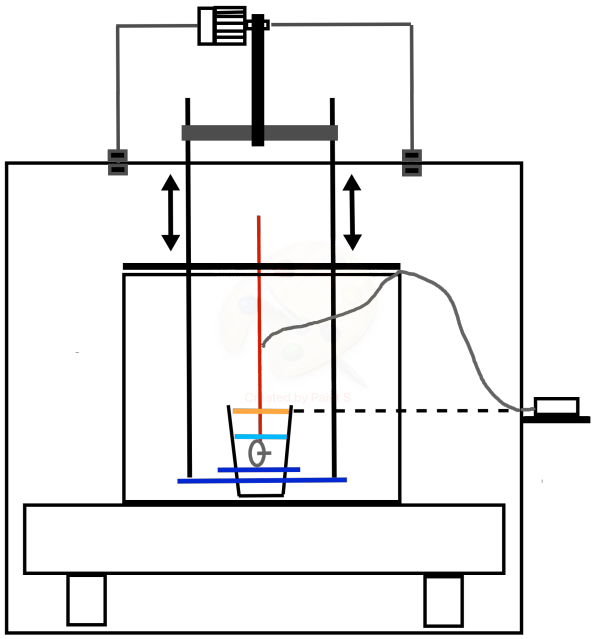
Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Information Technology and Electrical Engineering

Miriam Kopperstad Wolff

Comparison of Various Insulin Pumps with Respect to Accuracy of the Insulin Delivery

Master's thesis in Engineering and ICT
Supervisor: Martin Steinert
Co-supervisor: Anders Lyngvi Fougner
June 2021



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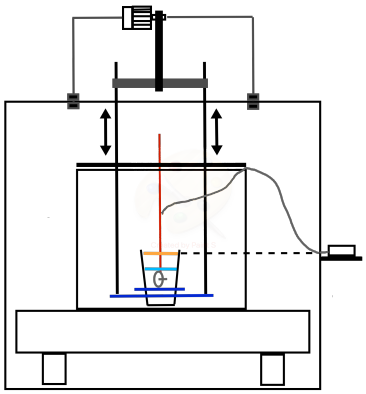

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Abstract

Insulin pumps are commonly used as part of the treatment for patients with Diabetes Mellitus type 1. Existing research indicates that the lower the insulin rates are, the lower the insulin delivery accuracy. Especially patients with low insulin demands might be significantly affected. There is no existing requirement for insulin delivery accuracy; therefore, this is up to the manufacturers to define. Manufacturers often promise accuracy levels of ±5%. In this master thesis, we will test the insulin delivery accuracy of different insulin pumps and discuss whether it is sufficient.

This master project is affiliated with Artificial Pancreas Trondheim (APT). APT is an interdisciplinary research group where developing a closed-loop glucose control system is the long-term goal. In the last years, several tries have been made to develop such systems by different researchers. A closed-loop system with automatic insulin delivery will require that the technical equipment is accurate and reliable.

The standard IEC 60601-2-24 describes how insulin pumps should be tested to verify accuracy and determine basic safety. During the autumn of 2020, we implemented this standard and established an experimental procedure. The project thesis can be found in appendix D. During this master thesis, the implementation of the IEC standard was further developed to achieve sufficient stability and reliable results.

Our experiment results verify that the higher insulin volume deliveries are more accurate than lower ones for insulin pumps from different manufacturers. However, following the IEC standard was challenging because it is very prone to disturbance. Especially when measuring low insulin rates, the relative margins of error are significant. We went through several iterations to optimize the experimental setup. Therefore, we suspect the standard to be poorly suited to test small insulin volumes. Further research should explore alternative methods of measuring insulin delivery accuracy to review the reliability of earlier studies of insulin pump accuracy.

Sammendrag

Insulinpumper er ofte brukt som en del av behandlingen for pasienter med Diabetes Mellitus type 1. Eksisterende forskning viser at jo lavere insulindoser, jo lavere er nøyaktigheten av insulinleveransen. Dette kan være spesielt farlig for pasienter med svært lavt insulinbehov. Det finnes ikke et krav for nøyaktighet av insulinleveranse, og dette er opp til insulinpumpeleverandøren å definere. Leverandørene lover ofte en nøyaktighet på ±5%. I denne avhandlingen skal vi teste nøyaktigheten på insulinleveransen hos forskjellige insulinpumper og diskutere om den er god nok.

Denne masteroppgaven er skrevet i samarbeid med Artificial Pancreas Trondheim (APT). APT er en tverrfaglig forskningsgruppe der det langsiktige målet er å utvikle et lukket-sløyfe glukose kontrollsystem. De siste årene har det blitt gjort flere forsøk på å utvikle et slikt system av forskjellige forskningsgrupper. Et lukket-sløyfe system med automatisk insulinleveranse vil stille enda høyere krav til at det tekniske utstyret er nøyaktig og pålitelig.

IEC 60601-2-24 standarden beskriver hvordan insulinpumper skal testes for å verifisere nøyaktigheten og sørge for grunnleggende sikkerhet. I løpet av høsten 2020 implementerte vi denne standarden og etablerte en eksperimentell prosedyre. Prosjektoppgaven kan bli funnet i appendiks D. Denne testmetoden trengte videre utvikling under masteroppgaven for å oppnå tilstrekkelig stabilitet og troverdige resultater.

De eksperimentelle resultatene bekrefter at de høye insulindosene er mer nøyaktige enn de lave for insulinpumper fra forskjellige leverandører. Det å følge IEC standarden var deimot utforende fordi den er veldig sårbar mot forstyrrelser. Spesielt når man måler lave doser er den relative feilmarginen betydelig. Derfor bør resultatene bli sett på som en indikator for en nøyaktighetsmåling, og som en mulighet til å sammenligne insulinpumper. Den totale leveransen over tid var nokså nøyaktig for de fleste insulinpumpene, til og med ved lave doser, så når man bruker systemer uten automatiske doseringer av insulin, er ikke avvikene nødvendigvis spesielt klinisk relevante. For lukket-sløyfe systemer derimot, krever hver individuelle leveranse et høyt nivå av nøyaktighet.

Preface

With this thesis, I finalize my Master of Science degree at the Norwegian University of Science and Technology (NTNU). Not once have I doubted this choice of career. It started as an integrated master in Engineering and ICT and led to a specialization in ICT and Mechanical Engineering. I also got the opportunity to be an exchange student at Universitat Politècnica de València (UPV) for a year. Together, the course of study has offered a wide range of new experiences and knowledge.

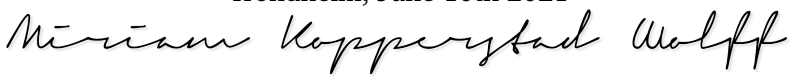
I would like to thank my supervisor Martin Steinert, and my co-supervisor, Anders Lyngvi Fougner, for their contributions and motivational support. All the help I have gotten from TrollLABS, both for academic and emotional support and for being an exceptional learning environment. The APT team, for much-needed constructive feedback, and especially Patrick Christian Bösch for valuable assistance and supply equipment.

I am grateful for my parents, Magnhild and Robert, that have been patiently listening when I incoherently tell them about my work. Especially my dad, that has been helping me with some practical tasks and his assistance as a chemical engineer. Thank you to my brother, Ruben, for guidance when it comes to writing. The students at the master's office have contributed with both humor and intellectual stimuli, making my everyday life enjoyable.

The outbreak of COVID-19 left its mark on my time at NTNU, when it first led to an early return from my stay in Spain and later a somewhat anticlimatic last year of a master's degree. This has, in many ways, been hard on most of us. On this occasion, I would like to thank NTNU for, in my opinion, handling the situation in such a good way. Quick and big decisions had to be made, and I am grateful that we could get through it without affecting my education in a major way.

My time at NTNU will be remembered with great pleasure for all the fun, the knowledge, and all the friends I have made along the way.

Trondheim, June 10th 2021



Miriam Kopperstad Wolff

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Chapter 1

Introduction

In this thesis, we present a comparison of various insulin pumps concerning the accuracy of insulin delivery. The evaluation is based on IEC 60601-2-24 (hereafter referred to as IEC). The IEC standard describes how insulin pumps should be tested to verify accuracy and determine basic safety. During the autumn of 2020, we implemented this standard and established an experimental procedure. The project thesis can be found in appendix D. During this master thesis, the implementation of the IEC standard was further developed to achieve sufficient stability and reliable results. Whether this standard is clinically relevant for evaluating basic safety in insulin pumps is up for discussion, and alternative methods are suggested. Several insulin pumps from different manufacturers are evaluated.

This chapter introduces the problem description, relevant background, and motivation to carry out the research. Further, we will define the scope of the project thesis, along with the limitations that apply. Lastly, an outline of the thesis contents is presented.

1.1 Background and Motivation

Insulin pumps are commonly used as part of the treatment for patients with Diabetes Mellitus type 1. Existing research indicates that the lower the insulin rates are, the lower is the accuracy of the insulin delivery [1] [2] [3]. If true, this might affect a wide span of patients, but especially those with very low insulin demand, like children. In this master thesis, we want to investigate insulin delivery accuracy at different insulin delivery rates for different insulin pump models.

The International Electrotechnical Commission (IEC) publishes international standards and provides certifications for electrical technologies. The IEC standard defines how to verify insulin delivery accuracy and provide basic safety in insulin pumps. Nevertheless, it does not mention any requirement for insulin delivery accuracy. Therefore the accuracy is up to the manufacturers to define. Manufacturers often

promise accuracy levels of ±5%.

The importance of a sufficient level of accuracy in insulin pumps has several aspects. In an artificial pancreas, a regulation system is made based on insulin pump deliveries together with glucose sensor values. Coefficients have to be individually programmed for each patient. When the coefficients are sufficient, future glucose levels can be predicted, leading to the possibility of automating insulin delivery. Unfortunately, glucose measurements and insulin delivery/absorption have both delays, and they are not perfectly accurate. Lower accuracy causes a lower quality artificial pancreas.

Insulin is a transparent liquid with the possibility of crystallization. Sometimes this will lead to a blockage of insulin delivery, also called an occlusion. Occlusions can appear for other reasons, such as inflammation. Insulin pumps usually implement ways to detect occlusions. A common problem in occlusion detection is delay and false positives. With a more reliable, accurate insulin delivery, the sensitivity of the occlusion alarms can be elevated. In this manner, a more accurate insulin pump can help to minimize the delay of occlusion alarms. Also, when it comes to occlusions, the most severely affected patient groups are the ones with the lowest insulin demands.

This master thesis is affiliated with Artificial Pancreas Trondheim (APT). APT is an interdisciplinary research group for whom developing a closed-loop glucose control system is the long-term goal. In the last years, several tries have been made to develop such systems by different researchers. A closed-loop system with automatic insulin delivery will require that the technical equipment is accurate and reliable.

1.2 Problem Description

The problem description for the thesis work is as follows:

> Patients with Diabetes Mellitus type 1 often use insulin pumps as part of the treatment. Most of these pumps have tubing and needle attached for infusion of insulin to the subcutaneous tissue. On the other hand, “patch pumps” are fixed directly to the skin without the use of tubing. In combination with blood glucose data from continuous glucose monitor (CGM) systems, we are looking into a future of automated insulin delivery.
>
> In this project, the student will measure the accuracy of insulin pumps based on the IEC 60601-2-24 standard and related test protocol. The student needs to ensure that the protocol is followed properly, that the measurements are representative, and that significant error sources are identified.
>
> Specifically, the student will perform the following tasks:

1. Literature review on:
    - The IEC standard for requirements for the basic safety and essential performance of infusion pumps and controllers.
    - Test methods for measuring accuracy of insulin bolus and basal rates.
    - Accuracy of insulin pumps.
    - Insulin pump technical specifications.
2. Implement an experimental setup and procedure.
3. Run experiments and analyze the results.
    - Run at least one experiment on 4 different insulin pump models.
    - One experiment consists of both bolus and basal rate measurements.
4. Write a scientific paper reviewing:
    - The accuracy of different insulin pumps.
    - The IEC standard and alternative ways of measuring insulin pump accuracy.
5. If time allows, the student should explore and aim to understand the cause of the obtained results.

1.3 Project Scope and Limitations

The main objective of this master thesis is to test the accuracy of insulin pumps from different manufacturers. To achieve this, we must further develop the experimental setup based on the IEC standard from the project thesis (appendix D). We have to be confident about the stability and reliability of the experimental results. It is necessary to establish a detailed experimental procedure to be able to compare insulin pumps righteously. When this is achieved, we will run experiments on insulin pumps from different manufacturers. Based on the experiences made during the project, we will discuss the pros and cons of the test method presented in the IEC standard and potential ways of improving it.

After obtaining experimental results, we will discuss them with a focus on clinical relevance. The questions to be addressed are: Is the insulin delivery accuracy sufficient in the different insulin pumps? Is it dangerous for patients with low insulin demand to use them? Lastly, we will propose how the research can further be developed.

The limitations of performing the study are primarily due to equipment. More expensive experimental equipment would make the results more accurate. In addition, it was necessary to borrow medical equipment, such as insulin pumps and insulin. Sometimes waiting for equipment was a bottleneck for the progress. Also,

building the experimental setups had its limitations with the quality of equipment. Those consisted of faulty and/or inaccurate temperature and humidity sensors and attempts to use motors that were broken.

The IEC standard was also a limitation in that it limits the freedom to be creative in testing insulin pump accuracy. To verify the performance of the insulin pumps, we had to perform tests under the same conditions as the manufacturers have done. However, the IEC standard does not necessarily present the most convenient method to obtain the most accurate results.

Last but not least, time and space were a limitation. We only had one analytical balance available, and every experiment took approximately one week. An even more quantified study would be preferable but unattainable. The experiments should optimally be performed in a room with temperature- and humidity control and as undisturbed as possible. This was not available for our experiments. However, benchmarking our results with other publications on the subject, the experimental environment has not significantly impacted our results.

1.4 Thesis Structure

Theory and related work

Chapter 3 presents a short overview of related work found on test setups for the accuracy of different types of insulin pumps. In addition, how to represent the results in a clinically relevant way is covered. Also, earlier tests of insulin pump accuracy are mentioned. Lastly, different methods for measuring the accuracy of small flows of liquid are presented.

Chapter 2 provides essential definitions and a theory foundation regarding insulin pumps, insulin, and the IEC standard for how to test the basic safety of insulin pumps.

Methodology and results

Chapter 4 presents the final test setup to measure insulin pump accuracy, including tests to determine whether the setup is stable. Procedures to prepare and carry out the tests are described in detail.

Chapter 5 presents test data from insulin pumps on early test setup. Further test results on the stability of the final test setup are presented.

Discussion and conclusions

Chapter 7 examines the thesis results and discusses possible sources of error. Challenges found during the establishment of the test setup are explained. The validity

and clinical relevance of the IEC standard are discussed. Various alternative solutions to the problem of injecting and measuring small volumes of insulin doses are proposed.

Chapter 8 contains the thesis conclusion and recommendations for future work.

Appendices

Appendix A contains the code files used to run experiments and to analyse experimental results. **Appendix B** contains the plots and tables from the different experiments testing bolus rates. **Appendix C** lists the plots and tables from the different experiments testing basal rates. The introductory work for the master thesis, from the project thesis during autumn 2020, can be found in **Appendix D**.

Chapter 2

Theoretical Framework

In this chapter, we will explain concepts and definitions that can be useful for understanding the thesis as a whole. First, we will look into what an insulin infusion system is, how they work, and how closed-loop systems work. Then we will provide some general information about the insulin pump models that are tested in this thesis. The characteristics and challenges of using insulin are explained. This information is relevant to the experiments and to appraise the clinical relevance of insulin delivery accuracy. Following, we summarize the relevant parts of the IEC standard to test the insulin accuracy of insulin pumps, which will be implemented in later chapters. Lastly, we will look into analytical balances and how to use them.

2.1 Insulin Infusion Systems

Insulin pumps are commonly used as part of the treatment for patients with Diabetes Mellitus type 1. Several brands are selling insulin infusion systems, but they are usually based on the same principles. Closed-loop systems are aiming to mimic the behavior of a pancreas. In Norway, the insulin pumps produced by Medtronic, Roche, and Rubin Medical are the ones used by patients in 2021 [4]. These are the brands we will test in this thesis, along with a no longer produced model by Johnson & Johnson.

2.1.1 System Description

A traditional insulin infusion system consists of an insulin pump and an insulin infusion set (see figure 2.1). A motor in the insulin pump is pushing a piston towards the insulin reservoir, resulting in an insulin flow through a plastic tube and a cannula inserted into the patient's body. Both the length of the plastic tubes and the cannulas are depending on the insulin infusion set. The cannulas are typically made of plastic or steel. The insulin pumps have buttons and a user

interface to insert insulin and choose user-specific settings.

Patch pumps, however, do not have a plastic tube. The adhesive tape is directly attached to the pump, with a cannula underneath, placed on the patient's body. To control the insulin patch pump, the patient needs a separate device with buttons and a user interface that communicates with the pump via Bluetooth.

Human beings should always have active insulin working in the body. Therefore insulin should periodically be injected. In an insulin pump, this is called the **basal rate** [U/h] because it is covering the basal need of insulin while carbohydrate intake is absent. The basal rate is fixed to a 24-hour profile for the specific patient. When the patient is about to eat, it is necessary to supplement with additional insulin injection, and these rates are called the **bolus rates** [U]. The volume of the dose depends on the meal and the time of the day.

Unfortunately, insulin demand is varying depending on many factors, such as activity levels and sleep patterns. This means that fixing a basal rate will only work to a certain degree. To solve this problem, manufacturers are trying to implement so-called hybrid-loop systems. These systems read continuous glucose sensor data, using control algorithms to predict future glucose levels and adjust basal rates. The patients still need to note carbohydrate intake and insert manual bolus doses, explaining why it is called a hybrid-loop system. For an entirely closed-loop system to work, glucose sensors must become more accurate, and delay in both glucose sensors and insulin absorption must be reduced or eliminated.

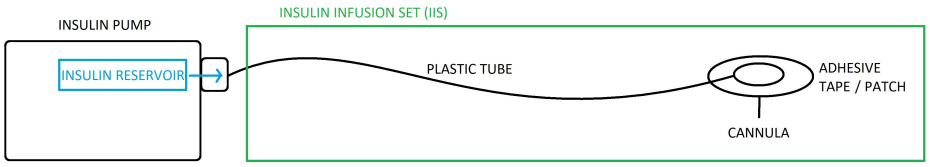


Figure 2.1: Illustration of an insulin infusion system sourced from the project thesis (appendix D).

2.2 Insulin Pump Models

In this section, we will give some general information about the insulin pumps used in this thesis's experiments.

2.2.1 MiniMed 640G and 640G

Medtronic 640G and 670G are among the most recent insulin pump models offered by Medtronic. It can be connected to a continuous glucose monitor and use this sensor data to predict the future glucose level. If there is a high risk of hypogly-

cemia, the insulin delivery will stop until the risk is over. The 670G provides an even more advanced algorithm that automatically adjusts as needed.

Delivery Accuracy and Speed

For basal rates and bolus rates ≥ 0.1 unit, Medtronic claims that this insulin pump model delivers an accuracy of ±5% [5]. However, for bolus volumes < 0.1 unit, they claim an accuracy of ±20%. The insulin delivery speed is 1.5 units per minute.

Increments

Basal rates are delivered quasi-continuously in increments (**??**):

- 0.025 U/h for basal amounts in the range 0 to 0.975 units
- 0.05 U/h for basal amounts in the range 1 to 9.95 units
- 0.1 U/h for basal amounts of 10 to 35 units

Minimal and Maximal Rates

The lowest possible bolus rate is 0.025U, and for basal rates, it is 0.025U/h. The max possible bolus is 75U, and the max possible basal rate is 35U/h.

2.2.2 Animas Vibe

The Animas Vibe pumps are currently off the market. Johnson & Johnson was the manufacturer, and it could be used together with a glucose sensor.

Delivery Accuracy and Speed

Animas Vibe claims that the delivery accuracy of both bolus and basal rates are ±5% [6]. The delivery rates are as following:

- Bolus, under 1U: 1.1 to 2.2U/sec
- Bolus, 1U or more (normal delivery speed): 0.5 to 0.9U/sec
- Bolus, 1U or more (slow delivery speed): 0.2 to 0.4U/sec

Increments

Delivery increments could not be found in the user manual.

Minimal and Maximal Rates

Basal rates can be set from $0.025U/h$ to $25U/h$, and bolus rates from $0.05U$ to $35U$.

2.2.3 Accu-Check Spirit Combo

Roche produces Accu-Check Spirit Combo. It has integrated Bluetooth technology so that it can be used together with a glucose meter.

Delivery Accuracy and Speed

The manual of this insulin pump is not given a max deviation for all rates but rather the results from testing different rates. Basal rates are only tested at $1U/h$, with an accuracy of ±5%. Bolus rates are tested at a minimal and maximal rate, resulting in an accuracy of ±30% and ±5%, respectively.

Increments

Basal rates are delivered quasi-continuously in increments (**??**).

Basal rates:

- 0.01 up to 1.00U/h
- 0.05 (up to 10.0U/h)
- 0.1 (up to 25.0U/h)

Increments for all boluses is 0.1U.

Minimal and Maximal Rates

This insulin pump can be set to give the basal rates $0.05U/h$–$25.0U/h$, and bolus rates $0.1U$-$50U$.

2.2.4 Tandem t:slim X2

The Tandem t:slim X2 is new on the market and produced by Rubin Medical. It is integrated with Dexcom G6 continuous glucose meter and has implemented an algorithm to adjust basal rate delivery automatically.

Delivery Accuracy and Speed

This insulin pump claims a level of accuracy of ±5% at all flow rates and volumes tested per the IEC standard. The delivery speeds specified are $2.97U/min$ at 25 unit bolus deliveries and $1.43U/min$ at 2.5 unit bolus deliveries. For all basal rates, basal rates are delivered every fifth minute.

Increments

The basal rate increments are $0.001U$ for rates greater or equal to $0.1U/h$. Bolus delivery increments are $0.001U$ for rates greater or equal to $0.05U$.

Minimal and Maximal Rates

Basal rates can be set from $0.1U/h$ to $15U/h$, and bolus rates from $0.05U$ to $25U$.

2.3 Insulin

Insulin is an enzyme produced in the pancreas in non-diabetic humans. Artificially produced insulin comes in many forms; they differ in absorption time, time of effect, and intensity curve. In insulin pump therapy, one uses the most rapid-acting insulin types. For this type of insulin, it is absorbed in the body after 10-20 minutes and affects for 2 to 5 hours [7]. It is a clear liquid, and if it is exposed to very low or high temperatures, it might crystallize. While stored, it should be placed in a fridge.

2.3.1 Amount Needed by Different Patient Groups

Diabetes patients have individual insulin demands. Typically the insulin demand will increase per body weight. In addition, factors such as food intake, activity level, sleep patterns, hormonal imbalances, and stress impact glucose levels and insulin demand. In many ways, blood glucose behavior is still a mystery. A rough estimate says that patients with diabetes type 1 need 0.5 to 1 units of insulin per kg per day [7]. Considering a baby weighing 4 kg, the absolute minimal insulin demand for a patient will be around two units per day. For an adult, the demand is around 60 units per day.

2.3.2 Insulin Characteristics

Pure insulin has a very high concentration. The density is:

$$\rho_I = 1.090 g/cm^3 \tag{2.1}$$

Pure insulin is, however, mixed with water before handed out to patients. An example of an insulin brand used today is NovoRapid U-100. This insulin contains 100 units of insulin aspart (equivalent of 3,5mg) per 1ml [8], which is a common concentration internationally. Considering the temperature is $21°C$, the density of water [9] is

$$\rho_W = 0.998 g/cm^3 \tag{2.2}$$

To calculate the density of NovoRapid U-100 we can use the following formula:

$$\rho_{mix} = \frac{m_I + m_W}{\frac{m_I}{\rho_I} + \frac{m_W}{\rho_W}} \tag{2.3}$$

where m_I and ρ_I is the mass and the density of insulin, while m_W and ρ_W is the mass and the density of water. Given that $m_I = 3,5mg$, and that the total mass is $1ml \approx 1g = 1000mg$. Following we have that $m_W = 1000mg - 3,5mg = 996,5mg$. Using this in equation 2.3.2 we get that

$$\rho_{mix} = 0.998g/cm^3 \tag{2.4}$$

which is equal to the density of water. Hence, the density of the insulin aspart in the insulin concentration is negligible.

Further we have that $1U = 0,01mL$, so that for insulin, $1U = 0,01mL = 0,00998g$. To convert a given insulin dose into the weight of insulin in grams, we can use the following equation:

$$m = \frac{\rho U}{100} \tag{2.5}$$

where m is the mass $[g]$, $\rho[g/cm^3]$ is the density of insulin, and $U[U]$ is the given insulin volume in units.

2.4 IEC 60601-2-24:2012

The IEC standard [10] describes the essential performance requirements for insulin pumps. This section summarizes the parts of the IEC standard that are relevant to our project experiments.

2.4.1 Navigation in the Standard

In our experiments, we will use insulin pumps available for patients and are intended to be carried continuously by the patient. The IEC standard has defined different types of insulin pumps and associated experimental setups and procedures. The category suited for our experiments is defined as "type 4: Profile Pump".

Table 201.102 in IEC can be used to navigate the relevant test setup and test procedures for our type of insulin pump. It also says that basal rates will be tested on the minimum and intermediate rates, while bolus rates will be tested on the minimum and maximum rates. The relevant test setup is illustrated in figure 201.104b. Testing the accuracy of basal rates is explained in 201.12.1.103 and for bolus rates in 201.12.1.105.

2.4.2 Test Setup

Figure 2.2 shows a model for the experimental setup to test insulin delivery accuracy in insulin pumps, sourced from the IEC standard [10]. An electronic balance with accuracy to at least five decimal places should be utilized to weigh the mass of insulin doses. The insulin pump shall be filled with "ISO 3696:1987 or a liquid which can be expected to give similar test results". Follow the instructions of the manufacturer to prepare the insulin pumps for the experiments.

The insulin doses should be inserted in a beaker filled with water and a layer of oil on top to minimize evaporation. Concerning avoiding the effect of hydrostatic pressure, the insulin pump shall be placed horizontally at the same height as the top of the liquid in the beaker.

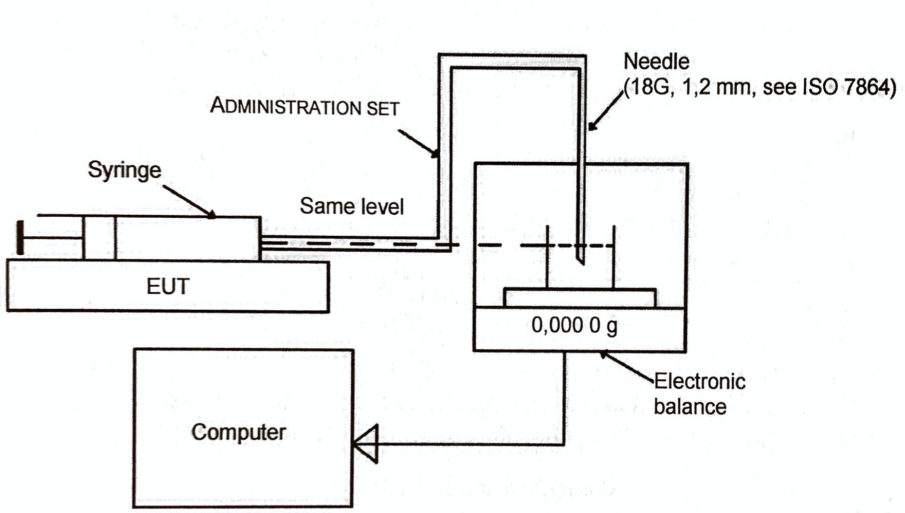


Figure 2.2: Setup for delivery accuracy test of insulin pumps, sourced from the IEC standard

2.4.3 Bolus Rate Accuracy Test

Before starting a bolus rate accuracy test, due to the IEC standard, either a correction factor must be calculated to compensate for an underlying basal rate, or the basal rate should be completely turned off. The experiment should be set up according to section 2.4.2.

Twenty-five successive bolus deliveries shall be measured at both minimum and maximum bolus rate for the insulin pump. The mean value and the percentage deviation from the set value shall be calculated.

To calculate the percentage deviation from the set value we use the following formula:

$$\sigma^2 = \frac{\mu_{avg} - \mu_{set}}{\mu_{set}} * 100 \tag{2.6}$$

where μ_{avg} is the average of the measure doses, and μ_{set} is the bolus rate that is expected from the injection. This value will demonstrate the accuracy of the discrete doses over time.

Next, the standard says to select the deliveries with the maximum positive (μ_{max}) and maximum negative (μ_{min}) deviation from the set value. These should be expressed as percentage deviation from the set value. This can respectively be calculated as

$$\sigma^2 = \frac{\mu_{max} - \mu_{set}}{\mu_{set}} * 100 \tag{2.7}$$

$$\sigma^2 = \frac{\mu_{min} - \mu_{set}}{\mu_{set}} * 100 \tag{2.8}$$

These numbers will reveal whether the variations between the insulin deliveries are significant.

2.4.4 Basal Rate Accuracy Test

Before starting a bolus rate accuracy test, a correction factor must be calculated to compensate for evaporation. The experiment should be set up according to 2.4.2. This test should be repeated twice, once using the minimum possible rate and once using an intermediate rate. The manufacturer must specify this rate. For comparability, we will use 1 U/h as the intermediate rate for all insulin pumps.

The first 24 hours of the experiment is called the stabilization period T_1. The following 25 hours is called the analysis period T_2. The sample interval S should be set to 15 minutes. Initially, the insulin pump should run non-stop through the stabilization and analysis period, and a measurement W_i shall be made every sample interval.

S: Sample interval (min)
d: Density of test liquid (g/ml)
T_1: Stabilization period (hours)
T_2: Analysis period (hours)
W: Measurement (g)
Q: Flow rate (g/h)
r: Set rate (g/h)
A: Overall mean error (%)
E_p: Percentage variation (%)
P: Observation window (min)
m: Maximum number of observation windows

Stabilization period

The stabilization period should be plotted in a graph showing flow against time at 30 minutes increments, see figure 2.3. The set rate r (g/h) should be indicated by a broken line. The flow can be calculated by the following equation:

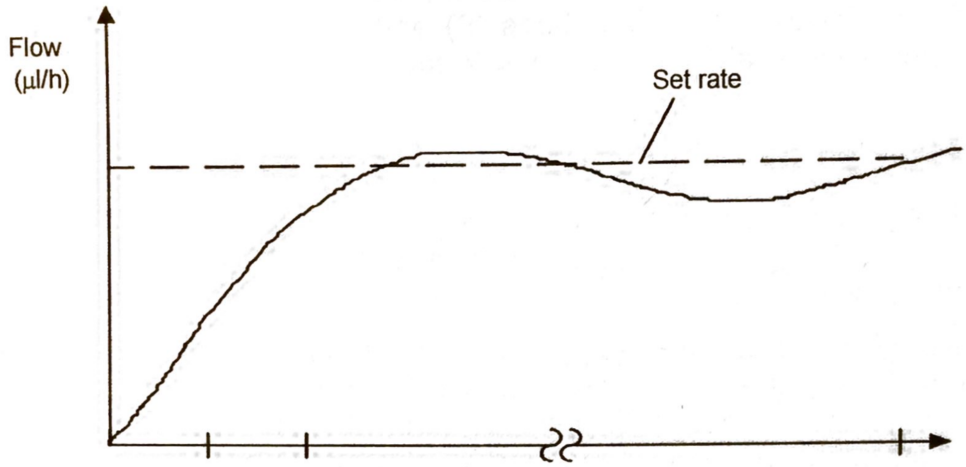


Figure 2.3: Start-up curve over the stabilization period for basal rate experiment, sourced from the IEC standard

$$Q_i = \frac{60(W_{2i} - W_{2(i-1)})}{2S * d} \tag{2.9}$$

We use every second measurement W_{2i} because the sample rate is 15 minutes, while the time increment in the plot is 30 minutes. The measurements shall be corrected for evaporation loss. d is the density of the test liquid at 20°C (g/ml).

