Towards an educational diabetes model

3TU. School for Technological Design

STAN ACKERMANS INSTITUTE

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Towards an educational diabetes model

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by

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Abstract

We are developing a mathematical model to serve as the heart of an educational diabetes simulator. The model is based on physiological principles and consists of three compartments: the gut, the plasma and the interstitial fluid. Glucose and insulin in- and outflow is described for all three compartments using integral/differential equations. The model can be adjusted to predict glucose and insulin concentrations for healthy persons, patients with diabetes type 1 or patients with diabetes type 2. The differences are accomplished by using different values for the parameters of the model.

We have performed parameter estimation on data of healthy persons and on data of patients with diabetes type 1. This gives us the values for the parameters for these two groups. The results are promising: for healthy people the data is almost perfectly fitted by our model and for patients with diabetes type 1 the trends of the data are predicted adequately. Unfortunately there was no data available to perform parameter estimation for patients with diabetes type 2.

The next steps will now be to obtain more data for patients with diabetes type 1 or 2. This will help us further improve the model, in particular the part that describes food uptake, and to incorporate exercise and emotions into the model. It will also enable us to determine the parameter values for the diabetes type 2 model, thus providing us with the last information needed to develop the educational diabetes simulator.

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Chapter 1

An introduction to diabetes

1.1 Diabetes Mellitus, a growing disease

Diabetes Mellitus is a so-called metabolic disease. It affects the way our body processes glucose, the carbohydrate that fuels the cells in our body. When you have diabetes, the glucose concentrations in your blood become too high. This may lead to both short-term and long-term complications, such as infections, ketoacidosis, blindness, kidney failure, blood vessel complications, coma and even death.

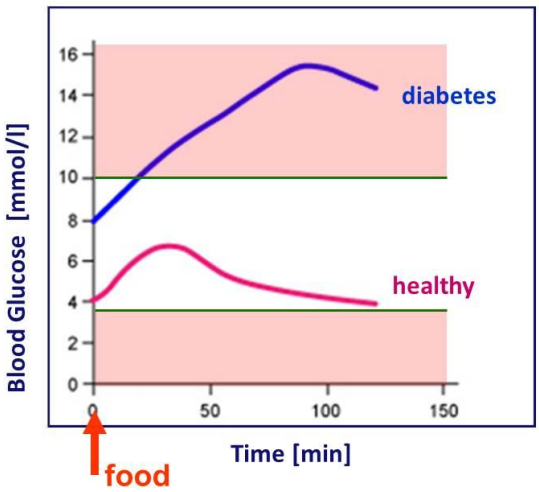


Figure 1: Graph showing the difference in glucose concentrations between healthy persons and diabetes patients after eating a

There are several forms of diabetes. The most common are diabetes type 1 and diabetes type 2. In patients with diabetes type 1, the pancreas does not produce insulin anymore, which is a necessary hormone for getting glucose into the cells. Diabetes type 1 is an auto-immune type disease and cannot be prevented. Almost 5% of all diabetes patients has diabetes type 1. In patients with diabetes type 2, the pancreas is still producing insulin, but not as much as is necessary for the body to regulate the glucose concentration. Diabetes type 2 is considered a welfare disease since it occurs mostly in overweight or obese patients that exercise too little. The assumption is that it can be prevented by an adequate regime of diet and exercise. Almost 95% of all diabetes patients have diabetes type 2, and this percentage is rising.

Diabetes Mellitus is a fast growing disease. In 2007 approximately 740.000 Dutch people had been diagnosed with the disease, and the estimation of the RIVM is that this will continue to grow to 1.3 million people in 2025. A large contributing factor to this is the increase in people with overweight. The health

expenditure related to diabetes is approximately 9% of the total health expenditure in the Netherlands, which amounts to approximately €2.9 million in the year 2010. To keep this number from growing ever larger, something has to be done.

1.2 A battle not won yet

Currently there is no cure for either diabetes type 1 or type 2. For patients with diabetes type 1, research is being conducted into pancreas or islet cell (which contain the insulin-producing cells) transplantation. Unfortunately patients often suffer from rejection symptoms and there is always a lack of donors. For patients with diabetes type 2, transplantation also would not be as effective since there the problem lies not only with the insulin production, but also with its usage. This is why a cure for diabetes type 2 is nowhere on the horizon yet.

