeft. Gisteren had ze een glucose van rond de 10,5, maar toen had ze geen calorische intake, dus zijn we geen insuline gestart. Om 12 uur gaan we weer prikken en dan zal haar glucose ook boven de 10 geraken omdat ze nu wel calorische intake krijgt. Bij deze patiënt was er dus een reden voor. Ik denk dat een opfris cursus helemaal niet slecht zou zijn. Ook omdat er volgens mij niet meer bekend is waarom we überhaupt gestart zijn met het protocol.

Q: Indien op gevoel: in welke mate speelt het protocol op de achtergrond een belangrijke rol? In hoeverre beïnvloedt het protocol nog steeds de manier waarop het bloed glucose niveau wordt gereguleerd?
A:

Q: Wat zijn uw ervaringen met het strict glucose protocol?
A:

Vragen omtrent het protocol zelf:
Q: Op welke patiëntenpopulatie is het strict glucose protocol gericht?
A: Bij mijn weten is dit protocol, zoals we hier gestart zijn is het voor elke IC patiënt

Q: naar welke bloedglucose waarde streven jullie?
A: 7.

Q: Wanneer wordt er gestart met het toedienen van Insuline?
A: Bij een glucose hoger dan 7.

Q: Hoe wordt de bloedglucosewaarde gemeten?
A: Via een bloed gas analyse spuitje. Arterieel, en als we het niet anders hebben, dan doen we het via de POC. De POC is wel handig om erbij te hebben, omdat er ook patiënten zonder arteriële lijn hebben. Als je iemand tussendoor nog een keer wilt prikken hoeft dat niet altijd met bloedgas.

Q: Hoe vaak wordt de bloedglucosewaarde gemeten? Hoe wordt de tijd tussen twee opeenvolgende metingen bepaald?
A: Dat ligt aan de hoogte van je glucose. Stel er een patiënt met hoge glucose van bijvoorbeeld 20, en ik start met insuline, dan wil ik ook al pakweg een uur later weten wat het resultaat is. Indien een patiënt stabiel is, dan is in feite 1 keer per dienst voldoende; 3 a 4 keer per dag.

Q: Op een andere afdeling gaven ze aan dat de tijd van een prik afhankelijk is van een strak prikschema. Is daar hier ook sprake van?
A: Nee, hier op de algemene IC hebben wij dat niet, omdat wij hier prikken naar de toestand van de patiënt. Het enige vaste prikmoment dat je hebt is de ochtendprik, waarbij nierfuncties, glucose etc. worden gemeten.

Q: Hoe wordt de dosering van insuline bepaald? Onderscheid perfusor / bolus?
A: We beginnen met een eenheid bij het opstarten en vervolgens wordt naar eigen inzicht verhoogd of verlaagd, hierbij wordt het protocol globaal gehandhaafd. Het toedienen van bolussen betreft toch een beetje natte vingerwerk. Er wordt natuurlijk wel in het achterhoofd gehouden welk resultaat de beoogde bolus toediening moet hebben. Op de IC heb je natuurlijk wel de mogelijkheid om bij te sturen.

Vragen omtrent invoeren van de Novorapid perfusor stand in het systeem.
Q: Hoe wordt de instelling van de Novorapid perfusor (dosis) opgeslagen in het systeem?
Q: Wordt een aanpassing in de stand van de perfusor direct aangepast in het systeem.
A: Het gaat handmatig, normaal gezien tellen/controleren wij de patiënt elke 2 uur. Maar de tijdsbalk kun je aanpassen zoals je zelf wilt. Dus als ik een tijdsgebied heb van elk uur dan staat die daar ook op. Ik tel bijvoorbeeld een perfusor elke 2 uur. Dan klik ik die aan en dan verschijnt er een kolom die precies hetzelfde is als de vorige kolom die ik bevestigd heb, deze zou ik dan moeten bevestigen of handmatig moeten wijzigen. In principe moet je ervan uit kunnen gaan dat als er een rare tijd staat aangegeven buiten de vaste uren dat er op dat moment een verandering is ingegaan. In principe mag je er ook van uitgaan de insuline de hele tijd loopt.

Het kan wel zo zijn dat je bijvoorbeeld een opdracht krijg om de insuline te stoppen om 11:40, dan vul ik in ICIP in 12:00 gestopt, omdat dat mijn volgende telronde is. Dan heb je dus eigenlijk een vertraging van 20 minuten. Voor de vochtbalans ben ik dan compleet, maar kwa scoren op perfect op tijd alles invoeren ben ik niet compleet. Stel ik prik nu bloed, over een kwartier heb ik de uitslag, dan is het ongeveer half 12, de glucose is aan de hoge kant. Ik zet de perfusor een standje hoger, rond 11:35-11:40. In ICIP zet ik het onder 12:00 omdat ik dan weer mijn telronde heb.

In ICIP kan ik een half uur van te voren een telling invoeren. Een telling wordt gedaan om te twee uur en bestaat eigenlijk uit het invoeren waardoor je laat zien dat je de medicaties hebt gecontroleerd en ze op een bepaalde stand lopen.

Q: Zou je me na afloop van het interview kunnen laten zien hoe het invoeren in zijn werk gaat?
A: Jazeker we lopen zo even richting het systeem.

Q: Wordt een bolus Insuline ingevoerd middels een opmerking of middels een toegevoegde medicatieopdracht?
A: Hierin zal ik je een beetje moeten teleurstellen. Het komt soms voor dat een bolus niet geregistreerd wordt in het ICIP. Bijvoorbeeld een bolus van 2, van iemand die start ergens met voeding en op een gegeven moment zien we een suiker van 10, 12, nog niet zo spectaculair in feite, dat er dan al 2 eenheden gebolust worden. Vaak worden die 2 eenheden niet gerapporteerd. Ik registreer het zelf wel altijd, want stel je zit er toch naast, dan weet je wel waarom je ernaast zit. Maar het komt regelmatig voor dat het bij overgang van de dienst mondeling gecommuniceerd wordt, en dan is het dus niet verwerkt in het systeem. Hoe vaak dit precies gebeurt, daar durf ik geen getal over te geven, maar ik zie het wel gebeuren.

Daarom zou ook weer zo een opfris cursus nodig zijn. Het is net zo als in elk bedrijf, je voert iets in, mensen raken enthousiast en werken daaraan mee. Op een gegeven moment krijg je dat het allemaal een beetje inzakt. Met een opfriscursus krijgen mensen weer een even een herinnering dat ze zichzelf beter moeten controleren. En nou is het toch nog altijd zoiets van tussen de 7 en de 15 is er eigenlijk nog niks aan de hand. Terwijl je eigenlijk toch meer naar de 7 zou moeten streven denk ik.

Additionele vragen
Q: Heeft u nog andere op of aanmerkingen omtrent het strict glucose control protocol?
A: Nee
Q: Mochten er nog additionele vragen komen, zou ik hierover dan contact met u kunnen opnemen? A: Vanzelfsprekend.

7.2.1 Interview with care-coordinator and nurse on E3

Algemene vragen:

Q: Op welke afdeling werkt u?
A: E3

Q: Hoe lang werkt u al op deze afdeling?
A: 34 jaar.

Q: Wat is uw functie? Wat zijn uw voornaamste taken?
A: Ik ben IC-verpleegkundige en unitleider.

Ervaringen omtrent gebruik van het strict glucose control protocol:
Q: Bent u op de hoogte van het strict glucose control protocol?
A: Ja, ik ben er van op de hoogte.

Q: Weet u waar het protocol terug te vinden is?
A: In ODIN.

Q: Is het protocol ook nog op de werkvloer terug te vinden?
A: We hebben een vaste plek op de werkvloer achter de balie, waar dit protocol ligt.

Q: Welk protocol wordt/werd er gebruikt? Een van de onderstaande versies of wellicht een andere waar ik nog geen hoogte van heb.
A: Richtlijn voor intraveneuze toediening van kortwerkende insuline (met de barcodes).

Q: Wanneer is het glucose protocol in gebruik genomen?
A: Dat zou ik niet meer precies weten, volgens mij is dat ergens begin jaren 2000 geweest. Dat is toen uit Leuven overgekomen, van het onderzoek van Van den Berghe.

Q: Wordt het strict glucose protocol tot op heden gebruikt?
A: Ja, het wordt nog altijd gebruikt.

Q: Indien niet, tot wanneer is het strict glucose protocol gebruikt?
-

Q: Indien wel, in welke mate wordt/werd het strict glucose protocol gebruikt?
A: Elke patient die hier komt, daar worden bloedsuikers bij gecontroleerd vanaf de opname, op regelmatige tijdstippen, en iedereen start de Actrapid (insuline) afhankelijk van het protocol. Dat wordt nog altijd heel strikt gehanteerd.

Q: Zijn alle medewerkers van het protocol op de hoogte?
A: Ja, iedereen doet het vanuit zijn eigen al, dat zit erin gebakken.

Q: Indien op gevoel: in welke mate speelt het protocol op de achtergrond een belangrijke rol? In hoeverre beïnvloedt het protocol nog steeds de manier waarop het bloed glucose niveau wordt gereguleerd?
-

Q: Wat zijn uw ervaringen met het strict glucose protocol?

A: In het begin toen het protocol er pas was, toen was het nog een beetje moeilijk. Misschien dat sommige mensen toen wel ten onrechte een hypo-glucose gekregen hebben. Maar ik moet zeggen, gaande de jaren, is het erin geraakt en levert het protocol op dit moment geen problemen op. Iedereen hanteert het en dat loopt eigenlijk vlot. En als we er niet goed uitkomen, hoe we het gaan doen, volgens het protocol, dan wordt hulp van de arts gevraagd.

Vragen omtrent het reguleren van de bloedglucose
Q: Op welke patiëntenpopulatie is het strict glucose protocol gericht?
A: Alle patiënten.

Q: Wanneer wordt er gestart met het toedienen van Insuline?
A: Gewoon volgens het protocol (>7 mmol/L). Er is soms een uitzondering, voor de mensen die hier opgenomen worden, die eigenlijk niet echt intensive care behoeftig zijn en die nog niet echt goed aan het eten zijn, en een iets hogere bloedglucose hebben, dan waarvoor ze volgens het protocol insuline zouden moeten krijgen. Daar starten we dan geen insuline op en wachten we even. Zodra die mensen weer gaan eten dan komt het toch wel goed weer. De overige IC-patiënten worden allemaal volgens protocol opgestart.

Q: Welke bloedglucose wordt er in de praktijk nagestreefd?
A: We hanteren gewoon de getallen die in het protocol staan. Daarvoor is het protocol en je maakt het jezelf daar natuurlijk ook gemakkelijk mee.

Q: Hoe wordt de bloedglucosewaarde gemeten?
A: Capillair (met de vingerprik). Accucheck. Als de patiënt op dat moment een bloedgas analyse dient te krijgen, dan wordt er natuurlijk ook een bloedglucose opgevraagd.

Q: Is de bloedglucose waarde direct zichtbaar bij het afnemen van een capillaire meting?
A: Ja, dat kunnen we rechtstreeks van het apparaat aflezen. Alleen als de uitslag extreem laag is dan sturen we voor alle zekerheid een bloedmonster naar het laboratorium, dit is een arterieel bloedmonster.

Q: Hoe vaak wordt de bloedglucosewaarde gemeten?
A: Minstens 1 keer per dienst, dus 3 maal per 24 uur. En als de insuline regelmatig aangepast dient te worden, dan gebeurd het vaker.

Q: Is er sprake van een vast prikschema?
A: Het enige vaste moment is 's-ochtends tussen kwart over 5 en half 6. Dan worden alle patiënten geprikt en worden alle analyses afgenomen. Hier is ook uiteraard een glucose bij.

Q: Hoe wordt de tijd tussen twee opeenvolgende metingen bepaald?
A: Afhankelijk van of de patiënt insuline heeft of niet of als de bloedglucose stabiel blijft met een bepaalde instelling van insuline. Indien de bloedglucose stabiel is over de laatste paar dagen, dan staat de perfusor goed ingesteld en hoeft er niet iedere 2-3 uur geprikt te worden.

Q: Zou ik een aanname kunnen maken over wanneer een patiënt als stabiel beschouwd kan worden?
A: Nee, want er kan ieder moment iets veranderen in de toestand van de patiënt. Bloedglucoses moeten toch met enige regelmaat gecontroleerd worden.

Q: Hoe wordt de dosering van insuline bepaald?
A: Volgens protocol

Vragen omtrent invoeren van de Novorapid perfusor stand in het systeem.
Q: Hoe wordt de instelling van de Novorapid perfusor (dosis) opgeslagen in het systeem?
Q: Wordt een aanpassing in de stand van de perfusor direct aangepast in het systeem.
A: Op het moment dat we de stand van de pomp veranderen, dan veranderen we het ook direct in het registratiesysteem. Anders ga je het vergeten, en kun je achteraf niet meer terug zien wanneer je het hebt aangepast. Je komt standaard op met een interval van 2 uur. Veronderstel om 10:30 verandert de instelling van de pomp. In het systeem klik je dan rechtsboven, of op het systeem zelf, en geef je aan 'nu aanpassen'. Over het algemeen wordt de exacte tijd genoteerd. Het is niet zo dat iemand om 10:20 de pomp verandert, en het pas om 12:00 uur verwerkt in het systeem. We doen het altijd op het moment zelf.

Q: Wordt een bolus Insuline ingevoerd middels een opmerking of middels een toegevoegde medicatieopdracht?
A: Discontinue medicatie, een nieuwe medicatie opdracht.