Analysis period

The analysis period should be plotted in a trumpet curve (see figure 2.4). Broken lines should indicate the set rate r (g/h) and the overall mean error A. The overall mean error can be calculated as

$$A = \frac{100(Q - r)}{r} \tag{2.10}$$

where

$$Q = \frac{60(W_j - W_k)}{T_2 * d} \tag{2.11}$$

W_j is the mass sample at the end of the analysis period, while W_k is the sample at the start of the analysis period.

Percentage variation $E_p(max.)$ and $E_p(min.)$ should also be plotted. These values must be calculated for observation windows $P = \{15, 60, 150, 330, 570, 930\}$

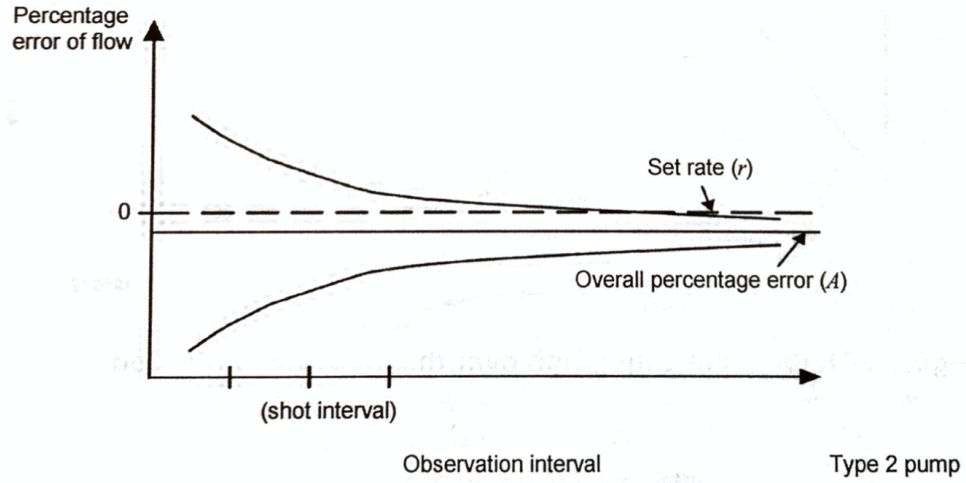


Figure 2.4: Trumpet curve plotted from the analysis period for basal rate experiment, sourced from the IEC standard

minutes. $E_p(max.)$ and $E_p(min.)$ are calculated as

$$E_p(max.) = MAX_{j=1}^{m} \left[\frac{S}{P} \sum_{i=j}^{j+\frac{P}{S}-1} 100 \frac{Q_i - r}{r} \right] [\%] \tag{2.12}$$

$$E_p(min.) = MIN_{j=1}^{m} \left[\frac{S}{P} \sum_{i=j}^{j+\frac{P}{S}-1} 100 \frac{Q_i - r}{r} \right] [\%] \tag{2.13}$$

where

$$Q_i = \frac{60(W_i - W_{i-1})}{S * d} \tag{2.14}$$

and r is the set rate (g/h).

m is the maximum number of observation windows, calculated as

$$m = \frac{T_2 - P}{S} + 1 \tag{2.15}$$

so that the maximum number of observation windows decreases as the duration of observation windows increases.

The trumpet plot is demonstrating how small or large the total error of insulin delivery is over time. The overall percentage error is indicated, showing if the total insulin delivery is below or above the expected.

2.5 Analytical Balances

2.5.1 Characteristics

This section will define some standard terms to describe the quality and precision of analytical balances.

Calibration

A calibration is when one compares the measurement output while measuring an object with a known weight. Then, one can adjust the instrument to obtain an agreement between the two [11].

Capacity

The capacity of a balance means the maximum amount the balance can measure.

Linearity

Linearity is the deviation from a straight line. For perfect linearity, the displayed value will increase at the same rate when adding an element with the same mass.

Readability

This is the minor division at which the scale or balance can be read, or the number of places after the decimal point that the scale can be read [11].

Repeatability

Amount of agreement between repeated measurements of the same quantity [11].

2.5.2 Best Practice When Using Analytical Balances

Rules

- The doors of the balance must be closed while measuring to avoid air flows.
- Use gloves while handling objects to be measured so that moisture, grease, and dirt do not affect the weight.
- The weight must always be clean from dust and chemicals.
- Environment due to temperature and humidity should be stable while making measurements.
- Measurements should be made immediately after a stabilization time given by the manufacturer of the balance.

Drifting and How to Avoid It

The drifting phenomenon is common in highly sensitive balances and might appear even in optimal environments. The consequence consists in the balance displays values changing in one direction or the other, possibly even without any load on the scale. The most common reason this happens is due to static electricity, or temperature changes [12]. Ideally, measurements should be made in a room with climate control. In dry air, the friction causes a buildup of static electricity. A level of humidity around 40% is preferable. Plastic beakers might create static electricity; glass or metal might be better. The operators of the analytical balances could also use an anti-static floor covering if having problems with static electricity.

Chapter 3

Related Work

This chapter presents a review of academic papers relevant to this master thesis. First, we will look at publications on implementations of the IEC standard. Secondly, we explore other methods for measuring flow. To add to that, we will compare academic papers on insulin pump accuracy reviews. Lastly, we will look into the possible factors that might affect insulin pump accuracy.

3.1 Measuring Flow and Insulin Pump Accuracy

3.1.1 Implementation of the IEC Standard

A paper by Kamecke et al. [13] presents an implementation of the IEC standard. In this paper, they explore whether it is possible to use the same standard to test patch pumps so that the accuracy evaluations will be comparable. They are pointing out that the IEC standard should claim accuracy criteria for the insulin pumps.

To fulfill the demands of the IEC standard, they have presented their basal rate experiments in trumpet plots and calculated the deviations of the bolus rates. They discuss the clinical relevance of the results, arguing that the presentations of the results that the IEC standard is demanding, difficult to read, easily misread, and not clinically relevant. Therefore, they additionally present the basal rates both in a scatter plot and in a boxplot. These plots have broken lines indicating the expected flow and the deviation of ±5%. These plots are based on insulin delivery rates for 1-hour windows. For bolus rates, they are not presenting any plots. However, they argue that every single dose should be taken into account when evaluating the quality of the insulin pump, as every individual bolus is clinically relevant.

The IEC standard claims that basal rates must be tested at an intermediate and lowest possible rate for the insulin pump model. Depending on the insulin pump brand, the lowest rates usually are around $0.05U/h$ or $0.025U/h$. Because of potential factors of error and accuracy of test equipment, Kamecke et al. concluded

that the lowest accessible basal rate to test would be $0.1U/h$ or more. They have used $1U/h$ as the intermediate rate in the paper, and they have not tested at other rates. The reason for this is not specified in the paper.

Borot et al. have implemented a test method that is based on the principles of the IEC standard. However, they have taken the liberty of making adjustments so that the experiment also can be applied on patch pumps [14]. To achieve this, they have attached a capillary to the insulin pump cannula submerged in water with a layer of paraffin oil on top. The balance they have used is a more accurate one than used in this master project, increasing the quality of the experiment results. Basal rates are still only tested on $1U/h$.

The two papers mentioned in this section have both implemented the IEC standard, with some adjustments. Kamecke et al. have focused on presenting the results in an intuitive and clinically relevant matter. In contrast, Borot et al. have made adjustments to the actual experimental setup so that it is possible to apply on patch pumps and traditional insulin pumps. However, they both have in common that they have ignored the demand of testing the lowest basal rate possible. None of them are explaining why they have made this decision.

3.1.2 Flow Measurements

For measuring flow, there are two common technologies: Flowmeters and load cells. These technologies both have their pros and cons [15]. We have listed the main properties in table 3.1. Which one is best suited depends on the problem to be solved.

It is not only in diabetic treatment that measuring tiny quantities is an interesting challenge. In different medical therapies, medicine in liquid form is continuously or quasi-continuously injected in the patient's body and is prone to clogging [16]. The Microthermal CMOSens Flow Sensors can measure down to single-digit nanoliters per minute [17]. The MiniMed 640G insulin pump has 1.5 units per minute as a standard delivery rate [5]. This equals $1.5U/min = 0,015ml/min = 15000nl/min$, and does following look promising to measure insulin delivery.

3.2 Accuracy of Bolus and Basal Rate Delivery of Different Insulin Pump Systems

Several publications on insulin pump accuracy have been made by Ziegler et al. [2] [1], and Freckmann et al. [3], all from the same research environment in Germany. The experiments are based on the IEC standard. Roche Diabetes Care funds the experiments. Roche Diabetes Care is an insulin pump manufacturer, so that the publications might be biased.

In 2018, Ziegler et al. published an evaluation of a basal rate of $0.1U/h$. They point out that "*Most manufacturers' specifications are limited to the accuracy of basal*

rates ≥1 U/h, while far lower basal rates are common in children." [1]. Their results are showing large deviations for accuracy of different insulin pumps and different infusion systems [1]. Therefore, they conclude that the accuracy of insulin delivery might not be as expected for patients with low insulin demand.

Further in 2019, Freckmann et al. published a review of both bolus and basal rates [3]. In this evaluation, the rates tested were boluses of $1U$ and $10U$, and a basal rate of $1U/h$, so lower rates was excluded. All insulin pumps showed similar results for these experiments and a high level of accuracy (except from in the first 12 hours of the experiments and for patch pumps in 1-hour windows). Also, in a poster later that year [2], a comparison between different bolus rates shows that rates over $1U$ are all accurate to a deviation of ±15%. For $0.1U$, the results are more unpredictable.

After reviewing several papers published on insulin pump accuracy and implementations of the IEC standard, we see that low insulin rates have mostly been excluded. However, when they were included, the authors have concluded that the accuracy decreases with the smaller insulin volume deliveries.

3.3 Factors That Might Affect Insulin Pump Accuracy

Several factors might impact insulin delivery accuracy, not only the quality of the insulin pump. First of all, the patient's usage of the insulin pump might impact insulin delivery. If a person is very active, lifting and lowering the insulin pump or losing it on the floor might provoke insulin delivery. Wear and tear might also have an impact on the electronics of the insulin pump. Additionally, an insulin pump is a complex instrument depending on the different parts delivered in perfect order and that the battery life is good. Which type of IIS used might impact the delivery as well.

Insulin reservoirs have friction, and the lower the volumes, the more significant the impact of the friction. A study of the impact of lubricant on insulin pump accuracy [18] shows that using lubricant might drastically reduce the need for force used to deliver insulin from a syringe. This might also help to eliminate the need for a stabilization period for the IEC standard.

Table 3.1: A comparison of measuring flow with flow meters versus load cell technology

	Flow Meters	Load Cell
Pros	Can tell how much liquid that has run through a pipe, because they are measuring the flow rate of a liquid through a specific point	Can handle any material (dry, containing air bubbles, corrosive etc.)
	Work on small quantities	Can handle large quantities
	Cheap	
Cons	Best suited for continuous flow applications	Complex technology, and therefore also expensive
		Sensitive to vibrations, because they are based on weight measurements

Chapter 4

Methods

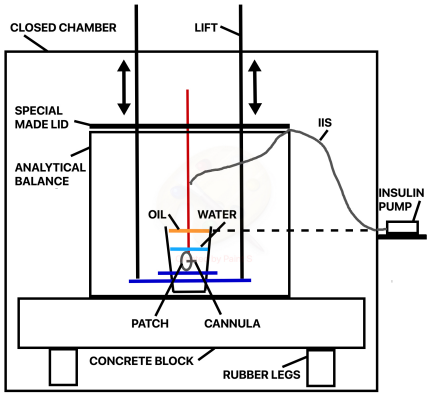
4.1 Experimental Setup

The test setup is based on IEC (2.4.2). Some details are added and will be explained in this section. Figure 4.1 shows a model of the experimental setup, including some essential definitions, along with a photo of the actual setup.

4.1.1 Equipment

Below is a list of the equipment used in the experiments:

1. **Closed chamber**
   The experimental setup is placed inside of a closed chamber. A lifting mechanism is attached to the chamber instead of directly to the balance. Consequently, the vibrations from the motor do not affect the measurements. Small holes create openings for the plastic tube of the insulin pump and power lines. A shelf is mounted at the same height as the top of the liquid in the beaker. There we place the insulin pump. Isolation tape is applied in the door frame to keep a stable environment for the experiments. Putting the weight inside this chamber also helps to avoid sensitivity against air flows on the system. The dimensions of the chamber are $40cmx40cmx60cm$.
2. **Concrete block**
   A heavy concrete block is cast and is standing on rubber legs to fit inside of the anti-vibration chamber. The heavy concrete and the rubber legs work to minimize vibrations on the system from the environment and the lifting mechanism. It has the dimensions $32cmx32cmx11cm$
3. **Marble table**
   The closed chamber is placed on a marble table. This is extremely heavy and helps to absorb potential vibrations from the room and the building.
4. **Ohaus Explorer Semi-Micro Balance EX225D**
   This high precision balance has a precision level of $0,01mg$ and $0,1mg$ for



(a) Setup model

(b) Photo of actual experimental setup

Figure 4.1: Illustration of experimental setup

the capacity of $120g$ and $220g$ respectively. Our experiments requires an accuracy of $0,01mg$. See table 4.1 for further specifications.

5. **Lifting mechanism**
   To make a measurement, it is necessary to lift the beaker off the scale, zero the balance, and put it back down. A lifting mechanism is built so that this can be done automatically. With this mechanism, we also avoid opening the chamber to avoid air flows and temperature changes. The lifting mechanism and the automated system are explained in detail in section 4.1.2.
6. **3D printed parts**
   The 3D printed files can be found in the attached folder *3D prints*. The part named *Tube Clam.stl* is a tube with an opening to insert the insulin tube to make it stiff and to stand still during the experiments. The use of the other parts is further explained in section 4.1.2.
7. **Laser cut parts**
   All parts that were laser cut are in Plexiglas. This material does not absorb water and hence will not affect the humidity during the experiments. A specially made lid to the balance is made, with slots for the insulin tube, lifting mechanism, and the 3D printed tube clam. The use of the other laser cut parts is further explained in section 4.1.2.
8. **Clams and duct tape**
   Clams are used to fasten the wire where the tube of the insulin pump is inserted. Duct tape is added where needed to reduce vibration when adding boluses on the insulin pump.
9. **Distilled water**
   $40ml$ is used in the beaker. Tap water contains minerals that might affect

the experiment.

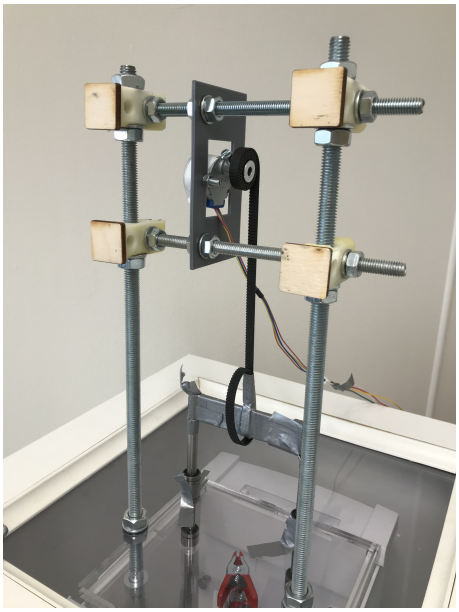
10. **Oil**
    $20ml$ is used in the beaker. The oil used is paraffin oil [19]. It is chemically stable and free from water [20]. This is important to minimize evaporation or other chemical reactions that might affect the weight. The vapor pressure is $0,13hPa$ when $20C$, which is low.
11. **Insulin**
    NovoRapid [8] insulin is used in the insulin pumps during the experiments.
12. **Insulin pumps and IIS**
    The specific insulin pumps and equipment used for the experiments are specified in chapter 5.
13. **Plastic beaker**
    The beaker that is used has a diameter of $5cm$ and holds $100ml$. The beaker should be as light as possible, with a large enough radius for the ISS not to touch the walls of the beaker.
14. **Plastic gloves**
    For high precision measurements, it is essential to maintain a sterile environment, and humidity or grease marks can affect the results. Plastic gloves are used for every experiment.
15. **Syringe**
    To carefully fill the plastic beaker with water and a layer of oil on top, syringes are used.
16. **Temperature- and humidity sensors**
    The temperature and humidity are measured outside of the closed chamber. A DHT22 temperature-humidity sensor is used. The sensor has an accuracy of $<\pm 0.5$°C and ±2%, and a resolution of 0.1°C and 0.1% [21].

Table 4.1: Specifications Ohaus Explorer Semi-Micro Balance EX225D

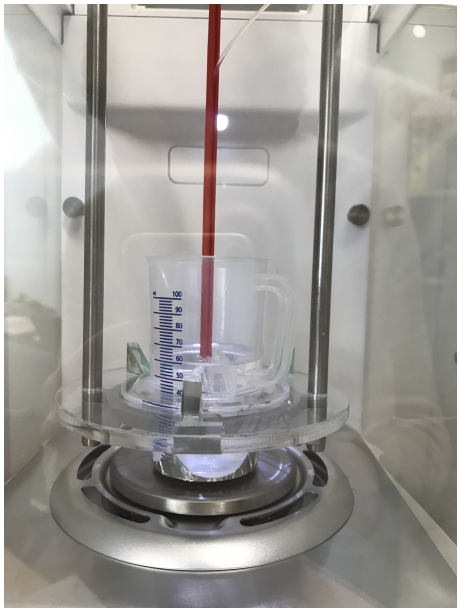
Model	EX225D
Capacity	120 g / 220 g
Readability d	0.01 mg / 0.1 mg
Repeatability (std. dev.) (20 g)	0.015 mg
Repeatability (std. dev.) (100 g)	0.02 mg / 0.1 mg
Linearity (g)	±0.1 mg

4.1.2 Automated Measuring System

The lifting mechanism consists of a 12V stepper motor lifting a piece connected to two rods that are attached to the closed chamber, see figure 4.2a. These rods go all the way down to the inside of the scale, where they are connected to the 3D printed part *3D Prints/Bottom Clam.stl*. On top of this 3D printed part is a laser cut circle with an empty hole in it. Another smaller laser-cut part is attached to



(a) Stepper motor and lifting mechanism attached to the closed chamber



(b) The beaker has a ring attached that gets lifted

Figure 4.2: Illustration of lifting mechanism

the beaker. In this way, when the motor lifts the rods, the beaker is also is lifted. Acrylic triangles are glued to the laser cut plateau so that the beaker always lands in the same place on the scale. Figure 4.2b shows the lower part of the lifting mechanism.

Several design solutions were considered. For how the insulin tube should be connected to the system, three solutions were tested: attached to the beaker, attached to the lifting mechanism rods, or the lid. The last alternative led to the most stable system. Stability was evaluated by repeatedly measuring the beaker filled with water and oil with an IIS attached to the system. The aim was to shorten the time for a measurement to stabilize and lower the standard deviation when measuring the same sample.

4.1.3 Running Python Script

The experiments are running automatically through a python script, which can be found in appendix A.1. The stepper motor and temperature-humidity sensor are connected to an Arduino Uno. The balance is controlled with the RS232 port. Instructions about the port communication and programming language for the balance are specified in the balance manual. Both the balance and the Arduino Uno are connected to the computer with a USB cable.

The script can be run from the terminal. A menu will appear, giving the user several

alternatives. To start a program, one first defines the time interval between each measurement and then names the excel file to be generated. The algorithm for each measurement goes as follows:

1. Zero balance
2. Lower beaker
3. Wait until the balance has stabilized
4. Save measurement
5. Lift beaker
6. Zero balance
7. Write measurement, date, time and environment data to excel

This algorithm is repeated with the given interval.

4.2 Setup Procedure

This section will describe how to prepare the experimental setup before diving into the experimental procedure. As we are working with a high precision balance, concerns about a stable environment, vibrations, and clean equipment should be taken into account at all times. The experiment is very prone to noise.

4.2.1 Preparing the insulin pump

Before every experiment, we provide the insulin pump with a new reservoir and IIS, following the manufacturer's instructions. In addition, we make sure that the battery life is sufficient.

Remember to push and pull the piston a couple of times on the reservoir before filling the reservoir to reduce friction. The piston is often lubricated, and this will help distribute the lube. The reservoir is following filled with rapid-acting insulin. For the experiments where insulin is used, the insulin should is kept at room temperature for at least 24 hours before it is filled in the reservoir to avoid crystallization. We are careful to make sure that there are no air bubbles in the tube.

4.2.2 Preparing the test setup

1. First, clean the balance from dust and chemicals.
2. Then, make sure that the balance is properly leveled by adjusting the legs. We also run an internal calibration regularly.
3. Place the insulin pump horizontally on the shelf so that it is placed at the same height as the top of the liquid in the beaker (see figure 4.3).
4. Insert the insulin tube in the slot of the stiff tube. Adjust the height so that the cannula will be submerged in water.
5. Place the beaker on the scale and carefully fill it with $40ml$ water and $20ml$ oil.

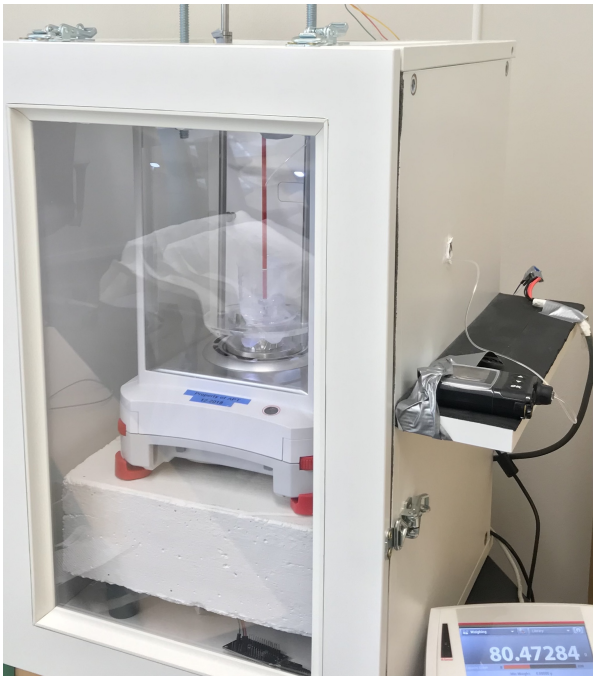


Figure 4.3: Test setup showing how the insulin pump is placed in the same height as the liquid in the beaker.

6. Close the door of the balance and the anti-vibration chamber.
7. Start a program to log the measurements automatically as explained in section 4.1.3.

4.3 Experimental Procedure

4.3.1 Measurements of Evaporation Rate

A correction factor must be calculated to be able to compensate for evaporation in the experiments. The beaker is filled with 40ml of water and 20ml of oil, and a measurement is made every 15 minutes. The evaporation rate is calculated as the slope of the linear regression of all the measurements. For the calculations and plots, we have used a python script.

4.3.2 Insulin Pump Experiments

For each basal rate tested, the procedure has been as follows:

1. Follow the setup procedure in section 4.2.
2. Set the insulin to deliver the desired basal rate.
3. Let the experiment run for 49 hours.
4. Change the basal rate to deliver 0 U/hr to prepare bolus rate tests.

5. For each bolus rate tested, 25 successive amounts will be delivered and measured. The time interval between each bolus delivery and measurement should be defined based on the bolus and flow rate size.

4.4 Analyzing the Experiment Results

In this section, we will show how we have implemented the formulas from section 2.4.4 and 2.4.4 into code. The code automatically generates plots and makes calculations to satisfy the demands of the IEC standard. We have also added some presentations of the experiment results, which will be further explained.

The experiment results are saved in an excel document with five columns: *Date*, *Time*, *Measurement [g]*, *Temperature* and *Humidity*. To generate plots and calculate relevant information, we have used python scripts that are reading directly from a given excel document. It is given that the excel file is placed in the same directory as the python script.

All measurements are made in grams. To be able to compare the expected insulin deliveries with the measured ones, insulin rates are converted to grams in the following function:

```
def fromUnitsToGrams(dose):
        # 1 Unit equals 0.01 ml
        # Density unit is g/cm^3
        # 1 ml = 1 cm^3
        return density*dose*0.01
```

As input, the variable *dose* should be the expected insulin rate in units. The function returns the expected insulin rate in grams.

To calculate the mean and standard deviation of the temperature and humidity, we have used the *statistics* library from python. The example below is from *basal.py*.

```
def getEnvData(col):
        # Returns the average and standard deviation from the values in a column

        # List of strings containing the values of a column minus title row
        list_of_values = sheet.col_values(col)[1:24*4+25*4]

        # Convert all values from string to float
        for i in range(0,len(list_of_values)):
                list_of_values[i] = float(list_of_values[i])

        return statistics.mean(list_of_values), statistics.stdev(list_of_values)
```

4.4.1 Bolus Rates

In this section, we will refer to functions in a python script called *bolus.py*. This can be found in appendix A.3. To analyze bolus rates, we are interested in the difference between each measurement. We correct for evaporation using the rate found in the evaporation rate experiment (see section 4.3.1). The function below is fetching the 26 measurements to calculate the 25 amounts delivered. *evaporation_rate* is given in g/min, so we multiply this with the interval between the measurements to get the correction factor. Then we iterate through the measurements and calculate the differences, compensating for evaporation.

```
def getBolusDeliveries():
        measurements = sheet.col_values(2)[1:27]

        [...]

        # Calculate evaporation correction factor
        correction_factor = evaporation_rate*interval

        for i in range(1,len(measurements)):
                [...]
                delivery = measurements[i] - measurements[i-1] + correction_factor
                bolus_deliveries.append(delivery)
        return bolus_deliveries
```

Bolus Analysis Table

As required in the IEC standard (see section 2.4.3), average delivery, the percentage deviation from the expected value, the percentage deviation from the maximum value, and the percentage deviation from minimum value is calculated. In addition, we have added the standard deviation of all the measurements in both absolute and percentage values.

In the *bolusAnalysis()*-function the mean delivery and the standard deviations are calculated using the *statistics* library. The formulas 2.6, 2.7 and 2.8 are implemented in the variables *dev_set_val*, *dev_max* and *dev_min* respectively.

```
def bolusAnalysis(bolus_deliveries, expected_rate):
        bolus_avg = statistics.mean(bolus_deliveries)
        st_dev_absolute = statistics.stdev(bolus_deliveries)
        st_dev_percentage = st_dev_absolute/expected_rate*100

        dev_set_val = (bolus_avg - expected_rate)*100/expected_rate
        dev_max = (max(bolus_deliveries) - expected_rate)*100/expected_rate
        dev_min = (min(bolus_deliveries) - expected_rate)*100/expected_rate

        return bolus_avg, st_dev_absolute, st_dev_percentage,
            dev_set_val, dev_max, dev_min
```

Scatter Plot

For every insulin pump and every bolus rate tested, we will make a scatter plot. In a scatter plot, we plot the insulin delivery against the index of the insulin delivery. A broken line in black is indicating the expected value. The broken blue lines indicate a deviation window of ±5%, and the red lines a deviation window of ±15%.

```
def getScatterPlot(bolus_deliveries, expected_rate):
        # Indexes of deliveries
        x = list(range(1,len(bolus_deliveries) + 1))

        # Broken line for expected rate
        exp = [expected_rate for i in range(len(bolus_deliveries))]

        plt.ylim([0, expected_rate*1.5])
        plt.xlabel('Bolus␣delivery␣index')
        plt.ylabel('Measurement␣[g]')

        plt.plot(x, bolus_deliveries, 'o', color='black', label="Measurement")

        # Broken indicator lines
        plt.plot(x, exp, color='black', label="Expected␣value")
        plt.plot(x, [el*1.05 for el in exp], color='blue', label="5%␣from␣target")
        plt.plot(x, [el*0.95 for el in exp], color='blue')
        plt.plot(x, [el*1.15 for el in exp], color='red', label="15%␣from␣target")
        plt.plot(x, [el*0.85 for el in exp], color='red')

        plt.legend()
        plt.show()
```

4.4.2 Basal Rates

In this section, we will refer to functions in a python script called *basal.py*. This can be found in appendix A.2. For all basal rate experiments, the interval between each measurement is 15 minutes, as required in the IEC standard (see section 2.4.4).

To analyse basal rates we are interested in the measured flow rates. We correct for evaporation using the rate found in the evaporation rate experiment (see section 4.3.1). The function below shows how we are implementing equation 2.9

and 2.14. The function takes in as an argument *observation_interval* which is the increments we want to calculate flow rates for in minutes.

```
def getFlowRateList(sheet, observation_interval):
        # Returns a list of the flow rates for a wanted observation interval
        measurements = sheet.col_values(2)[1:]
        measurements[0] = float(measurements[0])

        flow_rate_list = []

        # Calculate evaporation correction factor
        correction_factor = evaporation_rate*observation_interval

        fac = int(observation_interval/interval)

        # Convert all values from string to float
        for i in range(1,round(len(measurements)/fac)):
                measurements[fac*i] = float(measurements[fac*i])
                delivery = measurements[fac*i] - measurements[fac*(i-1)]
                    + correction_factor
                flow_rate = 60*(delivery)/(observation_interval*density)
                flow_rate_list.append(flow_rate)

        return flow_rate_list
```

Stabilization Plot

The measurements of the first 24 hours should be plotted in a graph showing flow against time at 30-minute increments. This period is called the stabilization period. See an example in figure 2.3. We are indicating the expected rate with a black, broken line. The broken blue lines indicate a deviation window of ±5%, and the red lines a deviation window of ±15%.

```
def getStabilizationPlot(flow_rate_list, expected_rate):
        # Stabilisation plot with observation interval of 30 minutes
        y = flow_rate_list[:24*2]
        x = list(range(0,len(y)))
        x = [t*2*interval for t in x]

        exp = [expected_rate for i in range(len(y))]

        plt.title('Stabilization Period')
        plt.xlabel('Time [min]')
        plt.ylabel('Flow rate [g/h]')

        # Broken indicator lines
        plt.plot(x, exp, color='black', label="Expected value")
        plt.plot(x, [el*1.05 for el in exp], color='blue', label="5% from target")
        plt.plot(x, [el*0.95 for el in exp], color='blue')
        plt.plot(x, [el*1.15 for el in exp], color='red', label="15% from target")
        plt.plot(x, [el*0.85 for el in exp], color='red')

        plt.plot(x, y, '-', color='black', label="Measurement")
        plt.legend()
        plt.show()
```

Trumpet Plot

In the trumpet plot we use the measurements from the analysis period (the 25 hours after the stabilization period), and implement the algorithm explained in section 2.4.4. The overall error is indicated with a red, broken line. A snippet of the implementation can be seen below:

```
def getAnalysisPlot(flow_rate_list, expected_rate, Q):
        Q_list = flow_rate_list[n_1:n_1 + n_2]

        # Total mean error
        A = 100*(Q - expected_rate) / expected_rate

        # Observation windows
        P = [15, 60, 150, 330, 570, 930]

        E_p_max_list = []
        E_p_min_list = []

        for observation_window in P:
                m = (T_2 - observation_window)/interval + 1
                E_p_list = []
                for j in range(1, int(m) + 1):
                        E_p = []
                        K = interval/(observation_window)
                        #K = 1/(int(j + observation_window/interval))
                        for i in range(j-1, int(j+observation_window/interval-1)):
                            E_p.append((Q_list[i]-expected_rate)*100/expected_rate)
                        E_p_list.append(K * sum(E_p))
                E_p_max_list.append(max(E_p_list))
                E_p_min_list.append(min(E_p_list))

        [...]
```

Cumulative Plot

We have added a plot that is not required according to the IEC standard. This plot is intuitive to read, where a black line is over time indicating the expected total amount delivered, and a red line is indicating the actual delivered amount. It is implemented as follows:

```
def getCumulativePlot(flow_rate_list, expected_rate):
        Q_list = flow_rate_list[n_1:n_1 + n_2]
        y = []

        for i in range(0,n_2):
                y.append(sum(Q_list[:i]))

        x = list(range(0,len(y)))
        x = [t*interval for t in x]

        set_rate_list = [expected_rate*i for i in range(len(y))]

        plt.title('Cumulative␣Plot␣of␣Analysis␣Period')
        plt.xlabel('Time␣[min]')
        plt.ylabel('Delivered␣insulin␣[g]')

        # Broken indicator lines
        plt.step(x, set_rate_list, color='red', label="Expected␣total␣delivery")
        plt.step(x, y, '-', color='black', label="Actual␣total␣delivery")
        plt.legend()
        plt.show()
```

Basal Analysis Table

In the *getStatistics()*-function the mean delivery and the standard deviations are calculated using the *statistics* library. For the statistics, the observation windows of the flow rates are 1 hour, so that the standard deviation is calculated for 1-hour windows. The measurements from the analysis period are used.

```
def getStatistics(flow_rate_list, expected_rate):
        # Calculate percentage deviation for every hour window
        # Printing only from analysis period
        Q_list = flow_rate_list[24:24 + 25]

        mean = statistics.mean(Q_list)
        st_dev_absolute = statistics.stdev(Q_list)
        st_dev_percentage = st_dev_absolute/expected_rate*100
        dev_set_val = (mean - expected_rate)*100/expected_rate

        return mean, st_dev_absolute, st_dev_percentage, dev_set_val
```

The table is formatted and printed in the *main()*-function.

