
CHAPTER 8

SIMULATION MODEL VERIFICATION

In this chapter the simulation model presented in Chapter 7 is applied and the quality of the predictions are evaluated. Verification is performed by comparing simulated results to measured data. Two evaluations were considered, namely long-term and short-term trials and the quality of both are determined according to certain evaluation criteria.

8.1 Introduction

The potential for successful application of the energy system simulation model presented in Chapter 7 is directly dependent on the verification study results. Therefore many simulations were performed for a variety of case studies in order to establish the accuracy of the simulation model's predictions. These results were compared to measured results to evaluate how precise reality could be modelled with the system.

The verification study was conducted with the following procedure:

- Firstly, two groups of volunteers (healthy and diabetic) performed many clinical tests and recorded many blood glucose response measurements due to a wide variety of external disturbances.
- Then a simulation model for each of the test subjects was constructed according to some of the measurements that were logged.
- The simulation models were then solved in order to generate simulated data points for the case studies that were not used for the simulation model construction phase.
- Lastly, the measured data was compared to simulated data and the validity of the model and the simulation system was evaluated according to predefined criteria.

This chapter consists of three main sections, namely:

- Reference data acquisition – where the methods and materials are described;
- The verifications study – where the measurements are compared to the simulations, and;
- The interpretation section – where the final verification results are discussed.

8.2 Reference data acquisition

Measurement data to verify the simulation model was collected over a series of separate trials. The original objectives of many of these trials were wide-ranging and not aimed at verification of this study as such. This however does not entail a disadvantage, but rather an advantage, since the

acquisition of the data represents glycaemic responses due to many every-day influences the accuracy and applicability of the model for normal human behaviour could be assessed better.

For the larger part of all the trials performed blood glucose levels of the test subjects were monitored under different circumstances. The blood glucose concentrations were usually obtained with the use of handheld glucose meters. These devices require small droplets of blood, normally acquired through pricking of a fingertip, and they then estimate the glucose concentration by either determining the impedance of the droplet in a certain chemical, or by measuring the colour change due to some chemical additive [1].

Extensive ongoing worldwide research is aimed at finding an easier and less painful method of determining current blood sugar levels. Many non-invasive methods have been introduced with varying success [2]. For this study however the normal invasive method of estimation by impedance was primarily employed.

Two distinct groups of test subjects were used for these trails. These are divided into a diabetic group and a healthy persons group. Furthermore, the conditions for which the measurements were taken can also be subdivided into two scenarios. These are long-term tests, mostly performed with the diabetic subjects, and short-term tests performed with both the volunteer groups.

The following paragraphs contain a short summary and discussion concerning the trials, the test subjects and the methods used to obtain the verification data.

8.2.1 Test subjects

During the three-year duration of the study both healthy and diabetic volunteers were asked to measure blood glucose levels while performing various tasks. All the volunteers were instructed in detail as to what the various procedures involved and what the purposes of the trials were. Where necessary, ethical clearance by two separate ethical committees was obtained for the trials.

Healthy subjects

The healthy subjects amounted to 18 volunteers. The group of subjects consisted of people with varying ages and body mass indexes (BMI). The following table presents a summary of the healthy individuals:

	Average	Range
Number	18	
Age	27	9 to 58
Length	1.74	1.0 to 1.98
BMI	23.9	19.6 to 30.8

Table 8.1 – Summary of the group of healthy subjects used for the clinical trials.

Diabetic subjects

The diabetic subjects amounted to 9 volunteers in total. There were 5 male and 4 female subjects of varying ages and body mass indexes (BMI). The following table presents a summary of the diabetic individuals:

	Average	Range
Number	9	
Age	44	32 to 52
Length	1.75	1.63 to 1.85
BMI	23.4	21.3 to 26.3

Table 8.2 – Summary of the group of diabetic subjects used for the clinical trials.

More details concerning the test subjects are presented in Appendix A.

8.2.2 Long-term trials

All the diabetic subjects and some of the healthy subjects were asked on several occasions to log their behaviour over long periods of time. These periods ranged from one day up to several days and even weeks on end, depending on the primary objective of the specific trials that were conducted. The people had to keep track of the following influences and responses:

- food consumption;
- exercise;
- insulin injections;
- stress and illness levels, and;
- blood sugar measurements.