Since there is no cure for diabetes, it is a life-long disease. Treatment is mainly focused on preventing complications by keeping the glucose concentration of a patient within normal range. For patients with diabetes type 1 this means they have to inject themselves with insulin. Patients with diabetes type 2 usually start with a diet and exercise program, often combined with oral medication that either heightens the amount of insulin the pancreas creates or lowers the insulin resistance of the cells. Once this is no longer effective, they also have to start injecting insulin.

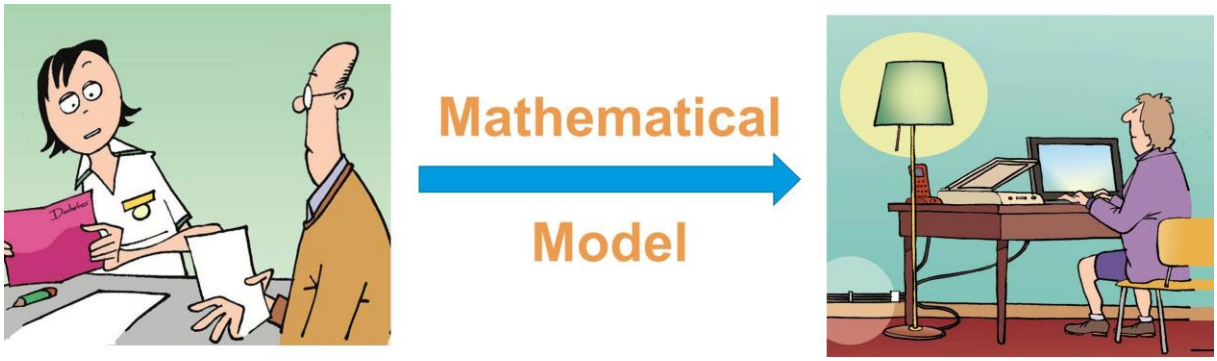
Education plays a large role in the treatment of diabetes. Patients have to learn how to help their own metabolic system, through eating properly, taking the right amount of medication, and adjusting both needs for exercise or emotional state. Research has shown that good diabetes education can reduce HbA1c, a measure for the average glucose concentration over the last 3 months. In the long run this should also reduce complications associated with poor diabetes control.

Currently in the Netherlands diabetes education is provided to the patient in several one-on-one sessions with a diabetes nurse, a dietician, or a podiatrist. This is a very intensive and costly way of teaching. Another downside is that the patient has no way of safely practicing with the newly acquired knowledge. This

makes that the patient still has to try to implement their new knowledge on a basis of trial and error. A good educational program would tackle these issues. Unfortunately there is no such program available yet.

1.3 Our aim

Our goal is to provide the diabetes patient with an educative diabetes simulator, which provides a safe environment to practice with the main factors that influence diabetic control: food, exercise, medication and emotional state. We want to pour this diabetes simulator in the form of a computer game that patients can play at home.



There are already several diabetes games on the market, for instance 'Time Out', 'Balance battle', or the games from Glymetrics. However, none of these games is based on realistic physiological processes. This means the educational value is fairly limited, since the numbers from the game do not correspond with the patient's numbers in reality. Also, most of these games only focus on patients with diabetes type 1, while there are much more patients with diabetes type 2. More information on these existing diabetes games can be found in Appendix J.

We intend to address these issues by feeding our diabetes simulator with a mathematical model that can calculate glucose and insulin values based on physiological processes. We will develop this model for both patients with diabetes type 1 and patients with diabetes type 2. The mathematical model will be validated on the glucose- and insulin concentrations of real patients to ensure the calculations are a good representation of the processes in the body. Next to educating patients with diabetes type 1 and 2, we will also aim our simulator at caregivers and healthcare professionals. A full project description is given in Appendix A.

In this report we will describe the process towards a mathematical diabetes model. In Chapter 2 we will first describe the physiological processes we want to capture in mathematics. We start with the metabolism of a healthy person and then describe the changes for patients with diabetes type 1 and 2. The next step is to convert this physiological process into a mathematical model. This is described in Chapter 3. Our mathematical model leaves us with a lot of parameters with unknown values. To obtain values for these parameters we perform parameter estimation on data acquired from literature and patients; this process is described in Chapter 4. Unfortunately, we do not have any data yet for patients with diabetes type 2. Therefore the results described in Chapter 5 only contain values for healthy people and patients with diabetes type 1. Here we will also discuss some of the limitations of our approach. Chapter 6 is then devoted to giving our preliminary conclusions and looking forward to the next stage of the project.