4.4.3 Comparison of Insulin Pumps

All the insulin delivery rates from all the insulin pump models are compared in a table by the total percentage of deviation from target along with the standard deviation. The format will be *<average value>±<standard deviation>%*. These values are read from the experiment results from the individual pumps and manually written into the table.

Chapter 5

Results

In this chapter, we present the results of the initial experiments and the experiments of the insulin pumps. The procedure presented in chapter 4 was followed strictly to make the results comparable.

5.1 Initial Experiments

5.1.1 Evaporation Rate Experiment

For the measurements made of the beaker filled with water and oil, the raw data can be found in $EvaporationRate.xls$. During this experiment, the temperature was 25.0±0.2°C, and the humidity was 25.3±0.7% inside the anti-vibration chamber. Using the python script $evaporation\_rate.py$, a linear regression is performed on the measurements, showing that $y = -0.000002157x + 79.663[g/min]$ and $R^2 = 0.98$. Hence, the evaporation rate is $0.000002157g/min$, or $0.00013g/hr$. See figure 5.1. The red curve presents the linear regression, while the blue lines are indicating the linearity acceptance of the balance (table 4.1).

5.2 Insulin Pump Experiments

5.2.1 Experiment details

This section will specify the IIS sets used for the different insulin pumps that are tested. We also will list the different rates tested on the different insulin pumps, depending on their lowest possible rates. All the insulin pumps are filled with NovoRapid $100U/ml$ insulin.

MiniMed 640G and 670G

Information about these insulin pumps can be found in section 2.2.1. The insulin pumps used in the experiment are demo pumps borrowed from a hospital. The

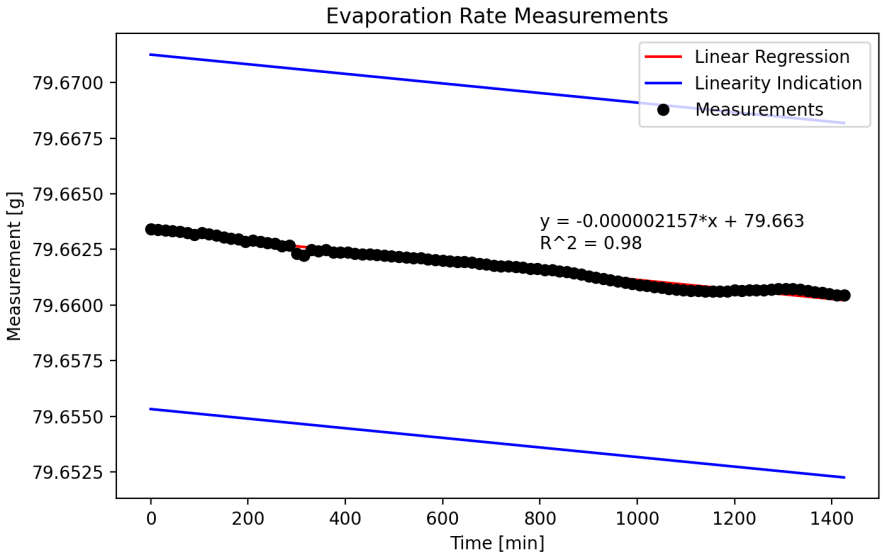


Figure 5.1: Plot of measurements made of the plastic beaker filled with water and oil every 15 minutes for 24 hours.

condition is almost as new and is most of the time not in use.

- IIS: Medtronic Quick-set
- Tube: 110cm
- Cannula: 9mm, teflon
- Minimal possible rates: 0.025U (bolus) and 0.025U/h (basal)

Animas Vibe

Information about the insulin pump tested in this experiment can be found in section 2.2.2. The insulin pump used in the experiment is in good condition and was produced in 2018. For some time, it has been used under normal conditions by a patient.

- IIS: Accu-Check FlexLink
- Tube: 80cm
- Cannula: 6mm, teflon
- Minimal possible rates: 0.05U (bolus) and 0.025U/h (basal)

Accu-Check Spirit Combo

Information about the insulin pump tested in this experiment can be found in section 2.2.3. The insulin pump used in the experiment is in good condition and has the production year of 2013. For some time, it has been used under normal

conditions by a patient.

- IIS: Accu-Check FlexLink
- Tube: 80cm
- Cannula: 6mm, teflon
- Minimal possible rates: 0.1U (bolus) and 0.05U/h (basal)

Tandem t:slim X2

Information about the insulin pump tested in this experiment can be found in section 2.2.4. The insulin pump used in the experiment is entirely new.

- IIS: AutoSoft 90 Infusion Set
- Tube: 60cm
- Cannula: 6mm, teflon
- Minimal possible rates: 0.05U (bolus) and 0.1U/h (basal)

5.2.2 Bolus Rate Experiments

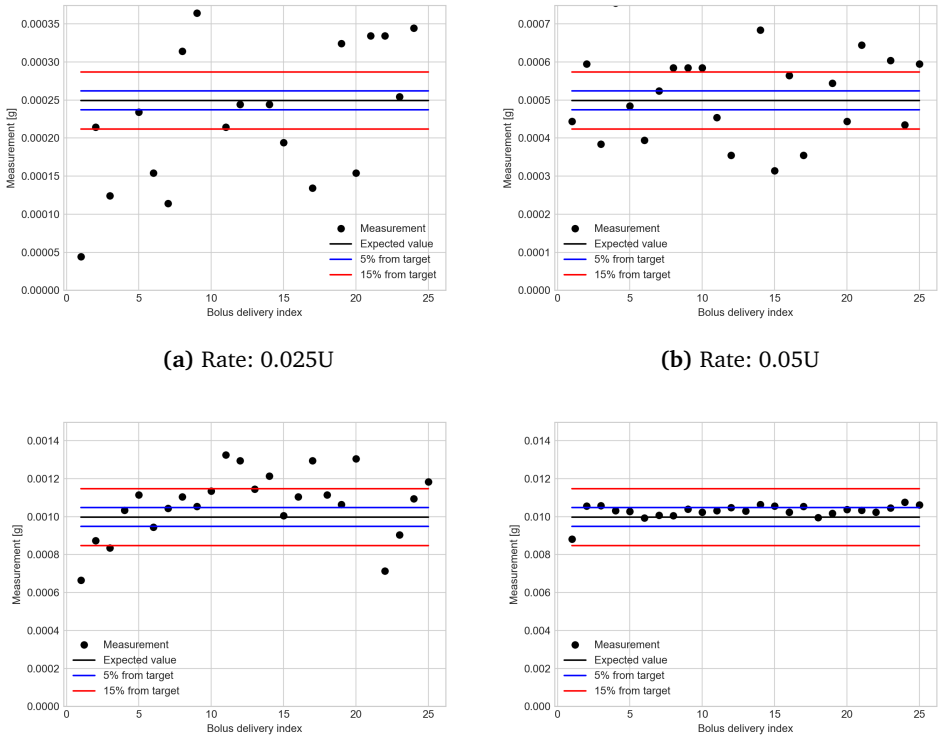
The bolus rates are tested with 26 successive readings to calculate 25 differences. The interval between each measurement is 2 minutes. Bolus rates are tested at 0.1U and 1U. If possible, they are also tested at 0.025U and 0.05U, depending on the lowest delivery rate of the insulin pump.

Figure 5.2 is sourced from **Appendix B.1**, showing an example of the graphical presentation of the bolus dose delivery measurements of MiniMed 640G. We observe that the percentage deviation is increasing for the lower bolus dose deliveries. The associated table from **Appendix B.2** is shown in figure 5.3. Deviations are calculated as specified in the IEC standard. We observe that the deviations from the expected values are below ±10% for all rates.

5.2.3 Basal Rate Experiments

The basal rates tested for all insulin pumps are 0.1U/h and 1.0U/h. Plots of the stabilization period, the first 24 hours of the experiment, can be seen for both rates tested in **Appendix C.1**. One example is fetched here, see figure 5.4. The 0.1U/h experiments are fluctuating outside of the ±15% deviation target throughout the period. In contrast, the 1.0U/h experiments are stabilizing after about 250-300 minutes.

The following 25 hours, the analysis period, are presented in trumpet plots in **Appendix C.2**, as required in the IEC standard. Additionally, we are showing the cumulative insulin deliveries during the analysis period up against the expected total insulin delivery, see figure 5.5. All of the cumulative plots can be found in **Appendix C.3**. In these, we also observe how the 1.0U/h experiments show approximately linear curves close to the target, compared to the 0.1U/h experiments



(a) Rate: 0.025U

(b) Rate: 0.05U

(c) Rate: 0.1U

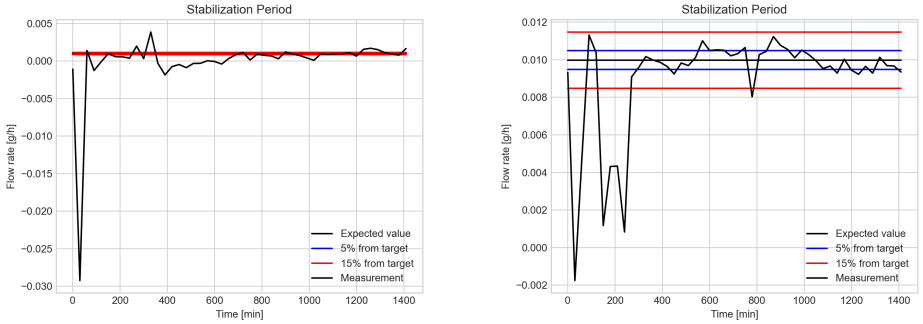
(d) Rate: 1U

Figure 5.2: Scatter plots of bolus rates for MiniMed 640G

	0.025U	0.05U	0.1U	1.0U
Expected [g*10^(−5)]	25	50	100	998
Average [g*10^(−5)]	26	53	109	1029
Standard deviation [g*10^(−5)]	14	23	21	38
Standard deviation [%]	54.1	45.6	21.2	3.8
Deviation from expected value [%]	5.1	6.0	9.2	3.1
Deviation from max. value [%]	134.2	123.3	68.8	7.9
Deviation from min. value [%]	−102.3	−129.2	−33.4	−11.7
Temperature [°C]	23.7±0.1	24.1±0.1	22.2±0.3	23.0±0.1
Humidity [%]	21.4±0.1	21.6±0.1	25.3±0.1	25.3±0.1

Figure 5.3: Table showing bolus accuracy for MiniMed 640G.

that are more characterized by fluctuations and total over-delivery by the end. Finally, tables in **Appendix C.4** show the total average delivery and the standard deviations for 1-hour windows, along with the mean and standard deviation for the temperature and humidity during the experiments.

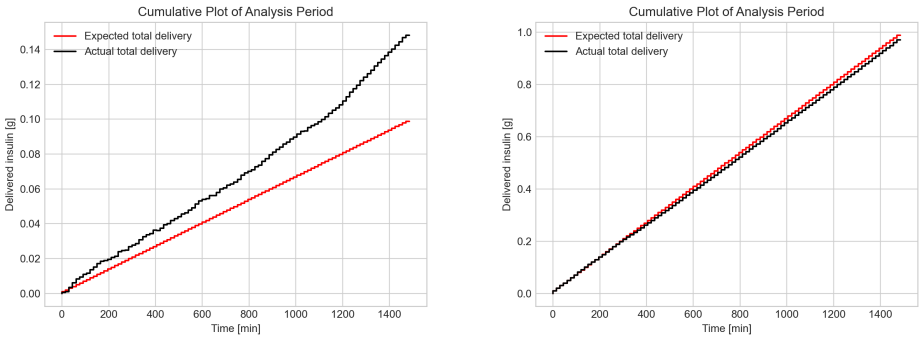


(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure 5.4: Plots of stabilization period for MiniMed 640G

5.3 Comparison of Insulin Pumps

The insulin pumps tested in section 5.2 are tested for both bolus and basal rates. This section will compare the total deviations from the expected deliveries for different insulin pumps and the standard deviations. Basal rates for the different insulin pumps tested are compared in table 5.2. The results for bolus rates are presented in table 5.1.



(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure 5.5: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period for MiniMed 640G

Table 5.1: Comparison of accuracy of bolus rate delivery of insulin pumps

	Bolus rates			
	0.025U	0.05U	0.1U	1U
640G	5±54%	6±46%	9±21%	3±4%
#1 670G	44±50%	14±28%	11±28%	4±8%
#2 670G	6±67%	4±39%	5±22%	0±21%
Animas Vibe	—	-6±22%	12±16%	4±2%
#1 Accu-Check	—	—	9±50%	-2±45%
#2 Accu-Check	—	—	-4±21%	-2±9%
Tandem	—	4±53%	-8±46%	3±12%

Table 5.2: Comparison of accuracy of basal rate delivery of insulin pumps

	Basal rates	
	0.1U/h	1U/h
640G	52±42%	-2±4%
#1 670G	90±131%	7±10%
#2 670G	33±62%	6±4%
Animas Vibe	49±100%	8±19%
#1 Accu-Check	39±136%	9±12%
#2 Accu-Check	15±50%	4±7%
Tandem	46±94%	-2±23%

Chapter 6

Scientific Paper

This chapter has attached the whitepaper we have written based on our experiences and experimental results throughout the project and master thesis. Rather than focusing on the performance of the insulin pumps in regards to the test results, we are arguing that the IEC standard is insufficient for testing small insulin volumes.

Established Methods for Measuring Insulin Pump Accuracy are Insufficient for Low Delivery Volumes

Abstract

Insulin pumps are frequently used as part of the treatment of diabetes mellitus type 1. Accurate insulin delivery is essential to provide good diabetes therapy. Research indicates that delivery of small insulin volumes (≤ 0.1 U bolus doses and ≤ 0.1 U/h basal rates) may be less accurate than intermediate insulin volumes in commercially available insulin pumps. If true, this might affect the quality of the treatment for patient groups with low insulin demands, like children.

We created an experimental setup to conduct accurate measurements of low insulin volumes (≤ 0.1 U bolus doses and ≤ 0.1 U/h basal rates) in compliance with IEC 60601-2-24. We implemented mitigating procedures to lessen the influence of drift, static electricity, atmospheric disturbance, and mechanical vibrations. The plastic measuring container was separated with metal tape to minimize the effects of static electrical buildup. A lifting mechanism was built to zero the balance between each measurement and run experiments automatically. Further, we use the experimental setup to test the insulin delivery accuracy of several commercially available insulin pumps. 5 different insulin pump models were tested on both bolus doses and basal rates.

Mean bolus delivery was observed to be within ± 10 % of target for all the tested rates, with lower rates showing higher deviations. Basal rate results generally show an over-delivery of more than 15 % for lower rates, while 1 U/h was within ± 10 % of target for all insulin pump models. The results show some unexpected behaviors, such as negative delivery rates for lower basal rates.

The tested insulin pumps show similar levels of intra-sample accuracy, with lower rates deviating more than intermediate rates. However, factors such as drifting, static electricity, and vibrations affected the reliability of the experimental results, especially for lower rates. The results are ambiguous, implying that the test method set out in IEC 60601-2-24 could be unreliable when testing insulin delivery volumes smaller than 1 U. Further testing using alternative methods of measuring insulin delivery accuracy should be conducted to review the reliability of earlier studies of insulin pump accuracy.

Introduction

Insulin delivery accuracy is an essential aspect of providing good diabetes therapy and patient safety. As such, verifying the accurate delivery of commercially available pumps has been of interest in numerous research projects. However, they mainly focus on testing that insulin volumes ≥ 1.0 U of different insulin pump models is within ± 5 % (Kamecke et al., 2018)

(Freckmann et al., 2019). Although there are similar publications focusing on lower insulin volume delivery (< 1.0 U) (Ziegler et al., 2018) (Ziegler et al., 2019) (Girardot et al., 2020), thorough comparisons and performance measures seem to be a lacking area of research. Ziegler et al. conclude that lower rates are less accurate (2018). If true, this would have significant implications for a wide range of patient groups, especially concerning those with low insulin demands.

A conventional insulin pump consists of an electromechanical motor, an electronic control system, a reservoir filled with rapid-acting insulin, and a patch with a cannula for subcutaneous infusion, connected through a flexible tube. The tube, patch, and cannula are together called an insulin infusion set (IIS). Patch pumps do not contain a flexible tube and are directly attached to the patient's body.

In insulin pumps, a distinction of the insulin delivery is made between basal rates and bolus doses. Basal rates are running quasi-continuously, meaning that small amounts of insulin are injected automatically at a given interval. The basal rates are set as flow rates in units per hour (U/h). On the other hand, bolus doses are delivered manually by the user to correct high glucose levels or ahead of meals. These amounts are discrete, given in units (U). One unit of insulin (1 U) is defined as 34.7 µg of the active substance. The standard concentration of insulin distributed from pharmacies is mixed so that 1ml of liquid contains 100 U of insulin. We use *insulin volumes* as a common term for both basal rates and bolus doses (an insulin volume of 1 U equals a basal rate of 1 U/h and a bolus dose of 1 U). Insulin demand is age dependent (Klinkert et al., 2008), and children might require basal rates of 0.1 U/h or even lower (Bachran et al., 2012). In a study made of insulin demands in adults (>18 years of age), the median basal rates ranged from 0.75 U/h to 0.9 U/h (Snider, 2018). Delivering and measuring small medicine volumes is challenging (Jungmann, 2017), and the accuracy is affected by both available technical equipment and the uncertainty associated with the in vivo environment.

IEC 60601-2-24 (hereafter IEC) defines how to test insulin pumps to provide basic safety. However, IEC does not state any accuracy requirements, leaving it up to the manufacturer to decide on an acceptable threshold. Manufacturers typically claim their insulin pump delivers accuracy within ± 5 %, especially for 1.0 U/h basal rates (Freckmann et al., 2019). On the other hand, IEC states that insulin pumps must be tested at their lowest possible delivery rates and doses. For the insulin pump models tested in this study, the lowest rates and doses are varying from insulin volumes between 0.025 U and 0.1 U. For this reason, we use *lower rates/doses* to refer to insulin volumes ≤ 0.1 U, while *intermediate rates/doses* refer to insulin volumes of 1 U.

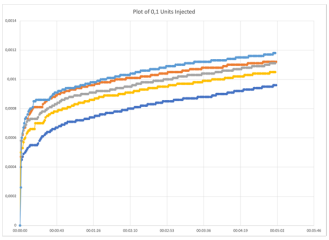
The IEC standard seemingly works well to test accuracy for intermediate insulin volumes but is challenging for lower volumes, requiring a balance displaying five decimal points of a gram (*IEC 60601-2-24:2012*, 2012). In evaluating how to test delivery accuracy of insulin pumps based on the IEC standard, Kamecke et al. conclude that the lowest assessable basal rate to test is 0.1 U/h or more (2018).

In this study, the IEC standard will be implemented to test bolus dose and basal rate delivery accuracy in vitro. Different insulin pump models will be tested on both lower and intermediate insulin volumes. Based on the results, we want to evaluate the IEC standard applied on lower insulin volumes.

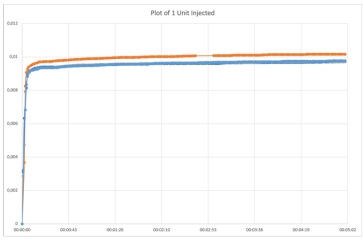
Test Setup

The experimental setup was implemented based on the previously mentioned IEC to enable comparative testing of *lower insulin delivery volumes*. The setup consists of a beaker on a precision balance into which the medium is pumped. Oil is added to the beaker to avoid evaporation. Lastly, the insulin pump is fixed to the height of the water column. Trials were run on the experimental setup. However, we were unable to produce credible results for the lower volumes of insulin delivery relying solely on the basic experimental setup described in the standard.

The ambiguity of the measurements emerged from the increasing significance of noise when approaching the balance's tolerance. The drifting phenomenon made it especially challenging to decide when to write down measurements for lower bolus doses after delivery as illustrated in Figure 1.



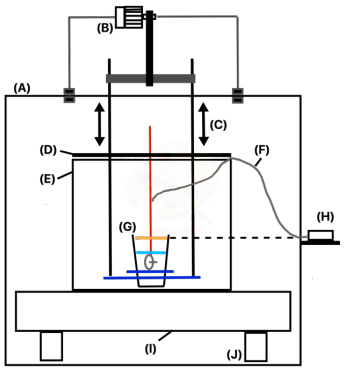
(I): 0.1U is injected five time. They stabilize on several plateaus after around 20-60 seconds. Further, the drifting is making the measurement ambiguous.



(II): 1.0U is injected five times. They are all stabilizing at a plateau after around 30 seconds, and with a level of drift that is unsignificant to the measurement reading.

Final Test Setup:

Figure 1 shows a schematic of the final test setup used to test insulin pump accuracy, along with the actual setup. The balance used is an Explorer SEMI-MICRO EX225D (Ohaus Corporation, New Jersey, USA), which has a readability of 0.01 mg with a maximum capacity of 120 g. Figure 2 (I) shows a model of how the insulin is added to the liquid through the insulin pump cannula. The beaker is filled with 40 ml of distilled water and 20 ml paraffin oil to avoid evaporation (see Figure 2 (II)). A precise lifting mechanism is implemented so that the beaker can be lifted from the balance, the balance can be zeroed, the beaker can be lowered, and a new measurement can be made.



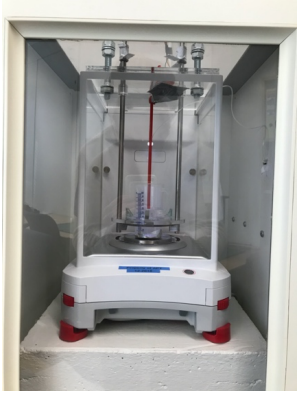
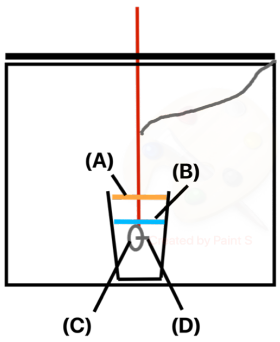


Figure 1:
(I): Model of the experimental setup. The analytical balance (E) is placed inside of a closed chamber (A). A motor (B) is lifting two rods, creating a lifting mechanism (C). The specially made lid (D) has an opening for the insulin tube. Outside of the closed chamber is a shelf to place the insulin pump (H) in liquid height. The IIS tube (F) is connected to the balance and submerged in the water in a plastic beaker (G). A concrete block (I) on rubber legs (J) is placed underneath the balance to absorb mechanical vibrations.

(II): Photo of the experimental setup.



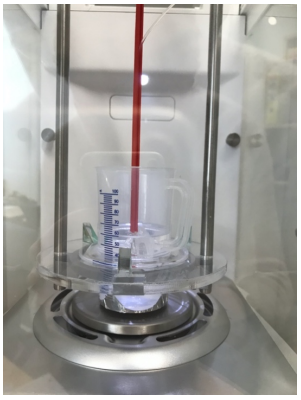


Figure 2:
(I): Closeup from model of the experimental setup. The beaker is filled with water (B) and a layer of oil (A) on top to avoid evaporation. The IIC patch (C) and cannula (D) is submerged in water. The red tube is 3D-printed and has a rail for the IIS tube to be inserted.

(II): Photo of beaker filled with water and oil, with the cannula submerged.

Every 15 minutes, for 24 hours, measurements were made without any insulin delivery. The purpose was to evaluate the stability of the test setup, and to measure evaporation rates.

Stabilization

To enable good repeatability of the readings, it is of utmost importance to create stable conditions for the balance and the measured medium, both regarding mechanical vibrations and static electricity. Ideally, the latter is avoided using a glass beaker to contain the measured fluid. However, due to the upper weight limit on the balance of 120 g, it was decided to use a plastic beaker. With no alterations, the plastic beaker resulted in long stabilization times, theorized to be caused by static electricity. The stabilization time was significantly reduced by adding aluminum tape to the bottom of the beaker.

Another challenge with stabilization was due to mechanical vibrations. Adding complexities, such as liquids in the beaker and the IIS, to the test setup increased the sensitivity to vibrations. Therefore, a concrete block was cast with rubber legs underneath to decouple and isolate the setup from said vibrations. Resulting in a setup less prone to vibrations. However, air flows were still a problem. Therefore, a closed chamber was built. The closed chamber was placed on an immense marble table, with the concrete block placed inside of it. The balance was placed on the top of the concrete block, resulting in a system considerably less sensitive to vibrations, movement of air, and static electricity.

Drift

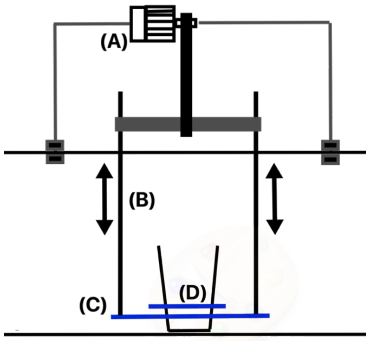
Several solid objects were measured for 24 hours to verify the stability of the setup. The measurements were not constant even though the system was closed, and the measured object was not touched or otherwise altered. According to the manufacturer of the balance, this was expected behavior. For long-time measurements, drifting will occur due to both internal and external temperature changes.

This test was repeated while tracking temperature and humidity, but a direct correlation between the drift and environmental data was not found. Traditionally when making a measurement, a balance is zeroed before placing the mass on the scale. Then, the measurement is made immediately after the balance has stabilized. A lifting mechanism was built to facilitate this procedure with repeated measurements over time. The lifting mechanism utilizes a stepper motor to raise and lower the beaker off and on the scale so that the balance can be zeroed between each measurement. The chamber can remain closed this way, mitigating external environmental factors such as mechanical vibrations, temperature changes, and air flows on the measurements. Additionally, the beaker can be repeatedly placed on the

same target for all measurements. The balance is in turn connected to a computer and controlled through a script. The experiments could thus run automatically for prolonged periods.

Lifting Mechanism Design Solution

Figure 3 (I) shows a model of the design solution for the lifting mechanism. A stepper motor attached through timing belts along linear rails ensures reproducible movement (Figure 3 (II)), and clearance between the lifting arm and beaker ensures accurate weight readings. The acrylic platforms make sure that the beaker is lifted without wobbling. We needed to ensure that the beaker would always be placed on the same spot on the scale. Therefore, a funnel-like guidance system was made on the attachment doughnut by fixing small triangular shapes along the edge (Figure 2 (II)).



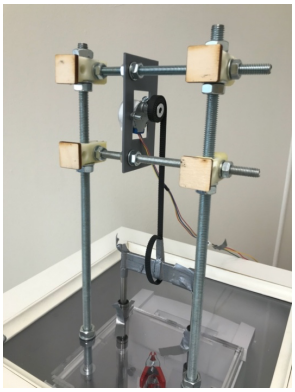


Figure 3:
(I): Model of the lifting mechanism. It consists of a stepper motor (A) pulling on a platform through a timing belt. Two rods (B) are attached to the platform through linear bearings to the chamber's top. The platform consists of a doughnut-shaped piece of acrylic (C). An extended acrylic rim was fixed to the beaker (D) to interlock the beaker with the rising platform.

(II): Closeup of the upper part of the lifting mechanism.

Materials and Procedures:

Five different insulin pump models from four different manufacturers were tested (Table 1). The IEC standard does not require repeating the experiments or testing insulin pumps from different production batches. Due to higher relevance in the modern market, the MiniMed 670G and Accu-Check Spirit Combo were tested twice. According to the manufacturer's

instructions, the insulin pumps were filled with insulin aspart (NovoRapid®; Novo Nordisk A/S, Bagsværd, Denmark).

Insulin Pump	Manufacturer	Infusion Set	Cannula	Tubing [cm]	Number of repetitions
Accu-Chek® Spirit Combo	Roche Diabetes Care GmbH	Accu-Check FlexLink	6 mm Teflon	80	2
MiniMed® 640G	Medtronic MiniMed	MiniMed® Quick-set®[a]	9 mm Teflon	110	1
MiniMed® 670G					2
Animas® Vibe®	Animas Corporation	Accu-Check FlexLink	6 mm Teflon	80	1
Tandem t:slim X2	Rubin Medical	AutoSoft 90 Infusion Set	6 mm Teflon	60	1

Table 1: *Overview over insulin pump systems tested including specifications of the IIS used.*

The lowest common denominator of insulin delivery is 0.1 U for both bolus doses and basal rates. Hence, bolus doses were tested at 0.1 U and 1.0 U, while basal rates were tested at 0.1 U/h and 1.0 U/h. For bolus doses, the measurements were made with a two-minute interval. Basal rate measurements were made at 15-minute intervals for 49 hours. According to the IEC standard, the first 24 hours are defined as the stabilization period. The following 25 hours are used in the analysis.

Insulin delivery rates were calculated based on the weight measurements increasing. First, the difference between the two measurements was calculated, then the difference was converted from grams to units of insulin, using a density of 0.998 g/cm^3. We assume that the difference between the density of U-100 insulin and water is negligible.

Results

Bolus dose accuracy

In Table 2, the total mean bolus dose delivery after 25 successive deliveries is presented for all the insulin pump models, along with the standard deviation. Figure 4 shows the measured boluses in scatter plots from the first experiment of the MiniMed 670G. The red, broken lines indicate a target of ±15 %, while the blue lines indicate a ± 5 % window.