Food consumption

Every item of food that the person ingested during the trials were carefully logged and recorded. As described previously, the simulation model employs food intake as the primary influencing factor of blood glucose levels, so careful consideration was required during this stage.

The detail record of the meals, together with drinks, included:

- the time of consumption as well as duration of ingestion of the meal;
- the amount of each part of the meal that was consumed (for example: 1 medium chicken breast, 1½ slice of white bread, etc.);
- the estimated nutritional value of the food, including calories, carbohydrates, protein and fat content as well as glycaemic index (GI);
- an estimated amount of ets contained in the meal (according to the volunteer).

The last log entry, i.e. the ets value of the meal, was asked of the volunteers in order to assess the user-acceptance and user-understanding of the ets concept. The concept could be evaluated to determine whether the idea of 'ets' could be rolled out as a marketable quantity for validating and evaluating foods.

Exercise

Since the simulation model also incorporates energy expenditure as an influencing factor of blood sugar levels, the exercises the test subjects performed were also logged. Normal energy expenditure during every-day activity was accounted for by evaluating the individuals' lifestyles. It was assumed to be part of the basal metabolism expenditure. Any extra and purposeful exercises, like gym, jogging, cycling, etc. were recorded.

The following information was important as input for verification of the simulation model:

- the starting time of the exercise;
- the duration of the exercise;
- a detailed description of the specific exercises that were performed;

- an estimation of the amount of calories used during the exercise;
- an estimation of the amount of ets that was used for the exercise (in the volunteer's opinion).

Exercises that were performed in quick succession had to be listed as separate exercises. For example, a single gym session containing 30 minutes of cycling and 20 minutes of jogging will be listed as two separate entries into the logbook. This is to ensure that the simulation model receives the correct external influence.

Furthermore, as with the food input, the volunteers' opinions were acquired to determine the applicability of the ets concept. Again the concept's user-acceptance was evaluated to determine the every-day value of using ets.

Insulin injections

Most of the long-term tests were performed by Type 1 diabetic patients. Because of their diabetic status they are required to inject insulin on a daily basis in order to adequately control their blood sugar levels [3],[4],[5]. The simulation model uses these injection dosage values as input to perform the simulations. Healthy people that performed these trials were not required to provide any information regarding this section.

The following information was required about the insulin injections:

- the exact time the injection was administered;
- the type of insulin that was used;
- the exact dosage that was taken;
- the amount of "negative ets" that the injected insulin is worth (volunteers' opinion).

The type of the insulin is very important since the release of effective insulin into the bloodstream is calculated for every time step throughout the solving process and every type of insulin has a different release response [6]. The release function, Equation (7.22), was used.

Furthermore, the user-understanding and user-acceptability was again assessed by evaluating the opinions of the subjects as to how much negative ets is contained in the insulin dosage taken.

Stress levels and illness

Some of the control system parameters of the simulation model are dependent on the level of stress or illness the person experiences. For this reason the subjects were asked to declare an estimation of their stress and illness conditions. For simplifications sake three possibilities were given to the subjects. These are: high, medium or low stress levels.

They also had to specify whether the stress condition was long-term or short-term stress or an illness (see Section 6.2). If short-term was the case the subjects were required to log the time in the same manner as the exercises described above. For any assumptions estimated values were used.

Blood sugar measurements

The subjects were required to record blood sugar levels with their glucose monitors throughout the trials. Since most of the subjects on the long-term trials were diabetic patients, they were required to take blood glucose measurements anyway in order to calculate required insulin dosages. These measurements as well as some others (as the specific trials demanded) were all used for the verification of the simulation output.

The exact times of the measurements were required for accurate verification of the long-term simulation results. The measured results are usually represented with one decimal value and were recorded as such.

8.2.3 Short-term trials

In contrast to the long-term trials, the short-term trials were not performed to evaluate the effects of every-day living conditions on blood sugar concentrations. With the long-term trials the aim was to integrate all the applicable external influences and investigate their effect. In contrast the short-term trials were primarily used to only determine the effects of isolated influences.