Q: Wordt een insuline bolus altijd opgeslagen in het systeem?
A: Discontinue medicatie, een nieuwe medicatie opdracht. Of als opmerking bij de huidige medicatieopdracht. Of in het verpleegkundig verslag. Hier is niet genoeg eenduidigheid over.

Q: Hoe wordt het toedienen van glucose in het geval van hypoglucose opgeslagen in het systeem?
A: Discontinue medicatie: Glucose 50%. Dit is altijd een opdracht van de arts.

Additionele vragen
Q: Heeft u nog andere op of aanmerkingen omtrent het strict glucose control protocol?
A: Wij hebben vanaf het begin het protocol gehanteerd. Het is goed ingeburgerd na al die jaren en het loopt eigenlijk vrij soepel. We hebben er weinig problemen mee.

7.3.1 Interview with care-coordinator on F3

Algemene vragen:

Q: Op welke afdeling werkt u?
A: F3.

Q: Hoe lang werkt u al op deze afdeling?
A: Bijna 13 jaar.

Q: Wat is uw functie? Wat zijn uw voornaamste taken?
A: Ik ben IC verpleegkundige, en daarbij ben ik unit leider geworden.

Ervaringen omtrent gebruik van het strict glucose control protocol:
Q: Bent u op de hoogte van het strict glucose control protocol?
A: Ik ben ervan op de hoogte in de zin dat ik er mee heb gewerkt.

Q: Weet u waar het protocol terug te vinden is?
A: Het protocol is terug te vinden op ODIN.

Q: Welk protocol wordt/werd er gebruikt? Een van de onderstaande versies of wellicht een andere waar ik nog geen hoogte van heb.
A: Richtlijn voor intraveneuze toediening van kortwerkende insuline op IC (D3, E3, F3). De inzichten in bloed glucose control zijn veranderd, zonder dat het protocol is aangepast. Het protocol is ingevoerd omdat het zou leiden tot een vermindering van complicaties. Er bleek na invoering dat er vaker hypo glycemie plaatvond. Hierdoor de target range naar omhoog aangepast.

Q: Protocollen worden regelmatig uitgewerkt in een process model. Is er een process model beschikbaar van het strict glucose control protocol?
A: Nee.

Q: Wanneer is het glucose protocol in gebruik genomen?
A: Naar schatting ongeveer 6-7 jaar geleden.

Wordt het strict glucose protocol tot op heden gebruikt? Het wordt gebruikt maar het wordt niet strict nageleefd. Het gebeurt meer op inzicht en ervaring van het verpleegkundig personeel. Ook zullen we bij een diabeet eerder insuline toedienen dan bij een niet diabeet.

Q: Indien niet, tot wanneer is het strict glucose protocol gebruikt?
A: Het protocol is ongeveer een half jaar gebruikt.

Q: Indien wel, in welke mate wordt/werd het strict glucose protocol gebruikt?
Q: Wat zijn uw ervaringen met het strict glucose protocol?
A: Het protocol werkt niet goed. Er wordt geen rekening gehouden met andere medicatie.

Vragen omtrent het protocol zelf:

(Vragen omtrent opslag van data is weggelaten. Dit gaat hetzelfde als op de andere afdelingen).

Q: Hoe vaak wordt de bloedglucosewaarde gemeten?
A: Daar durf ik geen harde uitspraak over te doen. Minimaal 1 maal per dag. Indien we starten met het toedienen van Insuline dan gaan we vaker meten.

Q: Hoe wordt de tijd tussen twee opeenvolgende metingen bepaald? Ik weet niet of die echt volgens richtlijnen bepaald wordt. Dit gebeurt meer op eigen inzicht.

Vragen omtrent de opslag van de data:
Q: Hoe worden de gemeten bloedglucose waarden opgeslagen in het systeem?
A: Dit gebeurt via het Lab, wanneer wij een bloedmonster naar boven sturen dan komen de metingen later in het systeem te staan. Wanneer de bloedglucose gemeten wordt met de handheld dan wordt alsnog de meting doorgestuurd naar het Lab. Hier wordt de meting geverifieerd en in het systeem verwerkt.

Q: Indien handmatig: worden de gemeten waarden direct ingevoerd in het systeem?
A: Nee dit kan niet.

Q: Komt het tijdstip van een meting zoals genoteerd in het systeem overeen met de werkelijkheid?
A: Het tijdstip van een meting zoals genoteerd in het systeem betreft het tijdstip wanneer de laborant het verwerkt heeft. Wanneer er een bloedmonster naar het lab gestuurd is dan zal er vertraging tussen zitten, omdat een laborant de testen moet uitvoeren. Deze vertraging betreft ongeveer 30 minuten. Wanneer een meting via de handheld gedaan wordt dan hoeft een laborant slechts te verifiëren en zal de vertraging een stuk kleiner zijn, ongeveer 10 minuten.

Q: Hoe wordt het toedienen van een insuline (Perfusor Novorapid) opgeslagen in het systeem?
A: Het toedienen van Insuline is een nieuwe medicatie opdracht.

Q: Indien handmatig: wordt een bolus ingevoerd middels een opmerking of middels een toegevoegde medicatieopdracht?
A: Beide is mogelijk.

Q: Komt het tijdstip van toediening van Insuline zoals genoteerd in het systeem overeen met de werkelijkheid? Wanneer de insuline dosis wordt veranderd dan wordt dit vrijwel direct aangegeven in het systeem.

Q: Hoe wordt het toedienen van een insuline bolus opgeslagen in het systeem?
A: Via een opmerking in de bestaande medicatieopdracht of via een nieuwe medicatie opdracht.

Q: Komt het tijdstip van toediening zoals genoteerd in het systeem overeen met de werkelijkheid?
A: Ja dit komt overeen.

Q: Hoe wordt het toedienen van glucose in het geval van hypoglucose opgeslagen in het systeem?
Indien handmatig: worden de toegediende doses direct ingevoerd in het systeem?
A: Dit is een nieuwe medicatie opdracht.

Komt het tijdstip van toediening van een glucose bolus zoals genoteerd in het systeem overeen met de werkelijkheid?
Ja. Bij het opslaan van een nieuwe medicatie opdracht wordt de daadwerkelijke tijd genoteerd.
Additionele vragen

Q: Heeft u nog andere op of aanmerkingen omtrent het strict glucose control protocol?

Q: Mochten er nog additionele vragen komen, zou ik hierover dan contact met u kunnen opnemen?
A: Natuurlijk, trek maar aan mijn jas.

7.3.2 Interview with nurse on F3

Algemene vragen:
Q: Op welke afdeling werkt u?
A: F3.

Q: Hoe lang werkt u al op deze afdeling?
A: 5 jaar.

Q: Dan heeft u wellicht net wel of net niet de introductie van het strict glucose control protocol meegemaakt?
A: Ja, het DIADAIM.

Q: Wat is uw functie? Wat zijn uw voornaamste taken?
A: Verpleegkundige, voornaamste taak is eigenlijk het observeren van alle vitale waardes van de patiënt.

Ervaringen omtrent gebruik van het strict glucose control protocol:
Q: Bent u op de hoogte van het strict glucose control protocol?
A: Ja, ik ken het wel. Ook met hoe vaak je moet prikken en hoe je moet verhogen of verlagen met insuline, alleen passen wij dat niet toe op die manier zoals het in het protocol staat beschreven.

Q: Weet u waar het protocol terug te vinden is?
A: Ja, in ODIN.

Q: Welk protocol wordt/werd er gebruikt? Een van de onderstaande versies of wellicht een andere waar ik nog geen hoogte van heb?
A: Richtlijn voor intraveneuze toediening van kortwerkende insuline op IC (D3, E3, F3).

Q: Wanneer is het glucose protocol in gebruik genomen?
A: Ik schat 5 jaar geleden.

Q: Wordt het strict glucose protocol tot op heden gebruikt?
A: Slecht.

Q: Indien niet, tot wanneer is het strict glucose protocol gebruikt?
A: Wat betreft insuline toediening, dat je zegt, dat je Novorapid start boven een glucose van 8. Dat wordt wel allemaal gedaan. Maar het strict afnemen van glucoses volgens protocol gebeurt niet. En dat heeft ook een bepaalde rede namelijk dat wij bij de postoperatieve OK patiënten een vast prikschema hebben.

Q: Indien op gevoel: in welke mate speelt het protocol op de achtergrond een belangrijke rol? In hoeverre beïnvloedt het protocol nog steeds de manier waarop het bloed glucose niveau wordt gereguleerd?
A: Ik ben het er niet mee eens dat het op gevoel gaat. Iedere patiënt, soms diabeet, soms niet diabeet reageert heel anders op insuline therapie. Het glucose niveau kan dus ontzettend fluctueren. Chronologisch prikken wij wanneer de patiënt binnenkomt een glucose, 2 uur daarna prikken we glucose, 2 uur daarna prikken we nog een keer glucose, daarna prikken we nog een keer 4 uur erna, en vervolgens nog een keer 's-ochtends. Standaard als een patiënt binnenkomt, prikken wij al 5 keer glucose.

Wanneer je glucose zou starten en je merkt dat ondanks de vaste prikken de glucose nog steeds hoog blijft of snel keldert, dan wordt er vaker gecontroleerd.

Vragen omtrent het protocol zelf:
Q: Op welke patiëntenpopulatie is het strict glucose protocol gericht?
A: Voornamelijk op diabeten, maar wij passen het eigenlijk op iedereen toe.

Q: Naar welke bloed glucose waarde streven jullie?
A: Tussen 4.5 en 8.

Q: Wanneer wordt er gestart met het toedienen van Insuline?
A: Bij een glucose hoger dan 8.

Q: Hoe wordt de bloedglucosewaarde gemeten?
A: Arterieel en af en toe met de POC.

Q: Hoe vaak wordt de bloedglucosewaarde gemeten?
A: Chronologisch prikken wij wanneer de patiënt binnenkomt een glucose, 2 uur daarna prikken we glucose, 2 uur daarna prikken we nog een keer glucose, daarna prikken we nog een keer 4 uur erna, en vervolgens nog een keer 's-ochtends.

Q: Hoe wordt de tijd tussen twee opeenvolgende metingen bepaald?
A: Stel je voor er komt iemand om 10:00 binnen. Dan is de eerstvolgende prik om 12:00, de prik daarna is om 14:00, de prik daarna om 18:00 en vervolgens weer om 6:00 in de ochtend. Vaak wordt er tussen 6 uur 's-avonds en 6 uur 's-ochtends ook nog 1 of 2 keer geprikt. Het start dus eigenlijk op het moment dat de patiënt hier binnenkomt.

Q: Hoe wordt de dosering van insuline bepaald? Onderscheid perfusor / bolus?
A: We beginnen meestal op 1 E/u. Vervolgens wordt het vaak met 1 eenheid verhoogt of verlaagt afhankelijk van de eerstvolgende waarde. Een bolus wordt eigenlijk bijna niet gedaan, tenzij je glucose boven de 15 of 20 hebt, dan gaat het in overleg met de arts. Dan wordt er geen protocol gevolgd.

Q: Wanneer wordt een glucose bolus toegediend?
A: Wanneer de glucose onder de 4.5 ligt.

Vragen omtrent invoeren van de Novorapid perfusor stand in het systeem.
Q: Hoe wordt de instelling van de Novorapid perfusor (dosis) opgeslagen in het systeem?
A:

Q: Wordt een aanpassing in de stand van de perfusor direct aangepast in het systeem.
A: Je doet ieder uur een update, maar doe je het verlagen of verhogen dan doe je het op het moment dat je het doet. Bij de verse patiënten doen we dat eigenlijk ieder uur. Bij de mensen die langer dan 24 uur liggen dan wordt vaak om te 2 uur geteld.

Q: Laat overzicht data zien. Het lijkt erop dat de data per 2 uur wordt opgeslagen?
Wanneer er een stand van de Novorapid perfusor wordt doorgegeven (bijvoorbeeld 2/11/16 08:00, 7:46). Wil dat zeggen om 7:46 is de perfusor ingesteld op 2 E/u of van 8:00 tot 10:00 staat de perfusor op 2 E/u.
A: Als voorbeeld is een stabiele patiënt genomen. Indien er niks verandert wordt er iedere 2 uur de stand van de Perfusor Novorapid ingevoerd. Onder Eigenschappen > Historie, staat het tijdstip dat het is ingevoerd in het systeem. 50 Eenheden is de

concentratie van de spuit en is niet van belang voor jou. Voor jou is enkel de dosis van belang die ingesteld staat.

Q: Het toegediend volume bedroeg 4 ml met een inloopsnelheid van 2 ml / uur. Dosis is dus 2 E/u. 7:46-9:46 2 E/u of van 8:00 tot 10:00 2 E/u.
A: Het toegediend volume betreft het toegediende volume sinds de instelling van de perfusor en het huidige telmoment. Wanneer de dosis van de perfusor wordt aangepast dan start het toegediend volume weer op 0.

Q: Zou je me na afloop van het interview kunnen laten zien hoe het invoeren in zijn werk gaat?
A: Zeker.

Q: Voor mijn gevoel loopt hij eigenlijk continue door en zou ik eigenlijk moeten kijken waar er een verandering is in de stand van de perfusor.
A: Klopt. Een verandering is geaccentueerd, dit is te herkennen aan de gele blokken met twee streepjes. Er staan dan meerdere opdrachten in. Bv om 18:15 is de stand verlaagd naar 1 eenheid.

