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Mathematical modeling of insulin response in encapsulated islets of Langerhans

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Title (English)

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Abstract

Transplantation of the islets of Langerhans is a promising technique for restoring the impaired insulin production in brittle type 1 diabetics. The downside is that the patient will have to take immunosuppressant drugs in order to protect the islet cells from the immune system. Donors are also sparse, making the quest of finding sufficient amounts of islets for transplantation hard. Encapsulation of the islets of Langerhans has been proposed as a means of protecting the cells from the immune system taking away the need for immunosuppresives. The most common encapsulation technique is extravascular capsules, which are categorized into micro- and macrocapsules. The microcapsules hold only one or a small set of islet whereas the macrocapsules hold a large quantity of islets.

This thesis investigates the encapsulation impact on the beta-cells rapid insulin response to rising plasma glucose levels. This was done by simulating the glucose-insulin system in MATLAB with included encapsulation of the islets. Two current macro-encapsulation set ups were used in the model, Beta-Air and ViaCyte devices, and they were compared against a normal case. The results showed that the Beta-Air device would not be able to restore normoglycemia in a T1DM patient but rather showed a delay in insulin response, while the ViaCyte device could mimic the normal case well.

Keywords

Encapsulation, glucose, insulin, secretion, islets, Type 1 diabetes mellitus

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Mathematical modeling of insulin response in encapsulated islets of Langerhans

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Populärvetenskaplig sammanfattning

500,000 barn, 0-14 år, lider idag av typ 1-diabetes världen över och i Europa diagnostiseras 20,000 nya fall varje år. Sjukdomen innebär att kroppen inte kan kontrollera glukosnivåerna i blodet på grund av skadad insulinproduktion vilket innebär att patienten dagligen måste injecera sig själv med insulin för att överleva. I komplexa fall av sjukdomen där glukosnivåerna är svårkontrollerade kan transplantation av de Langerhanska öarna vara ett alternativ. Vid denna behandling är det meningen att de insulinproducerande beta-cellerna från friska öar ska återställa insulinproduktionen. Det finns dock nackdelar med denna behandling, kroppen kommer att försöka stöta bort implantatet och immunhämmande medicinering måste användas vilket medför kända biverkningar. Inneslutning av öarna under ett membran, är en teknik för att skydda mot kroppens immunförsvar och således onödiggöra immunhämmande medicinering.

Projektet grundar sig i att simulera glukos-insulin-systemet med inkorporering av enkapsulering av de Langerhanska öarna. Detta för att utvärdera hur stor påverkan diffusionen av glukos samt insulin har på blodsocker-kontrollen men också hur mycket formen på inneslutningen påverkar resultatet. I huvudsak två olika inneslutnings-tekniker implementerades i modellen, Beta-Air (form av en disk) och ViaCyte (flak-formad), och användes för simuleringar. Beta-Air-anordningen visade på förhöjda glukos-värden medans ViaCyte imiterade utgången i jämförelse med en frisk person.

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Contents

List of Figures

List of Tables

Abbreviations

AUC	**A**rea **U**nder **C**urve
FDA	United States **F**ood and **D**rug **A**dministration
GLP-1	**G**lucagon-**L**ike **P**eptide-**1**
hESC	**h**uman **E**mbryonic **S**tem **C**ells
IEQ	**I**slet **EQ**uivalents
MATLAB	**MAT**rix **LAB**oratory
OGTT	**O**ral **G**lucose **T**olerance **T**est
STZ	**ST**repto**Z**otocin
T1DM	**T**ype **1** **D**iabetes **M**ellitus
T2DM	**T**ype **2** **D**iabetes **M**ellitus

Chapter 1

Introduction

1.1 Diabetes mellitus

Diabetes mellitus affects 382 million people worldwide today [2] and is predicted to be among the top seven of causes to death in 2030 [3]. The year 2013 saw 5.1 million deaths and a health care cost of USD 548 billion. In 2035 the number of people with the disease is expected to increase to about 592 million. 80 % of people having the disease live in low- middle-income countries, this is also where it has the most drastic effect. Hot-spots right now for the disease include countries in the Middle East, Western Pacific, sub-Saharan Africa and South-East Asia. Countries in these regions have recently gone through large economic developments and as a consequence changed lifestyle.