The main purpose was to investigate the blood glucose response to one influence, like a specific food or a certain exercise. These trials were therefore usually performed after long fasting periods or, if successive tests were conducted, the test would be done on the same time every day, etc. However, the blood glucose values obtained with these trials can be just as well applied for verification of the human energy system simulation model.

Mainly three distinctive tests were conducted on a short-term basis. These were to determine human blood glucose response due to:

- oral food ingestion;
- exercise energy expenditure, and;
- serum insulin injections.

The following paragraphs describe the three tests and their methods.

Food ingestion

The trials that were performed with various ingested foods (and drinks) were usually done for one of two purposes. It was either to determine the GI and henceforth the ets content of a food (see Section 2.4), or it was to characterise the specific test subject in order to construct a personalised simulation model. For both cases the measurement procedure was the same.

The procedure used is similar to any glucose tolerance test such as those performed for GI tests [7]. The test subjects have to fast for a sufficiently long period before the tests and make sure that their blood glucose concentrations are relatively constant. Then a basal blood sugar level is recorded with a “finger prick” blood test.

After the basal level is determined the test can begin. The subjects then ingest a certain food. For the next predetermined amount of time and at predetermined intervals blood glucose levels are measured and recorded. The concurrent changes in blood glucose concentrations are known as the “glycaemic response”.

In the case of the healthy individuals the tests are usually run until the subjects’ blood glucose levels are restored back to basal level. The duration of the trials with the diabetic subjects however depended on the objectives of the specific trials. These objectives were for example to investigate the blood glucose rise due to a certain food or to determine the time or efficiency of a specific person’s digestive system.

All this data was recorded and blood glucose response graphs were drawn and evaluated for both the effect of different foods on one person as well as the effect of different persons ingesting the same food.

Exercise energy expenditure

Exercise trials were conducted to determine the effect of strenuous exercise on glycaemic response. Two types of measurements were performed for these trials. These are firstly with a handheld glucometer like most of the trials and secondly with intravenous measurements [1].

The glucometer tests are similar to those described above for the food trials. The intravenous measurements however are slightly different. In that case a tube is inserted directly into the test subject's artery for drawing blood. The location of the tube is determined by the specific exercise that is performed for the trial in order to prevent excessive movement in the region of the tube. For example, if the subject is cycling on a stationary bicycle, therefore has significant leg movement, the blood is preferably draw from the arm region that is comparatively motionless.

In both test procedures the test subjects were required to exercise according to specific schedules while blood glucose measurements were taken at regular and predetermined intervals. Like with the food trials described above the recorded blood glucose levels were plotted and used to evaluate the effect vigorous energy expenditure has on blood glucose. The results were used to verify both the human energy system simulation model and the theoretical link between exercise and ets derived in Section 3.3.

Insulin injections

The healthy group of test subjects did not participate in the insulin injection trials. Only diabetic subjects were asked to measure their glycaemic response due to injected insulin. The objective was primarily to determine the consequent drop in blood glucose concentration after various types of insulin were injected. A secondary objective of the trials was to determine insulin sensitivities of the test subjects in order to characterise them and consequently construct accurate simulation models.

The trials were performed in a similar manner as the food trials described above. Instead of ingesting food though, the subjects were required to inject specific dosages of specific serum insulin. A prerequisite was that, before starting the tests, the subjects had to fast for relatively long periods and they had to ensure that their blood glucose levels were reasonably constant. Blood glucose levels were then determined with invasive impedance glucose meters [1].

Similar to the food and exercise trial results, both characterisation of the insulin and the persons could be performed. These responses were weighed against the results of the simulations and the human energy system simulation model was thereby verified.

8.3 Verification study

In order to verify the validity of the human energy system simulation procedure the following steps were followed:

- For the test subjects shown in Section 8.2.1 a separate simulation model was constructed for each person based on a few (but not all) of the trials the person performed. That model was then unique to that specific person. It is important to notice that not all the trial data obtained for the subject was used for the model construction phase.
- The next step was then to assess the new model. The model was solved to simulate the person's blood glucose response in reaction to a variety of external influences. These specific influences were the same as those the subject underwent in the trials that were not used for the model construction phase.
- Verification of the model was then accomplished by comparing the simulated results to the measured ones obtained from the trials. If the results compare well the simulation procedure is deemed successful.