Chapter 2

Physiological model

The next sections give a short description of the physiological processes of glucose metabolism in healthy persons and patients with diabetes type 1 or 2. A more extensive description, combining the physiological model and the mathematics, is given in Appendix B.

2.1 The healthy glucose metabolism

To be able to function properly, our body needs energy. This energy is mainly generated by the burning of glucose in our muscle and fat cells. The brain also needs a steady supply of glucose to function. To make sure the brain never runs out of glucose, in a healthy person the body makes sure the blood glucose concentration never drops below 4 mmol/L. It also keeps the blood glucose concentration lower than 7 mmol/L. It achieves this regulation by use of the hormone insulin, which acts as a key that enables glucose to enter the cells. There are also some other hormones that play a role in this balance, but we will only look at the dynamics of glucose and insulin to keep our model simple.

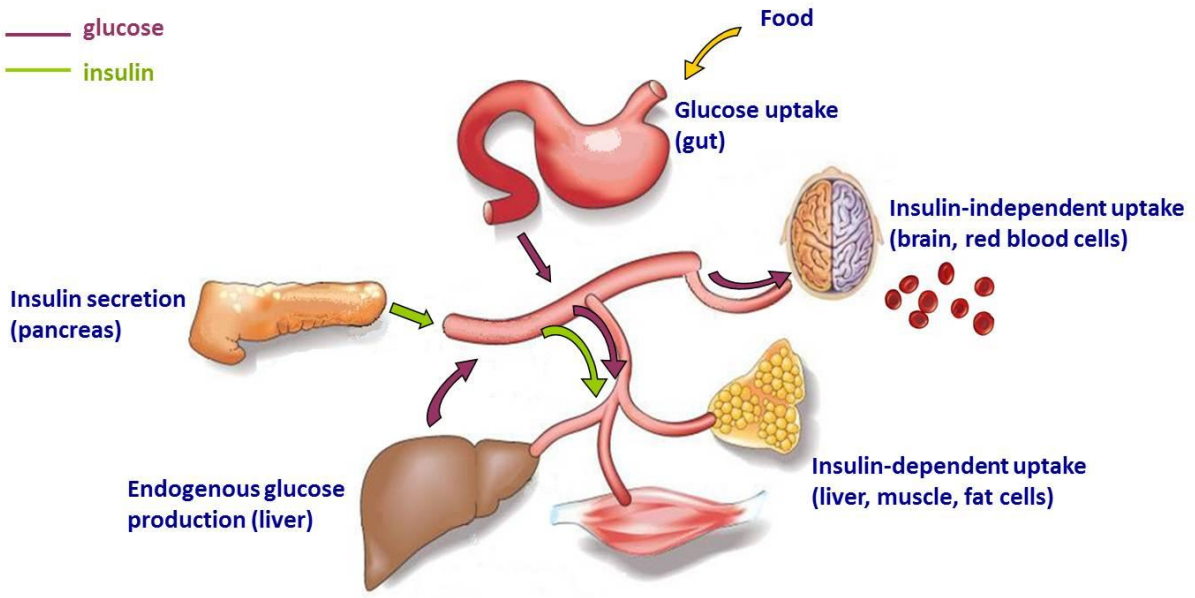


Figure 2: Physiological model describing the glucose metabolism in healthy persons

Glucose enters the blood stream from two different sources: through food intake (mainly in the form of carbohydrates which are converted to glucose in the gut) and through the release of glucose from storage in the liver (glycogenolysis). Glucose leaves the blood stream through absorption by the cells. This process differs for different kind of cells: red blood cells and the brain can take up glucose directly, for muscle cells, the liver and adipose tissue glucose is taken up through mediation by insulin. Insulin is created in the pancreas. All these functions and glucose- and insulin streams are shown schematically in Figure 2.

The amount of insulin the body generates is determined by the amount of glucose present. A higher amount of insulin then suppresses the release of glucose from the liver and enables glucose to enter the cells, thus removing glucose from the blood stream. If there is a low glucose concentration, insulin production is suppressed and the glucose release from the liver is increased. In this way the body maintains the correct glucose concentration, even during food intake, exercise or emotional stress.