The three main forms of diabetes are, type 1 (T1DM), type 2 (T2DM) and gestational diabetes. What they have in common is that persons affected can not produce enough insulin or use it effectively. Insulin is what makes the body being able to take up glucose and use it as an energy source. This thesis will focus on T1DM, which is believed to be caused by an autoimmune reaction that causes an attack on the insulin producing pancreatic beta cells. This leads to elevated levels of glucose which are harmful for the body unless treated. In order to survive, T1DM patients daily inject insulin to keep the glucose levels steady. Still this treatment is not problem free, hypoglycemia (low blood sugar) as a consequence of injecting to much insulin is always a risk, which can lead to difficult side effects such as coma or even death.

1.2 Pancreas transplantation

In certain cases of patients with severe T1DM, pancreatic transplantation is an option. The benefits from this kind of surgery is that normal glucose levels can be maintained without insulin injections, many side effects of the disease can be avoided by this. There are also downsides to this kind of surgery, since the body will reject the foreign transplant unless lifelong treatment with immunosuppresant drugs is conducted. Since the body's

immune system will be suppressed this opens up for lower resistance to viral and bacterial infections and also cancer. Often if a patient receives this kind of treatment it is part of an combined transplantation procedure with a kidney, since then immunosuppressives are already in use.
The first pancreatic transplantation was made in 1966 and the first which achieved insulin independence [4], conducted by the same group at the University of Minnesota, was made in the same year. Until now several advances has been made, better procedures and more effective immunosuppressives. Still the lack of organ donors is a problem for this method.

1.3 Islet transplantation

Transplantation of the islets of Langerhans is considered an option for curing T1DM. The insulin producing β-cells of the donor islets are to replace the lost β-cells in the native pancreas and restore normoglycemia. The islets are isolated from a donor pancreas, with a method which was first developed in the 1960s [5], and then infused into, most commonly, the patients liver. In the early 1970s, several studies supported that islet transplantation could reverse diabetes in non-human primates [6] and rodents [7, 8]. The first clinical trials were made in 1974 but the first successful case was reported in 1990 [9], where patients became insulin independent for some time.
At the end of the 1990s a group in Alberta, Edmonton, developed a new technique for islet transplantation[10], that is now called the Edmonton Protocol. This method has shown to be, if followed in a correct manner, quite successful for achieving insulin independence.
Though islet transplantation has been able to restore normoglycemia in subjects with T1DM, some issues still have to be solved. The available organ donors is not nearly enough to satisfy the need, the quality of the isolated islets are not always to satisfaction, and patients will only stay normoglycemic for a limited time, often about 12 months. Most important, life long treatment on immunosuppresives is necessary, which comes with known complications.
The shortage of donor islet cells has been suggested to be solved by using other animal pancreatic cells, such as pig islets. One potential problem with this treatment is the risk of viral infections and other complications. The upswing of stem cell research has also made it possible to solve the islet shortage problem, hESC are differentiated to islet cells and used for transplantation. This would bring an infinite supply of islets, however rejection is still a problem and if transplanted cells would revert to a more pluripotent state, these could induce tumor growth. Both alternatives mentioned to human donor islets require easy removal of the transplant in the case of something going wrong.
Although islet transplantation for brittle T1DM patients has been able to enhance quality of life of those treated, the procedure is still considered as experimental by the FDA.

1.4 Encapsulation

In order to protect transplanted islets of Langerhans from the immune-system, they can be encapsulated within a semi-permeable membrane. The idea is that the membrane will keep the agents of the immune-system away from the islet cells but still give access to glucose, oxygen and other nutrients. Insulin must also be able to diffuse in a rapid manner through the membrane for the islets to perform their task of glucose control. If working, this method would be able to restore insulin production without the need of immunosuppressives for the transplant.
The first reported study of encapsulation of islets was made in 1977 [11], where rats were made diabetic with infusion of STZ and then implanted with encapsulated rabbit neonatal pancreas. Glucose and insulin returned to normal when conducting OGTTs. When isolating an STZ-treated pancreas from an diabetic animal, it did not secrete any insulin and the removal of the encapsulated pancreas made the animals die of hyperglycemia within eight days. Also no rejection of the transplants could be seen. This demonstrated the potential of this concept and yielded further studies for clinical testing.

There are two types of encapsulation techniques, intra- and extra-vascular devices. Where the intravascular devices are directly connected to the vein and artery, which would give fast access to oxygen, glucose and other nutrients. One problem with this technique is that blood clots could be formed in the fibers.
The extravascular devices comes in two different forms, micro and macro setups. Microencapsulation means that one or a few set of islets are encapsulated, most commonly in alginate. The concept is illustrated in Figure 1.1.