As explained in Section 8.2 above, the trial data collected for this study was gathered during two distinct types of trials. These trials were long-term and short-term trials. Because the reference data was already structured in this fashion, it seemed logical to perform the simulations for verification in the same way. For this reason the assessment of the simulation results were done for two separate cases or scenarios, namely whole-day and isolated disturbance simulations.

All the measured data from the trials along with the corresponding simulated values are presented in Appendix B.

8.3.1 Whole-day simulations

The first set of simulations was performed for an entire day. The result is an integrated blood glucose response due to various inputs such as ingested food, exercises done, second meal effects,

waking effects, long- and short-acting insulin injections, stress situations, etc. All of these inputs were logged and provided to the simulation model as external influences experienced at the specific times of the day.

Simulation models were constructed for both healthy and diabetic subjects. Furthermore, many of the subjects logged several days. For all of these days the same simulation models were implemented but with different input criteria as logged by the subjects. The following figure shows a comparison between the simulated and measured data points throughout the whole day simulations.

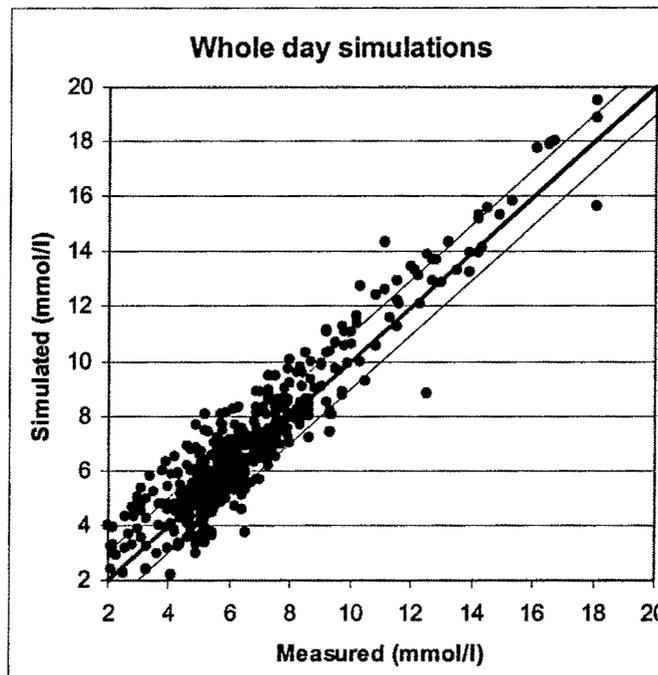


Figure 8.1 – Comparison between measured and simulated data for the whole-day simulations.

In total 532 data points were recorded and compared. Figure 8.1 furthermore shows a thick diagonal line that represents the optimum accuracy. The closer the data points are to this line, the more accurate the simulations are. Next to the optimum line Figure 8.1 also shows two thin diagonal lines. These represent the 1 mmol/l error band.

Error band	Fraction of data points within error band
0.5 mmol/l	41.7%
1.0 mmol/l	70.7%
2.0 mmol/l	95.5%

Table 8.3 – Accuracy of the whole-day simulations.

Table 8.3 shows the accuracy of the whole-day simulations output. The accuracy of the simulations is defined as the amount of data points that fall within a certain error band when compared to the measured data. For the whole-day simulations the 1.0 mmol/l error band, as shown in Figure 8.1, was considered to be acceptably accurate. Therefore, the simulations can be regarded as 70.7% accurate.

It should be noted though that many of the calculated errors (especially for the diabetic simulations) were deemed inaccurate while in actual fact the errors are only due to phase differences. Figure 8.2 presents an example of one of the whole-day simulations that was performed for one of the diabetic subjects.