Insulin Pump	0.1 U	1.0 U
Accu-Chek® Spirit Combo	109 ± 50 %	98 ± 45 %
	96 ± 21 %	98 ± 9 %
MiniMed® 640G	109 ± 21 %	103 ± 4 %

MiniMed® 670G	111 ± 28 %	104 ± 8 %
	105 ± 22 %	100 ± 21 %
Animas® Vibe®	112 ± 16 %	104 ± 2 %
Tandem t:slim X2	92 ± 46 %	103 ± 12 %

Table 2: *A table showing the total mean bolus dose delivery [%], ± the standard deviation.*

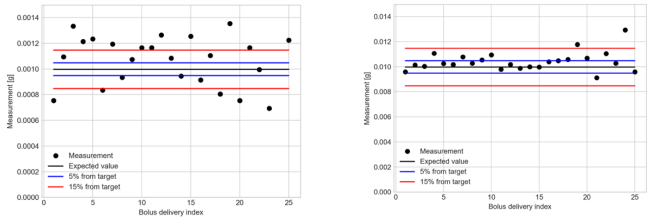


Figure 4:
(I): Scatter plot of repeated bolus doses of 0.1U in MiniMed 670G

(II): Scatter plot of repeated bolus doses of 1.0U in MiniMed 670G

Basal rate accuracy

The first 24 hours of the basal rate experiments are called the stabilization period. According to the IEC standard, this period must be plotted by flow rate over time. In this plot, it is expected that the deviation is considerable initially, smoothing out towards the expected value towards the end. As observed in Figure 5, this is the case when testing 1.0 U/h rates. On the contrary, the 0.1 U/h stabilization plots range outside of the target throughout the stabilization target without any pattern. The results in Figure 5 are from the experiment of MiniMed 670G as representative of the trends in our observations.

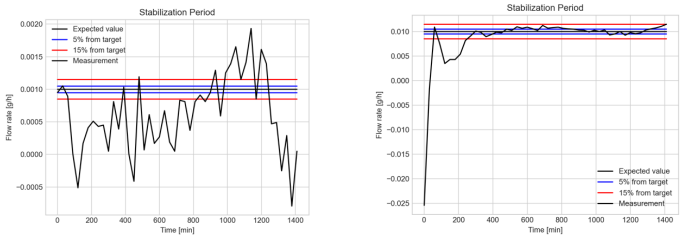


Figure 5:

(I): Stabilization plot for a basal rate of 0.1U/h in MiniMed 670G.

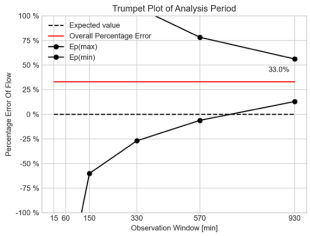
(II): Stabilization plot for a basal rate of 1.0U/h in MiniMed 670G.

The following 25 hours of measuring the basal rate is called the analysis period. When calculating the flow rates and standard deviation, a one-hour observation window is used. Table 3 is showing the total mean deviation for all the experiments calculated from the analysis period. The total mean deviation of 0.1 U/h bolus doses ranged from 15 % to 90 % from target, while for 1 U/h, it ranged from -2 % to 9 %.

Insulin Pump	0.1 U/h	1.0 U/h
Accu-Chek® Spirit Combo	139 ± 136 %	109 ± 12 %
	115 ± 50 %	104 ± 7 %
MiniMed® 640G	152 ± 42 %	98 ± 4 %
MiniMed® 670G	190 ± 131 %	107 ± 10 %
	133 ± 62 %	106 ± 4 %
Animas® Vibe®	149 ± 100 %	108 ± 19 %
Tandem t:slim X2	146 ± 94 %	98 ± 23 %

Table 3: *A table showing the total mean basal rate delivery [%] during the analysis period, ± the standard deviation calculated from 1-hour-windows.*

As required in the IEC standard, the analysis period is presented in trumpet plots, showing how the accuracy increases when expanding the observation windows. The mean deviation from the target is indicated with a red, broken line. Figure 6 is showing the trumpet plots from an experiment of MiniMed 670G. In addition to trumpet plots, cumulative plots show the total insulin delivery over time, against the expected total delivery, in figure 7. The trend was similar for all insulin pump models: 1 U/h showing approximately linear cumulative plots and trumpet plots with low deviations, and 0.1 U/h showing fluctuating cumulative plots and trumpet plots with large deviations.



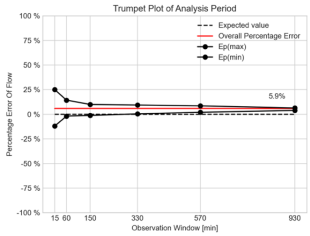


Figure 6:
(I): Trumpet plot for a basal rate of 0.1 U/h in MiniMed 670G.

(II): Trumpet plot for a basal rate of 1.0 U/h in MiniMed 670G.

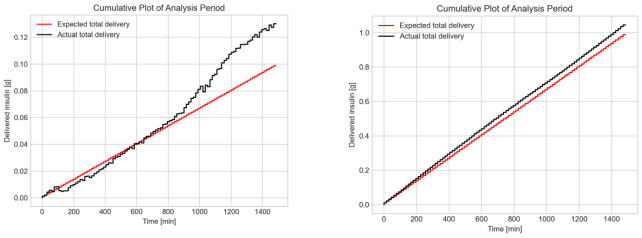


Figure 7:
(I): Cumulative plot for a basal rate of 0.1 U/h in MiniMed 670G, during the 25-hour analysis period.

(II): Cumulative plot for a basal rate of 1.0 U/h in MiniMed 670G, during the 25-hour analysis period.

Discussion

The bolus dose experiments show that the total insulin delivery falls within a target of ± 15 % for all doses in all insulin pump models. However, 1 U doses are, on average, more accurate than 0.1 U doses and have smaller deviations. Every individual dose is clinically relevant for bolus doses as they are individually injected with long intervals in between.

Low basal rates (0.1 U/h) are showing a total mean over-delivery of at least 15 % for all insulin pump models tested (see Table 3). Intermediate rates (1.0 U/h), however, have a maximal total deviation of ± 9 % from target. Compared to the bolus doses, this was not an expected result. We anticipated seeing a correlation between the insulin delivery accuracy of the same insulin volumes because basal rates are equivalent to several successive bolus dose deliveries. A possible theory to explain this is drifting due to temperature changes. However, the delivery increments between bolus doses and basal rates might differ, making our expectations unreasonable.

In the stabilization plots from the basal rate experiments, the 0.1 U/h measurements are fluctuating throughout the 24 hours, at times even below zero. In contrast, the 1.0 U/h measurements stabilize after about 250 minutes. The fact that the flow rate is calculated for half an hour observation windows might have affected the results, as the interval between insulin delivery increments is unknown. In the cumulative plots, the lower basal rates were winding and nonlinear for all the insulin pump models, unlike the smooth lines of the 1.0 U/h experiments. We observe some downward cracks in Figure 7 (I), which should not appear. Negative flow rates can appear due to noise in the measurements or underpressure in the insulin pump causing insulin to be sucked back into the tubing. As the experimental setup is left undisturbed during the experiments, the former reason is more probable.

Comparing the 0.1U/h stabilization period (Figure 5 (I)) with the cumulative plot (Figure 7 (I)) from the following 25 hours, we observe an under-delivery in the beginning, turning into an over-delivery during the analysis period. This might be caused by drifting due to external

and internal temperature changes. Other possible reasons may be contamination on the surface of the beaker evaporating in the startup period or buildup of static electricity. These observations call into question the reliability of the 0.1 U/h basal rate results.

After significant efforts to implement the IEC standard and correct for outside influences, the quality of the observations is still questionable, especially for lower insulin volumes. According to the manufacturer, the accuracy our balance can provide to weigh a given sample, can be calculated as $SF*R_{std}/UT$ (*Understanding Minimum Weight*, 2017), where SF is the security factor, R_{std} is the repeatability and UT is the uncertainty tolerance. We have a repeatability of 0.02 mg. Using SF=2 and UT=5%=0.05 we get a minimal weight sample of 2*0.02/0.05=0.8mg, corresponding to 0.08U of insulin. Concerning the complexity of the experimental setup, a higher SF would be preferable. Using a more accurate balance could have increased the confidence in the results. However, the main challenges were due to the behavior of the liquids, the lifting mechanism, and maximum weight limits – problems that may be expected to persist with a more sophisticated balance. Recently, Girardot et al. have published findings from a similar experiment on low volume delivery accuracy, employing a more sophisticated balance in conjunction with mass flowmetry, and also report significant inaccuracies in total deliveries (2020).

The current IEC standard has difficulties concerning implementation.
If one should look for alternative methods of testing insulin pump accuracy, some critical factors should be considered. First, a new method should be applicable to patch pumps as well as traditional insulin pumps. When the current IEC standard was released (2012), patch pumps were relatively new on the insulin pump market and have been a growing industry ever since. In 2018, patch pumps were used by around 5 % of patients using insulin pumps (Ginsberg, 2018). Second, a method that does not require a 24-hour stabilization period is preferable, as the first 24 hours of an IIS is a considerable amount of the IIS lifetime. One should also aim to find a method that does not require too expensive equipment and is easy to implement. An alternative way to measure insulin delivery accuracy with an analytical balance is to measure the insulin pump repeatedly. As the reservoir inside of the insulin pump gradually will be emptied with insulin, one can observe how the measurements decrease. Complications with the current experimental setup due to working with liquids would be eliminated. High precision flow meters are another alternative and may be used in other medical therapies such as pediatrics and neonatology (Jungmann, 2017).

The experiments in this study are done in vitro. In vivo use will cause noise on insulin delivery accuracy. Hence, working with tiny volumes is a general challenge. It is questionable whether a higher accuracy when delivering low rates would have an impact. The significance of the noise from in vivo use augments for patients with lower insulin demands. A possible solution to avoid the uncertainties of small insulin volumes is to use less concentrated insulin.

There is no official demand for insulin pump accuracy stated in the IEC standard. Hence, it is up to the manufacturer to consider whether an insulin pump is providing basic safety. This makes it difficult to conclude whether the quality of an insulin pump is sufficient. Insulin pump accuracy for all insulin volume deliveries is essential to provide safe diabetes therapy for all patient groups. Basal rates < 1.0 U/h span a wide range of patients, even adults. An evaluation of the clinical relevance of insulin delivery accuracy should be made. Further, a general accuracy criterion should be defined in the IEC standard.

Conclusion

The method specified in IEC 60601-2-24 to test insulin pump accuracy is seemingly working well for testing intermediate insulin volumes but appears to be insufficient for smaller, although clinically relevant, volumes. Factors such as drifting, static electricity, and vibrations invoke a significant relative error for lower insulin volumes. Nor is the current standard applicable on patch pumps. An evaluation of what level of accuracy is necessary for clinical settings should be made. Further, the IEC standard should define an accuracy criterion to ensure safe diabetes therapy for all patient groups. An immediate recommendation to mitigate the challenges concerning both measuring and delivering small insulin volumes, is to provide lower insulin concentrations – and thus larger total fluid volumes – for patients with low insulin demands.

References

Bachran, R., Beyer, P., Klinkert, C., Heidtmann, B., Rosenbauer, J., & Holl, R. W. (2012). Basal rates and circadian profiles in continuous subcutaneous insulin infusion (CSII) differ for preschool children, prepubertal children, adolescents and young adults. *Pediatric Diabetes*, *13*(1), 1–5. https://doi.org/10.1111/j.1399-5448.2011.00777.x

Freckmann, G., Kamecke, U., Waldenmaier, D., Haug, C., & Ziegler, R. (2019). Accuracy of Bolus and Basal Rate Delivery of Different Insulin Pump Systems. *Diabetes Technology & Therapeutics*, *21*(4), 201–208. https://doi.org/10.1089/dia.2018.0376

Ginsberg, B. H. (2018). Patch Pumps for Insulin. *Journal of Diabetes Science and Technology*, *13*(1), 27–33. https://doi.org/10.1177/1932296818786513

Girardot, S., Jacquemier, P., Mousin, F., Rendekeu, C., Hardy, S., & Riveline, J.-P. (2020). All Insulin Pumps Are Not Equivalent: A Bench Test Assessment for Several Basal Rates. *Diabetes Technology & Therapeutics*, *22*(6), 476–483. https://doi.org/10.1089/dia.2019.0486

IEC 60601-2-24:2012. (2012). https://www.standard.no/no/Nettbutikk/produktkatalogen/Produktpresentasjon/?ProductID=605278

Jungmann, S. (2017, November 16). *Yet Another Technical Gap Closed: Measuring Lowest Flow Rates in Medical Therapies*. https://www.sensirion.com/en/about-us/newsroom/sensirion-specialist-articles/measuring-lowest-flow-rates-in-medical-therapies/

Kamecke, U., Waldenmaier, D., Haug, C., Ziegler, R., & Freckmann, G. (2018). Establishing Methods to Determine Clinically Relevant Bolus and Basal Rate Delivery Accuracy of Insulin Pumps. *Journal of Diabetes Science and Technology*, *13*(1), 60–67. https://doi.org/10.1177/1932296818788349

Klinkert, C., Bachran, R., Heidtmann, B., Grabert, M., & Holl, R. W. (2008). Age-specific Characteristics of the Basal Insulin-rate for Pediatric Patients on CSII. *Experimental and Clinical Endocrinology & Diabetes*, *116*(2), 118–122. https://doi.org/10.1055/s-2007-990296

Snider, C. (2018, February 15). *Let's talk about your insulin pump data*. https://www.tidepool.org/blog/lets-talk-about-your-insulin-pump-data

Understanding Minimum Weight. (2017, August 22). https://us.ohaus.com/en-US/misc/newsletter-sign-up?n=0.2827956418669759

Ziegler, R., Kamecke, U., Waldenmaier, D., Haug, C., & Freckmann, G. (2018). Delivery of Low Basal Rates in Different Insulin Pumps—An Accuracy Evaluation. *Diabetes*, *67*(Supplement 1). https://doi.org/10.2337/db18-972-P

Ziegler, R., Waldenmaier, D., Mende, J., Haug, C., & Freckmann, G. (2019). 119-LB: Bolus Dosing Accuracy of Two Recent Insulin Pumps. *Diabetes*, *68*(Supplement 1).

https://doi.org/10.2337/db19-119-LB

Chapter 7

Discussion

7.1 Evaporation Rate

The results from the evaporation rate experiment can be seen in figure 5.1. As the R^2-number of the linear regression is close to 1, the graph has a high rate of linearity. The slope from the linear regression is negative, and $0.000002157g/min = 0.00013g/hr$. Consequently, the last decimal point will decrease with 13 increments during an hour. Some evaporation is observed, but it is quite small and will be compensated for in our experiments of insulin pump accuracy.

7.2 Insulin Pump Experiment Results

When we are to compare the accuracy performance of the different insulin pumps that are tested in this thesis, there are a couple of things we need to keep in the back of our minds. First of all, there is a considerable difference in the insulin pump production year. Also, the IIS and the tube length belonging to the different insulin pumps vary. We have only tested one insulin pump from each model so that potential faulty individual insulin pumps will not be discovered. The order in which the experiments have been performed might also impact the results. We continuously learn how to perform the experiments better. With all this said, the experiments have been performed carefully, and the procedure has been consistently followed. We are confident that, given our prerequisites, the results are credible.

7.2.1 Comparison of Insulin Pumps

Bolus Experiment Results

The plots and tables presenting the bolus rate results can be found in appendix B. There seems to be a slight trend for the bolus experiments that the deviations

from the expected value get higher for lower insulin volumes. The trend is even more significant for the standard deviation. However, the total insulin delivery deviation is, for the most part, within a target of 10%. For every single $1U$ test, the deviation was less than 5%. We can derive that the total delivered amount after successive bolus deliveries is accurate for all rates. However, for lower rates, a single delivery has a more unpredictable accuracy.

One experiment stood out negatively; the bolus accuracy for MiniMed 670G. We expect this insulin pump to have the same level of performance as the MiniMed 640G, as the only difference between them is the software. However, the deviation for all rates below $1U$ is higher than 10%, significantly worse than the others. In contrast, the second experiment of the same insulin pump shows significantly lower mean deviations for all delivery rates. There do not seem to be any considerable variations in the temperature and humidity data. This is a general trend; there is no correlation between temperature or humidity variations and deviation from the expected value. For other possible sources of errors, see section 7.3.

Basal Experiment Results

The plots and tables presenting the basal rate results can be found in appendix C. In general, we have less control of possible disturbance of the basal rate experiments because they are running automatically for 49 hours and consequently not continuously monitored. Another possible factor to affect the results is the following: Basal delivery is quasi-continuous. We do not know the interval between each insulin delivery for the different insulin pumps. This might affect the results of the individual measurements, as an insulin delivery might happen just as the measurement is made. However, in the long run, the measurement results will tell us whether the total insulin delivery is close to the target or not.

In the stabilization period plots, we expect the results to deviate initially and then gradually converge to the expected rate (indicated with a black line), which we observe when testing $1U/h$ for the different insulin pumps. On the other hand, for $0.1U/h$, the plots are heavily deviating and do not have a converging pattern. We can read that some of the flow rates calculated have negative values. This indicates that sources of error have affected the results because the measurements should always increase as insulin is delivered. Having that said, the results might also be a sign that low flow rates are less accurate and also less evenly delivered.

The analysis period is presented in trumpet plots, cumulative plots, and tables. We observe that for all $1U/h$ experiments, the deviations of the total expected deliveries are inside a target of 10%. The cumulative plots show that the delivery is smooth as the curves are almost linear. In contrast, the basal rates of $0.1U/h$ are showing large over deliveries, all from 14.8% to 89.9% from expected total delivery. The cumulative plots are varying. Some curves are relatively smooth and linear, while some have bends and bows. Two of the plots even have some downward cracks, which should not appear at all. These phenomenons must be due to

errors, as the measurements will increase with insulin delivery.

Overview

In the insulin pump accuracy experiments, we have measured both flow rates over time and individual insulin delivery rates based on weighing the delivered volumes and calculating differences. Some of the insulin pump manufacturers claim their products to deliver an accuracy of 5% for all rates. Our experiments are confirming or almost confirming this for intermediate rates ($1U$ or $1U/h$). However, the lower rates are characterized by large deviations and, at times, low accuracy. It is difficult to distinguish between deviations caused by sources of error and actual insulin delivery accuracy when it comes to smaller volumes.

We expect there to be some correlation between the accuracy of bolus and basal rates at the same rates. For basal rates, there is a clear tendency of a large over-delivery for $0.1U/h$. Compared to the $0.1U$ experiments of the bolus rates, this is not an expected result. The lower bolus rates are also performing worse than the intermediate ones but have no pattern of over-delivery. This confusion is again enlightening the challenge of both delivering and measuring small volumes of insulin.

Insulin Model Reviews

We have, in total, tested four different insulin pump models. Animas Vibe is only tested once because this insulin pump model is no longer on the market. Tandem t:slim X2 was also tested because we only got to borrow it for one week. The other models were tested several times. In this section, we will discuss the degree of correlation between experiments of similar insulin pump models.

The first three experiments can be considered as the same insulin pump model as the difference between MiniMed 640G and 670G most likely is due to software. Except for the lower bolus doses of the first MiniMed 670G experiment, they show a high level of accuracy for all bolus doses (within ±10% from the target for total delivery). In the same experiment for basal rates, the results are significantly worse when testing $0.1U/h$. The three experiments all show a total over-delivery of $0.1U/h$, while $1U/h$ has both negative and positive mean deviation from target, always inside ±6.8% from the target. However, the variations between the experiments are significant, putting to question the credibility of the results. Are the variations due to the performance of the insulin pumps or noise in the measurements?

Comparing the two experiments of the Accu-Check insulin pump, we see that, all though performing well for all bolus doses (within ±10% from target for total delivery), the first experiment has more considerable standard deviations. Also, for the experiments of $0.1U/h$ basal rates, the standard deviation is immense the first time compared to the second (135.8% versus 49.7%). The reason might be

that the first experiment was performed earlier than the second. Thus, experience with the setup was acquired in the meantime. However, it might also be due to the actual performance of the insulin pump during the experiments or due to external factors (see 7.3).

7.3 Possible Sources of Error

7.3.1 High Precision Measurements

Balances that are accurate to five decimal points are highly sensitive to external factors. Several of those factors are not visible to the human eye, nor are they simple to avoid. Some of the common factors that might slightly affect the measurements are:

- Buildup of static electricity
- Air flows
- External temperature- or humidity changes
- Internal temperature changes in the balance
- Erroneous internal calibration of the balance
- Stains of grease or liquid on the object that is to be measured, this will evaporate
- Bad leveling of the balance
- Placing an object at different places on the balance
- Pieces of dust falling on the balance
- The balance has been shocked (added weight out of capacity range)

The experimental method suggested in the IEC has some weaknesses when it comes to high precision measurements. Working with liquids might make the environment unstable due to humidity. One must be very careful not to spill anything. Liquids are also very sensitive to vibrations. The beaker must be raised and lowered. If they move too much, liquid might drain and affect the measurements. Also, liquids tend to evaporate and at a different speed for different temperatures. A correction factor is calculated and compensated for, but it is still considered a possible source of error.

The IEC standard demands to test the insulin pumps at the lowest possible rates. For insulin pumps delivering low insulin volumes, the balance used for the experiments requires readability to five decimal points. The balance has a repeatability of $0.02mg$, which creates an expected relative error for the lowest rates of 8%.

7.3.2 Insulin Infusion Systems

An insulin infusion system might provide sources of error that are not related to the quality of the actual insulin pump model. An insulin pump is a complex machine consisting of many parts that are possibly delivered from different man-

ufacturers, where all of them can be faulty. One insulin pump with low-quality behavior does not necessarily imply that all insulin pumps of this model are bad. All though this is considered unlikely, the IIS or reservoir might also be faulty. In our experiments, we have made sure that the reservoirs are adequately lubricated (see section 3.3). Insulin might also create problems if not adequately treated. It can crystallize or it can appear air bubbles in the system.

7.4 IEC 60601-2-24

7.4.1 Weaknesses in the IEC Standard

While implementing the IEC standard, we discovered some weaknesses. Some of them are mentioned in the section above and are due to challenges in high precision measurements. As we have seen in chapter 3, other papers have questioned what the minimal level of accuracy required to provide basic safety is. This is something that the IEC standard could have specified. As seen in section 2.5.2, drifting is a common phenomenon in analytical balances, making them unsuitable for running long time measurements.

For this reason, we decided to build a lifting mechanism, making the experimental setup much more complex and time-consuming. The IEC standard has defined some ways to present the experimental results that are not necessarily intuitive to read nor clinically relevant. We will reason for which presentations we prefer in section 7.5. Lastly, an experimental method that can be applied on patch pumps and traditional insulin pumps is preferable.

7.4.2 Alternative Experimental Methods to Determine Insulin Pump Accuracy

In this section we will present alternative methods to test insulin pump accuracy and discuss whether they can be superior to the current standard.

More Accurate Analytical Balances

The first alternative to enhance an experimental setup could be to buy a more accurate analytical balance. Existing balances have advanced temperature control and mechanisms to eliminate static electricity, which was some of the challenges we have struggled with in this master thesis. However, these balances are expensive. Several of the challenges we have experienced will remain, see section 7.3. Another disadvantage with this solution is that higher accuracy often goes at the expense of the upper limit of the weight of a measurement. This means that when we are required to measure a beaker filled with water and oil, it is likely that we will need to surpass the upper limit of a more accurate balance.

In section 3.1 we refer to a publication where they have tweaked the IEC standard to be applied on patch pumps. This was done by attaching a capillary to the insulin

pump cannula submerged into a small plastic prism filled with water and oil. They have successfully implemented this method with a more accurate analytical balance, but they have not tested on lower rates than $1U/h$ without elaborating why. We, therefore, conclude that this alternative is questionable.

Flow Sensors

Flow can be measured using a flow sensor. Based on the research made in section 3.1.2, the most suitable technology for a flow sensor in our context would be to use a flow meter. The advantages of this method of measuring flow are that flow meters are a lot cheaper than analytical balances. The experimental setup will be simple, and one can apply it on both patch pumps and traditional insulin pumps. However, we cannot know that it would work before it is applied in practice. A possible problem could be that, since flow meters depend on contact, it might affect the viscosity of the insulin and invoke crystallization.

Measuring the Insulin Pump

Let us turn the method presented in the IEC standard upside down. We might measure insulin delivery accuracy while eliminating several of the challenges in the current setup. This consists of measuring the insulin pump, letting the insulin be delivered outside of the system. The weight of the insulin pump should decrease when insulin is delivered, as the insulin reservoir will empty. We avoid the challenges concerning liquids, vibration, and humidity changes from the current experimental setup with this approach. This approach can also be applied to path pumps. While testing bolus rates, one has to lift the insulin pump off the scale and start a bolus, but that is not necessarily a problem.

Avoiding Small Volumes

As we have seen from our experiments and other publications on the subject, insulin delivery accuracy seems to become a problem when volumes are small. Measuring and delivering delivery both gets complicated. A possible solution is to increase the lowest possible insulin delivery rates in the insulin pump software. Further, insulin is mixed with water. This means that the insulin concentration can be decreased for patients with low insulin demands. In this manner, they can use the higher flow rates while getting a suitable quantity of insulin.

7.5 Reasoning

7.5.1 Implementation of IEC 60601-2-24

The IEC standard is not specifying every detail of the experiments, meaning that we have made some choices along the way that we will reason for in this section. A lifting mechanism was built, even though this was not specified in the

standard. The reason was that analytical balances are not meant for long time measurements. An alternative to the lifting mechanism could be to do it manually, but that would be very unpractical, especially for the basal rate experiments. Lifting the beaker by hand would also provide sources of error such as air flows, potential stains on the beaker, and vibrations. Another alternative would be to let the measurements run continuously and write down measurements without lifting the beaker and zeroing the balance first. However, drifting will appear in the balance and create noise in the measurements. It is impossible to discover a correction factor to compensate for drifting as drift does not have a linear behavior. The best practice for using an analytical balance consists of zeroing the balance before measurement and note down the measurement immediately after the balance has stabilized (see section 2.5.2). The manufacturer states the stabilization time for a specific balance.

By implementing an automatic system that saves the measurements to an excel sheet and uses a script to generate plots and tables automatically, we eliminate the possibility of manually writing down the wrong values.

The IEC standard says to run tests on the highest possible bolus rates of a specific insulin pump on 25 successive doses. For the insulin pumps tested in this thesis, the reservoir of the insulin pumps did not contain 25 doses of the largest possible bolus rates, and testing such a dose would take too much time. We have therefore chosen to test at an intermediate rate. Basal rates at the lowest possible delivery rate are also not tested because we consider $0.1U/h$ to be the lowest rate where the results can give an impression of delivery accuracy. For lower rates, possible sources of error will make the results too ambiguous.

7.5.2 Representation of Bolus Experiment Results

The IEC standard has demanded how to present the bolus experiment results. Those consist of calculating the average delivery, the average deviation from target, and the percentage maximum and minimum deviation from the target value. These demands are satisfied in this thesis. Nonetheless, the standard deviation can give the same insinuation as the maximum and minimum deviation in a more concise way, which is why we calculate this in addition. The standard deviation is an essential value because every single bolus rate is clinically relevant. We also add a scatter plot so that every single bolus rate accuracy can be visually analyzed.

7.5.3 Representation of Basal Experiment Results

According to the IEC standard, the first 24 hours of the basal experiment results is called the stabilization time. As we have seen in the results, the curves are unpredictable at the beginning of the stabilization time. This is why we consider the following 25 hours, the analysis period, more critical. A trumpet curve is plotted to satisfy the IEC standard. This plot is not intuitively read but gives insight into the total mean deviation and the mean accuracy given various observation windows.

We have added a plot showing the total delivered insulin over the expected total amount at a given time, which shows the size of the deviation and how linear or winding the curve is. A table is added, where we calculate the delivery accuracy in 1-hour windows, and the values used are the same as the ones in the bolus rate tables so that they can easily be compared.

7.6 Clinical Relevance of Insulin Pump Accuracy

How clinically relevant is it that the smallest volumes of insulin delivery are accurate? Many factors can affect insulin pump delivery accuracy, it being faulty hardware (see section 7.3.2), patient movements, or changes in the environment. The experiments performed in this thesis are performed in vitro, eliminating the countless effect of in vivo use of insulin pumps. As the insulin volumes decrease, the relevance of the insulin delivery accuracy also gets smaller. This is amplified by the fact that insulin absorption in the body varies with activity levels, type of food consumption, hormonal levels, etc.

But what about patients with low insulin demands? For these patients, the accuracy might significantly impact their diabetes management. The fact that the deliveries vary between 5%-10% is probably sufficient, and it seems like the larger doses do. Nevertheless, the lower rates should also perform this well. We cannot assume that the insulin pumps are not delivering this level of accuracy because the sources of error might have significantly impacted the experiment results. As we have seen in chapter 3, other research on the subject has either neglected to test lower rates or concluded that the accuracy for lower rates is worse than for higher rates. Usually, basal rate tests were made on 1U/h, a medium/high rate for adults. For the future of artificial pancreas systems to work well, insulin delivery accuracy for lower rates will get an even higher matter.

Chapter 8

Conclusions

In this master thesis, we wanted to verify the accuracy of insulin delivery in different insulin pump models. While reading on related research on the subject, we found that very few publications were made on insulin pump accuracy regarding rates lower than $1U/h$. The publications on lower rates were posters for seminars; hence they were not detailed. We found this interesting and wanted to investigate the area further.

In the project thesis, during the autumn of 2020, we started implementing the IEC standard for testing insulin pump accuracy. It was important to us to stay as close to the standard as possible to compare our experimental results with other publications on the subject. However, implementing the standard was more challenging and time-consuming than predicted. The setup required adaptations such as making a specially made lid, 3d-printing parts to keep the insulin tube in place, and building a lifting mechanism. To run the experiments automatically for several days, we also had to program a script that communicated between the balance and the lifting mechanism. First off, the plan was to spend the first couple of weeks implementing the IEC standard and spending the rest of the semester running quantified experiments on different insulin pump models.

Unfortunately, we never reached a point where we were completely confident in the experimental results of the lowest insulin rates. However, given our equipment and the restrictions due to following the IEC standard, we find this an exciting discovery. Our results from testing lower rates are ambiguous as the possible sources of errors are significant. This is after spending several months implementing an experimental setup and procedure. Given that the IEC standard was last updated in 2012, it is probably not well suited for testing the lowest rates that insulin pumps today can deliver. Neither is the standard applicable on patch pumps, as these were relatively new on the market in 2012. The big questions are: How have the insulin pump manufacturers implemented the IEC standard? Do the insulin pump manufacturers claim to deliver a higher level of accuracy than they do in

reality?

8.1 Further Research

In the research made in this master thesis, we did not manage to become confident about our experimental results for the lowest flow rates. To upgrade the equipment used in our experiments would be expensive, leading us to believe that the method should change completely. Thus, for further research, we recommend exploring other methods of measuring small volumes of flow.

The aim should be to renew the IEC standard. First, we must investigate different technologies to measure the flow rates of small insulin volumes. We have listed some suggestions in section 7.4.2. The strengths and weaknesses of the alternative methods must be established. Then, we must decide which one is best suited given our context; It is important to ensure that the new experimental setup can be applied on patch pumps and traditional pumps to be compared righteously. It would be favorable to eliminate the stabilization time of the experiments, as the first 24 hours are a significant part of the equipment usage. The setup should also be as cheap as possible. Lastly, we must define a detailed experimental setup, including how to present the experimental results in a clinically relevant manner.

A separate study should be made on the clinical relevance of insulin delivery accuracy. Based on the results, the IEC standard should define specific insulin pump accuracy demands to ensure that insulin pumps are safe to use for all patient groups.