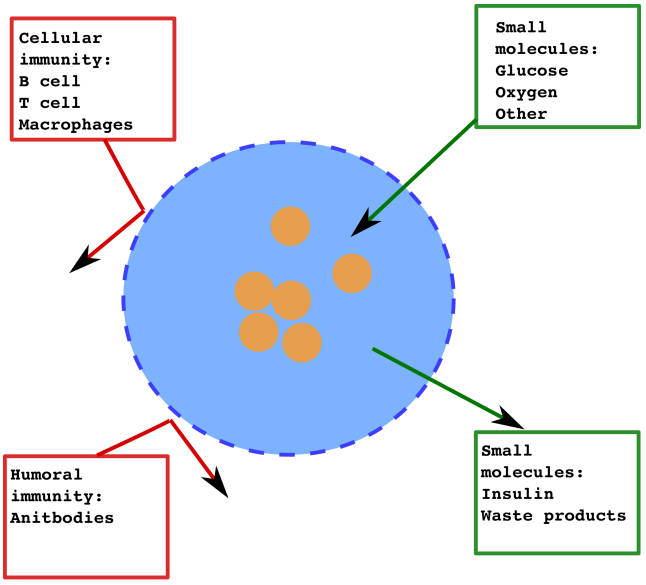

FIGURE 1.1: A basic microencapsulation setup

In macroencapsulation, all the islets are held in the same compartment. These devices

come in various forms, disc, rods, sheets etc. One device that will be discussed in this thesis is *Beta* 0_2 *Technologies* Insulin Bioreactor, β-Air [12, 13]. This device has gone through some preclinical [14–16] as well as clinical trials [17].

Another device that will be discussed in this thesis is ViaCyte's, Encaptra drug delivery

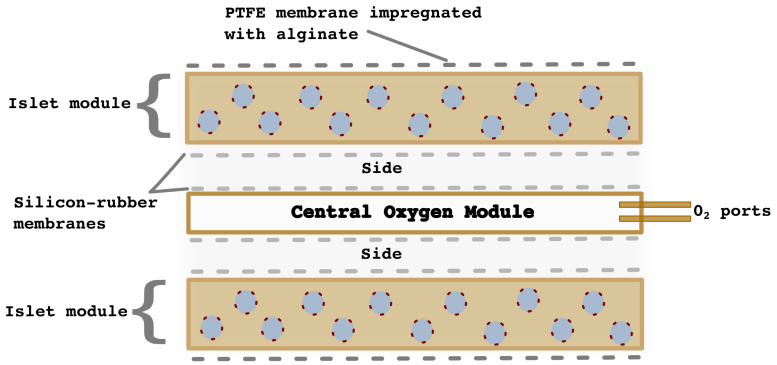

FIGURE 1.2: A cross section of the Beta-Air device

system, which has the shape of a sheet [18]. An illustration of the Encaptra device can be seen in Figure 1.3. This device uses pancreatic precursor cells, PEC-01, differentiated from hESC. The product combination of the PEC-01 cells and device is called VC-01.

When developing these encapsulation techniques some parameters are of great importance. The diffusion constants for both glucose and insulin are of importance to not delay the rapid response of insulin to rising blood glucose levels. The membrane should also let other important nutrients through, as well as oxygen, but still keep the immune system out. Also it is important that the membrane is biocompatible, since otherwise it will enhance the forming of fibrous tissue blocking transfer of bio-molecules across the membrane which will eventually kill the encapsulated cells.

Another factor that will highly affect the diffusion capabilities of the device is the surface-area-to-volume ratio. With a larger area of the device there will be more diffusion opportunities and the gradient of glucose will increase faster and the insulin will have a faster response. Also the packing density of the islets are of importance, since packing them too densely will increase the rate of cell necrosis due to hypoxia or that important nutrients are consumed by the outer cells.

Yet another factor that can be of importance is the easy retrieval of the encapsulation device after transplantation. If any complications should rise with the transplant, for example if transplanting pig islets or differentiated hESC, it can be very important to be able to remove them. This can be easily done with an macro-encapsulation device, but will be impossible with a micro-encapsulation set up.