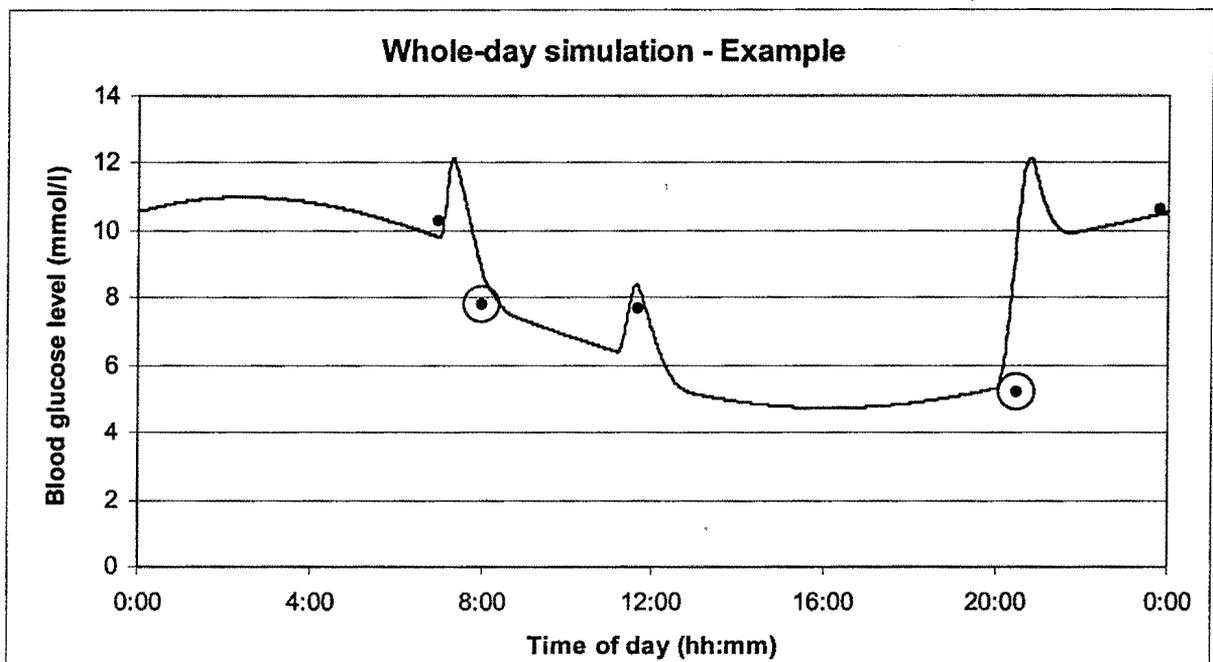


Figure 8.2 – Example of a whole-day simulation performed for a diabetic subject.

In the figure the solid line represents the simulation output for the entire day, while the dots represent the blood glucose measurements taken by the subject. The closer the dots are to the line, the more accurate the simulation is.

It is evident that at the measurements recorded at 8:00 and at 20:30 in Figure 8.2 (encircled dots), the simulation result (solid line) is relatively close to the measurements, suggesting an accurate simulation. However, the errors that were calculated for these two data points are relatively large. This is due to the phase of the simulation being different from the phase of the measurements.

The error is calculated at the time of the measurement and for both the aforementioned data points at that time, the simulated blood glucose values are very different from the measured ones. Since the trend of the blood glucose response is however simulated to an acceptable extent the inaccuracy, as suggested by Table 8.3, is not the best measure for verifying the simulation output. The method is nevertheless used due to its simplicity.

8.3.2 Isolated disturbance simulations

Simulation models were furthermore constructed for all the test subjects that participated in the short-term trials described in Section 8.2.3. For the people who participated in both trials the same models that were used for the whole-day verification were also used for the isolated simulations. The specific models were then implemented to simulate glycaemic response due to various isolated external influences or disturbances.

The disturbances (or a combination of the disturbances) were isolated according to each scenario that was simulated. The term “isolated” implies that the influences of other excitations were eliminated. For example, the subjects were required to fast for long periods before glucose tolerance tests were conducted for food consumption. The fasting “isolated” the test by eliminating any effects previous meals might have on the ones taken for the test. When performing the simulations, the models were provided with the same inputs as required from the test subjects.