2.2 Diabetes type 1

For patients with diabetes type 1, the pancreas does no longer produce insulin. Without insulin, glucose cannot be taken up by the insulin-dependent tissue and the glucose concentrations rise to enormous heights (a glucose concentration of 25 mmol/L or more is not uncommon in untreated patients). The body has only one line of defense against such high glucose concentrations: from approximately 10 mmol/L the body starts to excrete glucose through the kidneys. Unfortunately this gets rid of only a small amount of glucose.

To model patients with diabetes type 1 we therefore have to remove the insulin secretion from the pancreas, add insulin injections and add the excretion of glucose through the kidneys. This is depicted in Figure 3.

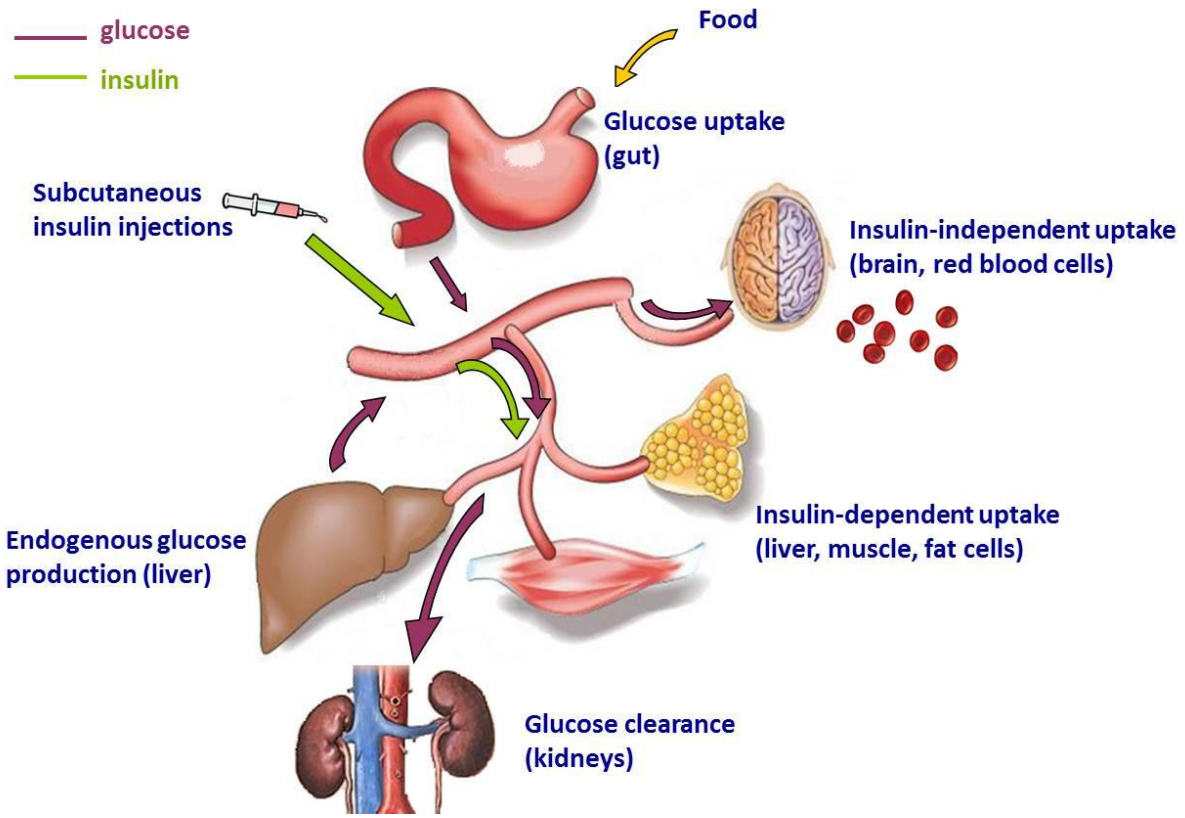


Figure 3: Physiological model describing the glucose metabolism in patients with diabetes type 1