Q: klopt het tijdstip dan ook met de werkelijkheid?
A: waarschijnlijk als je weer onder eigenschappen zult kijken blijkt dat het toch niet helemaal overeenkomt. Het zal rond het tijdstip gedaan zijn dat het is ingevoerd in het systeem. Maar om het overzichtelijker te maken, wordt er meestal op het hele of halve uur afgerond. Overigens wordt er op een bloedgas meting over het algemeen snel gereageerd.

Q: Laat overzicht data zien. In de data blijkt dat er een toegediend volume, inloopsnelheid en dosis gegeven is. Wanneer toegediend volume 4ml bedraagt, de inloopsnelheid 2 ml per uur dan is het logisch dat de dosis 2 eenheden per uur betreft. Dit blijkt echter vaak niet het geval (VOORBEELD 2-11 14:00 of 16:00).
Hoe moet ik dit zien. Is het puur en alleen de dosis waar het om draait?
A: Toegediend volume betekent de hoeveelheid dat de patiënt heeft gekregen

Q: Wordt een bolus Insuline ingevoerd middels een opmerking of middels een toegevoegde medicatieopdracht?
A: Nee dan heb je een aparte opdracht. Zou je een bolus moeten geven dan hoort eigenlijk een opdracht van de arts aangemaakt te worden.

Q: Hoe wordt het toedienen van glucose in het geval van hypoglucose opgeslagen in het systeem?
A: Medicatieopdracht.

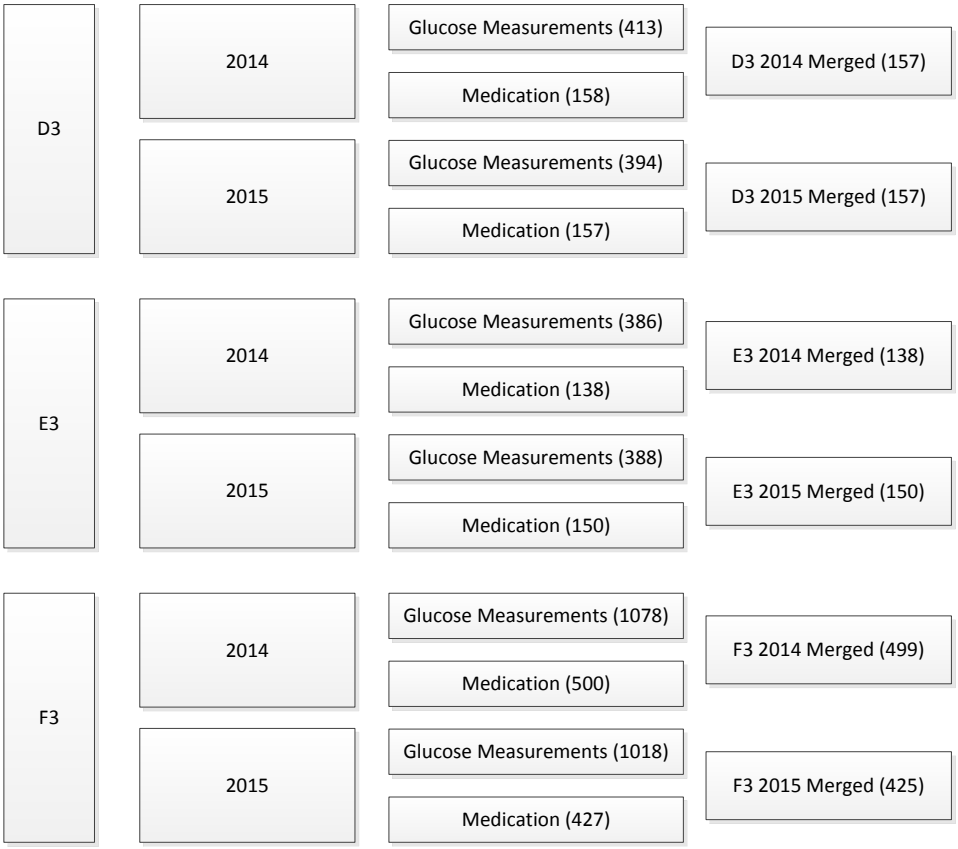
Additionele vragen
Q: Heeft u nog andere op of aanmerkingen omtrent het strict glucose control protocol?
A: Nee.

Q: Mochten er nog additionele vragen komen, zou ik hierover dan contact met u kunnen opnemen?
A: Natuurlijk.

Appendix 8: Data file structure

Appendix 8.1: Provided data structure

Appendix 8.2: Pre-processed data structure



Appendix 9: Overview decision trees

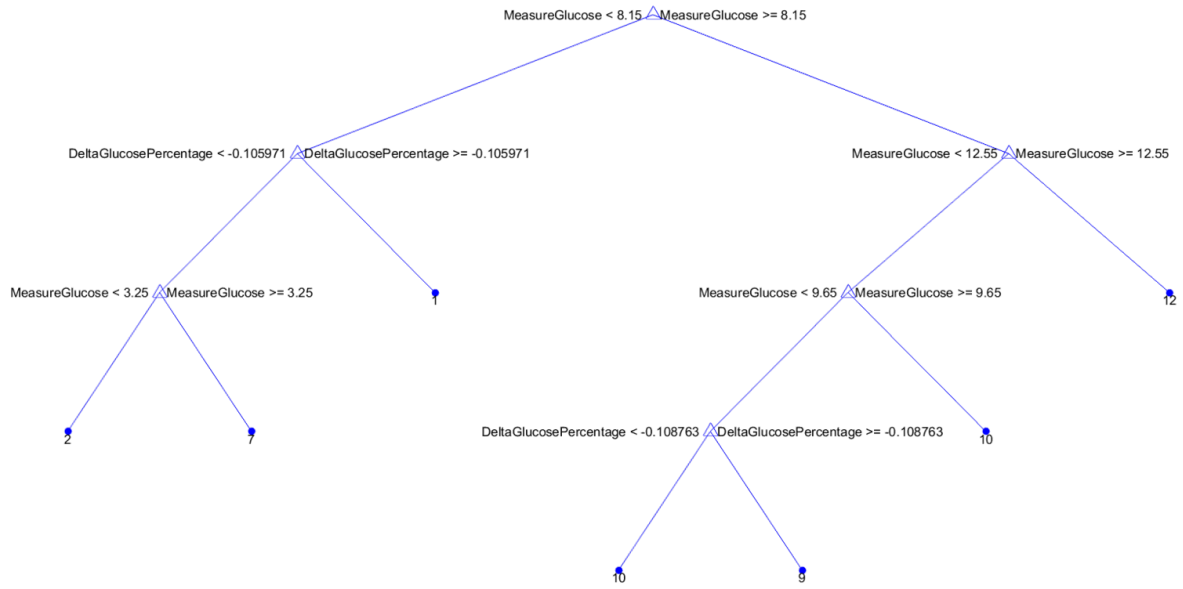
Decision trees: D3

Novorapid perfusor setting (D3)

Description	Class	#	%
Maintain current Novorapid setting	1	8344	82.46
Stop Novorapid perfusor	2	176	1.74
Decrease Novorapid perfusor with 3 or more	3	44	0.43
Decrease Novorapid perfusor with 2.5	4	12	0.12
Decrease Novorapid perfusor with 2	5	73	0.72
Decrease Novorapid perfusor with 1.5	6	50	0.49
Decrease Novorapid perfusor with 1	7	192	1.90
Decrease Novorapid perfusor with 0.5	8	175	1.73
Increase Novorapid perfusor with 0.5	9	285	2.82
Increase Novorapid perfusor with 1	10	521	5.15
Increase Novorapid perfusor with 1.5	11	37	0.37
Increase Novorapid perfusor with 2	12	161	1.59
Increase Novorapid perfusor with 2.5	13	4	0.07
Increase Novorapid perfusor with 3 or more	14	47	0.46

Classes and frequencies Novorapid perfusor setting (D3)

The maximum number of observations allowed per class in the undersampling phase was set to 200.



Decision tree Novorapid perfusor (D3)

Rules					Balanced train set			Test set		
								Accuracy: 47.27%		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN next Novorapid perfusor**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
5	1	<8.15	>-10.6	Keep current	25.22	24.94	12.23	45.38	93.55	11.14
7	12	>12.55	-	+2	9.78	17.53	4.82	5.14	14.62	13.03
8	2	<3.25	<-10.6	Stop perfusor	1.65	65.38	54.2	0.91	26.09	24.39
9	7	[3.25-8.15]	<-10.6	-1	27.76	23.34	11.14	20.40	3.88	1.94
11	10	[9.65-12.55]	-	+1	17.47	28.73	16.02	11.30	14.69	9.55
12	10	[8.15-9.65]	<-10.9	+1	3.68	34.48	21.77	2.73	14.49	9.35
13	9	[8.15-9.65]	>-10.9	+.5	14.42	37.44	24.73	14.15	6.98	4.14

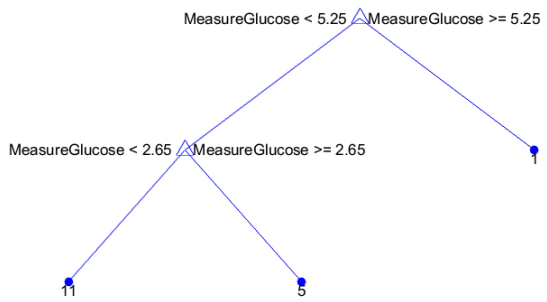
Extracted rules for next Novorapid perfusor setting (D3)

The next glucose bolus (D3)

Description	Class	#	%
0 mL Gluc 50%	1	10092	99.42
5 mL Gluc 50%	2	0	0.00
10 mL Gluc 50%	3	1	0.01
15 mL Gluc 50%	4	0	0.00
20 mL Gluc 50%	5	14	0.14
25 mL Gluc 50%	6	0	0.00
30 mL Gluc 50%	7	5	0.05
35 mL Gluc 50%	8	0	0.00
40 mL Gluc 50%	9	0	0.00
45 mL Gluc 50%	10	0	0.00
50 mL Gluc 50%	11	39	0.38

Classes and frequencies glucose bolus (D3)

The maximum number of observations allowed per class in the undersampling phase was set to 20.



Decision tree glucose bolus (D3)

Rules					Balanced train set			Test set		
								Accuracy: 90.38		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN next glucose bolus**	**Support (%)**	**Confi dence**	**Confidence difference**	**Support (%)**	**Confi dence**	**Confidence difference**
3	1	>5.25	-	0	50	63.33	30	90.30	99.87	0.0046
4	11	<2.65	-	50	15	88.89	55.56	.43	27.27	26.92
5	5	[2.65-5.25]	-	20	35	57.14	33.81	9.26	0.85	0.73

Extracted rules for next glucose bolus (D3)

Decision tree rule extraction for determining the next insulin bolus

Unfortunately, as to be seen in table 16, the number of insulin boluses that were captured in the ICIP IC system is very low. Therefore insulin boluses could not be considered in this research.

Description	Class	#	%
0 unit bolus	1	10133	99.82
1 unit bolus	2	1	0.01
2 unit bolus	3	0	0.00
3 unit bolus	4	4	0.04
4 unit bolus	5	0	0.00
5 unit bolus	6	0	0.00
6 unit bolus	7	1	0.01
7 unit bolus	8	0	0.00
8 unit bolus	9	0	0.00
9 unit bolus	10	0	0.00
10 unit bolus	11	8	0.08
11 unit bolus	12	0	0.00
12 unit bolus	13	0	0.00
13 unit bolus	14	0	0.00
14 unit bolus	15	0	0.00
15 unit bolus	16	2	0.02

Classes and frequencies insulin boluses (D3)

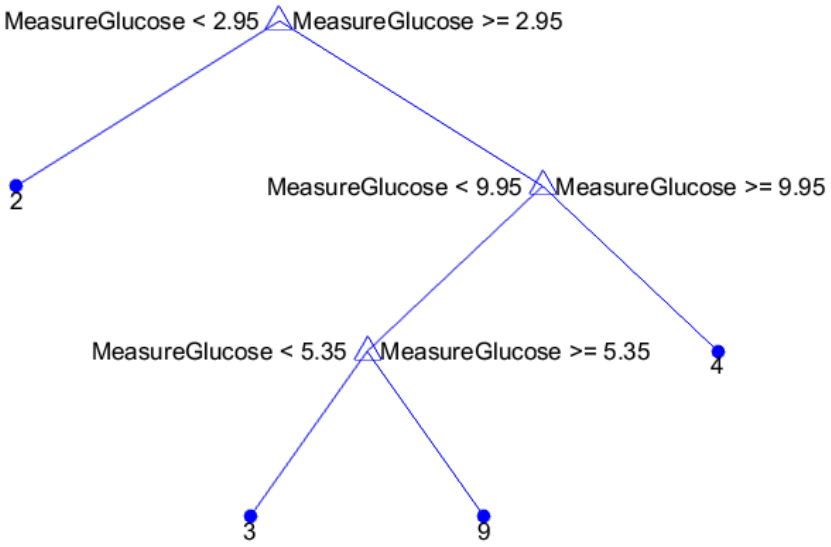
Decision trees: E3

Duration to next measurement (E3)

Class	1	2	3	4	5	6	7	8	9
Time interval	0-30	30-60	60-90	90-120	120-150	150-180	180-210	210-240	>240
# instances	342	228	406	701	842	797	886	847	6089

Classes and frequencies time to next measurement (E3)

The maximum number of observations allowed per class in the undersampling phase was set to 300.