1.5 Aim of this thesis

This projects aim was to model the glucose-insulin system, with included encapsulation of the islets of Langerhans. This to evaluate the outcome of transplanted encapsulated islets to T1DM patients in comparison to a healthy normal case. The parameters of

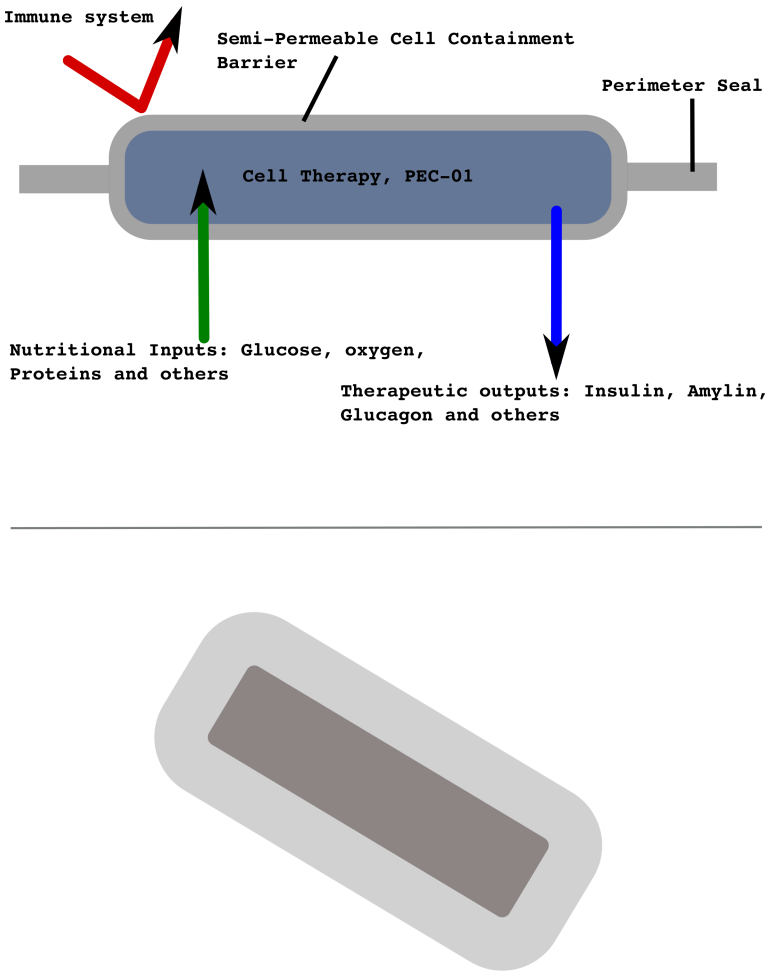

FIGURE 1.3: Top: Cross section of the Encaptra device. Bottom: Showing the sheet-like form.

the encapsulation will be investigated in order to find the optimal shape for getting a successful result. All the simulations have been done using MATLAB.

Chapter 2

Method

2.1 The model

The meal glucose-insulin system implemented in this project is based on earlier work [19]. Here they implemented their earlier described model [1] in MATLAB, and also designed a window interface that can simulate a 24-hour meal scheme. The model is illustrated in Figure 2.1 and consists of a glucose and insulin sub-system. These two systems interact by glucose being controlled by insulin secretion and insulin by glucose utilization and endogenous insulin production. The different parts of the model will be described in this section. The changes that were made, in order to include encapsulation, are covered in section 2.1.1.