Three different types of isolated disturbance simulations were performed. Simulation for the healthy subjects included a wide range of food tolerance tests as well as some exercise response tests. The diabetic simulation verifications were done for blood sugar response due to ingested food, exercises and also for short-acting insulin response.

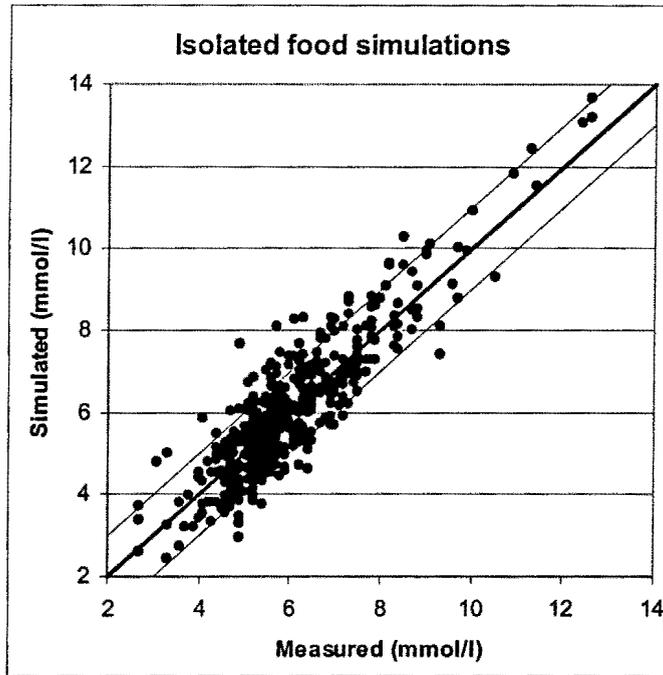


Figure 8.3 – Comparison between measured and simulated data for the isolated food simulations.

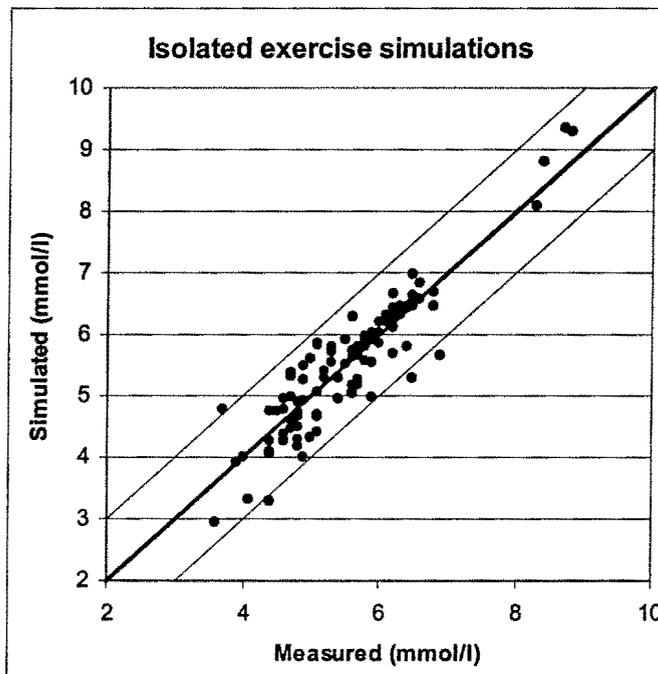


Figure 8.4 – Comparison between measured and simulated data for the isolated exercise simulations.