Decision tree duration to next measurement (E3)

Rules					**Balanced train set**			**Test set**		
								Accuracy: 46.52		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN perform next glucose measurement within**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
2	2	<2.95	-	30 – 60	1.86	44.90	36.22	0.57	37.50	35.49
5	4	>9.95	-	90 – 120	19.14	15.11	3.69	14.83	8.47	2.19
6	3	[2.95-5.35]	-	60 – 90	12.52	18.84	7.42	10.81	5.32	1.65
7	9	[5.35-9.95]	-	> 240	66.48	14.31	2.89	73.78	60.27	5.60

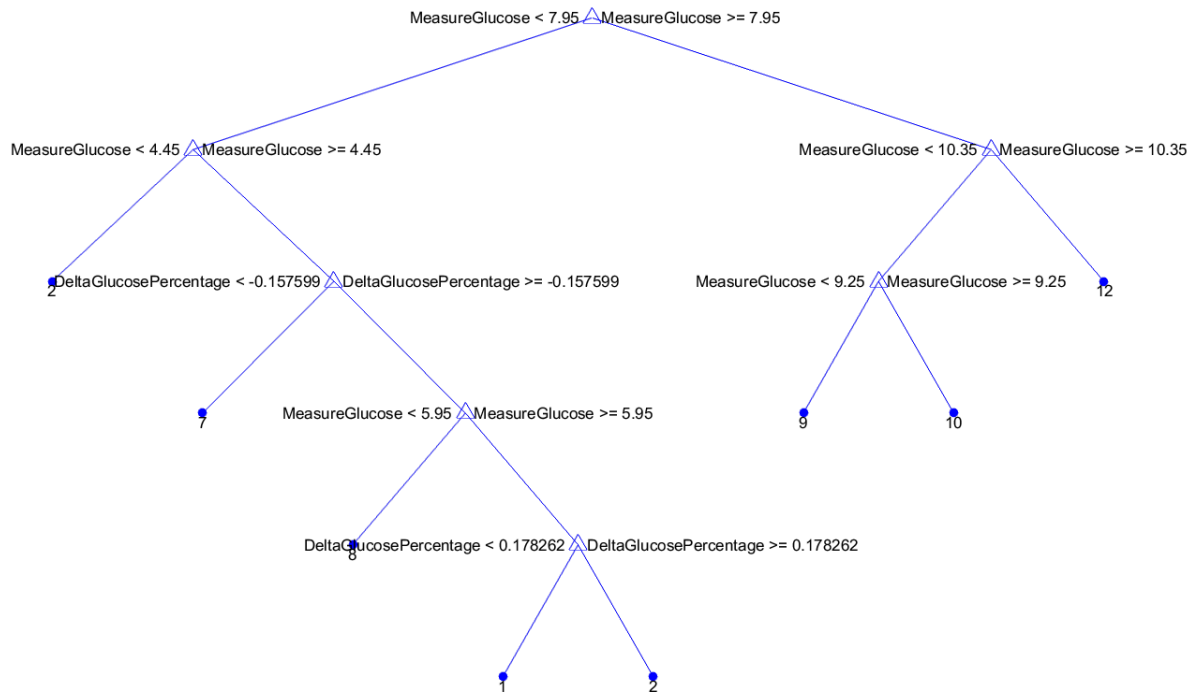
Extracted rules for duration to next glucose measurement (E3)

Required change in the Novorapid perfusor setting (E3)

Description	Class	#	%
Maintain current Novorapid setting	1	9068	81.92
Stop Novorapid perfusor	2	241	2.18
Decrease Novorapid perfusor with 3 or more	3	44	0.40
Decrease Novorapid perfusor with 2.5	4	10	0.09
Decrease Novorapid perfusor with 2	5	87	.79
Decrease Novorapid perfusor with 1.5	6	49	.44
Decrease Novorapid perfusor with 1	7	276	2.49
Decrease Novorapid perfusor with 0.5	8	176	1.59
Increase Novorapid perfusor with 0.5	9	251	2.27
Increase Novorapid perfusor with 1	10	535	4.83
Increase Novorapid perfusor with 1.5	11	47	0.42
Increase Novorapid perfusor with 2	12	228	2.06
Increase Novorapid perfusor with 2.5	13	7	0.06
Increase Novorapid perfusor with 3 or more	14	51	0.46

Classes and frequencies Novorapid perfusor setting (E3)

The maximum number of observations allowed per class in the undersampling phase was set to 200.



Decision tree Novorapid perfusor (E3)

Rules					Balanced train set			Test set		
								Accuracy: 33.14%		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN next Novorapid perfusor**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
4	2	<4.45	-	Stop perfusor	7.42	52.42	40.45	4.41	18.03	15.86
7	12	>10.35 -		+2	20.41	39.30	27.33	13.34	10.57	8.51
8	7	[4.45 7.95]	<-15.8	-1	20.71	28.90	16.93	11.42	10.76	8.23
10	9	[7.95 9.25]	-	+0.5	15.98	27.72	15.75	18.36	4.53	2.25
11	10	[9.25 10.35]	-	+1	11.25	34.04	22.07	8.64	15.90	11.06
12	8	[4.45 5.95]	>-15.8	-0.5	7.90	31.06	20.53	9.94	3.27	1.72
14	1	[5.95 7.95]	[-15.8 17.8]	Maintain	12.27	40.49	28.52	28.19	95.51	13.58
15	2	[5.95 7.95]	>17.8	Stop perfusor	4.07	23.53	11.56	5.71	4.43	2.26

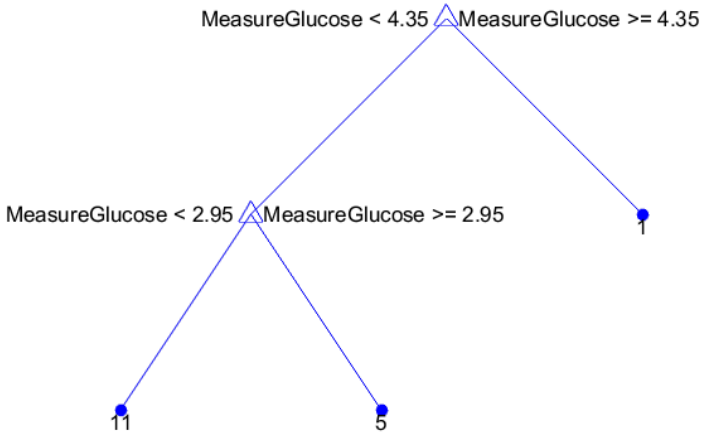
Extracted rules for next Novorapid perfusor setting (E3)

The next glucose bolus (E3)

Description	Class	#	%
0 mL Gluc 50%	1	11072	99.41
5 mL Gluc 50%	2	0	0.00
10 mL Gluc 50%	3	3	0.03
15 mL Gluc 50%	4	0	0.00
20 mL Gluc 50%	5	29	0.26
25 mL Gluc 50%	6	0	0.00
30 mL Gluc 50%	7	2	0.02
35 mL Gluc 50%	8	0	0.00
40 mL Gluc 50%	9	4	0.04
45 mL Gluc 50%	10	0	0.00
50 mL Gluc 50%	11	28	0.25

Classes and frequencies glucose boluses (E3)

The maximum number of observations allowed per class in the undersampling phase was set to 20.



Decision tree glucose bolus (E3)

Rules					Balanced train set			Test set		
								Accuracy: 96.41		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN next glucose bolus**	**Support (%)**	**Confi dence**	**Confidence difference**	**Support (%)**	**Confi dence**	**Confiden ce differenc e**
3	1	>4.35	-	0	39.13	74.07	45.08	96.37	99.89	0.50
4	11	<2.95	-	50	40.58	57.14	28.15	0.61	11.76	11.51
5	5	[2.95-4.35]	-	20	20.29	78.57	49.58	3.02	2.38	2.13

Extracted rules for next glucose bolus (E3)

Decision tree rule extraction for determining the next Insulin bolus (E3)

Description	Class	#	%
0 unit bolus	1	11114	99.78
1 unit bolus	2	0	0.00
2 unit bolus	3	0	0.00
3 unit bolus	4	3	0.03
4 unit bolus	5	3	0.03
5 unit bolus	6	0	0.00
6 unit bolus	7	0	0.00
7 unit bolus	8	0	0.00
8 unit bolus	9	0	0.00
9 unit bolus	10	0	0.00
10 unit bolus	11	18	0.16

Classes and frequencies insulin boluses (E3)

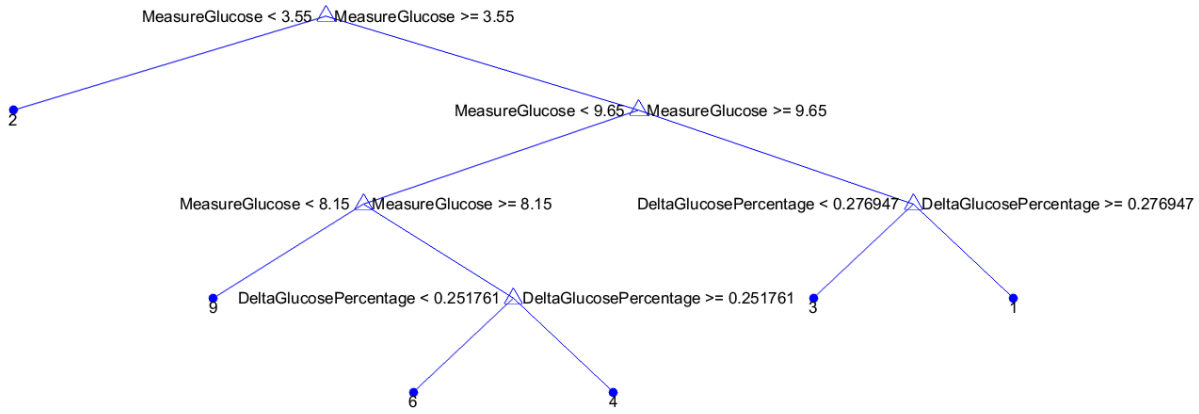
Decision trees: F3

Duration to next measurement (F3)

Class	1	2	3	4	5	6	7	8	9
Time interval	0-30	30-60	60-90	90-120	120-150	150-180	180-210	210-240	>240
# instances	802	160	406	920	1039	816	813	712	7464
%	6.11	1.22	3.09	7.01	7.91	6.21	6.19	5.42	56.84

Classes and frequencies time to next measurement (F3)

The maximum number of observations allowed per class in the undersampling phase was set to 300.



Decision tree duration to next measurement (F3)

Rules					Balanced train set			Test set		
								Accuracy: 40.15		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN perform next glucose measurement within**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
2	2	3.55	-	30 – 60	1.72	31.82	25.53	1.31	9.30	8.08
6	9	[3.55-8.15]	-	> 240	55.45	14.86	2.97	61.29	61.28	4.41
8	3	> 9.65	< 27.7%	60 – 90	14.76	16.67	4.96	11.05	4.63	1.56
9	1	> 9.65	> 27.7%	0 – 30	6.17	20.25	8.54	4.78	10.83	4.74
10	6	[8.15-9.65]	< 25.2%	150 – 180	18.08	17.49	5.78	17.67	6.55	0.34
11	4	[8.15-9.65]	> 25.2%	90 – 120	3.83	21.43	9.72	3.78	7.26	0.25

Extracted rules for duration to next glucose measurement (F3)

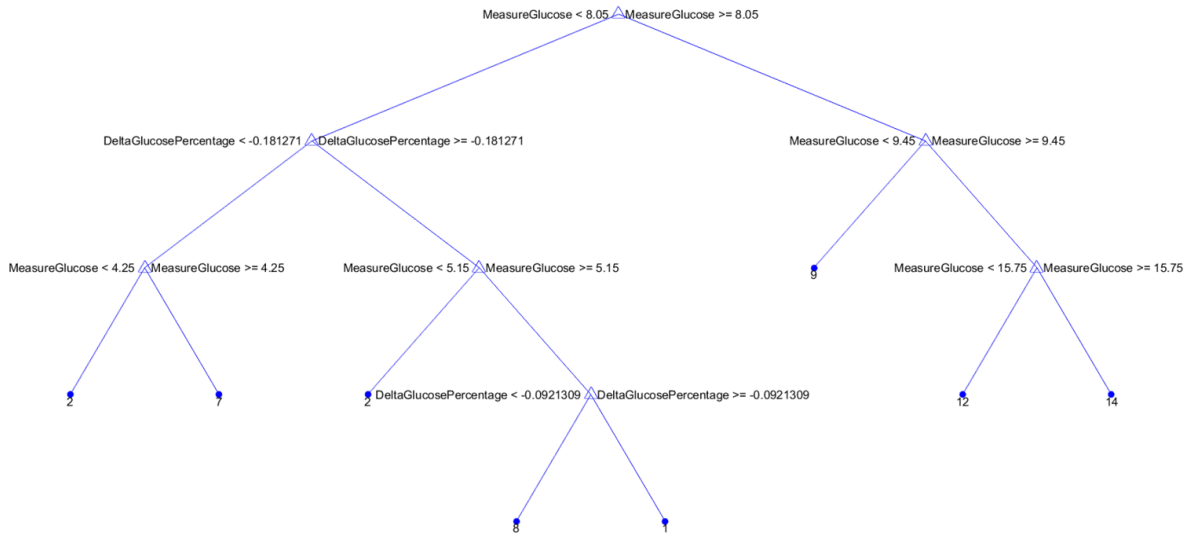
Required change in the Novorapid perfusor setting (F3)

Description	**Class**	**#**	**%**
Maintain current Novorapid setting	1	9679	73.95
Stop Novorapid perfusor	2	580	4.43
Decrease Novorapid perfusor with 3 or more	3	44	0.34

Decrease Novorapid perfusor with 2.5	4	10	0.08
Decrease Novorapid perfusor with 2	5	111	0.85
Decrease Novorapid perfusor with 1.5	6	80	0.61
Decrease Novorapid perfusor with 1	7	386	2.95
Decrease Novorapid perfusor with 0.5	8	274	2.09
Increase Novorapid perfusor with 0.5	9	341	2.61
Increase Novorapid perfusor with 1	10	1107	8.46
Increase Novorapid perfusor with 1.5	11	80	0.61
Increase Novorapid perfusor with 2	12	327	2.50
Increase Novorapid perfusor with 2.5	13	6	0.05
Increase Novorapid perfusor with 3 or more	14	63	0.48

Classes and frequencies Novorapid perfusor setting (F3)

The maximum number of observations allowed per class in the undersampling phase was set to 200.