With a renewed test setup, we may detect the insulin delivery accuracy for the lowest rates with confidence. If we then discover that the insulin delivery accuracy is insufficient, we should aim to figure out why this is and improve it.

Bibliography

[1] R. Ziegler, U. Kameche, D. Waldenmaier, C. Haug and G. Freckmann, 'Delivery of low basal rates in different insulin pumps—an accuracy evaluation,' *American Diabetes Association*, Jul. 2018. [Online]. Available: https://diabetes.diabetesjournals.org/content/67/Supplement_1/972-P?utm_source=TrendMD&utm_medium=cpc&utm_campaign=Diabetes_TrendMD_0.

[2] R. Ziegler, D. Waldenmaier, J. Mende, C. Haug and G. Freckmann, 'Bolus dosing accuracy of two recent insulin pumps,' *American Diabetes Association*, Jun. 2019. [Online]. Available: https://diabetes.diabetesjournals.org/content/68/Supplement_1/119-LB.

[3] G. Freckmann, U. Kamecke, D. Waldenmaier, C. Haug and R. Ziegler, 'Accuracy of bolus and basal rate delivery of different insulin pump systems,' *Diabetes Technology Therapeutics*, p. 8, Apr. 2019. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6477586/#B9.

[4] *Insulinpumper, cgm og forbruksmateriell*, [Online; accessed 05-05-2021]. [Online]. Available: https://sykehusinnkjop.no/nasjonale-avtaler/insulinpumper-cgm-og-forbruksmateriell-#produkter-pa-avtale/.

[5] *Minimed 640g system user guide*, [Online; accessed 15-March-2021]. [Online]. Available: https://www.medtronic-diabetes.co.uk/sites/uk/medtronic-diabetes.co.uk/files/minimed640gifu2015mp6025957-024_a_en_mmol.compressed.pdf.

[6] *Animas vibe owner's booklet*, [Online; accessed 29-April-2021]. [Online]. Available: https://www.manualslib.com/manual/832372/Animas-Vibe.html#manual.

[7] I. B. Hirsch, *Type 1 diabetes mellitus and the use of flexible insulin regimens*, [Online; accessed 19-September-2020], Nov. 1999. [Online]. Available: https://www.aafp.org/afp/1999/1115/p2343.html.

[8] *Novorapid*, [Online; accessed 17-September-2020], Mar. 2020. [Online]. Available: https://www.felleskatalogen.no/medisin/novorapid-novorapid-flexpen-novorapid-penfill-novorapid-pumpcart-novo-nordisk-562204.

[9] *Water density*, [Online; accessed 17-September-2020]. [Online]. Available: https://www.usgs.gov/special-topic/water-science-school/science/water-density?qt-science_center_objects=0#qt-science_center_objects.

[10] 'Medical electrical equipment - part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers (iec 60601-2-24:2012),' 2012.

[11] *Types of balances and scales, common terms, and care*, [Online; accessed 7-March-2021]. [Online]. Available: https://www.grainger.com/know-how/equipment-information/kh-laboratory-balance-scale-types-care-terms.

[12] *Analytical balances drift and its importance*, [Online; accessed 8-March-2021]. [Online]. Available: https://www.pharmaguideline.com/2014/11/drift-and-its-importance-in-analytical-balances.html.

[13] U. Kamecke, D. Waldenmaier, C. Haug, R. Ziegler and G. Freckmann, 'Establishing methods to determine clinically relevant bolus and basal rate delivery accuracy of insulin pumps,' *Journal of Diabetes Science and Technology*, pp. 60–67, Jul. 2018. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313283/.

[14] S. Borot, S. Franc, J. Cristante, P.-Y. Benhamou, B. Guerci, H. Hanaire, E. Renard, Y. Reznik, C. Simon and G. Charpentier, 'Accuracy of a new patch pump based on a microelectromechanical system (mems) compared to other commercially available insulin pumps,' *Journal of Diabetes Science and Technology*, Nov. 2014. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455475/.

[15] *Measuring flow: Load cells vs. flow meters*, [Online; accessed 28-April-2021]. [Online]. Available: https://www.crossco.com/resources/articles/measuring-flow-load-cells-vs-flow-meters/.

[16] *Yet another technical gap closed: Measuring lowest flow rates in medical therapies*, [Online; accessed 28-April-2021]. [Online]. Available: https://www.sensirion.com/en/about-us/newsroom/sensirion-specialist-articles/measuring-lowest-flow-rates-in-medical-therapies/.

[17] *Liquid flow meters*, [Online; accessed 28-April-2021]. [Online]. Available: https://www.sensirion.com/en/flow-sensors/liquid-flow-meters/.

[18] 'How lubricant choice affects dose accuracy in insulin pumps,' Sep. 2017, [Online; accessed 7-March-2021]. [Online]. Available: https://www.ondrugdelivery.com/lubricant-choice-affects-dose-accuracy-insulin-pumps/.

[19] *Parafinolje, 100 %*, [Online; accessed 23-January-2021]. [Online]. Available: https://www.biltema.no/bygg/maling/treolje/parafinolje-100--2000019182.

[20] *Sikkerhetsdatablad parafinolje*, [Online; accessed 23-January-2021]. [Online]. Available: `https://www.biltema.no/BiltemaDocuments/SecuritySheets/nb/361414_SDB.pdf`.

[21] *Dht22–temperature and humidity sensor*, [Online; accessed 14-April-2021]. [Online]. Available: `https://www.sparkfun.com/datasheets/Sensors/Temperature/DHT22.pdf`.

Appendix A

Code Files

A.1 main.py

Code listing A.1: Main program to run automatic measurements and logging, *main.py*

```
import urllib.request
import time
import datetime
import serial
import xlwt

# CONNECTION WITH ARDUINO FOR TEMPERATURE AND HUMIDITY AND STEPPER MOTOR

def connectToArduino():
        # SERIAL PORT CONNECTION ARDUINO
        port_name_arduino = '/dev/cu.usbmodem14201'
        serial_arduino = serial.Serial(port_name_arduino, 1200, timeout = 1)
        if not serial_arduino.isOpen():
                serial_arduino.open()
        return serial_arduino

def raiseBeaker():
        print("Raising beaker...")
        serial_arduino.write(b'U')
        serial_arduino.readlines()
        print("Beaker raised.")
        print('')

def lowerBeaker():
        print("Lowering beaker...")
        serial_arduino.write(b'L')
        serial_arduino.readlines()
        print("Beaker lowered.")
        print('')

# Temperature outside of chamber
def getTemperature():
        serial_arduino.write(b'Temp')
        time.sleep(1)
```

```
        val = serial_arduino.readlines()
        try:
                return str(val[0], 'utf-8')
        except:
                return ""

# Humidity outside of chamber
def getHumidity():
        serial_arduino.write(b'Hum')
        time.sleep(1)
        val = serial_arduino.readlines()
        try:
                return str(val[0], 'utf-8')
        except:
                return ""


# CONNECTION WITH BALANCE

def connectToBalance():
        # SERIAL PORT CONNECTION BALANCE
        port_name = '/dev/cu.usbserial-1410'
        baud_rate = 9600
        # If trying to read/write value for more than one second, run new iteration
        timeout = 1
        serial_balance = serial.Serial(
                port_name, baud_rate,
                parity=serial.PARITY_NONE,
                stopbits=serial.STOPBITS_ONE,
                bytesize=serial.EIGHTBITS,
                timeout=timeout,
                write_timeout=timeout)
        if not serial_balance.isOpen():
                serial_balance.open()
        return serial_balance

def getMeasurement():
        while True:
                serial_balance.reset_input_buffer()
                serial_balance.write(b'P\r\n')
                val = serial_balance.readlines()

                if len(val) > 2:
                        # Measurementvalue from print,
                        # decoded from bytes, stripped from whitespace,
                        # then split so we can remove units
                        measurement_list = val[1].decode('utf-8').strip().split()
                        # Get the measurement with right format for exel number
                        try:
                                # Make sure that element is measurement
                                float(measurement_list[0])
                                #return measurement_list[0].replace(".", ",")
                                return measurement_list[0]
                                break
                        except:
                                print("Fetched␣element␣was␣" + measurement_list[0])

def tareBalance():
        print("Taring...")
        serial_balance.write(b'T\r\n')
```

```
        print("Balance tared.")
        print('')

def zeroBalance():
        print("Zeroing...")
        serial_balance.write(b'Z\r\n')
        print("Balance zeroed.")
        print('')


# MENU FUNCTIONS

def getMenu():
        print('MAIN MANU')
        print('S: Status Update')
        print('P: Play Program')
        print('U: Raise Beaker')
        print('L: Lower Beaker')
        print('Z: Zero Balance')
        print('T: Tare Balance')

        print('What do you want to do?')
        choise = input()
        print('')

        if choise == "S":
                getStatusUpdate()
        elif choise == "U":
                raiseBeaker()
        elif choise == "L":
                lowerBeaker()
        elif choise == "P":
                playProgram()
        elif choise == "Z":
                zeroBalance()
        elif choise == "T":
                tareBalance()
        else:
                print('')
                print("Please choose one of the elements in the menu!")
                print('')
        getMenu()

def getStatusUpdate():
        print("STATUS UPDATE")
        print('.................................................')
        print("Time: " + datetime.datetime.now().strftime("%X"))
        print("")
        print("Environment data")
        print("Temperature: " + getTemperature() + " C ")
        print("Humidity: " + getHumidity() + "%")
        print("")
        print("Measurement: " + getMeasurement() + "g")
        print('.................................................')
        print("")

def getIntervalStatus(measurement, temperature, humidity):
        print("INTERVAL STATUS")
        print('.................................................')
        print("Time: " + datetime.datetime.now().strftime("%X"))
```

```
        print("")
        print("Environment data")
        print("Temperature: " + temperature + " C ")
        print("Humidity: " + humidity + "%")
        print("")
        print("Measurement: " + measurement + "g")
        print('.....................................................')
        print("")


def playProgram():
        print('STARTING PROGRAM')
        print('.....................................................')
        #print('How many minutes should each interval be?')
        interval = input('Interval: ')
        while not interval.isdigit():
                print('Please insert an integer as interval:')
                interval = input()

        print('')
        print('Interval is successfully set to ' + interval + ' minutes')
        print('')

        fileName = input("Filename: ")
        fileName = fileName + ".xls"

        wb, ws = initiateExel()

        startDateTime = datetime.datetime.now()
        startTime = startDateTime.strftime("%X")
        startDate = startDateTime.strftime("%x")
        count = 0

        while True:
                minFromStart = datetime.timedelta(minutes = (int(interval)*count))
                nextInterval = startDateTime + minFromStart

                if nextInterval <= datetime.datetime.now():

                        # Zeroing the balance
                        zeroBalance()
                        time.sleep(8)

                        # Lowering the beaker
                        lowerBeaker()
                        time.sleep(8) # Stabilisation time of balance is 8 seconds

                        # Making a measurement when balance is stable
                        measurement = getMeasurement()
                        time.sleep(2)

                        # Raising the beaker
                        raiseBeaker()
                        time.sleep(2)

                        # Fetch environment data
                        temperature = getTemperature()
                        humidity = getHumidity()

                        zeroBalance()
```

```
                        time.sleep(2)

                        getIntervalStatus(measurement, temperature, humidity)
                        count = count + 1

                        writeRowExel(
                                wb,
                                ws,
                                count,
                                fileName,
                                measurement,
                                temperature,
                                humidity)


# MANAGING EXEL DOCUMENTATION

def initiateExel():
        wb = xlwt.Workbook()
        ws = wb.add_sheet("measurements")

        # Write title row
        columns = ("Date", "Time", "Measurement␣[g]", "Temperature", "Humidity")
        ws.write(0, 0, columns[0])
        ws.write(0, 1, columns[1])
        ws.write(0, 2, columns[2])
        ws.write(0, 3, columns[3])
        ws.write(0, 4, columns[4])

        return ws, wb

def writeRowExel(ws, wb, row_index, filename, measurement, temp, hum):
        # Current date mm/dd/yy
        ws.write(row_index, 0, datetime.datetime.now().strftime("%x"))
        # Current time 00:00:00
        ws.write(row_index, 1, datetime.datetime.now().strftime("%X"))
        ws.write(row_index, 2, measurement)
        ws.write(row_index, 3, temp)
        ws.write(row_index, 4, hum)
        wb.save(filename)


serial_balance = connectToBalance()
serial_arduino = connectToArduino()

print('')
print('')
print('')
print('')
print('')
print('EXPERIMENT␣CONTROLLER')
print('................................................')

getMenu()
```

A.2 basal.py

Code listing A.2: Program to print plots and tables for basal rate experiments, *basal.py*

```
import xlrd
import statistics
import matplotlib.pyplot as plt
plt.style.use('seaborn-whitegrid')
import numpy as np
from matplotlib.ticker import FormatStrFormatter
from tabulate import tabulate


def getEnvData(sheet, col):
        # Returns the average and standard deviation from the values in a column

        # List of strings containing the values of a column minus title row
        list_of_values = sheet.col_values(col)[1:24*4+25*4+1]

        # Convert all values from string to float
        for i in range(0,len(list_of_values)):
                list_of_values[i] = float(list_of_values[i])

        return statistics.mean(list_of_values), statistics.stdev(list_of_values)


def getFlowRateList(sheet, observation_interval):
        # Returns a list of the flow rates for a wanted observation interval
        measurements = sheet.col_values(2)[1:]
        measurements[0] = float(measurements[0])

        flow_rate_list = []

        # Calculate evaporation correction factor
        correction_factor = evaporation_rate*observation_interval

        fac = int(observation_interval/interval)

        # Convert all values from string to float
        for i in range(1,round(len(measurements)/fac)):
                measurements[fac*i] = float(measurements[fac*i])
                delivery = measurements[fac*i] - measurements[fac*(i-1)]
                        + correction_factor
                flow_rate = 60*(delivery)/(observation_interval*density)
                flow_rate_list.append(flow_rate)

        return flow_rate_list


def getTotalFlow(sheet):
        # Returns a list of the flow rates for a wanted observation interval
        measurements = sheet.col_values(2)[1:]

        # Calculate evaporation correction factor
        correction_factor = evaporation_rate*interval

        # Convert all values from string to float
        for i in range(0,round(len(measurements))):
                measurements[i] = float(measurements[i])

        # Total flow compansated for evaporation rate
```

```
        Q = 60*(measurements[24*4 + 25*4] - measurements[24*4]
                + correction_factor*(n_2))/(density*T_2)
        return Q


def getStabilizationPlot(flow_rate_list, expected_rate):
        # Stabilisation plot with observation interval of 30 minutes
        y = flow_rate_list[:24*2]
        x = list(range(0,len(y)))
        x = [t*2*interval for t in x]

        exp = [expected_rate for i in range(len(y))]

        plt.title('Stabilization Period')
        plt.xlabel('Time [min]')
        plt.ylabel('Flow rate [g/h]')

        # Broken indicator lines
        plt.plot(x, exp, color='black', label="Expected value")
        plt.plot(x, [el*1.05 for el in exp], color='blue', label="5% from target")
        plt.plot(x, [el*0.95 for el in exp], color='blue')
        plt.plot(x, [el*1.15 for el in exp], color='red', label="15% from target")
        plt.plot(x, [el*0.85 for el in exp], color='red')

        plt.plot(x, y, '-', color='black', label="Measurement")
        plt.legend()
        plt.show()


def getAnalysisPlot(flow_rate_list, expected_rate, Q):
        Q_list = flow_rate_list[n_1:n_1 + n_2]

        # Total mean error
        A = 100*(Q - expected_rate) / expected_rate

        # Observation windows
        P = [15, 60, 150, 330, 570, 930]

        E_p_max_list = []
        E_p_min_list = []

        for observation_window in P:
                m = (T_2 - observation_window)/interval + 1
                E_p_list = []

                for j in range(1, int(m) + 1):
                        E_p = []
                        K = interval/(observation_window)
                        for i in range(j-1,int(j+observation_window/interval-1)):
                                E_p.append((Q_list[i]-expected_rate)*100/expected_rate)
                        E_p_list.append(K * sum(E_p))

                E_p_max_list.append(max(E_p_list))
                E_p_min_list.append(min(E_p_list))

        # Set rate is when percentage e rror is 0
        exp = [0 for i in range(len(P))]
        mean_error_list = [A for i in range(len(P))]

        plt.title('Trumpet Plot of Analysis Period')
```

```
        plt.ylim([-100, 100])
        plt.xlabel('Observation␣Window␣[min]')
        plt.ylabel('Percentage␣Error␣Of␣Flow')

        # Broken indicator lines
        plt.plot(P, exp, '--', color='black', label="Expected␣value")
        plt.plot(P, mean_error_list, color='red', label="Overall␣Percentage␣Error")
        plt.plot(P, E_p_max_list, '-o', color='black', label="Ep(max)")
        plt.plot(P, E_p_min_list, '-o', color='black', label="Ep(min)")

        overall_error = "{err:.1f}%".format(err = A)
        plt.text(830, A - 10, overall_error)

        plt.legend()
        plt.gca().yaxis.set_major_formatter(FormatStrFormatter('%d␣%%'))
        plt.show()


def getCumulativePlot(flow_rate_list, expected_rate):
        Q_list = flow_rate_list[n_1:n_1 + n_2]
        y = []

        for i in range(0,n_2):
                y.append(sum(Q_list[:i]))

        x = list(range(0,len(y)))
        x = [t*interval for t in x]

        set_rate_list = [expected_rate*i for i in range(len(y))]

        plt.title('Cumulative␣Plot␣of␣Analysis␣Period')
        plt.xlabel('Time␣[min]')
        plt.ylabel('Delivered␣insulin␣[g]')

        # Broken indicator lines
        plt.step(x, set_rate_list, color='red', label="Expected␣total␣delivery")
        plt.step(x, y, '-', color='black', label="Actual␣total␣delivery")
        plt.legend()
        plt.show()


def getStatistics(flow_rate_list, expected_rate):
        # Calculate percentage deviation for every hour window
        # Printing only from analysis period
        Q_list = flow_rate_list[24:24 + 25]

        mean = statistics.mean(Q_list)
        st_dev_absolute = statistics.stdev(Q_list)
        st_dev_percentage = st_dev_absolute/expected_rate*100
        dev_set_val = (mean - expected_rate)*100/expected_rate

        return mean, st_dev_absolute, st_dev_percentage, dev_set_val


def fromUnitsToGrams(dose):
        # 1 Unit is 0.01 ml
        # Density is in g/cm^3
        # 1 ml = 1 cm^3
        return density*dose*0.01
```

```
def main():
        data = {'': [
                "Expected [g*10^(-5)]",
                "Average [g*10^(-5)]",
                "Standard deviation (1-h-windows) [g*10^(-5)]",
                "Standard deviation (1-h-windows) [%]",
                "Deviation from expected delivery [%]",
                "Temperature [ C ]",
                "Humidity [%]"
        ],
        }

        while True:
                print('')
                fileName = input('Filename: ') + '.xls'

                wb = xlrd.open_workbook(fileName)
                sheet = wb.sheet_by_index(0)

                expected_unit_rate = float(input('Expected rate [U]: '))
                # Write in insulin units, convert to grams
                expected_rate = fromUnitsToGrams(expected_unit_rate)

                # Get average and standard deviation of environment data
                temp_avg, temp_dev = getEnvData(sheet, 3)
                temperature = (str(round(temp_avg, 1))+"  "+str(round(temp_dev, 1)))
                hum_avg, hum_dev = getEnvData(sheet, 4)
                humidity = (str(round(hum_avg, 1))+"  "+str(round(hum_dev, 1)))

                flow_rate_list = getFlowRateList(sheet, 60)
                mean, st_dev_absolute, st_dev_percentage, dev_set_val
                        = getStatistics(flow_rate_list, expected_rate)


                data[str(round(expected_unit_rate, 3)) + 'U/h'] = [
                        str("{num:.0f}".format(num = expected_rate*10**5)),
                        str("{num:.0f}".format(num = mean*10**5)),
                        str("{num:.0f}".format(num = st_dev_absolute*10**5)),
                        str("{num:.1f}".format(num = st_dev_percentage)),
                        str("{num:.1f}".format(num = dev_set_val)),
                        temperature,
                        humidity]

                flow_rate_list = getFlowRateList(sheet, 30)
                getStabilizationPlot(flow_rate_list, expected_rate)

                flow_rate_list = getFlowRateList(sheet, interval)
                Q = getTotalFlow(sheet)
                getAnalysisPlot(flow_rate_list, expected_rate, Q)
                getCumulativePlot(flow_rate_list, expected_rate)

                keepRunning = input('Add more files (y/n)? ')
                if keepRunning == "n":
                        break

        print(tabulate(data, headers = 'keys', tablefmt = 'fancy_grid'))


# Constants
```

```
density = 0.998 # g/cm^3
evaporation_rate = 0.000002157 # g/min
interval = 15 # Interval betweeen measurements in minutes

# n = number of measurements in stabilization / analysis period
# T = amount of minutes in stabilization / analysis period
n_1 = 24*4
T_1 = n_1*interval
n_2 = 25*4
T_2 = n_2*interval


print('')
print('')
print('')
print('')
print('')
print('BASAL␣RATE␣ACCURACY␣EXPERIMENT')
print('................................................')


main()
```

A.3 bolus.py

Code listing A.3: Program to print plots and tables for bolus rate experiments, *bolus.py*

```
import xlrd
import statistics
import matplotlib.pyplot as plt
plt.style.use('seaborn-whitegrid')
import numpy as np
from tabulate import tabulate


def getEnvData(sheet, col):
        # Returns the average and standard deviation from the values in a column

        # List of strings containing the values of a column minus title row
        # To 27 because null indexed and we want first 26 results = 25 differences
        list_of_values = sheet.col_values(col)[1:27]

        # Convert all values from string to float
        for i in range(0,len(list_of_values)):
                list_of_values[i] = float(list_of_values[i])

        return statistics.mean(list_of_values), statistics.stdev(list_of_values)


def getBolusDeliveries(sheet, interval):
        # List of strings containing the values of a column minus title row
        # To 27 because null indexed and we want first 26 results = 25 differences
        measurements = sheet.col_values(2)[1:27]

        # Convert from string to float
        measurements[0] = float(measurements[0])
```

```
        bolus_deliveries = []

        # Calculate evaporation correction factor
        correction_factor = evaporation_rate*interval

        for i in range(1,len(measurements)):
                # Convert from string to float
                measurements[i] = float(measurements[i])

                delivery = measurements[i] - measurements[i-1] + correction_factor
                bolus_deliveries.append(delivery)
        return bolus_deliveries


def bolusAnalysis(bolus_deliveries, expected_rate):
        bolus_avg = statistics.mean(bolus_deliveries)
        st_dev_absolute = statistics.stdev(bolus_deliveries)
        st_dev_percentage = st_dev_absolute/expected_rate*100

        dev_set_val = (bolus_avg - expected_rate)*100/expected_rate
        dev_max = (max(bolus_deliveries) - expected_rate)*100/expected_rate
        dev_min = (min(bolus_deliveries) - expected_rate)*100/expected_rate

        return bolus_avg, st_dev_absolute, st_dev_percentage,
                dev_set_val, dev_max, dev_min


def main():
        data = {'': [
                "Expected [g*10^(-5)]",
                "Average [g*10^(-5)]",
                "Standard deviation [g*10^(-5)]",
                "Standard deviation [%]",
                "Deviation from expected value [%]",
                "Deviation from max. value [%]",
                "Deviation from min. value [%]",
                "Temperature [ C ]",
                "Humidity [%]"
        ],
        }

        interval = int(input('Interval between each measurement [min]: '))

        while True:
                print('')
                fileName = input('Filename: ') + '.xls'

                wb = xlrd.open_workbook(fileName)
                sheet = wb.sheet_by_index(0)

                expected_unit_rate = float(input('Expected rate [U]: '))
                # Write in insulin units, convert to grams
                expected_rate = fromUnitsToGrams(expected_unit_rate)

                # Get average and standard deviation of environment data
                temp_avg, temp_dev = getEnvData(sheet, 3)
                temperature = (str(round(temp_avg, 1))+"  "+str(round(temp_dev, 1)))
                hum_avg, hum_dev = getEnvData(sheet, 4)
                humidity = (str(round(hum_avg, 1))+"  "+str(round(hum_dev, 1)))
```

```
                bolus_deliveries = getBolusDeliveries(sheet, interval)
                bolus_avg, st_dev_absolute, st_dev_percentage, dev_set_val, dev_max,
                        dev_min = bolusAnalysis(bolus_deliveries, expected_rate)

                data[str(round(expected_unit_rate, 3)) + 'U'] = [
                        str("{num:.0f}".format(num = expected_rate*10**5)),
                        str("{num:.0f}".format(num = bolus_avg*10**5)),
                        str("{num:.0f}".format(num = st_dev_absolute*10**5)),
                        str("{num:.1f}".format(num = st_dev_percentage)),
                        str("{num:.1f}".format(num = dev_set_val)),
                        str("{num:.1f}".format(num = dev_max)),
                        str("{num:.1f}".format(num = dev_min)),
                        temperature,
                        humidity]

                getScatterPlot(bolus_deliveries, expected_rate)
                keepRunning = input('Add more files (y/n)? ')
                if keepRunning == "n":
                        break

        print(tabulate(data, headers = 'keys', tablefmt = 'fancy_grid'))


def getScatterPlot(bolus_deliveries, expected_rate):
        # Indexes of deliveries
        x = list(range(1,len(bolus_deliveries) + 1))

        # Broken line for expected rate
        exp = [expected_rate for i in range(len(bolus_deliveries))]

        plt.ylim([0, expected_rate*1.5])
        plt.xlabel('Bolus delivery index')
        plt.ylabel('Measurement [g]')

        plt.plot(x, bolus_deliveries, 'o', color='black', label="Measurement")

        # Broken indicator lines
        plt.plot(x, exp, color='black', label="Expected value")
        plt.plot(x, [el*1.05 for el in exp], color='blue', label="5% from target")
        plt.plot(x, [el*0.95 for el in exp], color='blue')
        plt.plot(x, [el*1.15 for el in exp], color='red', label="15% from target")
        plt.plot(x, [el*0.85 for el in exp], color='red')

        plt.legend()
        plt.show()


def fromUnitsToGrams(dose):
        # 1 Unit equals 0.01 ml
        # Density unit is g/cm^3
        # 1 ml = 1 cm^3
        return density*dose*0.01


# Constants
density = 0.998 # g/cm^3
evaporation_rate = 0.000002157 # g/min
```

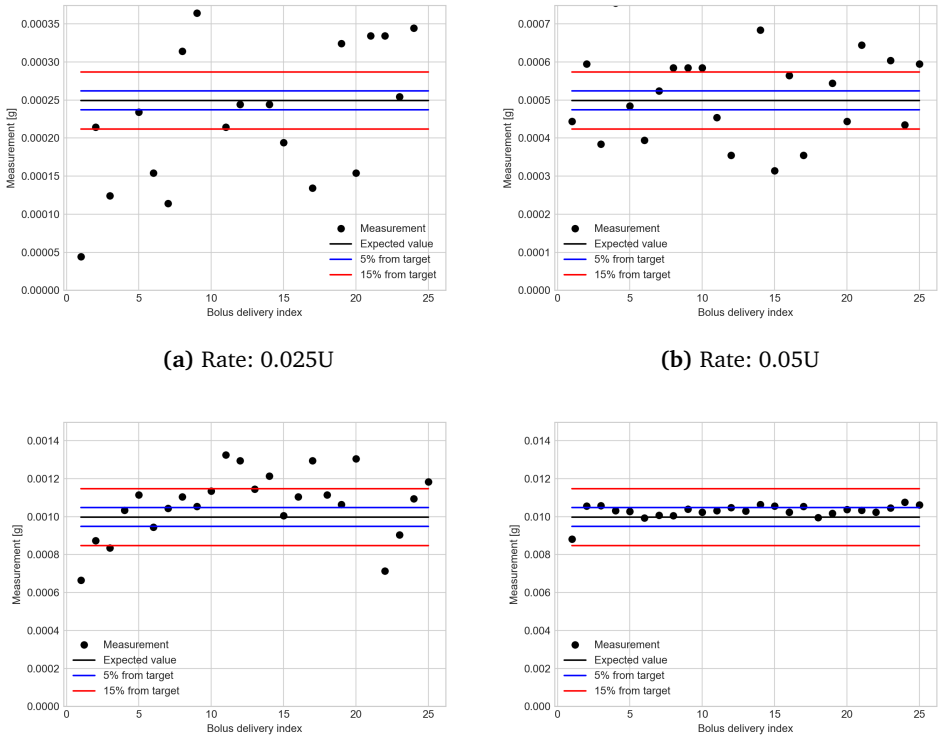
```
print('')
print('')
print('')
print('')
print('')
print('BOLUS␣RATE␣ACCURACY␣EXPERIMENT')
print('.................................................')
print('')

main()
```

Appendix B

Bolus Experiment Results

The raw data from the experiments can be found in the attached files in the folder *Results/Bolus rates*.