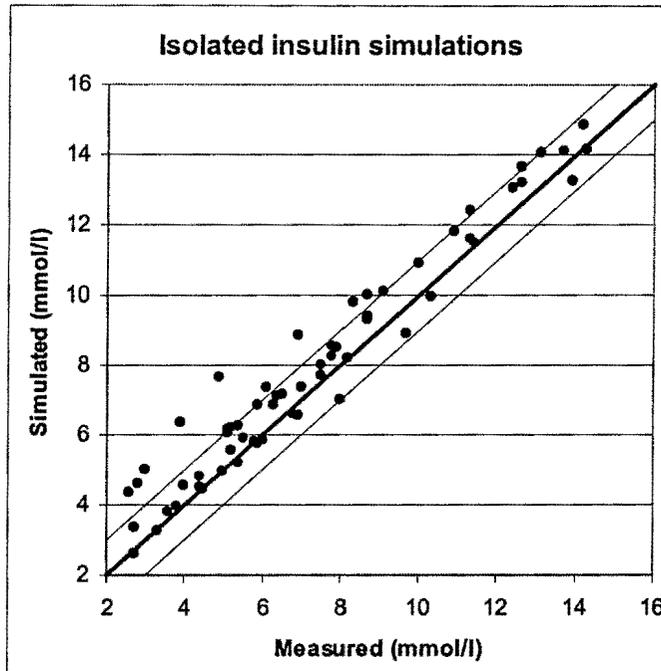


Figure 8.5 – Comparison between measured and simulated data for the isolated insulin simulations.

For all three measurements (food, exercise and insulin) both the measured and the simulated results were recorded and compared. The above graphs show the comparisons between the simulated and measured data.

Figure 8.3 to Figure 8.5 show the comparisons between the measured and simulated data collected for the isolated trials. In all three instances the closer the data points are to the thick diagonal line (which is the optimum answer), the more accurate the simulation. The two thin lines alongside the thick one again represent the 1.0 mmol/l error band. Again the data points within the 1.0 mmol/l band are considered accurately simulated, while all the data point outside the band are deemed inaccurate. The following table provides a summary of the results:

Isolated trial	Number of data points	Error bands and fractions of the data points that fall within the specific error bands		
		0.5 mmol/l	1.0 mmol/l	2.0 mmol/l
Food ingestion	454	45.6%	81.5%	98.9%
Exercise	109	74.3%	96.3%	100.0%
Insulin injections	66	40.9%	81.8%	95.5%

Table 8.4 – Accuracy of the isolated simulations.

Table 8.4 shows the accuracies of the three simulation types. The values represent the percentage fraction of the data points that fall within the various error bands (0.5, 1.0 and 2.0 mmol/l) as shown. As can be seen, the isolated simulations were deemed more than 80% accurate according to the 1 mmol/l error band.

As with the whole-day simulations some of the calculated error may be misleading. Often the calculated error is large due to phase difference and not due to inaccurate simulation. The absolute (and resultant) changes in blood sugar concentrations are however calculated relatively well.

8.4 Interpretation of the results

The criteria for evaluation, are the following: For the simulation results to be deemed accurate, the simulations for the integrated whole-day simulations had to be within the 1.0 mmol/l error band for at least 70% of the simulated data points. Concurrently, due to relatively higher degree of simplicity, the isolated simulation results had to be within the 1.0 mmol/l error band for at least 80% of the data points generated. As can be seen from Table 8.3 and Table 8.4, the whole-day simulations as well as the isolated simulations do indeed comply with these specifications.

It was explained in Sections 8.3.1 and 8.3.2 that many of the large errors found were due to phase differences between the measured and simulated data. The implications of the phase difference are however both positive and negative.

It might be argued that the phase difference presents a false perception of inaccurate simulation. Even though the results reflect badly in terms of falling within or outside the acceptable error band, the trends and significant influences on the blood glucose levels were nevertheless indicated quite

well. The simulations can therefore still be applied to suggesting insulin dosages for diabetics. After all, the absolute drop in blood glucose concentration due to injected insulin is still relatively correct.

However, there is a negative implication due to the phase difference that exists between measured and simulated data. For example, if a diabetic patient has a low blood sugar level due to a slight overdose of insulin, the simulation would suggest eating a certain amount of ets in order to counter the effect of the insulin. If the simulation phase is, for instance, 30 minutes slow the suggested ets dose might be too large because, according to the simulation, the effect of the insulin has not worn off yet. The overdose of ets could then induce hyperglycaemia, which has further negative consequences.

In spite of all this, the results are far better than what is currently available. The accuracy of all the simulations suggests that the simulation model and its results may yet be implemented for various applications. Albeit drug discovery, clinical testing or interactive blood sugar control, the proposed simulation and modelling of the human energy system is successful enough for further development and implementation.

In the following and concluding chapter a summary of all the findings in this study will be discussed, along with some recommendations for future work.

8.5 References

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