Decision tree Novorapid perfusor (F3)

Rules					Balanced train set			Test set		
								Accuracy: 38.49%		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN next Novorapid perfusor**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
6	9	[8.05 9.45]	-	+0.5	21.18	30.00	18.85	20.45	6.28	3.68
8	2	<4.25	<18.1	Stop perfusor	2.51	17.34	6.19	1.53	44.00	39.54
9	7	[4.25 8.05]	<18.1	-1	22.30	19.75	8.6	11.34	12.40	9.46
10	2	<5.15	>18.1	Stop perfusor	2.68	45.83	34.68	3.21	7.62	3.16
12	12	[9.45 15.75]	-	+2	21.63	32.73	21.58	16.91	9.04	6.57
13	14	>15.75	-	+3 or more	2.23	47.50	43.93	1.59	13.46	12.97
14	8	[5.15 8.05]	[-18.1 -9.2]	-0.5	10.09	30.94	19.79	8.87	5.52	3.41
15	1	[5.15 8.05]	>-9.2	Maintain	17.39	30.13	18.98	36.11	90.43	16.48

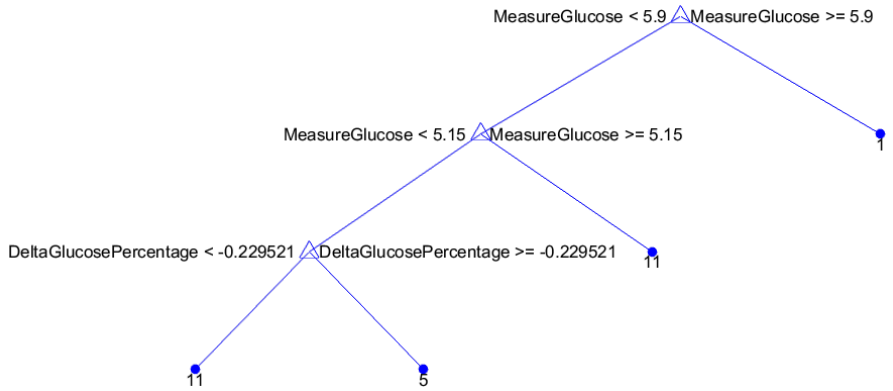
Extracted rules for next Novorapid perfusor setting (F3)

The next glucose bolus (F3)

Description	Class	#	%
0 mL Gluc 50%	1	13059	99.44
5 mL Gluc 50%	2	0	0.00
10 mL Gluc 50%	3	8	0.06
15 mL Gluc 50%	4	0	0.00
20 mL Gluc 50%	5	23	0.18
25 mL Gluc 50%	6	0	0.00
30 mL Gluc 50%	7	8	0.06
35 mL Gluc 50%	8	0	0.00
40 mL Gluc 50%	9	1	0.01
45 mL Gluc 50%	10	0	0.00
50 mL Gluc 50%	11	33	0.25

Classes and frequencies glucose boluses (F3)

The maximum number of observations allowed per class in the undersampling phase was set to 30.



Decision tree glucose bolus (F3)

Rules					Balanced train set			Test set		
								Accuracy: 84.31		
Node	**Class**	**IF glucose level**	**AND delta percentage glucose level (%)**	**THEN next glucose bolus**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
3	1	>5.9	-	0	40.40	70.00	39.70	84.28	99.86	0.43
5	11	[5.15 5.90]	-	50	9.09	77.78	47.48	8.29	0	-0.24
6	11	<5.15	<-23.0	50	23.23	43.48	13.18	3.14	0.97	0.73

Extracted rules for next glucose bolus (F3)

Decision tree rule extraction for determining the next Insulin bolus (F3)

Description	Class	#	%
0 unit bolus	1	13117	99.89
1 unit bolus	2	0	0.00
2 unit bolus	3	1	0.01
3 unit bolus	4	0	0.00
4 unit bolus	5	6	0.05
5 unit bolus	6	0	0.00
6 unit bolus	7	0	0.00
7 unit bolus	8	0	0.00
8 unit bolus	9	1	0.01
9 unit bolus	10	0	0.00
10 unit bolus	11	7	0.05

Classes and frequencies insulin boluses (F3)

Appendix 10: Overview Fuzzy Inference Systems

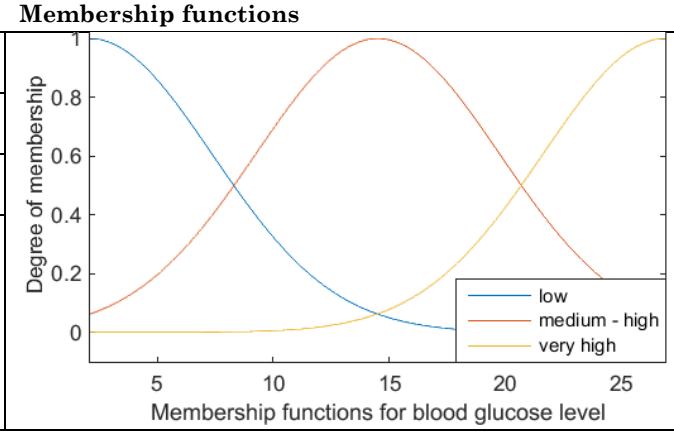
Fuzzy Inference Systems: D3

Duration to next measurement (D3)

Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters
low	[5.264 2.1]
medium - high	[5.26 14.4]
very high	[5.272 26.9]

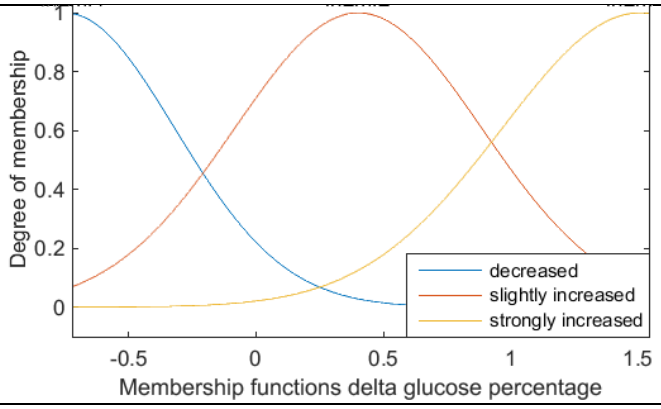
Membership functions



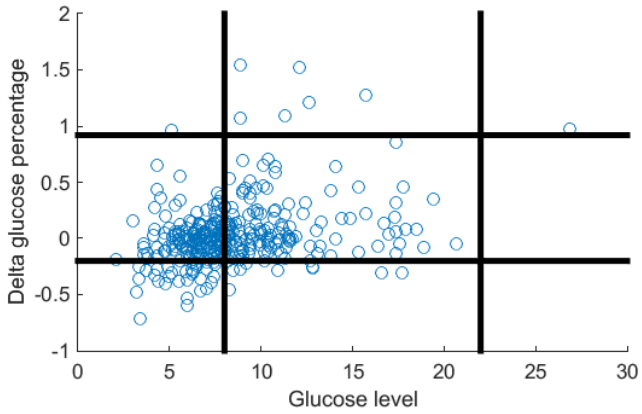
Linguistic variable: delta glucose percentage (dgp)

Linguistic value	Parameters
Decreased	[0.4307 -0.7482]
Slightly increased	[0.4861 0.4018]
Strongly increased	[0.5426 1.508]

Membership functions



Membership functions for independent variables



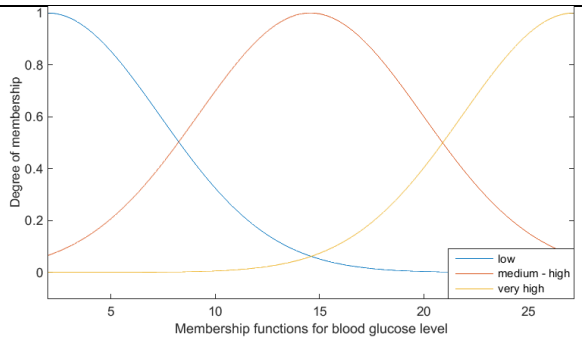
Scatterplot independent variables

IF glucose measurement	AND delta glucose %	THEN time to next measurement
low	decreased	1.24
low	slightly increased	5.11
medium to high	decreased	4.41
medium to high	slightly increased	2.07
medium to high	strongly increased	3.72

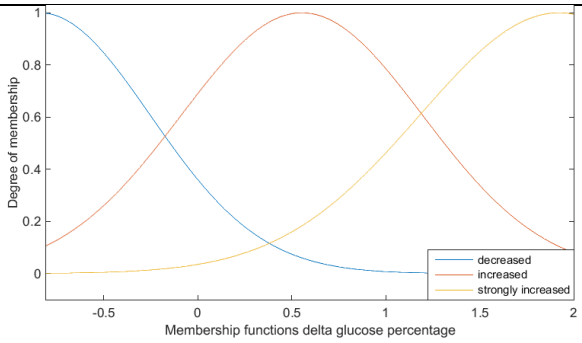
Extracted rules for duration to next glucose measurement (D3)

Novorapid perfusor setting (D3)

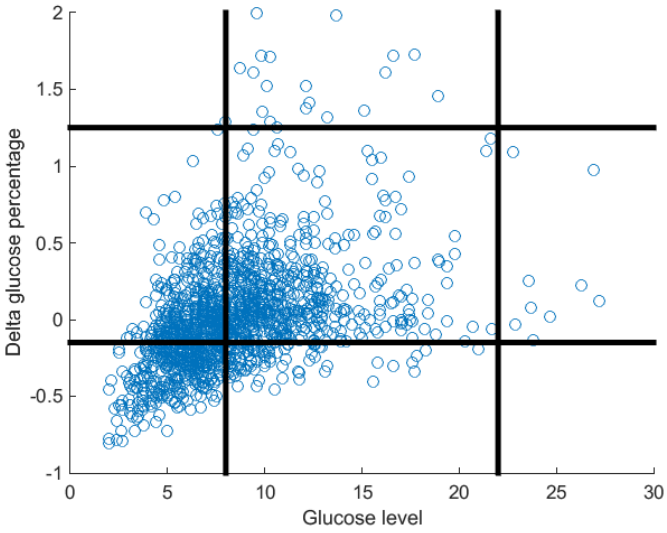
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
low	[5.352 1.985]	
medium - high	[5.39 14.6]	
high	[5.341 27.21]	

Linguistic variable: Delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.5875 -0.8387]	
increased	[0.6425 0.5545]	
strongly increased	[0.742 1.922]	

Membership functions for independent variables



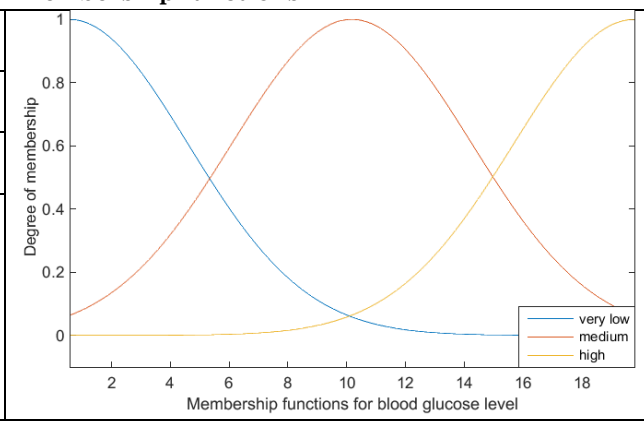
Scatterplot independent variables

IF glucose measurement	AND delta glucose %	THEN Novorapid perfusor setting
low	decreased	-2.40
low	increased	-1.11
medium - high	decreased	2.45
medium - high	increased	1.44
medium - high	strongly increased	1.36
very high	increased	7.38

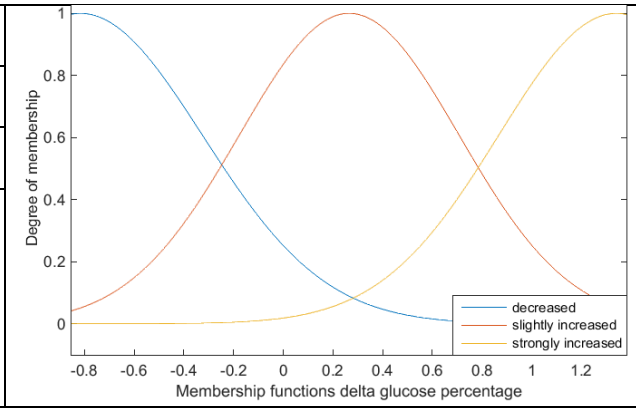
Extracted rules for determining the next Novorapid perfusor setting (D3)