2.3 Diabetes type 2

The physiological model for patients with diabetes type 2 is the most extensive. These patients still have some insulin production by the pancreas, but it is not enough to keep the glucose concentration within normal limits. This is because the pancreas is less sensitive to high blood glucose levels and therefore produces less insulin than needed and releases it at a slower rate. Another problem occurring in diabetes type 2 is so-called insulin resistance, where the insulin-dependent tissues respond less to insulin. You then need more insulin to take up the same amount of glucose from the bloodstream. Both conditions gradually set on over the years, with beta-cell function slowly decreasing and insulin resistance increasing. To battle these effects, patients with diabetes type 2 can take insulin injections (supplying the necessary extra insulin) or oral medication. There are several types of oral medication, all with their own function in the metabolic system. The main effects are suppression of the release of glucose by the liver and an increase in the amount of insulin released from the pancreas. A more detailed description of all types of oral medication and the ways to incorporate them into the physiological model is given in

Appendix C. A schematic representation of the physiological model for patients with diabetes type 2 is given in Figure 4.

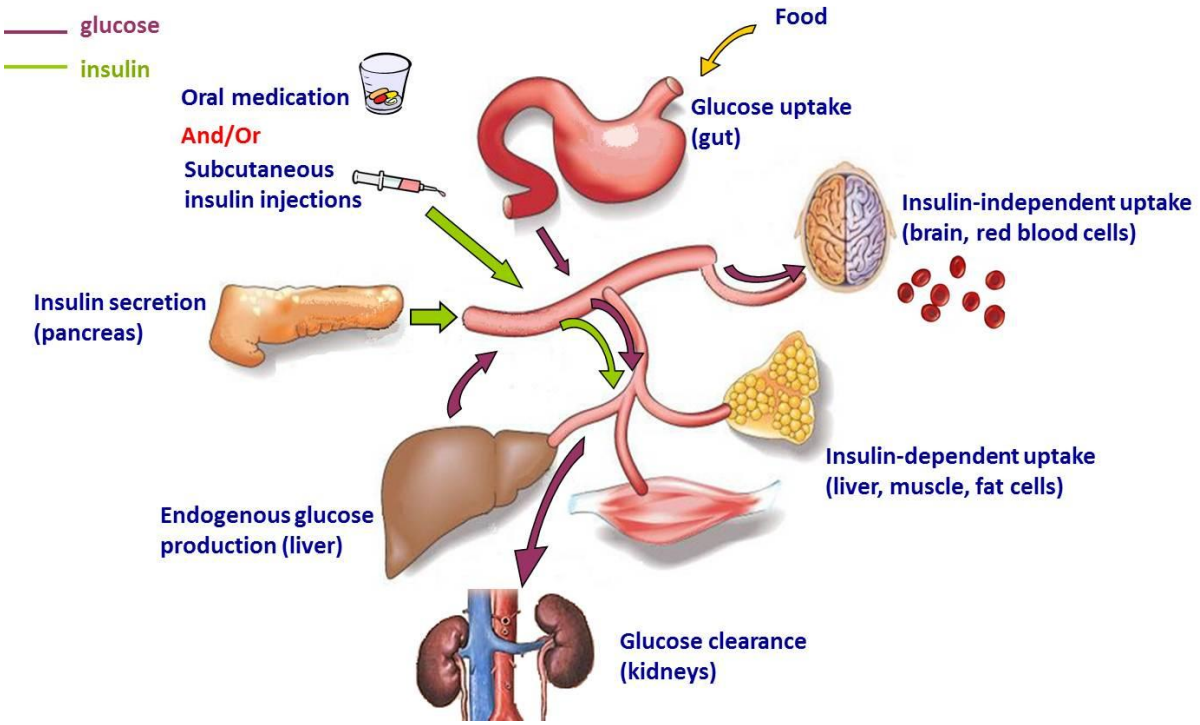


Figure 4: Physiological model describing the glucose metabolism in patients with diabetes type 2

Chapter 3

From physiology to mathematics

In this Chapter we will give a short overview of the steps taken from the physiological model to a mathematical model. A more extensive text on this, including the mathematics, is given in Appendix B.

3.1 Conversion into mathematics: the three compartment model

The first step towards a mathematical model is trying to divide the physiological model into compartments. Every compartment represents a place where conversions take place. Looking at our physiological model we can define three such compartments: the gut (where food is converted into glucose), the plasma (where glucose and insulin from the different sources comes together) and the interstitial fluid (where insulin is used by the cells to convert glucose into energy). When we use insulin injections, two extra compartments enter to account for insulin storage in the different layers of the skin. The three compartment model is represented in Figure 5. The arrows in this picture show the flows of glucose and insulin from one compartment to the next.