B.1 Scatter Plots



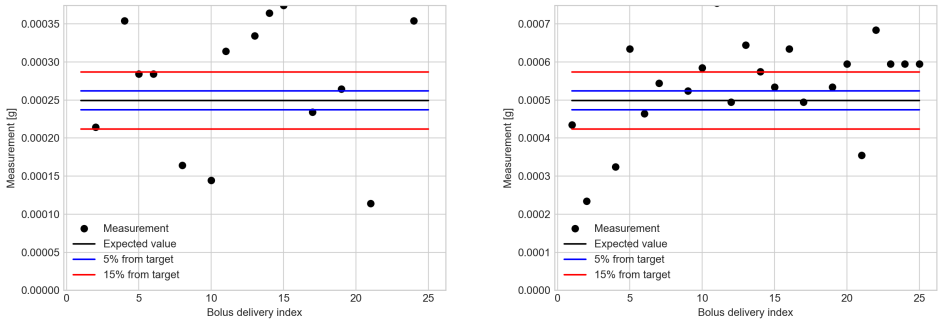
(a) Rate: 0.025U

(b) Rate: 0.05U

(c) Rate: 0.1U

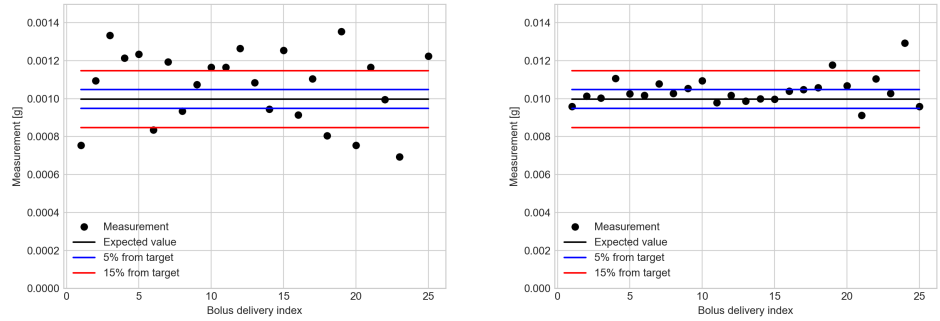
(d) Rate: 1U

Figure B.1: Scatter plots of bolus rates for MiniMed 640G



(a) Rate: 0.025U

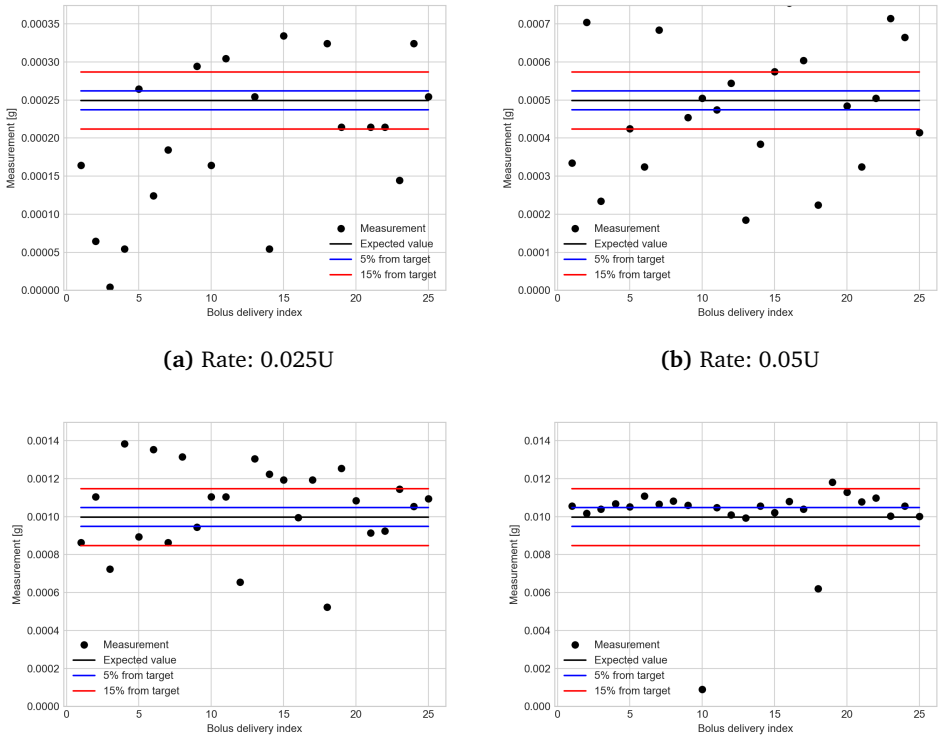
(b) Rate: 0.05U



(c) Rate: 0.1U

(d) Rate: 1U

Figure B.2: Scatter plots of bolus rates from the first experiment of MiniMed 670G



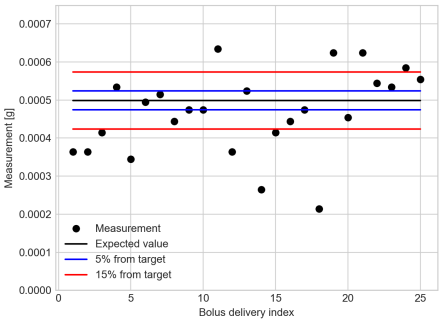
(a) Rate: 0.025U

(b) Rate: 0.05U

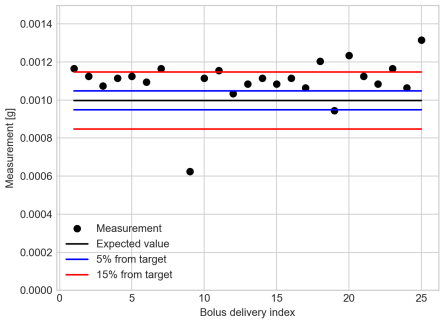
(c) Rate: 0.1U

(d) Rate: 1U

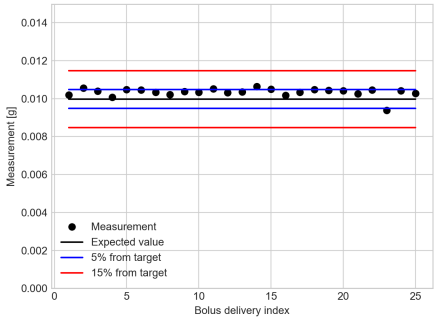
Figure B.3: Scatter plots of bolus rates from the second experiment of MiniMed 670G



(a) Rate: 0.05U

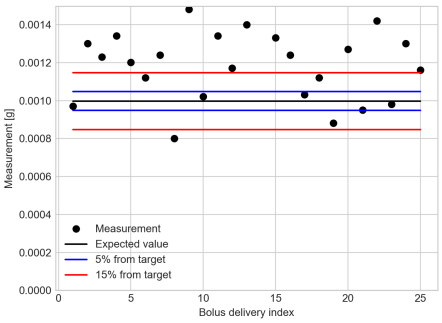


(b) Rate: 0.1U

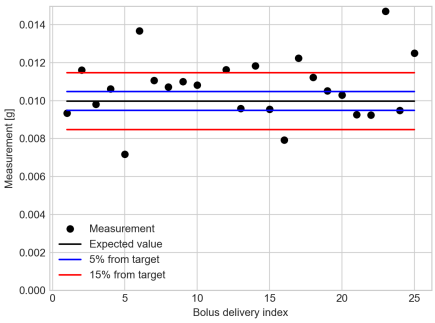


(c) Rate: 1U

Figure B.4: Scatter plots of bolus rates for Animas Vibe

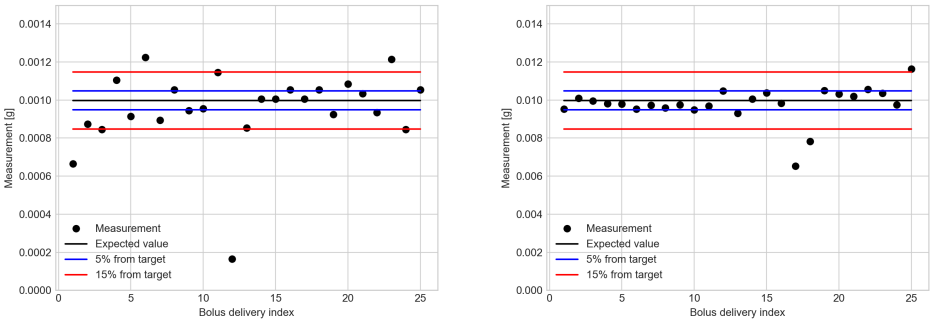


(a) Rate: 0.1U



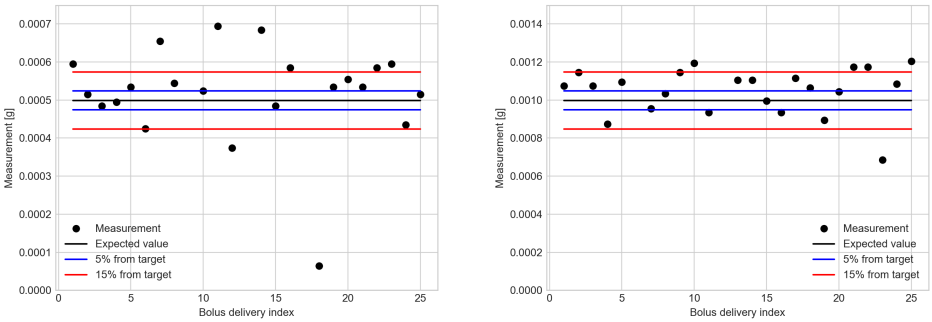
(b) Rate: 1U

Figure B.5: Scatter plots from the first experiment of bolus rates for Accu-Check Spirit Combo

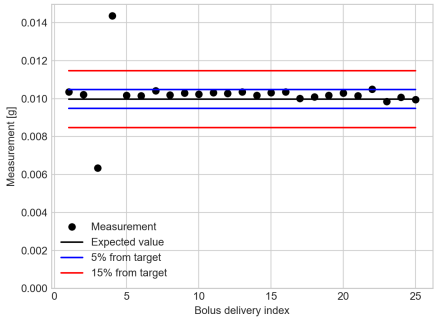


(a) Rate: 0.1U **(b)** Rate: 1U

Figure B.6: Scatter plots from the second experiment of bolus rates for Accu-Check Spirit Combo



(a) Rate: 0.05U **(b)** Rate: 0.1U



(c) Rate: 1U

Figure B.7: Scatter plots of bolus rates for Tandem t:slim X2

B.2 Bolus Result Tables

	0.025U	0.05U	0.1U	1.0U
Expected [g*10^(−5)]	25	50	100	998
Average [g*10^(−5)]	26	53	109	1029
Standard deviation [g*10^(−5)]	14	23	21	38
Standard deviation [%]	54.1	45.6	21.2	3.8
Deviation from expected value [%]	5.1	6.0	9.2	3.1
Deviation from max. value [%]	134.2	123.3	68.8	7.9
Deviation from min. value [%]	−102.3	−129.2	−33.4	−11.7
Temperature [°C]	23.7±0.1	24.1±0.1	22.2±0.3	23.0±0.1
Humidity [%]	21.4±0.1	21.6±0.1	25.3±0.1	25.3±0.1

Figure B.8: Table showing bolus accuracy for MiniMed 640G.

	0.025U	0.05U	0.1U	1.0U
Expected [g*10^(−5)]	25	50	100	998
Average [g*10^(−5)]	36	57	111	1042
Standard deviation [g*10^(−5)]	12	14	28	76
Standard deviation [%]	49.7	28.1	28.2	7.6
Deviation from expected value [%]	43.9	13.7	10.9	4.4
Deviation from max. value [%]	126.2	63.2	110.9	29.5
Deviation from min. value [%]	−54.2	−53.0	−30.4	−8.6
Temperature [°C]	22.5±0.2	22.9±0.2	22.9±0.2	22.6±0.1
Humidity [%]	23.7±0.3	23.7±0.3	23.3±0.3	23.9±0.2

Figure B.9: Table showing bolus accuracy from the first experiment of MiniMed 670G.

	0.025U	0.05U	0.1U	1.0U
Expected [g*10^(−5)]	25	50	100	998
Average [g*10^(−5)]	26	52	105	1002
Standard deviation [g*10^(−5)]	17	20	22	214
Standard deviation [%]	66.8	39.1	22.0	21.4
Deviation from expected value [%]	5.6	4.1	5.1	0.4
Deviation from max. value [%]	178.3	83.2	38.7	18.5
Deviation from min. value [%]	−98.3	−63.1	−47.5	−91.0
Temperature [°C]	23.9±0.1	23.9±0.1	24.3±0.2	24.5±0.1
Humidity [%]	28.6±0.9	28.5±0.3	28.4±0.2	27.5±0.3

Figure B.10: Table showing bolus accuracy from the second experiment of MiniMed 670G.

	0.05U	0.1U	1.0U
Expected [g*10^(−5)]	50	100	998
Average [g*10^(−5)]	47	112	1034
Standard deviation [g*10^(−5)]	11	16	24
Standard deviation [%]	21.6	15.5	2.4
Deviation from expected value [%]	−6.4	12.1	3.6
Deviation from max. value [%]	27.1	58.7	6.6
Deviation from min. value [%]	−57.1	−37.4	−6.0
Temperature [°C]	22.8±0.1	23.0±0.1	23.3±0.1
Humidity [%]	25.1±0.3	25.8±0.3	25.5±0.4

Figure B.11: Table showing bolus accuracy for Animas Vibe.

	0.1U	1.0U
Expected [g*10^(−5)]	100	998
Average [g*10^(−5)]	109	982
Standard deviation [g*10^(−5)]	50	452
Standard deviation [%]	50.1	45.3
Deviation from expected value [%]	8.8	−1.6
Deviation from max. value [%]	48.4	47.5
Deviation from min. value [%]	−216.2	−204.0
Temperature [°C]	21.4±0.2	20.3±0.8
Humidity [%]	20.4±0.2	19.1±0.2

Figure B.12: Table showing bolus accuracy from the first experiment for Accu-Check Spirit Combo.

	0.1U	1.0U
Expected [g*10^(−5)]	100	998
Average [g*10^(−5)]	95	979
Standard deviation [g*10^(−5)]	21	94
Standard deviation [%]	20.7	9.4
Deviation from expected value [%]	−4.4	−1.9
Deviation from max. value [%]	22.7	16.5
Deviation from min. value [%]	−83.5	−34.6
Temperature [°C]	23.1±0.1	22.9±0.0
Humidity [%]	38.4±0.2	38.1±0.1

Figure B.13: Table showing bolus accuracy from the second experiment for Accu-Check Spirit Combo.

	0.05U	0.1U	1.0U
Expected [g*10^(−5)]	50	100	998
Average [g*10^(−5)]	52	92	1023
Standard deviation [g*10^(−5)]	27	46	117
Standard deviation [%]	53.4	45.9	11.7
Deviation from expected value [%]	3.5	−7.5	2.5
Deviation from max. value [%]	121.3	20.7	44.0
Deviation from min. value [%]	−187.3	−185.7	−36.4
Temperature [°C]	25.8±0.0	25.7±0.0	25.6±0.0
Humidity [%]	42.5±0.7	42.8±0.4	41.8±0.2

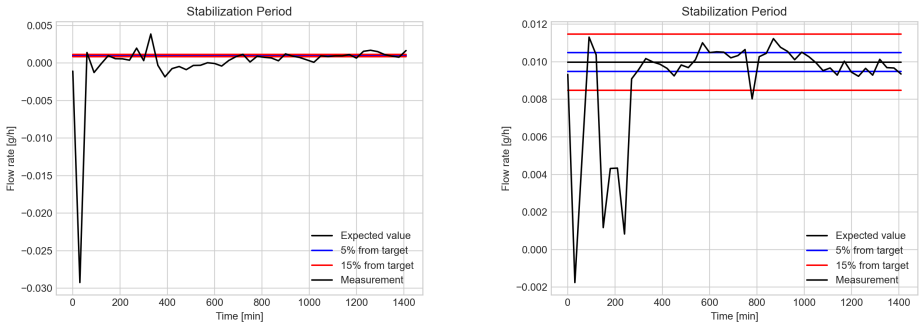
Figure B.14: Table showing bolus accuracy for Tandem t:slim X2.

Appendix C

Basal Experiment Results

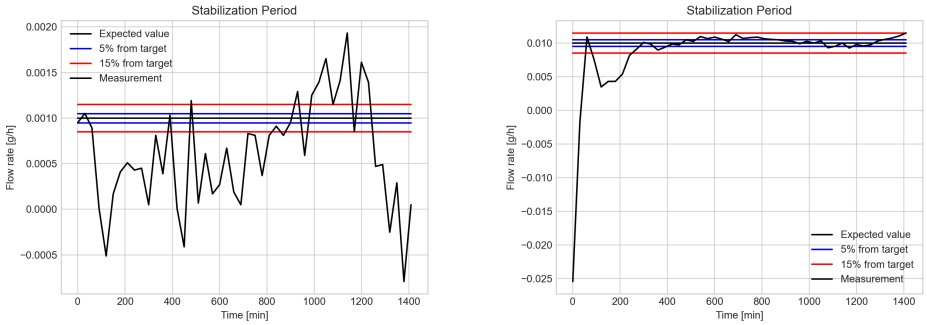
The raw data from the experiments can be found in the attached files in the folder *Results/Basal rates*.

C.1 Stabilization Period



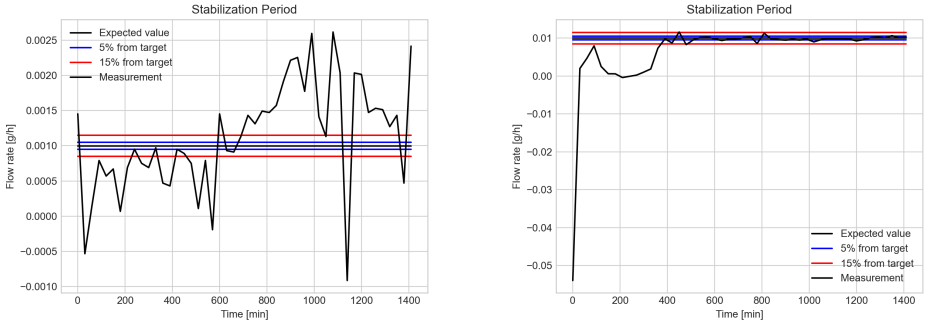
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.1: Plots of stabilization period for MiniMed 640G



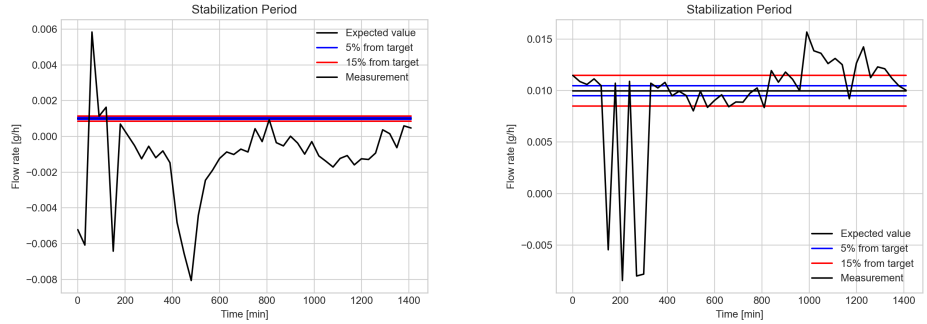
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.2: Plots of stabilization period from the first experiment of MiniMed 670G



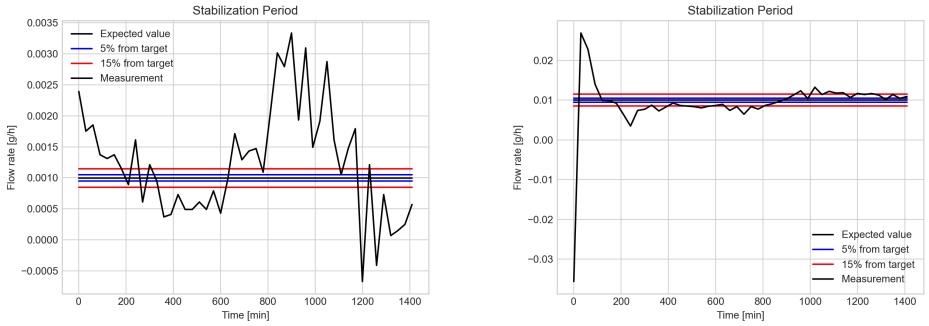
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.3: Plots of stabilization period from the second experiment of MiniMed 670G



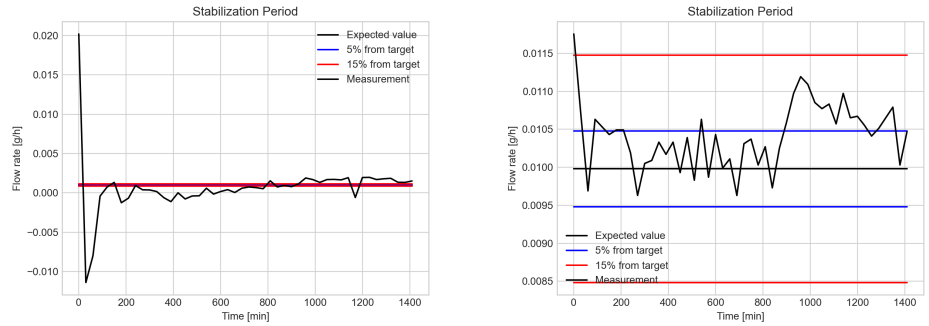
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.4: Plots of stabilization period for Animas Vibe



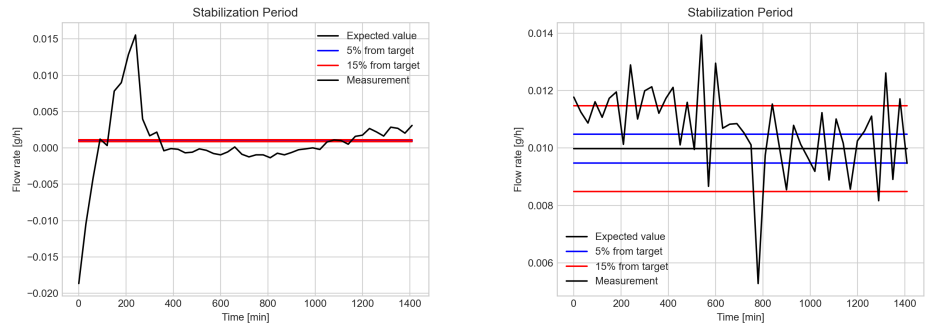
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.5: Plots of stabilization period from first experiment of Accu-Check Spirit Combo



(a) Rate: 0.1U/h **(b)** Rate: 1U/h

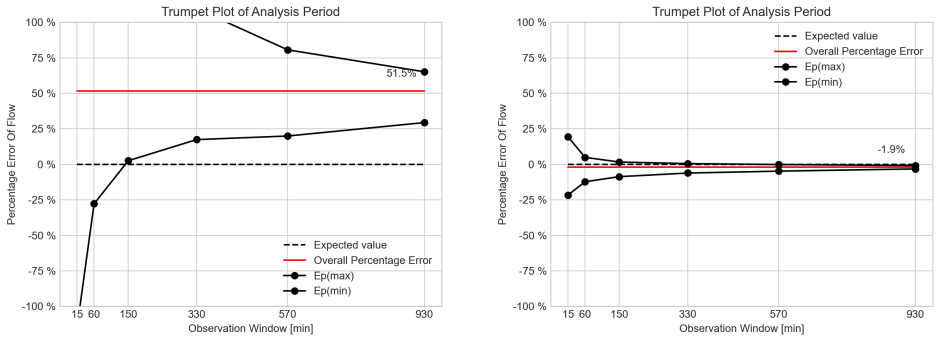
Figure C.6: Plots of stabilization period from second experiment of Accu-Check Spirit Combo



(a) Rate: 0.1U/h **(b)** Rate: 1U/h

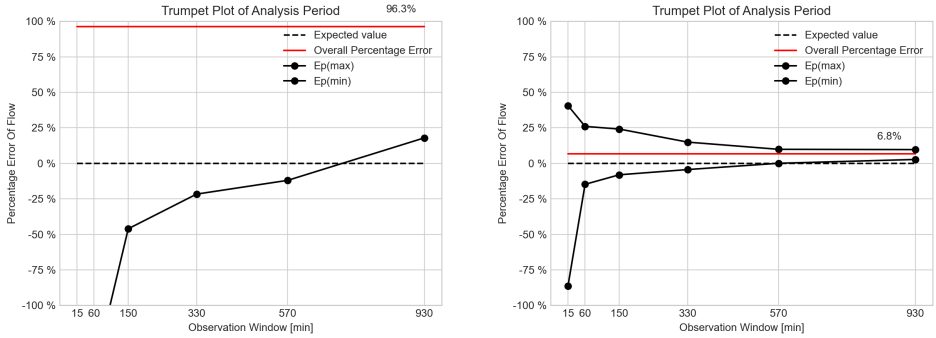
Figure C.7: Plots of stabilization period for Tandem t:slim X2. Note; because of an auto-off setting that was turned on, the experiment for 1.0U/h had already been installed for some hours before the experiment started.

C.2 Trumpet Curves



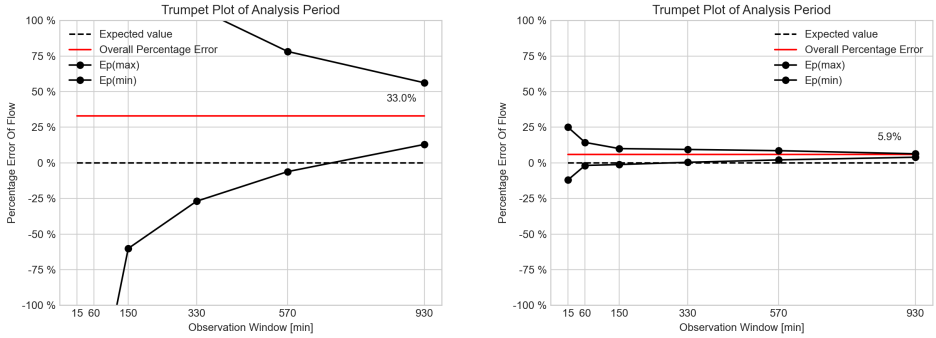
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.8: Trumpet plots of analysis period for MiniMed 640G



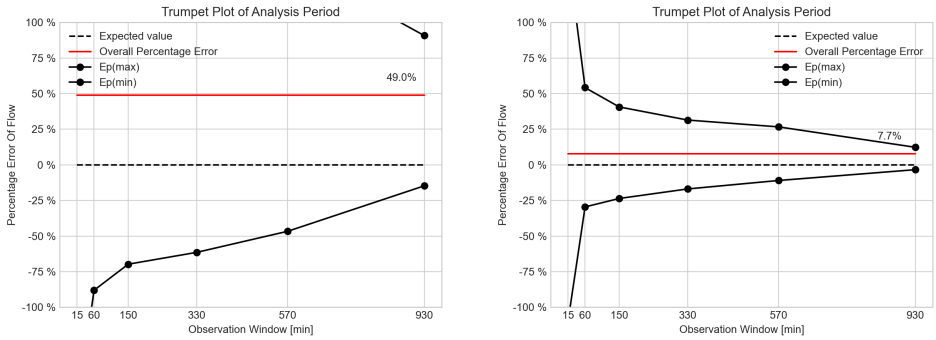
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.9: Trumpet plots of analysis period from the first experiment of MiniMed 6470G



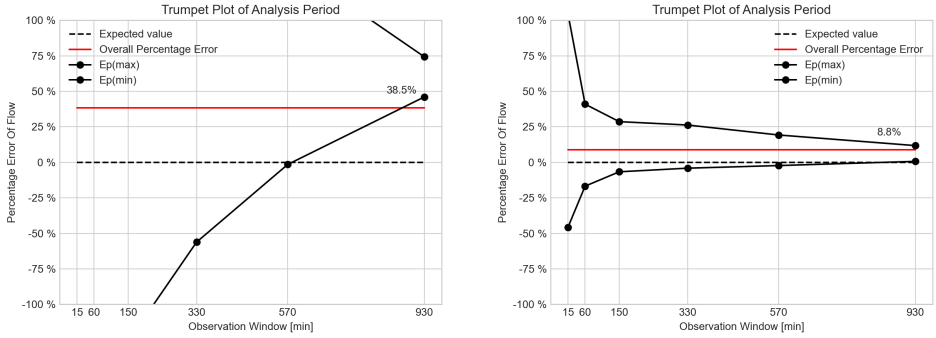
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.10: Trumpet plots of analysis period from the second experiment of MiniMed 6470G



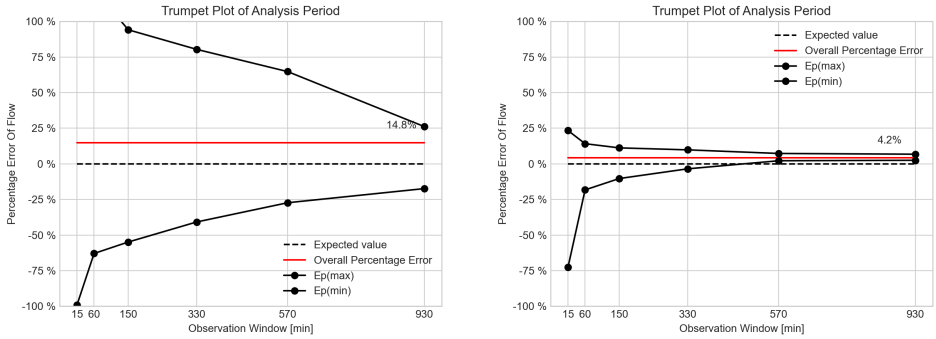
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.11: Trumpet plots of analysis period for Animas Vibe



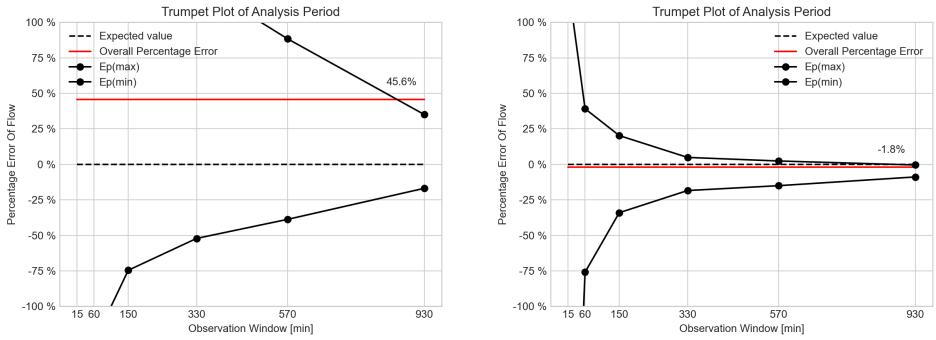
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.12: Trumpet plots of analysis period from first experiment of Accu-Check Spirit Combo



(a) Rate: 0.1U/h **(b)** Rate: 1U/h

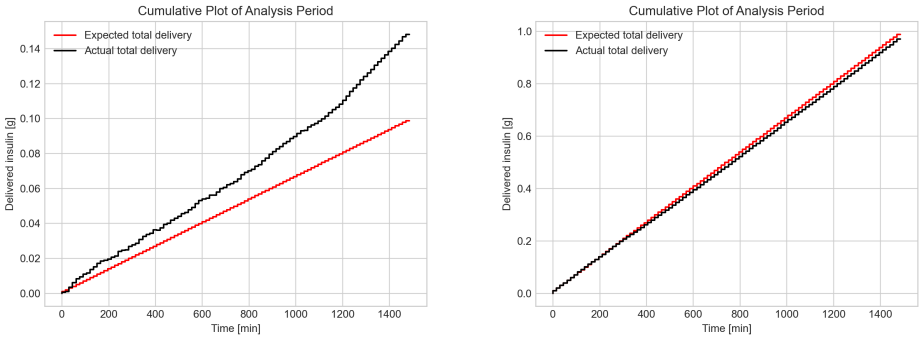
Figure C.13: Trumpet plots of analysis period from second experiment of Accu-Check Spirit Combo



(a) Rate: 0.1U/h **(b)** Rate: 1U/h

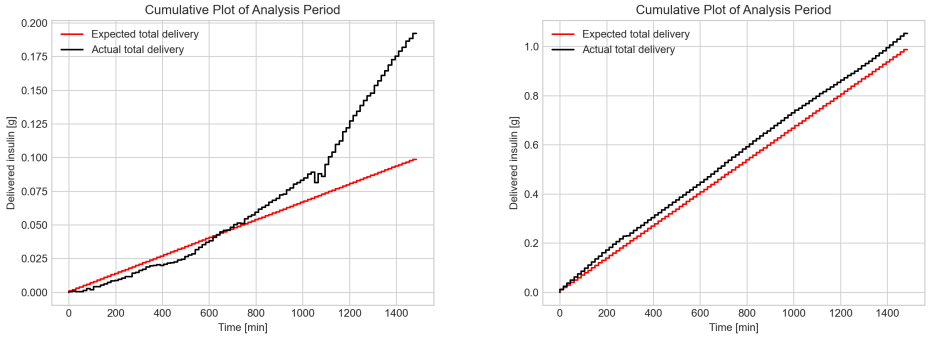
Figure C.14: Trumpet plots of analysis period for Tandem t:slim X2

C.3 Cumulative Plots



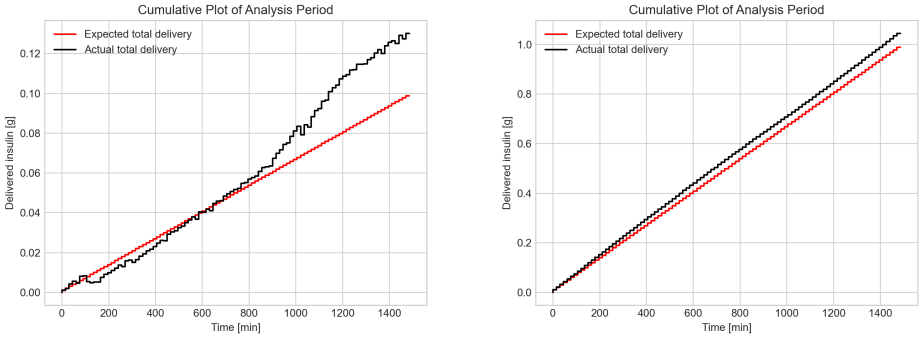
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.15: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period for MiniMed 640G