Glucose bolus (D3)

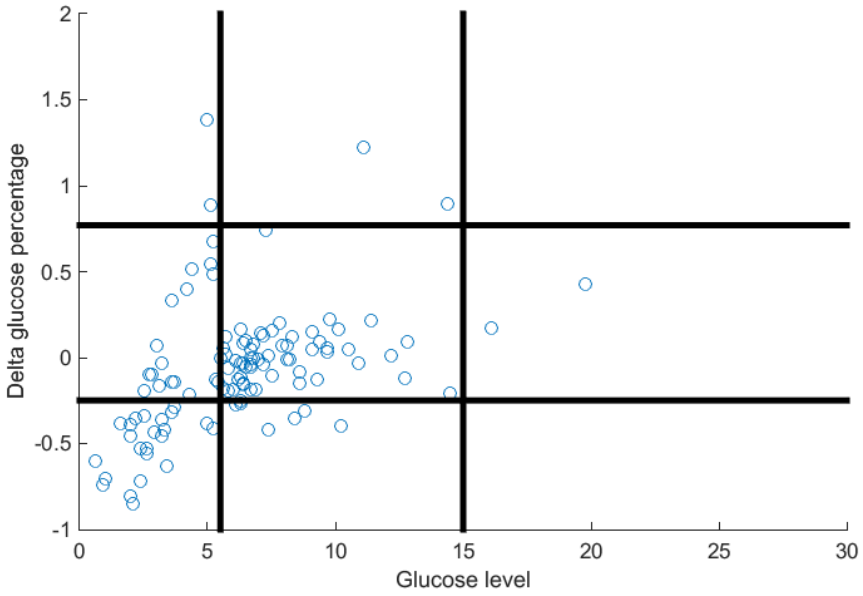
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
very low	[4.033 0.5632]	
medium	[4.088 10.18]	
high	[4.099 19.79]	

Linguistic variable: Delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.4914 -0.8158]	
slightly increased	[4.033 0.5632]	
strongly increased	[4.099 19.79]	

Membership functions for independent variables



Scatterplot independent variables

QQ

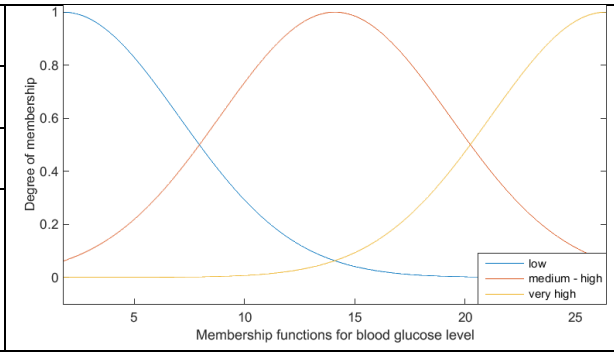
IF glucose measurement	**AND delta glucose %**	**THEN glucose bolus**
very low	decreased	45.81
very low	slightly increased	6.96
medium	decreased	-11.34 -> 0
medium	slightly increased	0.06

Extracted rules for determining the next Glucose bolus (D3)

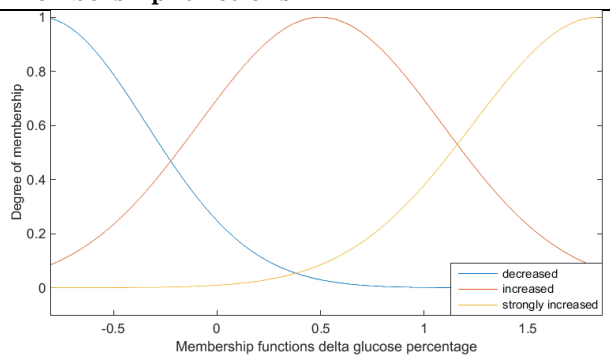
Fuzzy Inference Systems: E3

Duration to next glucose measurement (E3)

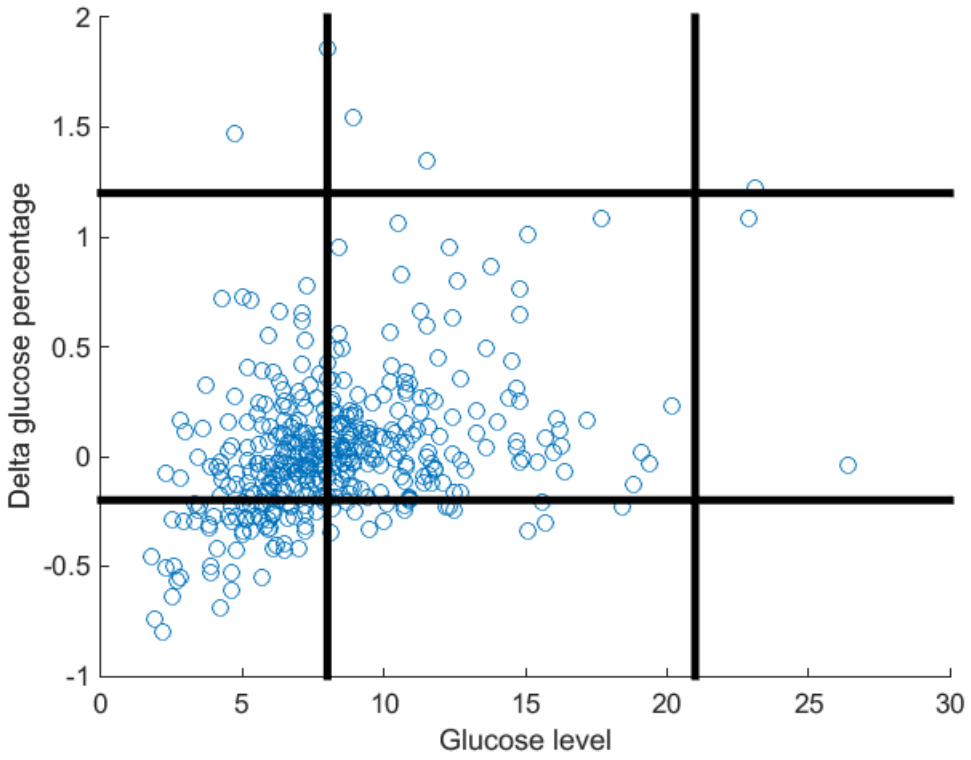
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
low	[5.225 1.804]	
medium - high	[5.22 14.1]	
very high	[5.23 26.6]	

Linguistic variable: delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.5099 -0.8517]	
increased	[0.5864 0.4983]	
strongly increased	[0.604 1.84]	

Membership functions for independent variables



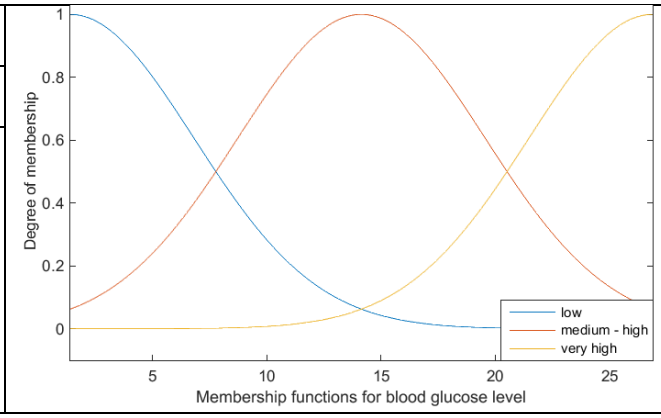
Scatterplot independent variables

IF glucose measurement	**AND delta glucose %**	**THEN time to next measurement**
low	decreased	0.76
low	increased	4.78
medium - high	decreased	2.09
medium - high	increased	2.58

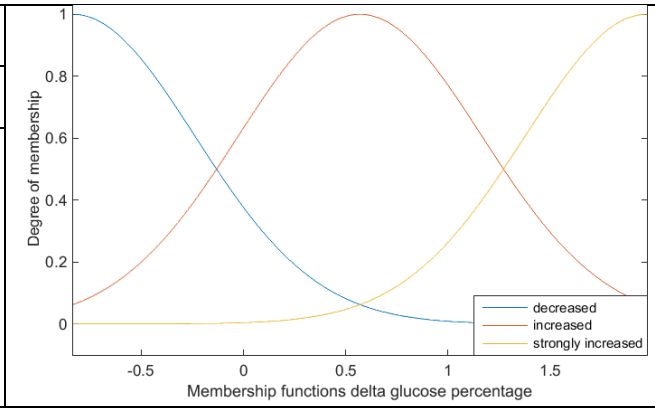
Extracted rules for duration to next glucose measurement (E3)

Novorapid perfusor setting (E3)

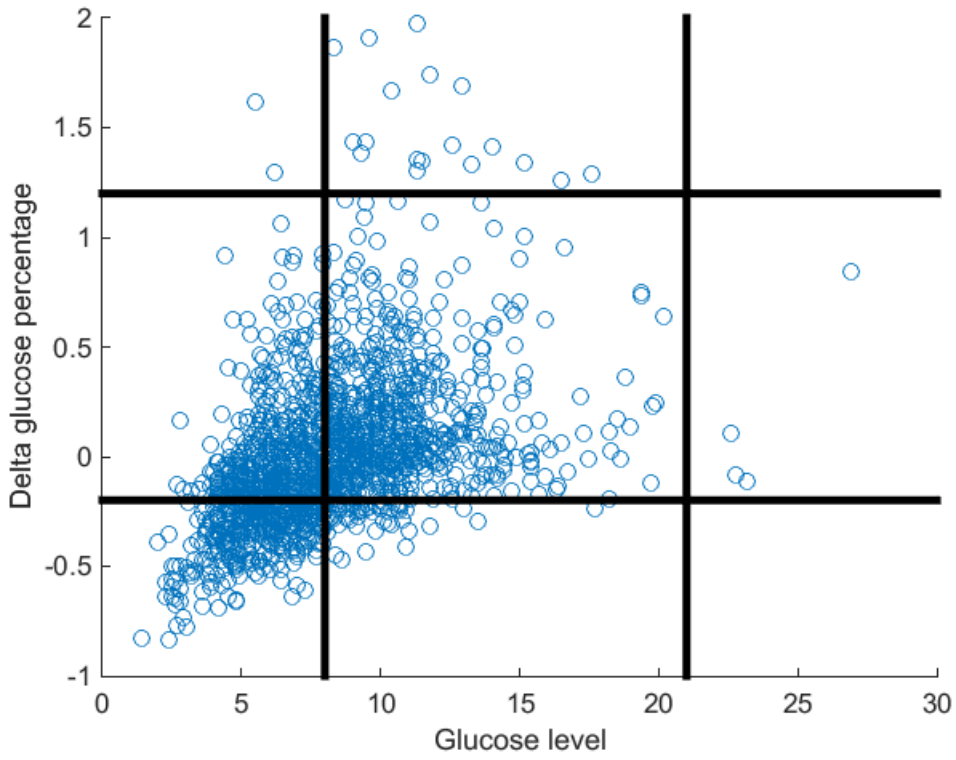
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
low	[5.429 1.417]	
medium - high	[5.409 14.16]	
very high	[5.422 26.9]	

Linguistic variable: Delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.5475 -0.8897]	
increased	[0.6205 0.5303]	
strongly increased	[0.6067 1.97]	

Membership functions for independent variables



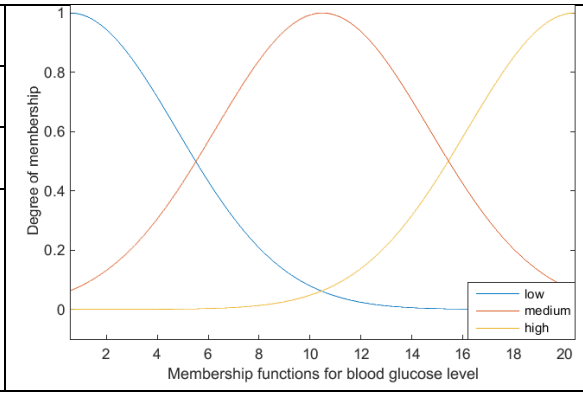
Scatterplot independent variables

IF glucose measurement	**AND delta glucose %**	**THEN Novorapid perfusor setting**
low	decreased	-2.75
low	increased	-1.26
medium - high	decreased	1.089
medium - high	increased	1.81
medium - high	strongly increased	1.47
very high	increased	2.49

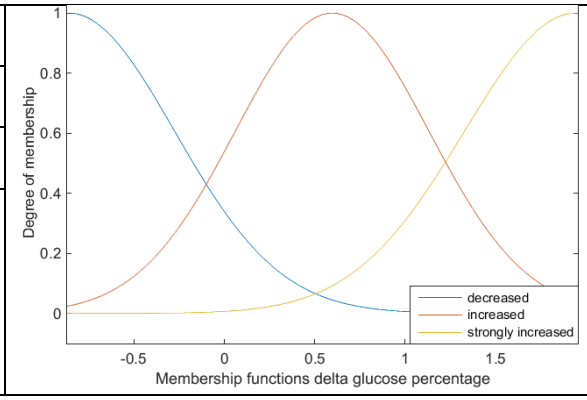
Extracted rules for determining the next Novorapid perfusor setting (E3)

Glucose bolus (D3)