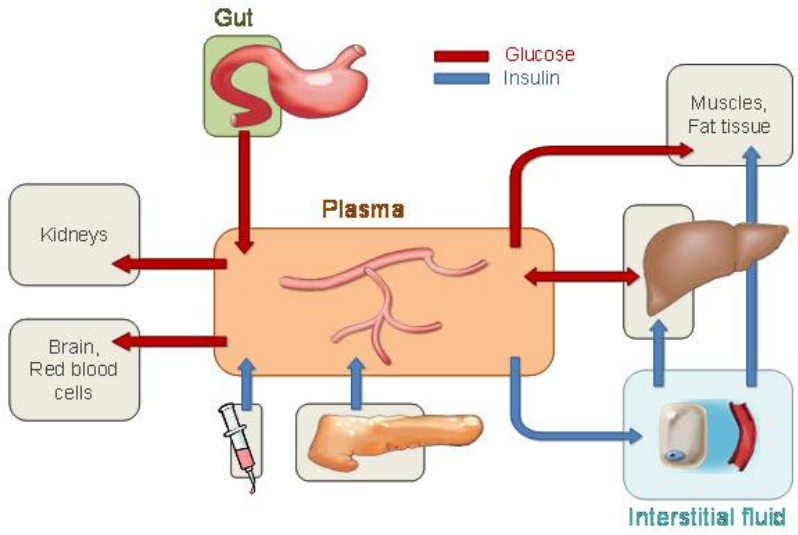


Figure 5: Three compartment model

3.2 Description of the mathematical model

For every compartment we can look at the glucose and insulin flowing in and out; by describing these flows in mathematical equations we get a

mathematical model. Not every compartment has both glucose and insulin in- and outflow; in the gut there is no insulin present, and in the interstitial fluid and the dermal layers we have only insulin present. For every compartment we define a differential equation that describes the change in glucose or insulin resulting from the different in- and outflows of that compartment. Doing this for every compartment gives us 4 differential equations: one describing glucose in the gut, one describing glucose in the plasma, one describing insulin in the plasma and one describing insulin in the interstitial fluid. The insulin injections give us an extra two differential equations. Some of these equations, for instance the ones for glucose and insulin in plasma, are coupled: the outcome of one equation is used as input for the other. The differential equations sometimes also contain differentials or integrals themselves, making the total system more complex.

In most cases the quantitative amount of in- or outflow depends on the current level of glucose or insulin. This current level is then multiplied by a constant rate to get at the quantitative amount. These rates are represented by parameters. In total we have ranging between 14 and 17 unknown parameters in our model, depending on whether we are looking at the healthy person model, the diabetes type 1 model or the diabetes type 2 model. For a healthy person, all parameters describing inflow of insulin from insulin injections are set to zero and the parameter describing the renal clearance is also zero. For a patient with diabetes type 1 the parameter describing insulin inflow from the pancreas is zero, but the parameters describing renal clearance and insulin injections do have non-zero values. And for a patient with diabetes type 2 all parameters have non-zero values, but the values might be different from the values for the other models.

As we have shown, the values of the parameters determine the behavior of the model in response to certain inputs. Unfortunately the values for these parameters are unknown, and they cannot be measured directly. But we do have a way to estimate these values, which is described in the next Chapter.

Chapter 4

Parameter estimation

4.1 Method of parameter estimation

Although the parameters of the model have some physiological significance, they are not measurable. This means we have to use another method to determine their value. We do this by performing a parameter estimation. In short this means we insert starting values into our model, use them to calculate a prediction, compare this prediction to actual data and then adjust the parameter values of the model to produce a better prediction.

Before performing parameter estimation we try to minimize the number of parameters that we have to estimate. We first check whether any parameters are coupled, which would mean we can calculate one from knowing the other. Through sensitivity analysis we see if there are any parameters of which the influence on the outcome is so small, we can easily leave it out or give it a (arbitrary) constant value. We also check whether we can perform parameter estimation on only a small part of the model at once. This would increase the accuracy of the estimation for the parameters contained in this sub-model, and would reduce the number of parameters that have to be estimated at once.

In our case our data consists of glucose and insulin concentrations in plasma after a meal. We have these concentrations for healthy persons and patients with diabetes type 1; we have no data yet for patients with diabetes type 2. We used both the glucose data and the insulin data to optimize our models. The parameter estimation process is described in more detail in Appendix E (for healthy persons) and in Appendix F and G (for patients with diabetes type 1).