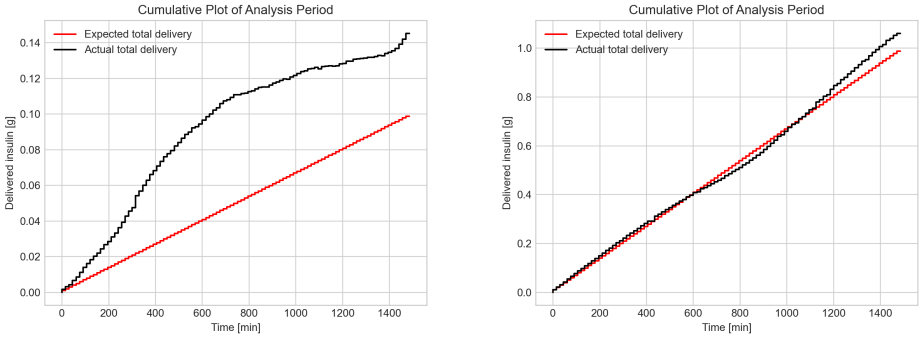
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.16: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period from the first experiment of MiniMed 670G



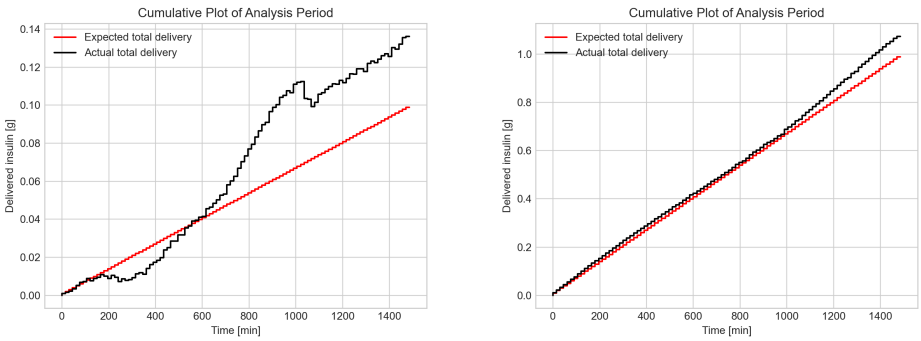
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.17: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period from the second experiment of MiniMed 670G



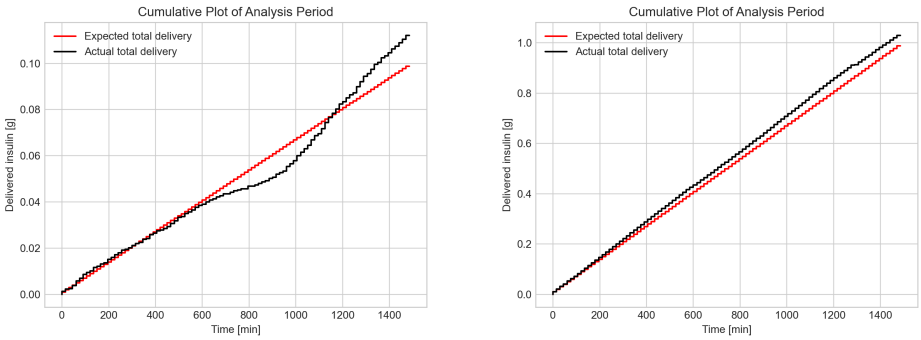
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.18: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period for Animas Vibe



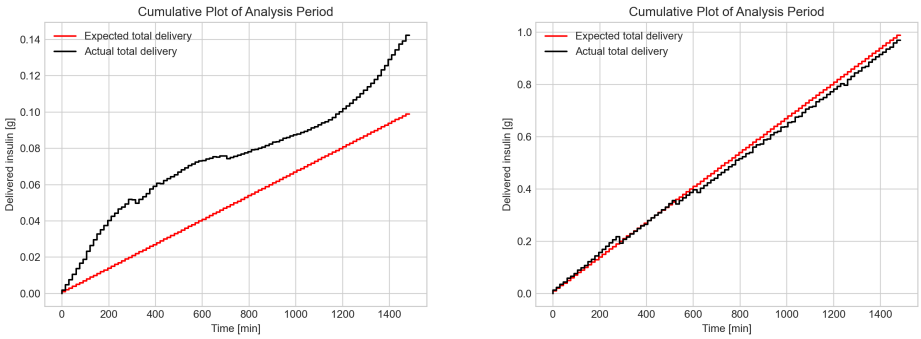
(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.19: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period from first experiment of Accu-Check Spirit Combo



(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.20: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period from second experiment of Accu-Check Spirit Combo



(a) Rate: 0.1U/h **(b)** Rate: 1U/h

Figure C.21: Cumulative plot of insulin delivery versus expected insulin delivery in analysis period for Tandem t:slim X2

C.4 Basal Result Tables

	0.1U/h	1.0U/h
Expected [g*10^(-5)]	100	998
Average [g*10^(-5)]	151	979
Standard deviation (1-h-windows) [g*10^(-5)]	42	36
Standard deviation (1-h-windows) [%]	42.4	3.6
Deviation from expected delivery [%]	51.5	-1.9
Temperature [°C]	23.3±0.2	23.4±0.4
Humidity [%]	22.3±1.7	20.8±1.2

Figure C.22: Table showing basal accuracy for MiniMed 640G.

	0.1U/h	1.0U/h
Expected [g*10^(-5)]	100	998
Average [g*10^(-5)]	189	1066
Standard deviation (1-h-windows) [g*10^(-5)]	131	103
Standard deviation (1-h-windows) [%]	130.9	10.3
Deviation from expected delivery [%]	89.9	6.8
Temperature [°C]	20.1±1.8	22.2±0.9
Humidity [%]	27.4±1.9	19.2±2.3

Figure C.23: Table showing basal accuracy from the first experiment of MiniMed 670G.

	0.1U/h	1.0U/h
Expected [g*10^(-5)]	100	998
Average [g*10^(-5)]	133	1054
Standard deviation (1-h-windows) [g*10^(-5)]	61	36
Standard deviation (1-h-windows) [%]	61.5	3.6
Deviation from expected delivery [%]	33.0	5.6
Temperature [°C]	23.4±0.5	24.4±0.6
Humidity [%]	28.1±3.2	30.4±1.3

Figure C.24: Table showing basal accuracy from the second experiment of MiniMed 670G.

	0.1U/h	1.0U/h
Expected [g*10^(-5)]	100	998
Average [g*10^(-5)]	149	1075
Standard deviation (1-h-windows) [g*10^(-5)]	100	187
Standard deviation (1-h-windows) [%]	99.9	18.8
Deviation from expected delivery [%]	49.0	7.7
Temperature [°C]	20.1±1.6	20.5±1.4
Humidity [%]	26.0±2.6	24.3±1.9

Figure C.25: Table showing basal accuracy for Animas Vibe.

	0.1U/h	1.0U/h
Expected [g*10^(−5)]	100	998
Average [g*10^(−5)]	138	1086
Standard deviation (1−h−windows) [g*10^(−5)]	136	121
Standard deviation (1−h−windows) [%]	135.8	12.1
Deviation from expected delivery [%]	38.5	8.8
Temperature [°C]	19.6±0.8	19.9±1.6
Humidity [%]	23.5±3.3	24.1±1.8

Figure C.26: Table showing basal accuracy from first experiment of Accu-Check Spirit Combo.

	0.1U/h	1.0U/h
Expected [g*10^(−5)]	100	998
Average [g*10^(−5)]	115	1040
Standard deviation (1−h−windows) [g*10^(−5)]	50	67
Standard deviation (1−h−windows) [%]	49.7	6.7
Deviation from expected delivery [%]	14.8	4.2
Temperature [°C]	22.8±0.7	23.8±0.9
Humidity [%]	29.9±4.0	34.8±2.1

Figure C.27: Table showing basal accuracy from second experiment of Accu-Check Spirit Combo.

	0.1U/h	1.0U/h
Expected [g*10^(−5)]	100	998
Average [g*10^(−5)]	145	980
Standard deviation (1−h−windows) [g*10^(−5)]	94	236
Standard deviation (1−h−windows) [%]	94.4	23.7
Deviation from expected delivery [%]	45.6	−1.8
Temperature [°C]	25.4±1.0	24.6±1.0
Humidity [%]	31.5±3.7	34.0±2.1

Figure C.28: Table showing basal accuracy for Tandem t:slim X2.

Appendix D

Project Thesis

Student thesis

NTNU
Norwegian University of Science and Technology
Faculty of information Technology and Electrical Engineering

Miriam Kopperstad Wolff

Establishing Methods to Determine Delivery Accuracy of Insulin Pumps

Student thesis in Engineering and ICT
Supervisor: Martin Steinert
December 2020

NTNU
Norwegian University of Science and Technology

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NTNU
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Science and Technology

Abstract

Patients with Diabetes Mellitus type 1 often use insulin pumps as treatment. Most of these pumps have a tubing and needle attached for infusion to the subcutaneous tissue. There is no official requirement for accuracy of insulin delivery of the insulin pumps. Manufacturers often promise accuracy levels of ±5%. Research shows that lower insulin doses tend to be less accurate than the larger insulin doses. Non-biased parties should verify that the insulin pumps deliver what they promise for all levels of insulin rates. In order to do so, adequate methods for testing and comparing insulin pumps must be established.

The standard IEC 60601-2-24 describes how insulin pumps should be tested to verify accuracy and determine basic safety. In this project the test method will be implemented and discussed, to later be able to verify whether the insulin pumps deliver a sufficient level of accuracy. For the future of artificial pancreas closed-loop systems with automated insulin delivery, this technology must be safe. Earlier tests have been done, but mainly by manufacturers. Hence a non-biased verification should be performed.

In this thesis we present a test setup and procedure to measure insulin pump accuracy based on IEC 60601-2-24. How results of the tests should be presented in a clinically relevant manner is discussed and suggested. The test setup went through several iterations where necessary details were added, so that the setup was stable and capable of measuring different scenarios.

Several challenges occurred while working with the project. IEC 60601-2-24 proposes to use a high precision balance to weight insulin drops delivered from pumps. However, not all details were specified and had to be resolved. High precision weighing requires high levels of care. Working with liquids offers problems with evaporation and oxidation, as well as the liquid being sensitive to vibrations and air flows. In the end we managed to set up a system that was completely stable.

Contents

Figures

Tables

Chapter 1

Introduction

In this thesis we present a test setup and procedure to measure insulin pump accuracy based on IEC 60601-2-24 (hereafter referred to as IEC). How results of the tests should be presented in a clinically relevant manner is discussed and suggested. The test setup went through several iterations where necessary details were added so that setup was stable and capable of measuring different scenarios.

This chapter introduces the problem description, relevant background and motivation to carry out the project. The scope to answer the problem is defined, along with the limitations that apply. Lastly, an outline of the thesis contents is given.

1.1 Background and Motivation

People with Diabetes Mellitus type 1 often use insulin pumps as part of the treatment. The IEC standard describes requirements for these pumps, but in a general and technical manner. Clinical impact is up to the manufacturers of the pumps to consider, where they usually promise accuracy levels of ±5%. Research shows that lower insulin doses tend to be less accurate than the larger insulin doses [1] [2] [3]. Non-biased parties should verify that the insulin pumps deliver what they promise for all levels of insulin rates. In order to do so, adequate methods for testing and comparing insulin pumps must be established.

Artificial Pancreas Trondheim (APT) has a long term aim to develop a robust closed-loop glucose control system and commercialize an artificial pancreas based on these results. Such a system would contain continuous glucose sensor data combined with insulin pumps with automatic insulin infusion calculated by control engineering algorithms. This would require insulin delivery to be accurate and safe for all patient groups. In this thesis we will focus on how to be able to determine this.

1.2 Problem Description

The problem description for the thesis work is as follows:

> This term project is affiliated with Artificial Pancreas Trondheim (APT).
>
> Patients with Diabetes Mellitus type 1 often use insulin pumps as part of the treatment. Most of these pumps have a tubing and needle attached, for infusion of insulin to the subcutaneous tissue (on the other hand, "patch pumps" are fixed directly to the skin without the use of tubing). In combination with blood glucose data from continuous glucose monitor (CGM) systems, we are looking into a future of automated insulin delivery.
>
> In this project, the student will explore methods to measure the accuracy of insulin pumps. The method should strive to be accurate even at the lowest possible insulin injection rates of the insulin pumps. The student will need to make sure that the measurements are representative and that possible sources of error are identified.
>
> Specifically, the student will perform the following tasks:
>
> 1. Literature review on:
>   - The IEC standard for requirements for the basic safety and essential performance of infusion pumps and controllers
>   - Test methods for measuring accuracy of insulin bolus and basal rates
>   - Accuracy of insulin pumps (from both manufacturers and independent publishers)
>   - Insulin pump technical specifications
> 2. Build an initial test setup
> 3. Define an initial test procedure
> 4. The student will also perform pilot tests to estimate and improve the accuracy of both the test setup and the procedure.
> 5. Based on the initial results a full test setup and procedure will be proposed to be deployed during the master project.

1.3 Project Scope

To fulfill the scope of this project we must establish a method that is showing good performance of stability. The procedure to implement the test setup will be explained in detail. Pilot tests of the initial test setup and procedure will be performed, and the results will be presented. After the initial tests are done, a full test setup will be proposed, even though not necessarily tested. A complete final setup will be deployed during the master project.

Relevant questions for research in this context are many, such as: Is the promise of accuracy levels of ±5% a suitable requirement for insulin pumps? And do pumps actually deliver this level of accuracy? Is the presented method in IEC for testing insulin pump accuracy suited for all insulin infusion rates? And how should insulin pump accuracy be presented in a clinically relevant way? Answering all of these questions is not inside of the scope of the project, but some of them will be discussed.

Limitations of performing a feasible study is to get hold of medical equipment and other necessary equipment. Orders might take time. IEC can also be considered a limitation in the way that it limits freedom to be creative in the way of testing insulin pump accuracy. To be able to verify the performance of the insulin pumps, we have to perform tests under the same conditions as the manufacturers have done.

1.4 Thesis Structure

Theory and related work

Chapter 2 gives a short overview of related work found on test setups for the accuracy of different types of insulin pumps, and how to represent the results in a clinically relevant way. Earlier tests of insulin pump accuracy are included.

Chapter 3 provides essential definitions and a theory foundation regarding insulin pumps, insulin and the IEC standard for how to test the basic safety of insulin pumps.

Methodology and results

Chapter 4 presents the final test setup to measure insulin pump accuracy, including tests to determine whether the setup is stable. Procedures to prepare and carry out the tests are described in detail.

Chapter 5 presents test data from insulin pumps on early test setup. Further test results on the stability of the final test setup is presented.

Discussion and conclusions

Chapter 6 examines the thesis results and discusses possible sources of error. Challenges found during the establishment of the test setup are explained. The validity and clinically relevance of the IEC standard is discussed. Some alternative solutions to the problem of injecting and measuring small volumes of insulin doses are proposed.

Chapter 7 contains the thesis conclusion and recommendations for future work.

Appendices

Appendix A contains the raw test data that are presented in the results.

Chapter 2

Related Work

This chapter presents an extensive review of academic papers discussing earlier tests of insulin pump accuracy. The research found is primarily written by a research group in Germany, which was founded by Roche Diabetes Care GmbH. Consequently, the articles should be read having in mind that they might be biased. Raw data from some of the tests are not published, which is a limitation of the analysis of earlier research.

2.1 Methods to Determine Clinically Relevant Bolus and Basal Rate Delivery Accuracy of Insulin Pumps

Kamecke et. al. [4] proposes an approach on how to test, evaluate, and present bolus and basal rate accuracy of insulin pumps from a clinical perspective. The article criticises IEC 60601-2-24 for proposing a presentation of the test results that are not intuitively understandable, nor clinically relevant. The article mentions that the lack of an accuracy criteria makes it difficult to make conclusions about the sufficient performance of an insulin pump.

In terms of the graphical presentations of basal rate accuracy, they added a scatter plot indicating the expected flow and the deviation of ±5% as horizontal lines, as well as what is proposed in IEC 60601-2-24 (3.3.2). They also suggest that average accuracy over hourly windows, not only over 24 hours or more, is additionally meaningful from a clinical perspective. For boluses every single one should be regarded. Averaging multiple boluses might decrease delivery error.

According to IEC the test of basal rate must be done at the lowest possible basal rate for the individual insulin pumps. Kamecke et al. concluded that the lowest accessible basal rate to test would be 0.1 U/h or more. For lower rates the expected weight increases was below the resolution of the balance. However, they chose to run tests at 1 U/h. On the insulin pumps tested in this thesis, lowest possible basal rate is 0.05 U/h and 0.025 U/h.

2.2 Accuracy of Bolus and Basal Rate Delivery of Different Insulin Pump Systems

It has been shown that the precision of individual boluses are higher with larger boluses [2] [3]. Ziegler et al. tested the delivery of low basal rates in different insulin pumps [1]. They concluded that the basal doses might not be delivered as expected for insulin pumps used by children with low insulin demand. However, for larger boluses all pumps delivered 100% of the doses within ±15% of target [2].

The results of the boluses are presented in tables where Ziegler et al. calculate the amount of boluses within different targets for the different insulin pumps, as well as in block plots. For basal rates the research group use tables, presenting the deviation in different time windows, in addition to scatter plots. They omit trumpet curves required from IEC 60601-2-24 and reasons about why this is not a clinically relevant representation.

Chapter 3

Theoretical Framework

In this chapter we provide background knowledge to understand the thesis as a whole. Primarily we will explain how insulin infusion systems work and define some important vocabulary. The theory about insulin and its characteristics is to be seen in context with the clinically relevance of insulin injection accuracy, and also characteristics relevant to the experiments. Lastly we will summarize what is considered the requirements for the basic safety and essential performance of infusion pumps according to IEC 60601-2-24.

3.1 Insulin Infusion Systems

The usage of insulin pumps is a common way to treat patients with Diabetes Mellitus type 1. There are several insulin pump manufacturers on the market, and even more insulin pump models. In this section we use the MiniMed 670G as a reference, because this is one of the pumps that will be given to patients in Norway in 2021 [5].

3.1.1 System Description

An insulin infusion system consists of several parts (Figure 3.1). The insulin pump is managed through a user interface where you can add customized settings and choose to inject insulin. It has a changeable reservoir that is filled with insulin. From the reservoir the insulin is carried through the plastic tube and the cannula, all the way into the patients body. The adhesive tape is applied on the patients skin, and the cannula reaches 6 - 9 mm under the skin. The plastic tube can vary in length. Both the reservoir and the insulin infusion set (IIS) is advised to be changed every second or third day [6].

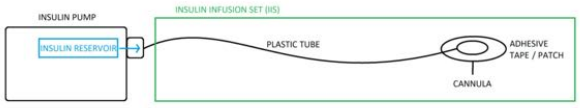


Figure 3.1: Illustration of an insulin infusion system.

3.1.2 Insulin Injection

For every hour of the day, the patient sets a rate of insulin (U/h) adapted to his need. This rate is called the basal dose, and is running automatically. The basal rate is quasi-continuous, which means that it is delivered in discrete small volume increments at predetermined intervals. Both the shot volume and the interval are changed when a new set rate is selected.

In addition to the basal dose, the patient is given the opportunity to manually inject discrete amounts of insulin. These injections are called bolus doses. Bolus doses are also split into small volume increments when injected by the pump. Bolus doses are typically injected before a meal or to adjust high glucose levels.

The injection increments in MiniMed 670G works as follows [7]:

- 0.025 units for basal and bolus amounts in the range of 0.025 to 0.975 units
- 0.05 units for basal and bolus amounts in the range of 1 to 9.95 units
- 0.05 units for bolus amounts of 10.0 units or larger
- 0.1 units for basal amounts of 10.0 units or larger
- Max basal rate: 35 units per hour
- Max bolus: 75 units

3.1.3 Accuracy of Bolus and Basal Rate Delivery

There are no mandatory accuracy requirements or acceptance criteria for insulin pumps.

Medtronic claims that the MiniMed 670G provides a delivery accuracy of insulin within ±5% of the set basal or bolus insulin rate [8]. However, smaller doses tend to be less accurate than larger doses [2].

3.2 Insulin

There exists several types of insulin on the market that vary in absorption time, time of effect and intensity curve. Insulin pumps are typically filled with rapid acting insulin. One type of insulin may have different effect on different patients.

The effect of rapid acting insulin starts after 10-20 minutes, and lasts for about 2 to 5 hours [9]. Examples of rapid acting insulin types are Novorapid and Humalog.

3.2.1 Amount Needed for Different Group of Patients

Each patient has a different insulin need. The patients insulin need will vary through the patients life and is affected by several factors, such as food, activity level, stress, hormonal imbalances etc.

Patients with diabetes type 1 typically require an insulin dosage of 0.5 to 1 Unit per kg per day [9]. This corresponds to minimum 2 Units per day for a baby weighing 4 kg, or 10 Units per day for a child weighing 20 kg. Insulin has an active effect for 3-5 hours after injection, and a patient should always have active insulin in their body.

3.2.2 Insulin Characteristics

Insulin is mixed with water. The most common insulin used today contains 100 units of insulin aspart (equivalent of 3,5 mg) per 1 ml [10]. Considering the temperature is $21°C$, the density of water [11] and insulin [12] respectively is

$$\rho_W = 0.998 g/cm^3 \tag{3.1}$$

$$\rho_I = 1.090 g/cm^3 \tag{3.2}$$

Following we have that $1U = 0,01mL$, so that for insulin, $1U = 0,01mL = 0,01090g$. For water $1U = 0,01mL = 0,00998g$. To convert a measurement of the weight of a liquid in grams to units of insulin, we can use the following equation:

$$U = \frac{m}{\rho} 100 \tag{3.3}$$

In the equation, m is the mass [g] and $\rho[g/cm^3]$ is the density of the measured liquid.

Insulin will crystallize or loose its effect if not handled correctly. It should be stored in a dark place, which holds a temperature of 2-8°C. Before it is put in the insulin pump reservoir, it should be room temperature. Furthermore, the reservoir and IIS should be changed after a maximum of 7 days [10]. The patient should follow the instructions provided by the manufacturers to minimize air bubbles in the reservoir and IIS.

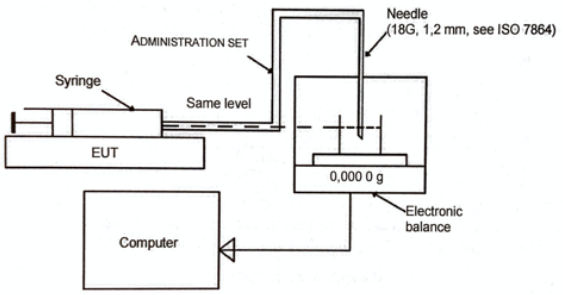


Figure 3.2: Setup for delivery accuracy test of insulin pumps in IEC 60601-2-24

3.3 IEC 60601-2-24:2012

IEC 60601-2-24 [13] describes the essential performance requirements for insulin pumps. Among other things, IEC provides methods for testing the insulin delivery accuracy of an insulin pump. In this section we have picked out the essential information for our experiment.

3.3.1 Test Setup

Figure 3.2 is the model for the test setup, sourced from the IEC standard [13]. The balance is required to be accurate to five decimal places for pumps with low minimum rates. The insulin pump should be at the same level as the liquid surface. In the model the syringe equals the insulin pump, and the administration set equals the IIS. The liquid is not specified. According to the IEC standard the insulin pump shall be filled with "ISO 3696:1987 or a liquid which can be expected to give similar test results".

3.3.2 Basal Dose Accuracy Test

The relevant basal dose accuracy test is explained in section 201.12.1.104 of the IEC standard. For the basal dose accuracy test, only one basal rate that is chosen by the manufacturer is required to test.

First you have to calculate the shot pattern by measuring the time t, taken in minutes for, 20 successive shot cycles. Calculate the shot cycle as:

$$S = t/20 \tag{3.4}$$

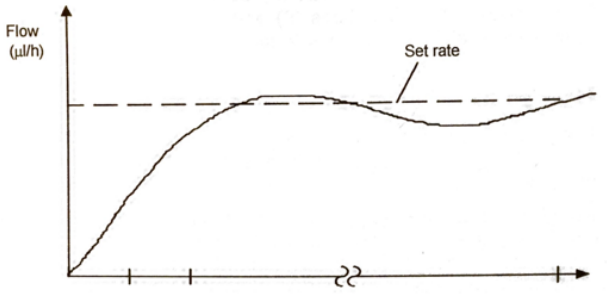


Figure 3.3: Start-up curve over the stabilization period for quasi-continuous output pumps

Stabilization period

Let the pump run for 24 hours, or for the time to empty half the container, whichever is the shorter. This is the stabilization period $T_S[min]$.

Choose an integer n so that

$$nS \approx 30 \tag{3.5}$$

Calculate the average flow for every successive nS samples over T_S. This is calculated as

$$Q_i = \frac{60(W_{ni} - W_{n(i-1)})}{nSd}[U/h] \tag{3.6}$$

where d is the density of the test liquid, and W_i is the ith mass sample.

Plot the flow as a function of elapsed time. Indicate the basal rate on the graph by means of a broken line. Figure 3.3 shows the illustrated example from the IEC standard.

Analysis period

After the stabilization period continue the test for a futher 100 sample intervals S, and measure the mass W_i delivered at each sample interval. This is the analasys period T_A. There is a maximum of m successive samples such that

$$m = \frac{(T_2 - P)}{S} + 1 \tag{3.7}$$

$E_p(max.)$ and $E_p(min.)$ is to be calculated for different observation windows to create a trumpet curve. Observation windows are defined as $P = S, 2S, 5S, 11S, 19S$ and $31S$ minutes. $E_p(max.)$ and $E_p(min.)$ are calculated as

$$E_p(max.) = MAX\left[\frac{S}{P}\sum_{j=1}^{j+\frac{P}{S}-1} 100\frac{Q_i - r}{r}\right][\%] \tag{3.8}$$

$$E_p(min.) = MIN\left[\frac{S}{P}\sum_{j=1}^{j+\frac{P}{S}-1} 100\frac{Q_i - r}{r}\right][\%] \tag{3.9}$$

where

$$Q_i = \frac{60(W_{ni} - W_{n(i-1)})}{Sd}[U/h] \tag{3.10}$$

and r is the basal rate (U/h).

The overall percentage flow can be calculated as

$$A = \frac{100(Q - r)}{r} \tag{3.11}$$

where

$$Q = \frac{60(W_{ni} - W_{n(i-1)})}{T_A d}[U/h] \tag{3.12}$$

Plot the percentage variation obtained against the observation window duration T_A. Indicate the zero error by means of a broken line and the overall percentage flow A by means of solid lines. See figure 3.4 as an example.

3.3.3 Bolus Dose Accuracy Test

The bolus dose accuracy test is explained in section 201.12.1.105 in the IEC standard. 25 successive bolus deliveries shall be measured at both minimum and maximum bolus rate for the insulin pump. Following, the mean value and the percentage deviation shall be calculated. The maximum positive and negative deviation should then be expressed as percentage deviations from the set value.

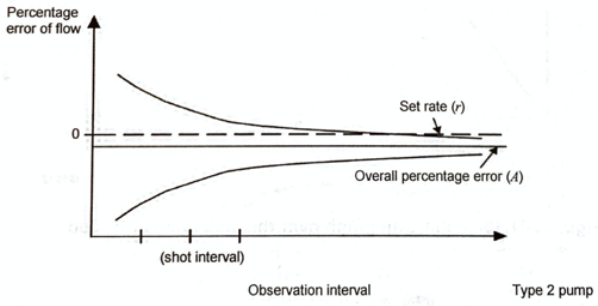


Figure 3.4: Trumpet curve plotted from data after the stabilization period for quasi-continuous pumps

Chapter 4

Methods

4.1 Test Setup

Test setup is based on IEC 60601-2-24 (3.3.1). Some details are added and will be explained in this section. Figure 4.1 shows a model of the experimental setup including some essential definitions.

4.1.1 Equipment

Below is a list of the equipment used in the experiment:

1. **Distilled water**
   $75ml$ is used in the beaker. Tap water contains minerals that might affect the experiment.
2. **Rapid acting insulin**
   The insulin pump should be filled with rapid acting insulin.
3. **Oil**
   $50ml$ is used in the beaker. The oil used is Universal Powered By McCulloch OLO008 Chain Oil (Bio) [14]. It is chemically stable and free from water. This is important to minimize evaporation or other chemical reactions that might affect the weight.
4. **Ohaus Explorer Semi-Micro Balance EX225D**
   This high precision balance has a precision level of $0,01mg$ and $0,1mg$ for the capacity of $120g$ and $220g$ respectively. This experiment requires an accuracy of $0,01mg$. See table 4.1 for further specifications.
5. **Lid**
   A special made lid with a rail opening for the tube of the insulin pump (see figure 4.1.1). The lid has a double layer and is completely solid to avoid vibrations in the system. This is necessary to reduce air flows.
6. **Thin wire, duct tape, thread and clams**
   The wire should be as thin as possible to minimize waves while submerged

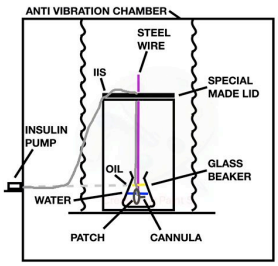


Figure 4.1: Model of experimental setup

in the liquid, but stiff enough to avoid vibrations. Duct tape should be used to attach the tube to the wire (see figure 4.3a). Thread should be used to attach the tube to the wire where the wire is submerged in liquid. Duct tape is added where needed to reduce vibration when adding boluses on the insulin pump. Clams should be used to support the wire onto the lid (see figure 4.3b).

7. **Glass beaker**
   The beaker should be as light as possible, with a radius that is large enough for the ISS not to touch the walls of the beaker. The beaker used is triangular and holds $100ml$.
8. **Anti vibration chamber**
   This is a closed chamber where small holes create openings for the plastic tube of the insulin pump and power lines. Inside the chamber is a table hanging in steel springs made based on a passive vibration isolation system [15]. See figure 4.1.1.
9. **Psychrometer or hygrometer**
   To measure the humidity during the experiment, ideally both inside and outside of the chamber.
10. **Thermometer**
    To measure the temperatures during the experiment, ideally both inside and outside of the chamber.

4.1.2 Setup Procedure

High precision weighing requires caution and a stable environment. Small variations or noises can have significant impact. Make sure that the environment is stable considering temperatures, humidity, vibrations and air flows during the whole process. In this section we describe in detail how to carry out the test.

Figure 4.2: Customized double layer lid

Environment

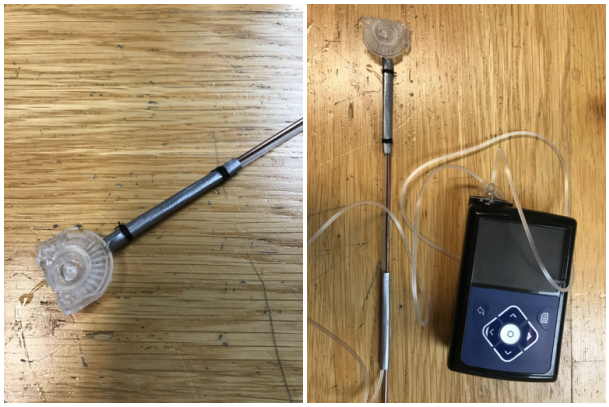
Start measuring the temperature and the humidity inside the anti vibration chamber. Values should be measured every 15 minutes and expressed with its mean and deviation in the introduction of test results.