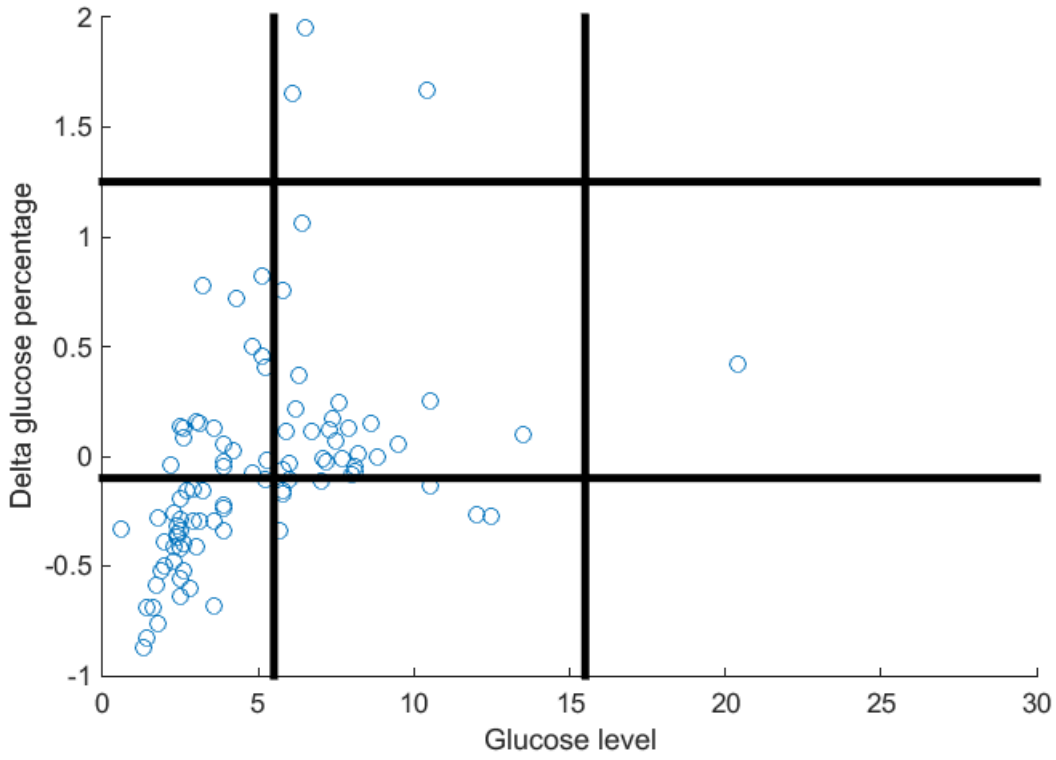
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
very low	[4.186 0.5803]	
medium	[4.213 10.49]	
high	[4.217 20.4]	

Linguistic variable: Delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.5843 -0.8593]	
increased	[0.5358 0.5956]	
strongly increased	[0.617 1.94]	

Membership functions for independent variables



Scatterplot independent variables

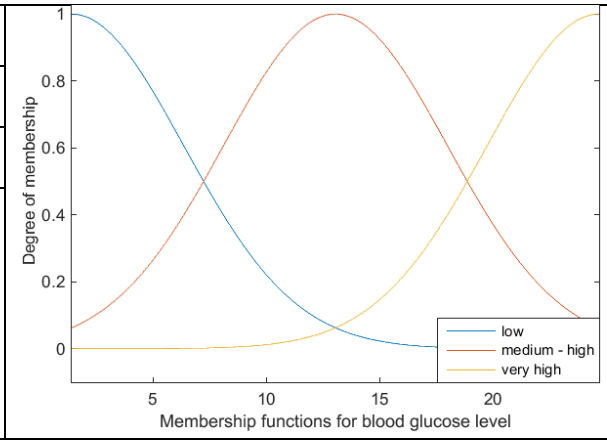
IF glucose measurement	AND delta glucose %	THEN glucose bolus
very low	decreased	55.56
very low	increased	22.98
medium	increased	8.56

Extracted rules for determining the next Glucose bolus (E3)

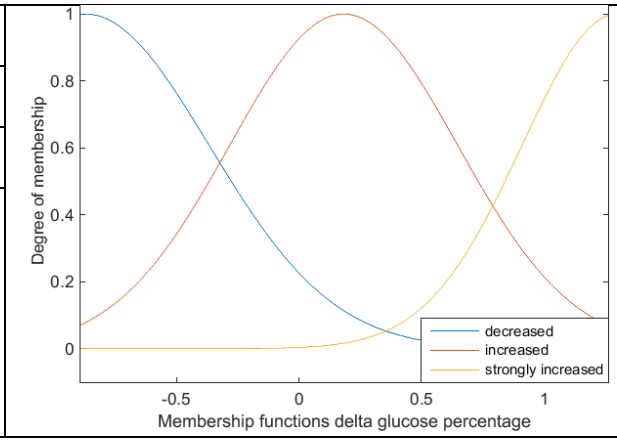
Fuzzy Inference Systems: F3

Duration to next glucose measurement (F3)

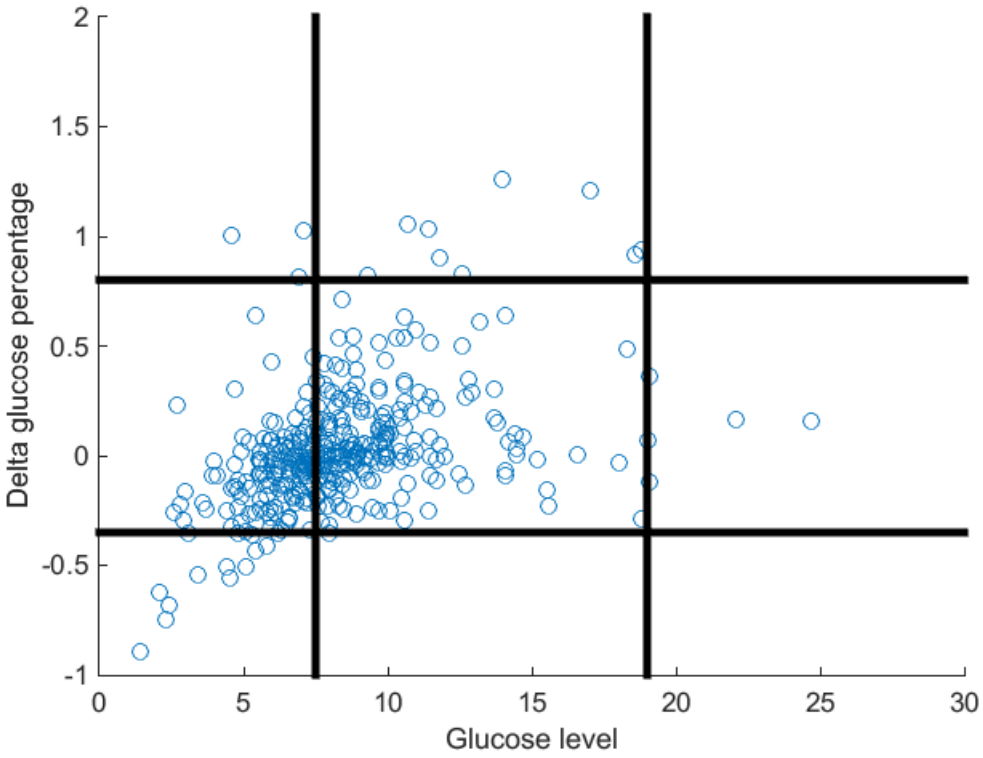
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
low	[4.95 1.55]	
medium - high	[4.947 13.05]	
very high	[4.948 24.7]	

Linguistic variable: delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.5039 -0.8699]	
increased	[0.4652 0.1811]	
strongly increased	[0.3881 1.295]	

Membership functions for independent variables



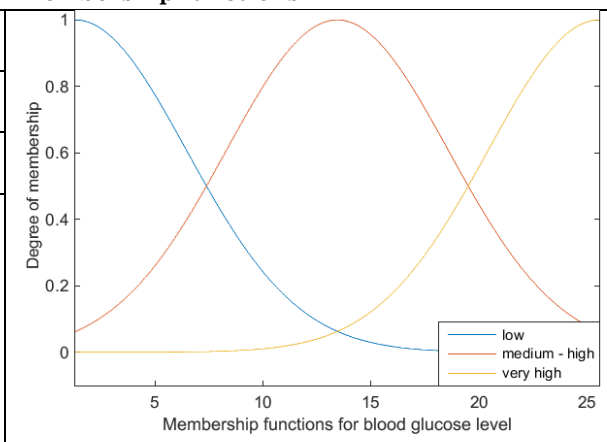
Scatterplot independent variables

IF glucose measurement	AND delta glucose %	THEN time to next measurement
low	decreased	-.019
low	increased	4.62
medium – high	increased	2.06
medium – high	strongly increased	2.71
very high	increased	1.43

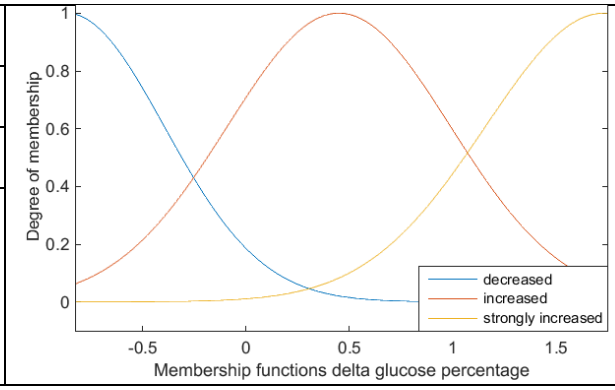
Extracted rules for duration to next glucose measurement (F3)

Novorapid perfusor setting (F3)

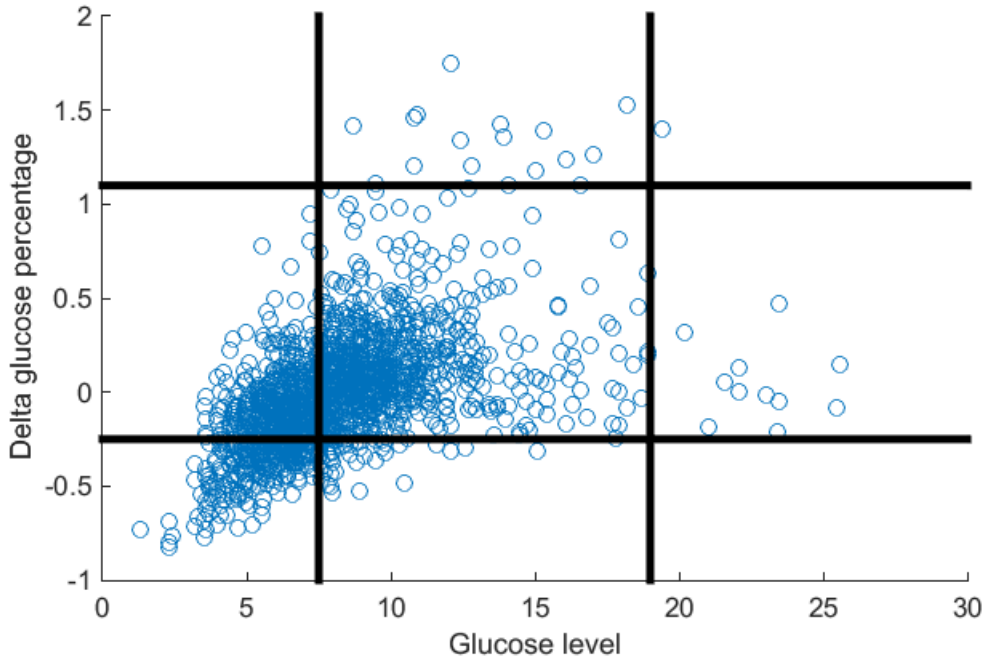
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
low	[5.164 1.306]	
medium - high	[5.156 13.46]	
very high	[5.159 25.6]	

Linguistic variable: Delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.4724 -0.8673]	
increased	[0.5418 0.45]	
strongly increased	[0.5748 1.734]	

Membership functions for independent variables



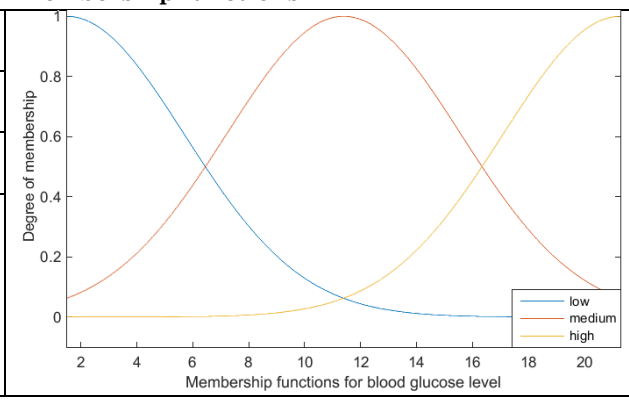
Scatterplot independent variables

IF glucose measurement	**AND delta glucose %**	**THEN Novorapid perfusor setting**
low	decreased	-2.69
low	increased	-2.04
medium - high	decreased	0.34
medium – high	increased	2.25
medium – high	strongly increased	1.41
very high	increased	3.46