4.2 Influences on the outcome

Parameter estimation is a very powerful tool to determine values for a mathematical model. However, it is only as good as the information you put into it. In our case this does not only encompass the data you estimate on or

the starting values for the parameters, although these of course have a large influence on the outcome. We also have to pick starting values and basal values for the physical quantities we are estimating on. Tweaking these starting and basal values can have large effects on the outcome. The process of choosing what values to take is described in Appendix G.

Chapter 5

Results and limitations

In this section we describe the results from the parameter estimation process. These can be found in more detail in Appendix E for the healthy person model and in Appendix G for the diabetes type 1 model. In Appendix H we compare the parameter values of both models.

5.1 Results for the healthy person model

We first wanted to check whether our basis, the healthy person model, functions correctly. To do this we gathered data from literature containing the glucose and insulin concentrations after eating a meal. We performed a parameter estimation on this data set and plotted the outcome of this parameter estmation against the actual data points. The results are shown in Figure 6. The prediction for the glucose concentration is shown in red on top; the prediction for insulin is shown in blue on the bottom. As can be seen from these plots the model fits the data almost perfectly. This serves as a check for the physiological basis of our model; if we forgot to include an important physiological process, this will show up for healthy persons since their glucose metabolism functions as should be. We can therefore be quite certain that our model incorporates the most important metabolism functions concerning glucose and insulin.

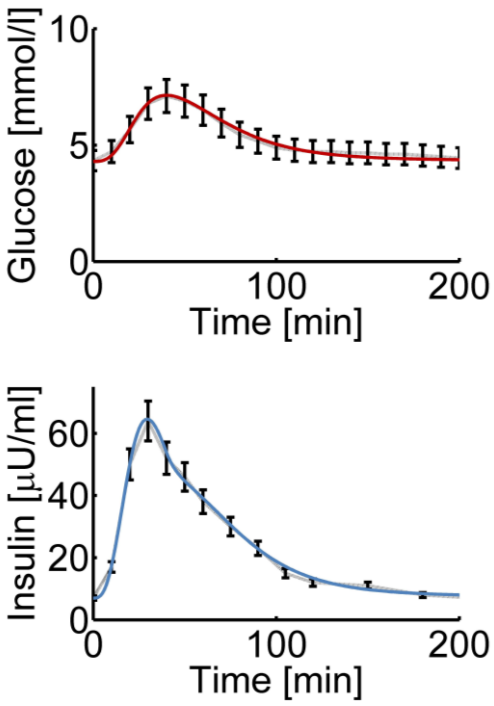


Figure 6: Outcome of the parameter estimation process for healthy persons

5.2 Results for the diabetes type 1 model

After we established our model works well for healthy people, we continued with the model for patients with diabetes type 1. We obtained data for 10 patients for two different days. One of these patients had a very high daily dosage of insulin when corrected for bodyweight. This can be an indication of insulin resistance. Since that factor is not taken into account in our model for diabetes type 1, we decided to exclude this patient from our data set. We performed parameter estimation on the breakfast data of the first day for the remaining 9 patients, and used the breakfast data of the second day for validation. We state the model calculation is accurate if more than 65% of all data points lies within a region of 25% above or below the model calculation.