Setup balance for automatic logging

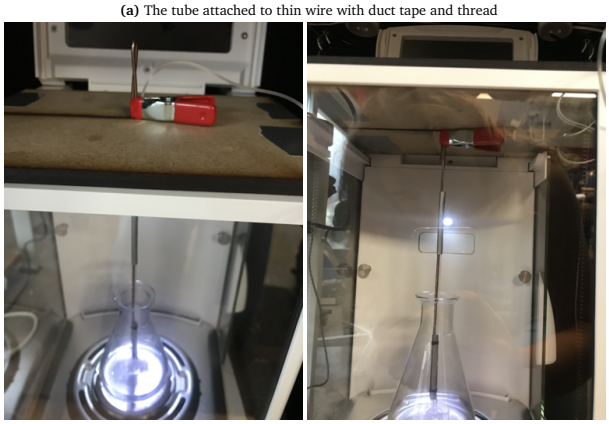
The balance can be set up to log measurements automatically at a given time interval. Go to the menu and click "Communication". Make sure that "Save to USB flash drive" is "On". Then go to "USB" –> "Print Settings" –> "Auto Print", where you can set the measurement interval (4.1.2). When the settings are correct, go to the home screen, put in the flash drive and click print.

Table 4.1: Specifications Ohaus Explorer Semi-Micro Balance EX225D

Model	EX225D
Capacity	120 g / 220 g
Readability d	0.01 mg / 0.1 mg
Repeatability (std. dev.) (20 g)	0.015 mg
Repeatability (std. dev.) (100 g)	0.02 mg / 0.1 mg
Linearity (g)	±0.1 mg

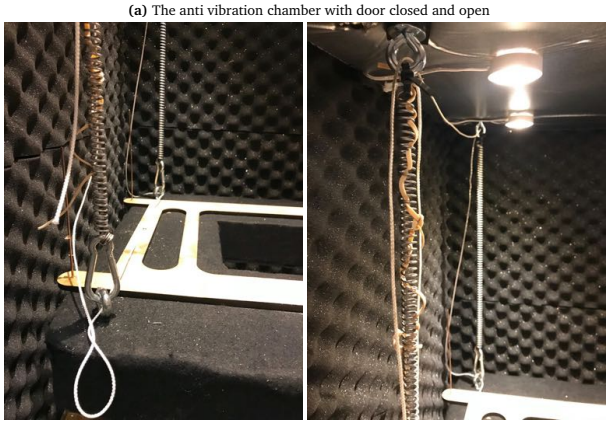


(a) The tube attached to thin wire with duct tape and thread



(b) A steel wire fixed to the lid with clams

(a) The anti vibration chamber with door closed and open



(b) The anti vibration chamber with closeup on the springs

Figure 4.5: Auto Print settings on the balance

Make sure the oil is chemically stable

Verify that the oil used in the experiment is chemically stable by placing the glass beaker carefully at the middle of the weight. Make sure the weight is clean and leveled. Fill the beaker with the same amount of distilled water and oil that you are going to use in the experiment (≥5 mm). Measure the stability for one hour, every 5 minutes. If the weight shows no tendency of continuously increasing or decreasing, the oil is sufficiently chemically stable.

Preparing the insulin pump

The insulin pump batteries, reservoir and IIS should be changed for each experiment. Set up the equipment in accordance with the manufacturer's instruction for use. To avoid crystallization, the insulin should be kept at room temperature for 24 hours before it is filled in the reservoir.

Preparing the test setup

1. First make sure that the weight is cleaned with alcohol.
2. Chop off the bottom of the patch (see figure 4.1.2), so it can go as close to the bottom of the beaker as possible with minimum amount of water. If necessary include the sides to fit into the glass beaker.
3. Place the weight in the anti vibration chamber.
4. Level the weight by adjusting the legs, and turn on the weight. Make sure it stabilizes.
5. Carefully place the glass beaker on the center of the weight and place the lid with the wire and tube attached on top of the weight.
6. Adjust the wire so that the patch is just above the ground.
7. Fill the beaker with water and oil according to the amount specified in 4.1.1 (see figure 4.7). Note that the cannula should be submerged under water

Figure 4.6: Patch of the IIS before and after the bottom is chopped off

as in 4.1.

8. Level the weight again.
9. Close the door to the anti vibration chamber and place the insulin pump in the same height as the top of the liquid in the beaker (see figure 4.8).
10. Let the system stabilize for one hour. If evaporation is observed, add some more oil in the beaker and repeat from step 8.

Measure stability of the measurement setup

For this stability test, an arbitrary insulin pump can be used. This only needs to be done once. All insulin delivery must be stopped on the insulin pump. Measure the stability for 24 hours, every 15 minutes. If any evaporation occurs, calculate the evaporation rate r_{ev} as

$$r_{ev} = \frac{1}{24} \sum_{j=2}^{24\times4} ((m_j - m_{j-1}) \times 4)[g/h] \tag{4.1}$$

where m_j is the current measurement.

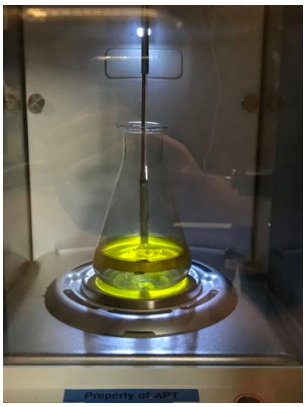


Figure 4.7: The beaker filled with a layer of water, a layer of oil and the patch submerged

Figure 4.8: Experimental setup where the insulin pump is leveled at the same heigh as the top of the liquid

4.2 Test Procedures

4.2.1 Testing Bolus Rates

Initially repeat the steps from section 4.1.2 and section 4.1.2. The bolus tests should be performed according to 3.3.3. The time interval between each bolus delivery and measurement should be defined based on the size of the bolus and flow rate. Bolus doses from all delivery increments should be included, not only at minimum and maximum rates.

In addition to what was described in IEC 60601-2-24, results should be represented in a table, calculating the amount of boluses (in %) that were inside a deviation of ±15%, ±10% and ±5% of expected delivery. Each insulin pump and bolus rate should be presented separately.

4.2.2 Testing Basal Rates

Initially repeat the steps from section 4.1.2 and section 4.1.2. The basal rate tests should be performed according to 3.3.2. Basal rates from all delivery increments should be included, not only at minimum and maximum rates. The test can run for a maximum of 72 hours.

In addition to what was described in IEC 60601-2-24, results should be represented in a scatter plot, where expected values are clearly marked as a horizontal line, and the deviations of ±5%, ±10% and ±15% as well. Additionally the results should be represented in a table, where the amount of basal doses (in %) are delivered in a 1-hour, 3-hour, 6-hour and 12-hour window, inside a deviation of ±15%, ±10% and ±5% of expected delivery. Each pump and basal rate should be represented separately.

4.2.3 Quantification of the Testing

Ideally all of the insulin pumps used in the experiments should be completely new. Also, identical pumps from different production batches should be compared to avoid any individual pump weaknesses. Different types of IIS and insulin types should be tested and compared to clarify if this might affect the results.

Chapter 5

Results

In this chapter we present the test results of the stability of the preliminary experimental setup. The test setup went through several iterations where details to the procedure were added. Tests of the insulin pumps included in this chapter were performed on the early iterations of the project, hence the procedure presented in chapter 4 was not followed strictly. The tests of the stability were performed on the final experimental iteration, where most of the procedure was followed strictly. Some details and standardisation was added after the final test, including temperature and humidity measurements.

5.1 Test of Insulin Pump Boluses on Early Experimental Setup

The first tests of insulin pumps were performed before we knew the IEC standard in detail. We also had less experience with the experimental setup. The tests were made on two old (pump B and C) and one relatively new (pump A, within a year old) insulin pump that were filled with water. To some extent, we consider these results unverified. For this reason the results will not be presented as detailed as explained in section 4.2.

Only bolus doses were tested. A bolus was injected manually from the insulin pump, and the size is referred to as "Expected dose [U]". The "# of repetitions"-tab shows amount of successive bolus deliveries. Between each bolus we waited for 5, 10 or 15 minutes depending on the size of the bolus. Table 5.1 shows the average amount delivered compared to the expected one, and the standard deviation relative to the average. Table 5.2 shows the amount of boluses delivered within a given deviation. To determine the size of the bolus in units from the measurement of the balance, we use equation (3.2.2). In appendix A.1, all of the test result measurements are listed.

5.2 Stability of the Oil on Final Experimental Setup

The test was performed with a layer of oil of approximately $0.7mm$. Measurements were registered every 5 minutes. The first test was performed while the weight was standing on the floor. The second test was performed while the weight was in the anti vibration chamber. The test was performed before the exact amount of water and oil was defined, and instead a layer of oil of $0.7mm$ was used. See table 5.3.

For both tests there is no sign of continuous increase or decrease, but some fluctuations that are probably due to vibrations and/or air flows in the system. The test in the chamber shows better stability. No measurable level of evaporation appeared using this oil.

5.3 Stability of Final Experimental Setup

During the stability test, the temperature and humidity was not measured. The insulin pump was filled with distilled water, using a new IIS and battery, and the measurements were made every 15 minutes as explained in section 4.1.2. The insulin pump used was relatively new (pump A) and in good condition. After the test rig was set up, it needed around an hour for the oil to drain from the wire and the beaker, and to stabilize. No doses were injected from the pump during the test. The stability test showed perfect stability during the 24 hours, and consequently no evaporation rate needs to be calculated. Stability test results can be found in section A.2.

Table 5.1: Average amount and standard deviation of bolus doses in three different insulin pumps

Expected dose [U]	Insulin pump	# of repetitions	Average [U]	Standard Deviation [%]
0.025	A	30	0.019	158
	B	10	0.011	136
	C	-	-	-
0.050	A	20	0.041	78
	B	10	0.017	76
	C	10	0.027	81
0.100	A	20	0.099	23
	B	10	0.090	10
	C	10	0.081	9
1.000	A	2	0.994	2
	B	-	0.897	1
	C	10	0.807	1
5.000	A	-	-	-
	B	4	4.949	1
	C	-	-	-

Table 5.2: Amount of bolus doses inside of range in three different insulin pumps

Expected dose [U]	Insulin pump	# of repetitions	Within ± 15% [%]	Within ± 5% [%]
0.025	A	30	0	0
	B	10	0	0
	C	-	-	-
0.050	A	20	20	0
	B	10	0	0
	C	10	10	10
0.100	A	20	50	25
	B	10	80	30
	C	10	40	10
1.000	A	2	100	50
	B	-	-	-
	C	10	100	50
5.000	A	-	-	-
	B	4	100	100
	C	-	-	-

Table 5.3: Measurements of stability of water and oil in beaker

Time [min]	Measurements (on floor) [g]	Measurements (in chamber) [g]
0	0.00000	0.00000
5	0.00043	0.00000
10	0.00058	0.00000
15	0.00055	0.00000
20	0.00051	0.00000
25	0.00043	0.00000
30	0.00039	0.00000
35	0.00037	0.00000
40	0.00030	-0.00004
45	0.00023	0.00000
50	0.00018	0.00000
55	0.00013	0.00000
60	0.00012	0.00000

Chapter 6

Discussion

In this chapter we will reason about the decisions made while establishing the experimental setup and the procedure explained in chapter 4. Adjustments and additions we have made to the IEC standard are explained. In chapter 5 test results were presented, and will here be further analysed. Possible sources of error in the experiment results are identified, along with the challenges that might cause them. Ultimately, ideas on possible workarounds of the challenges with insulin pump accuracy will be presented.

6.1 Reasoning for Representation of Bolus and Basal Rate Results

In chapter 4 we have defined how accuracy test results of insulin pumps should be presented. To satisfy IEC 60601-2-24, results should be presented as specified in the standard. However, the presentation the IEC demands might not be clinically relevant. Therefore we have added some additional graphical representations to present the test results, that we consider more relevant.

For boluses, every single dose is important. According to the IEC standard, results should be represented as the average amount delivered by the measured boluses, and the standard deviation. This way, extreme deviations might become invisible. Also, the standard deviation is calculated relatively to the average value, which means that erroneous values might have a positive effect. Values inside of the actual target might have a negative effect on the standard deviation depending on the average.

We have included a requirement of presenting the amount of boluses delivered that are inside of a given target. This makes it possible to compare the accuracy of the insulin pumps with the accuracy that the manufacturers of the insulin pumps promise to deliver. Most manufacturers promise an accuracy within ±5% of the expected dose, both for the boluses and the basal rates (3.1.3).

6.2 Test Results of the Insulin Pumps on Early Experimental Setup

The test results in section 5.1 should be considered as a test of the experimental setup, as well as the accuracy of the insulin pumps. The evaporation rate is not considered, because the accuracy tests on the early experimental setup were performed before the evaluation of the stability.

We observed a clear tendency that both the insulin delivery accuracy and the standard deviation is worse for the smaller boluses. See table 5.1 and 5.2. The reason for the lower accuracy for lower volumes might be friction in the insulin pump piston when injecting. It can also be due to lack of sensitivity in the balance or other weaknesses in the experimental setup.

In further research, the accuracy of insulin rates should be investigated more thoroughly. Systematic and quantified tests should be performed. Deliveries within ±5%, as the insulin pump manufacturers promise, only occurred for the largest bolus tested (5.000 U).

6.3 Challenges

Making the weight stabilize at such high precision measurements, working with liquids, caused several challenges. As showed in the results, the beaker filled with oil and water showed perfect stability, while adding the insulin pump did not.

6.3.1 Possible Sources of Error

High precision weighing should ideally be done without shocking the balance (applying more than tolerated weight), but this is very challenging to avoid during the setup procedure. Oil and/or water might also have been spilled, which might have affected the results, regardless of whether this was intended to avoid. In theory, the plastic tube should not cause the insulin to leak while it is still, and no insulin delivery is applied. However, there might be some leakage affecting the stability.

6.3.2 Adjustments and Additions to IEC 60601-2-24

According to IEC 60601-2-24 one should fill the insulin pumps with water instead of insulin during the experiments. Water might behave slightly different then insulin, which can affect the test result. We added a test with insulin to the test method, preferably with several different types of rapid acting insulin.

Because of vibrations making the weight fluctuate, even when the weight was standing on a solid marble table, we ended up putting the weight in an anti vibration chamber. This chamber was locked, so that the potential air flows through the

special made lid were also removed. However, to then be able to level the insulin pump with the liquid surface, a plastic tube of around 120 cm is required.

6.3.3 Evaporation

During the testing of several test setups, a common problem was the weight continuously decreasing, because of evaporation. Testing several types of cups and beakers, we found that a glass beaker provided less evaporation of the water than a plastic cup. The evaporation was even worse when a paper cup was used. We also found that the type of oil was essential. For one type of oil tested, we observed that the weight continuously increased, probably due to oxidation. Others evaporated. The oil must be chemically stable and not contain water. The layer of oil on top of the water must also be sufficiently thick.

6.3.4 Maximum Weight Range

A balance that is accurate to five decimal places is required. For the weight used, this is valid for weighing up to 120 g. The closer the measurement is to the maximum range, the less reliable it is.

When using a glass beaker to avoid evaporation, the weight increases more than if a plastic cup is used. It is therefore important to not add a lot of water and oil in the beaker. The beaker must have a small radius so that less liquid is necessary. Cutting of parts of the patch around the cannula, allows using a smaller beaker, and still avoiding the patch to touch the walls of the beaker.

6.3.5 Vibrations

Vibrations that affected the fluctuations of the weight could among other factors be caused by construction work, traffic or people walking in the room. Because the test period is stretched out over several days, it is difficult to avoid noise during the test period. Therefore, the tests should preferably run during the weekends.

When you inject insulin you have to use the buttons on the insulin pump. This causes vibrations in the plastic tube, that causes vibrations in the liquid on the weight and also fluctuations in the weight. This is solved by taping the plastic tube to the lid, and also nearby the insulin pump end. If you could remotely inject insulin in the pump, for example from your phone, that would have been optimal. This function is unfortunately not provided by the insulin pumps we have used for testing.

6.4 IEC 60601-2-24

For this thesis we wanted to stay true to the IEC standard, as it is the international standard that the manufacturers of insulin pumps have to comply with to enter

the market. However, there are some details in the design solution presented that are missing. Among them are which liquid (we used oil on top of water) applied where you submerge the cannula, and how to obtain a stable system without the IIS or the cannula touching the beaker.

The standard requires that the insulin pumps can deliver 1 U/h as a minimum basal rate. But most pumps have a minimum basal rate of 0.05 U/h or 0.025 U/h. For 0.025 U/h this equals 0.00025 g/h. Weighing at such a high precision level can easily be affected by different factors, such as temperature and humidity. IEC 60601-2-24 does not mention any criteria for test environment. It is reasonable to raise doubts whether the standard is meant for such small volumes as the minimum rates in the insulin pumps today.

There is not presented any specific requirement regarding how accurate insulin delivery should be in order to be accepted. Also, the standard only requires to test one basal rate. It is questionable if this can represent the accuracy of the rates using the smallest increments of insulin injection. For bolus doses it is not defined any amount of time to wait between each measurement. A more detailed procedure would have made insulin pump verification simpler.

6.5 Alternative Solutions to the Accuracy Problem

Working with very small volumes is a challenge. It seems to be a common problem that small insulin rates perform a lower accuracy. Measurements of very small volumes are also less accurate then the larger ones. Consequently the accuracy tests will be less reliable for smaller volumes. A solution to this problem can be to make the minimum insulin delivery rates larger.

Insulin given to patients contains water, and the concentration can be adjusted. The insulin given to patients today is usually 100 U/ml. One can argue that, rather than trying to make the insulin pumps more accurate at low rates, patient groups with a low insulin demand should be given insulin with a lower concentration.

Manufacturers of insulin pumps should also explore the clinical results of using larger increments and injection intervals, even for small basal and bolus rates (3.1.2). Comparing results of the same basal rates using different increments is especially interesting in regards to artificial pancreas and closed loop systems. In such systems, insulin delivery will be partly automated, so if the accuracy of the expected insulin delivery is low, the system will work poorly.

Chapter 7

Conclusions

In this thesis we have established a test setup and procedure to measure insulin pump accuracy based on IEC 60601-2-24. How results of the tests should be presented in a clinically relevant manner is discussed and suggested. The test setup went through several iterations where necessary details were added so that the test setup stabilized. Different insulin pumps were used to run pilot tests on the experimental setup.

7.1 The Thesis Projects Objective

In section 1.2 the problem description is presented. Concrete tasks are specified in five bullet points. The main objective for the project is to establish a test setup and procedure for measuring insulin pump accuracy.

In task 1 we needed to perform a literature review on several topics creating a foundation for the project and to find relevant research. This is summarized in chapter 2 and 3. The articles we found related to this subject is mainly published by the manufacturers or people related to them. Hence, the articles might be biased. In these articles we found that insulin pump accuracy in general is sufficient compared to the level of accuracy promised by the manufacturers. Results on minimum rates are not published. Yet, some sources claim that minimum rates may be less accurate. A publication on test setups based on IEC 60601-2-24, criticizes the standard for not being detailed enough, nor clinically relevant.

Task 2 and 3 states that the student shall build an initial test setup and to define an initial test procedure. During the project a test setup based on IEC 60601-2-24 was built and tested several times. For each test iteration, details to both the setup and the procedure were added, until a stable setup was established. The final test setup and procedure is described in detail in chapter 4, which is the answer to task 5.

In chapter 5, the pilot test results are presented as an answer to task 4. Improvements on the tests based on experiences from the pilot tests were implemented in the final tests. Results also showed that lower rates showed low accuracy in delivery. However, these tests were performed on an early stage of the experimental setup. Same tests should be performed again on final test setup. Ultimately, stability tests on the final test setup were made, and showed that the test setup was perfectly stable.

7.2 Additional Remarks

Challenges were shown during the implementation and the deployment of IEC 60601-2-24, due to lack of details presented in the standard. The problems that occurred while creating a stable test setup were due to evaporation, vibrations and air flows affecting the weight. If the presented method for testing is suitable for the insulin pumps at the minimum delivery rates, is questionable. The IEC standard defines how the results of the experiments should be presented. We have discussed whether the definition in the standard is clinically relevant, and we suggest some adjustments based on this discussion.

7.3 Recommendations for Further Research

7.3.1 Testing the Accuracy of Several Pumps

Now that a sufficiently precise and stable test setup is found, the accuracy of several insulin pumps on the market should be tested. To be sufficiently representative, identical pumps from different production batches should be compared. Both tests on basal rates and bolus rates should be performed. The clinical consequence of the level of accuracy observed should then be reviewed. The future of automatic insulin delivery might require a higher level of accuracy for the control algorithms to be reliable.

Further research on accepting criteria for insulin pump accuracy should be performed, and discussed with health personal. Based on these reviews, clinically relevant representation of test results can be determined.

Several dimensions of testing the insulin pumps could be added. Boluses could be tested while a basal dose is running, and not only in the absence of one. The effect of moving the pump up and down could be measured to observe whether this evokes insulin delivery. Movements in the pump are relevant to simulate daily use by the patients. Environments of the tests could be changed, such as testing during low or high temperatures. The IEC standard states that water can be used in the insulin pumps during testing. Tests using different types of insulin and water should therefore be done to determine whether water is a good substitute or not.

Patch pump accuracy should also be tested, and whether the test setups for them

are comparable to the test setups for infusion pumps should be examined.

7.3.2 Building an Insulin Pump

An insulin pump could be build to be able to test different types of technologies behind the pump mechanisms. These mechanisms cannot affect the flow and trigger insulin crystallization. If one type of pump mechanism is used in all insulin pumps, this makes it easier to get it CE approved, and this tendency might prevent further developments. Building an insulin pump would also give full control over the pump software. This way different bolus and basal dose increments and frequencies could be compared with the established test setup in the thesis.

7.3.3 Exploring Different Test Methods

If the test setup appears to not be suitable to determine accuracy of minimum insulin infusion rates, new ways to test accuracy should be explored, compared and maybe recommended to substitute the existing setup in IEC 60601-2-24. Preferably this new test setup should be suitable for both infusion pumps and patch pump so that they can be properly compared.

Bibliography

[1] R. Ziegler, U. Kameche, D. Waldenmaier, C. Haug and G. Freckmann, 'Delivery of low basal rates in different insulin pumps—an accuracy evaluation,' *American Diabetes Association*, Jul. 2018. [Online]. Available: https://diabetes.diabetesjournals.org/content/67/Supplement_1/972-P?utm_source=TrendMD&utm_medium=cpc&utm_campaign=Diabetes_TrendMD_0.

[2] R. Ziegler, D. Waldenmaier, J. Mende, C. Haug and G. Freckmann, 'Bolus dosing accuracy of two recent insulin pumps,' *American Diabetes Association*, Jun. 2019. [Online]. Available: https://diabetes.diabetesjournals.org/content/68/Supplement_1/119-LB.

[3] G. Freckmann, U. Kamecke, D. Waldenmaier, C. Haug and R. Ziegler, 'Accuracy of bolus and basal rate delivery of different insulin pump systems,' *Diabetes Technology Therapeutics*, p. 8, Apr. 2019. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6477586/#B9.

[4] U. Kamecke, D. Waldenmaier, C. Haug, R. Ziegler and G. Freckmann, 'Establishing methods to determine clinically relevant bolus and basal rate delivery accuracy of insulin pumps,' *Journal of Diabetes Science and Technology*, pp. 60–67, Jul. 2018. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313283/.

[5] H. Bratke, *Dette er de nye pumpene og sensorene*, [Online; accessed 18-November-2020], Nov. 2020. [Online]. Available: https://www.diabetes.no/for-helsepersonell/diabetesfag/dette-er-de-nye-pumpene-og-sensorene/.

[6] Medtronic, *Komme i gang med minimed 670g-systemet*, [Online; accessed 18-November-2020], Feb. 2019. [Online]. Available: https://www.medtronic-diabetes.no/sites/no/medtronic-diabetes.no/files/pdf/minimed_670g_komme_i_gang_med_uc201903112_no.pdf.

[7] *Medtronic – minimed 640g*, [Online; accessed 18-November-2020], Jan. 2019. [Online]. Available: https://www.diabetes.co.uk/diabetic-products/pumps/medtronic-minimed-640g.html.

[8] *Summary of safety and effectiveness data (ssed)*, [Online; accessed 18-November-2020], Jun. 2016. [Online]. Available: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017B.pdf.

[9] I. B. Hirsch, *Type 1 diabetes mellitus and the use of flexible insulin regimens*, [Online; accessed 19-September-2020], Nov. 1999. [Online]. Available: https://www.aafp.org/afp/1999/1115/p2343.html.

[10] *Novorapid*, [Online; accessed 17-September-2020], Mar. 2020. [Online]. Available: https://www.felleskatalogen.no/medisin/novorapid-novorapid-flexpen-novorapid-penfill-novorapid-pumpcart-novo-nordisk-562204.

[11] *Water density*, [Online; accessed 17-September-2020]. [Online]. Available: https://www.usgs.gov/special-topic/water-science-school/science/water-density?qt-science_center_objects=0#qt-science_center_objects.

[12] M. M. Harding, 'The crystal structure of insulin,' *Journal of Molecular Biology*, Mar. 1966.

[13] 'Medical electrical equipment - part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers (iec 60601-2-24:2012),' 2012.

[14] *Universal powered by mcculloch olo008 chain oil (bio) - 1 litre*, [Online; accessed 26-November-2020]. [Online]. Available: https://www.365reservedeler.no/olo008-chain-oil-bio-1-litre/product.pl?pid=1798870.

[15] G. L. Hermsdorf, S. A. Szilagyi, S. Rösch and E. Schäffer, 'High performance passive vibration isolation system for optical tables using six-degree-of-freedom viscous damping combined with steel springs,' *American Institute of Physics*, Jan. 2019. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/30709215/.

Appendix A

Test Result Listings

A.1 Insulin Pump Early Tests

The tables below shows all the measurement readings after a delivered bolus for insulin pump A (table A.1), B (table A.2) and C (table A.3).

A.2 Stability Readings

Table A.4 below shows all the measurement readings during the stability test. Start time is given relative to start of test, where we start at 00:00 Measurements were done with a interval of 15 minutes for 24 hours.

Table A.1: Insulin Pump A

Injected Bolus [U]	Measurement Reading [g]
	0.00019
	0.00000
	0.00000
	0.00064
	0.00044
	0.00000
	0.00000
	0.00085
	0.00000
	0.00000
	0.00074
	0.00000
	0.00000
	0.00000
0.025	0.00064
	0.00000
	0.00000
	0.00000
	0.00084
	0.00000
	0.00000
	0.00000
	0.00000
	0.00000
	0.00000
	0.00000
	0.00000
	0.00062
	0.00061

Insulin Pump A

Injected Bolus [U]	Measurement Reading [g]
0.050	0.00011
	0.00033
	0.00018
	0.00018
	0.00021
	0.00043
	0.00086
	0.00000
	0.00107
	0.00000
	0.00038
	0.00046
	0.00045
	0.00041
	0.00099
	0.00025
	0.00036
	0.00096
	0.00055
	0.00000
0.100	0.00122
	0.00138
	0.00088
	0.00119
	0.00047
	0.00072
	0.00081
	0.00101
	0.00099
	0.00103
	0.00100
	0.00106
	0.00107
	0.00130
	0.00133
	0.00095
	0.00090
	0.00063
	0.00109
	0.00084

Insulin Pump A

Injected Bolus [U]	Measurement Reading [g]
0.500	0.00461
	0.00575
	0.00484
	0.00526
	0.00495
	0.00528
	0.00495
	0.00525
	0.00435
	0.00524
1.000	0.00923
	0.00983

Table A.2: Insulin Pump B

Injected Bolus [U]	Measurement Reading [g]
0.025	0.00000
	0.00000
	0.00041
	0.00000
	0.00021
	0.00000
	0.00019
	0.00000
	0.00000
	0.00031
0.050	0.00000
	0.00030
	0.00021
	0.00029
	0.00012
	0.00022
	0.00000
	0.00000
	0.00035
	0.00017
0.100	0.00087
	0.00104
	0.00096
	0.00098
	0.00094
	0.00087
	0.00085
	0.00077
	0.00076
	0.00093

Insulin Pump B

Injected Bolus [U]	Measurement Reading [g]
0.500	0.00479
	0.00459
	0.00466
	0.00436
	0.00454
	0.00468
	0.00475
	0.00448
	0.00455
	0.00465
5.000	0.04953
	0.04928
	0.04886
	0.04989

Table A.3: Insulin Pump C

Injected Bolus [U]	Measurement Reading [g]
0.050	0.00051
	0.00000
	0.00077
	0.00009
	0.00023
	0.00035
	0.00031
	0.00007
	0.00022
	0.00015
0.100	0.00096
	0.00072
	0.00073
	0.00072
	0.00085
	0.00085
	0.00082
	0.00080
	0.00076
	0.00086
1.000	0.00926
	0.00943
	0.00957
	0.00941
	0.00924
	0.00936
	0.00954
	0.00954
	0.00948
	0.00950

Table A.4: Stability Readings

Time [hours]	Measurement Reading [g]
00:00	0.00000
00:15	0.00000
00:30	0.00000
00:45	0.00000
01:00	0.00000
01:15	0.00000
01:30	0.00000
01:45	0.00000
02:00	0.00000
02:15	0.00000
02:30	0.00000
02:45	0.00000
03:00	0.00000
03:15	0.00000
03:30	0.00000
03:45	0.00000
04:00	0.00000
04:15	0.00000
04:30	0.00000
04:45	0.00000
05:00	0.00000
05:15	0.00000
05:30	0.00000
05:45	0.00000
06:00	0.00000
06:15	0.00000
06:30	0.00000
06:45	0.00000
07:00	0.00000
07:15	0.00000
07:30	0.00000
07:45	0.00000
08:00	0.00000
08:15	0.00000
08:30	0.00000
08:45	0.00000

Stability Readings

Time [hours]	Measurement Reading [g]
09:00	0.00000
09:15	0.00000
09:30	0.00000
09:45	0.00000
10:00	0.00000
10:15	0.00000
10:30	0.00000
10:45	0.00000
11:00	0.00000
11:15	0.00000
11:30	0.00000
11:45	0.00000
12:00	0.00000
12:15	0.00000
12:30	0.00000
12:45	0.00000
13:00	0.00000
13:15	0.00000
13:30	0.00000
13:45	0.00000
14:00	0.00000
14:15	0.00000
14:30	0.00000
14:45	0.00000
15:00	0.00000
15:15	0.00000
15:30	0.00000
15:45	0.00000
16:00	0.00000
16:15	0.00000
16:30	0.00000
16:45	0.00000
17:00	0.00000
17:15	0.00000
17:30	0.00000
17:45	0.00000

Stability Readings

Time [hours]	Measurement Reading [g]
18:00	0.00000
18:15	0.00000
18:30	0.00000
18:45	0.00000
19:00	0.00000
19:15	0.00000
19:30	0.00000
19:45	0.00000
20:00	0.00000
20:15	0.00000
20:30	0.00000
20:45	0.00000
21:00	0.00000
21:15	0.00000
21:30	0.00000
21:45	0.00000
22:00	0.00000
22:15	0.00000
22:30	0.00000
22:45	0.00000
23:00	0.00000
23:15	0.00000
23:30	0.00000
23:45	0.00000

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