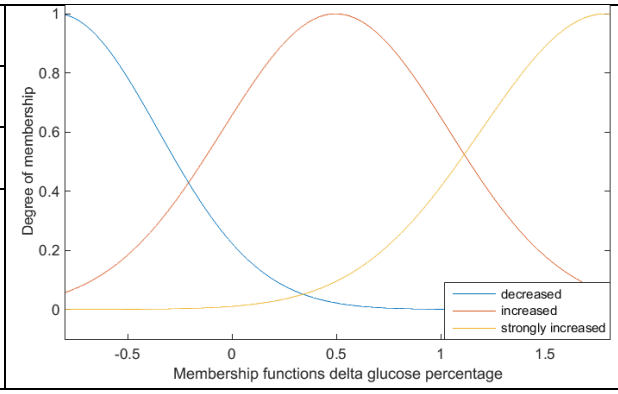
Extracted rules for determining the next Novorapid perfusor setting (F3)

Glucose bolus (F3)

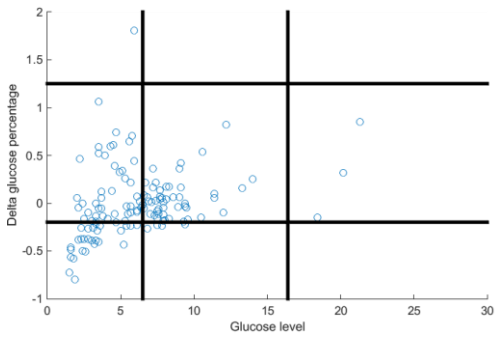
Linguistic variable: glucose measurement (gm)

Linguistic value	Parameters	Membership functions
very low	[4.202 1.498]	
medium	[4.205 11.4]	
high	[4.206 21.3]	

Linguistic variable: Delta glucose percentage (dgp)

Linguistic value	Parameters	Membership functions
decreased	[0.4843 -0.8381]	
unchanged	[0.542 0.497]	
increased	[0.5942 1.788]	

Membership functions for independent variables



Scatterplot independent variables

IF glucose measurement	AND delta glucose %	THEN glucose bolus
low	decreased	40.5
low	increased	32.5
medium	increased	17.82
high	increased	-1.43 -> 0

Extracted rules for determining the next Glucose bolus (F3)

Appendix 11: Protocol deviations

Red = deleted rule

Green = rule more or less according to the protocol

Orange = rule not according to the protocol

Black = neutral

Rules					Balanced train set			Test set		
								Accuracy: 49.90		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**thenperform next glucose measurement within**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
N2	2	<3.95	-	30 – 60	4.31	32.00	23.90	2.76	11.43	10.05
N5	4	>14.45	-	90 – 120	6.55	21.93	10.44	2.92	12.16	7.98
N7	7	[8.75-14.45]		180 -210	26.94	14.93	3.44	21.96	6.46	0.79
N8	6	[3.95-8.75]	<-28.7	150 – 180	4.88	21.18	9.69	4.73	2.50	-2.78
N9	9	[3.95-8.75]	>=-28.7	> 240	57.32	15.43	3.94	67.64	70.51	4.49

Extracted rules for duration to next glucose measurement (D3)

Rules					Balanced train set			Test set		
								Accuracy: 47.27%		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then Novorapid perfusor**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
5	1	<8.15	>-10.6	Keep current	25.22	24.94	12.23	45.38	93.55	11.14
7	12	>12.55	-	+2	9.78	17.53	4.82	5.14	14.62	13.03
8	2	<3.25	<-10.6	Stop perfusor	1.65	65.38	54.2	0.91	26.09	24.39
9	7	[3.25-8.15]	<-10.6	-1	27.76	23.34	11.14	20.40	3.88	1.94
11	10	[9.65-12.55]	-	+1	17.47	28.73	16.02	11.30	14.69	9.55
12	10	[8.15-9.65]	<-10.9	+1	3.68	34.48	21.77	2.73	14.49	9.35
13	9	[8.15-9.65]	>-10.9	+.5	14.42	37.44	24.73	14.15	6.98	4.14

Extracted rules for Novorapid perfusor setting (D3)

Rules					Balanced train set			Test set		
								Accuracy: 90.38		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then glucose bolus**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
3	1	>5.25	-	0	50	63.33	30	90.30	99.87	0.0046
4	11	<2.65	-	50	15	88.89	55.56	.43	27.27	26.92
5	5	[2.65-5.25]	-	20	35	57.14	33.81	9.26	0.85	0.73

Extracted rules for glucose bolus (D3)

If glucose measurement	and delta percentage glucose level (%)	then perform next glucose measurement within
low	decreased	1.24
low	slightly increased	5.11
medium to high	decreased	4.41
medium to high	slightly increased	2.07
medium to high	strongly increased	3.72
MAPE: 1.1378		

Extracted rules for duration to next glucose measurement (D3)

If glucose measurement	and delta percentage glucose level (%)	then Novorapid perfusor
low	decreased	-2.40
low	increased	-1.11
medium - high	decreased	2.45
medium - high	increased	1.44
medium - high	strongly increased	1.36
very high	increased	7.38
MAPE: 0.6482		

Extracted rules for Novorapid perfusor setting (F3)

If glucose measurement	and delta percentage glucose level (%)	then glucose bolus
very low	decreased	45.81
very low	slightly increased	6.96
medium	decreased	-11.34 -> 0
medium	slightly increased	0.06
MAPE: 10.8696		

Extracted rules for glucose bolus (F3)

Red = deleted rule
Green = rule according to the protocol
Orange = rule not according to the protocol
Black = neutral

Rules					Balanced train set			Test set		
								Accuracy: 46.52		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then perform next glucose measurement within**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
2	2	<2.95	-	30 – 60	1.86	44.90	36.22	0.57	37.50	35.49
5	4	>9.95	-	90 – 120	19.14	15.11	3.69	14.83	8.47	2.19
6	3	[2.95-5.35]	-	60 – 90	12.52	18.84	7.42	10.81	5.32	1.65
7	9	[5.35-9.95]	-	> 240	66.48	14.31	2.89	73.78	60.27	5.60

Extracted rules for duration to next glucose measurement (E3)

Rules					Balanced train set			Test set		
								Accuracy: 33.14%		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then Novorapid perfusor**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
4	2	<4.45	-	Stop perfusor	7.42	52.42	40.45	4.41	18.03	15.86
7	12	>10.35 -		+2	20.41	39.30	27.33	13.34	10.57	8.51
8	7	[4.45 7.95]	<-15.8	-1	20.71	28.90	16.93	11.42	10.76	8.23
10	9	[7.95 9.25]	-	+0.5	15.98	27.72	15.75	18.36	4.53	2.25
11	10	[9.25 10.35]	-	+1	11.25	34.04	22.07	8.64	15.90	11.06
12	8	[4.45 5.95]	>-15.8	-0.5	7.90	31.06	20.53	9.94	3.27	1.72
14	1	[5.95 7.95]	[-15.8 17.8]	Maintain	12.27	40.49	28.52	28.19	95.51	13.58
15	2	[5.95 7.95]	>17.8	Stop perfusor	4.07	23.53	11.56	5.71	4.43	2.26

Extracted rules for Novorapid perfusor setting (E3)

Rules					Balanced train set			Test set		
								Accuracy: 96.41		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then glucose bolus**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
3	1	>4.35	-	0	39.13	74.07	45.08	96.37	99.89	0.50
4	11	<2.95	-	50	40.58	57.14	28.15	0.61	11.76	11.51
5	5	[2.95-4.35]	-	20	20.29	78.57	49.58	3.02	2.38	2.13

Extracted rules for glucose bolus (E3)

If glucose measurement	and delta percentage glucose level (%)	then perform next glucose measurement within
low	decreased	0.76
low	increased	4.78
medium - high	decreased	2.09
medium - high	increased	2.58
MAPE: 1.1606		

Extracted rules for duration to next glucose measurement (E3)

If glucose measurement	and delta percentage glucose level (%)	then Novorapid perfusor
low	decreased	-2.75
low	increased	-1.26
medium - high	decreased	1.089
medium - high	increased	1.81
medium - high	strongly increased	1.47
very high	increased	2.49
MAPE: 0.6409		

Extracted rules for Novorapid perfusor setting (E3)

If glucose measurement	and delta percentage glucose level (%)	then glucose bolus
very low	decreased	55.56
very low	increased	22.98
medium	increased	8.56
MAPE: 11.0660		

Extracted rules for glucose bolus (E3)

Red = deleted rule
Green = rule according to the protocol
Orange = rule not according to the protocol
Black = neutral

Rules					Balanced train set			Test set		
								Accuracy: 40.15		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then perform next glucose measurement within**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
2	2	< 3.55	-	30 – 60	1.72	31.82	25.53	1.31	9.30	8.08
6	9	[3.55-8.15]	-	> 240	55.45	14.86	2.97	61.29	61.28	4.41
8	3	> 9.65	< 27.7%	60 – 90	14.76	16.67	4.96	11.05	4.63	1.56
9	1	> 9.65	> 27.7%	0 – 30	6.17	20.25	8.54	4.78	10.83	4.74
10	6	[8.15-9.65]	< 25.2%	150 – 180	18.08	17.49	5.78	17.67	6.55	0.34
11	4	[8.15-9.65]	> 25.2%	90 – 120	3.83	21.43	9.72	3.78	7.26	0.25

Table 45: Extracted rules for duration to next glucose measurement (F3)

Rules					Balanced train set			Test set		
								Accuracy: 38.49%		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then next Novorapid perfusor**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
6	9	[8.05 9.45]	-	+0.5	21.18	30.00	18.85	20.45	6.28	3.68
8	2	<4.25	<18.1	Stop perfusor	2.51	17.34	6.19	1.53	44.00	39.54
9	7	[4.25 8.05]	<18.1	-1	22.30	19.75	8.6	11.34	12.40	9.46
10	2	<5.15	>18.1	Stop perfusor	2.68	45.83	34.68	3.21	7.62	3.16
12	12	[9.45 15.75]	-	+2	21.63	32.73	21.58	16.91	9.04	6.57
13	14	>15.75	-	+3 or more	2.23	47.50	43.93	1.59	13.46	12.97
14	8	[5.15 8.05]	[-18.1 -9.2]	-0.5	10.09	30.94	19.79	8.87	5.52	3.41
15	1	[5.15 8.05]	>-9.2	Maintain	17.39	30.13	18.98	36.11	90.43	16.48

Table 46: Extracted rules for Novorapid perfusor setting (F3)

Rules					Balanced train set			Test set		
								Accuracy: 84.31		
Node	**Class**	**If glucose level**	**and delta percentage glucose level (%)**	**then next glucose bolus**	**Support (%)**	**Confidence**	**Confidence difference**	**Support (%)**	**Confidence**	**Confidence difference**
3	1	>5.9	-	0	40.40	70.00	39.70	84.28	99.86	0.43
5	11	[5.15 5.90]	-	50	9.09	77.78	47.48	8.29	0	-0.24
6	11	<5.15	<-23.0	50	23.23	43.48	13.18	3.14	0.97	0.73
7	5	<5.15	>-23.0	20	27.27	51.85	28.62	4.29	2.84	2.68

Table 47: Extracted rules for glucose bolus (F3)

If glucose measurement	and delta percentage glucose level (%)	then perform next glucose measurement within
low	decreased	-.019 → 0
low	increased	4.62
medium – high	increased	2.06
medium – high	strongly increased	2.71
very high	increased	1.43
MAPE: 1.2223		

Table 48: Extracted rules for duration to next glucose measurement (F3)

If glucose measurement	and delta percentage glucose level (%)	then Novorapid perfusor
low	decreased	-2.69
low	increased	-2.04
medium - high	decreased	0.34
medium – high	increased	2.25
medium – high	strongly increased	1.41
very high	increased	3.46
MAPE: 0.6686		

Table 49: Extracted rules for Novorapid perfusor setting(F3)

If glucose measurement	and delta percentage glucose level (%)	then glucose bolus
low	decreased	40.5
low	increased	32.5
medium	increased	17.82
high	increased	-1.43 → 0
MAPE: 12.6006		

Table 50: Extracted rules for glucose bolus (F3)

Appendix 12: Survey questions and results

1. Op welke afdeling werkt u?
2. Hoe veel jaar werkt u al op deze afdeling?
3. Bent u op de hoogte van het strict glucose control protocol?
4. Is het strict glucose control protocol nog beschikbaar op de afdeling?
5. Indien ja, waar?
6. In welke mate wordt het strict glucose protocol gevolgd?
7. Wat is de ondergens van de bloedglucose streefwaarden?
8. Wat is de bovengens van de bloedglucose streefwaarden?
9. Bij welke bloedglucose wordt de Perfusor Novorapid gestart?
10. In hoeverre bent u het eens met de volgende stelling: "Het reguleren van de bloedglucose gaat volgens eigen inzicht van de verpleegkundige."?
11. In hoeverre bent u het eens met de volgende stelling: "Het reguleren van de bloedglucose is een protocollaire handeling."?
12. In hoeverre bent u het eens met de volgende stelling: "Het strict glucose control protocol wordt niet meer gehanteerd."?
13. In hoeverre bent u het eens met de volgende stelling: "Het zou revelant zijn om een opfris cursus omtrent het reguleren van de bloedglucose te krijgen."?
14. In hoeverre bent u het eens met de volgende stelling: "Er wordt gestart met het toedienen van insuline zoals het staat voorgeschreven in het protocol."?
15. In hoeverre bent u het eens met de volgende stelling: "De bepaling van een insuline bolus verloopt conform het protocol."?
16. In hoeverre bent u het eens met de volgende stelling: "Het toedienen van glucose bij een hypoglycemie verloopt conform het protocol."?
17. In hoeverre bent u het eens met de volgende stelling: "De stand van de Novorapid perfusor wordt aangepast conform het protocol."?
18. Heeft u nog additionele opmerkingen omtrent het strict glucose control protocol?