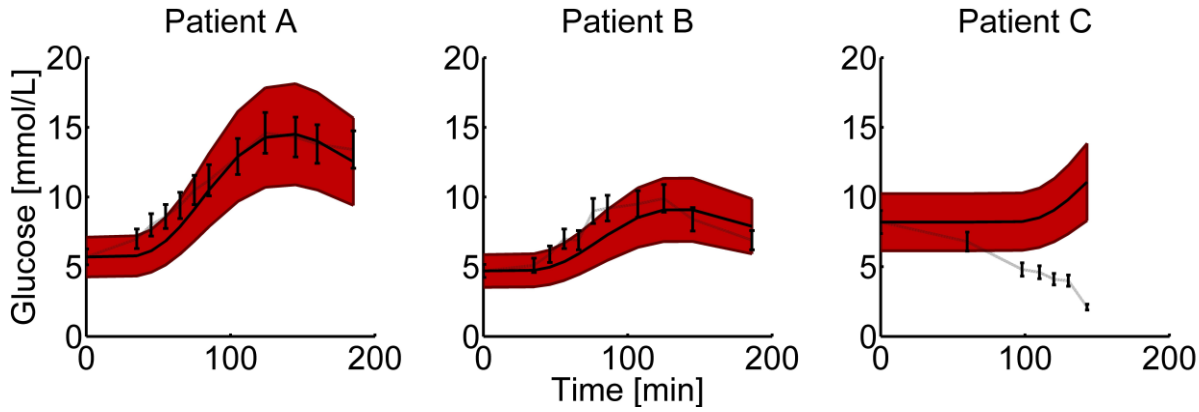


Figure 7: Validation graphs for three patients with diabetes type 1

Figure 7 shows three typical cases for the validation of the type 1 model. The model prediction (black full line) is compared with the data (black dotted line). The red areas show the acceptable model region (model ± 25%). For patient A and B the model shows a good prediction of the data. Almost all data points lie within the acceptable model region and the trend of the data corresponds well with the trend of the model prediction.

However, for some cases (like patient C) the model prediction is inaccurate because the patient glucose profile differs too much from other patients. This is clearly visible from the examples in Figure 2: both patient A and B have a rising glucose concentration after eating their breakfast, while patient C has a decreasing glucose concentration. This could be explained by looking at the insulin level and seeing whether this is much higher for patient C; however this

proved not to be the case. This would mean another process (for instance a hormonal reaction related to stress or exercise) is at work here, which is not (yet) covered by our mathematical model.

Over all patients the acceptable model region contains 66% of the data used for validation. When leaving out an outlier like patient C, this number goes up to 75% of all data points. This is a satisfactory result, considering we will use the model for educational purposes.

5.3 Limitations of our approach

The model shows to be able to predict blood glucose and insulin values fairly accurate. We did set the limits for accepting the model quite wide. This can be justified if we look at the purpose of the model: it will not be used for treatment, but only as an educational tool. Therefore the trend of our predictions is much more important than the absolute values, and these trends correspond quite well for most patients. Nonetheless, there are still some points open for discussion.

First of all it would be very helpful if we could use more data points for parameter estimation. This would be possible if we could use continuous glucose monitoring (CGM) measurements. For the patients with diabetes type 1, we had both laboratory data and CGM. But when we compared these two, it turned out that CGM was not very accurate. This is why we decided to use the laboratory measurements only (see also Appendix I).

The second limitation is the method chosen for modelling food intake. In our model we now model food intake only by the total amount of carbohydrates ingested. This is mainly because of the simplicity for our model calculations. However, a more extended model for food intake, for instance also incorporating the influence of proteins and lipids or the effect of simple versus complex carbohydrates, might increase the accuracy of the model. A first literature study into this topic revealed the possibility of perhaps using the glycemic index to model different types of food (see also Appendix D). Yvonne Rozendaal looked into this in her internship; her findings are summarized in her

end report. She showed that an extra term in the model for food intake can dramatically improve the model. This has not been tested on the full model yet.

A third limitation is that we now do not yet take into account both exercise and emotional state. These are expected to have quite a large impact on the model outcome. Getting these influences into the model should get high priority.

Chapter 6

The way forward

6.1 Conclusions

We successfully converted a physiological model describing the glucose and insulin balance in the body into a mathematical model. This mathematical model can be used to describe the glucose metabolism in healthy people, but also in patients with diabetes type 1 or diabetes type 2. By using parameter estimation, we can make the model suitable for predicting the glucose behavior in different scenarios. We have already estimated parameters for healthy persons and for patients with diabetes type 1. For healthy persons, the fit is almost perfect. For patients with diabetes type 1, the trend of the data is followed correctly and 66% of our data points lie within the acceptable region of the model (model ±25%). For a model developed as an educational tool this is very promising. For patients with diabetes type 2, the model has been completed but we now need data to perform a parameter estimation for this group as well.

6.2 Looking forward

There are several steps we would like to take next. We would like to perform another parameter estimation on the data for patients with diabetes type 1 to also be able to predict glucose and insulin concentrations after lunch and dinner. We would also like to incorporate both exercise and stress into our model. And we also want to perform parameter estimation for patients with diabetes type 2. For all these steps we need extra data; that is why we are now setting up another study with 100 patients to obtain the data necessary to continue our work.

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