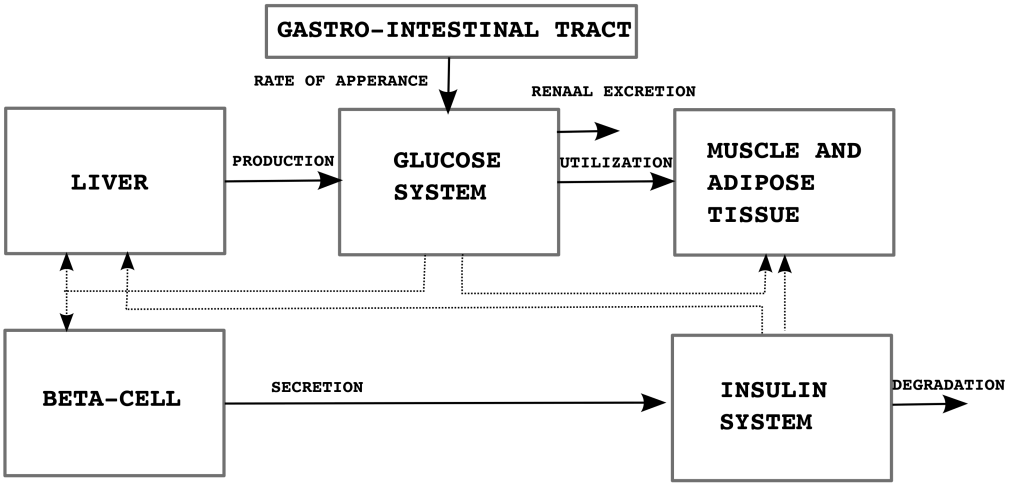

FIGURE 2.1: The model used and described in literature [19]

Glucose Subsystem
This system is divided into two compartments [20], slowly and rapidly equilibrating

tissue. The equations 2.1-2.4 building this part of the model can be seen below. Here G_p (mg/kg) is the mass of glucose in plasma and rapidly equilibrating tissue whereas G_t (mg/kg) is the mass of glucose in slowly equilibrating tissue. The concentration of glucose in plasma is denoted as G (mg/dl) and the suffix b stands for basal state. The endogenous glucose production is denoted by EGP (mg/kg/min) and the glucose rate of appearance in plasma is represented by Ra $(mg/kg/min)$. The glucose renal excretion is denoted by E $(mg/kg/min)$, insulin-dependent and -independent utilization is represented by U_{id} and U_{ii} $(mg/kg/min)$ respectively. The total distribution volume of glucose is here denoted by V_g (dl/kg), k_1 and k_2 (min^{-1}) are rate parameters of the glucose kinetics. The last equation expresses the steady-state for endogenous glucose production, which is the the sum of glucose utilization (U_b) and renal excretion (E_b).

$$\frac{dG_p(t)}{dt} = EGP(t) + Ra(t) + U(t) - E(t) - k_1 \cdot G_p(t) + k_2 \cdot G_t(t), \qquad G_p(0) = G_{pb} \tag{2.1}$$

$$\frac{dG_t(t)}{dt} = -U_{id}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t), \qquad G_t(0) = G_{tb} \tag{2.2}$$

$$G(t) = \frac{G_p}{V_g}, \qquad G(0) = G_b \tag{2.3}$$

$$EGP_b = U_b + E_b \tag{2.4}$$

Insulin subsystem

As the glucose sub-system, this system is also divided into two compartments as described in literature [21]. In this part of the model, I_l and I_p $(pmol/kg)$ denotes insulin masses in the liver and plasma respectively, I $(pmol/L)$ represents plasma insulin concentration. As before, b stands for the basal state.

The insulin secretion is denoted as S $(pmol/kg/min)$ and the total distribution volume is denoted as V_I (L/kg). The rate parameters of the insulin system are represented by m_1, m_2 and m_4 (min^{-1}). The equations representing this part of the model can be seen below.

$$\frac{dI_l(t)}{dt} = -(m_1 + m_3(t)) \cdot I_l(t) + m_2 \cdot I_p(t) + S(t), \qquad I_l(0) = I_{lb} \tag{2.5}$$

$$\frac{dI_p(t)}{dt} = -(m_2 + m_4) \cdot I_p(t) + m_1 \cdot I_l(t), \qquad I_p(0) = I_{pb} \tag{2.6}$$

$$I(t) = \frac{I_p}{V_I}, \qquad I(0) = I_b \tag{2.7}$$

The following equations states the hepatic extraction of insulin HE as time course dependent of secretion S.

$$HE(t) = -m_5 \cdot S(t) + m_6, \qquad HE(0) = HE_b \tag{2.8}$$

$$m_3(t) = \frac{HE(t) \cdot m_1}{1 - HE(t)} \tag{2.9}$$

Basal steady-state is given by,

$$m6 = m5 \cdot S_b + HE_b \tag{2.10}$$

$$m_3(0) = \frac{HE_b \cdot m_1}{1 - HE_b} \tag{2.11}$$

$$S_b = m_3(0) \cdot I_{lb} + m_4 \cdot I_{pb} \tag{2.12}$$

$$S_b = D_b \tag{2.13}$$

$$m_4 = \frac{2}{5} \cdot \frac{S_b}{I_{pb}} \cdot (1 - HE_b) \tag{2.14}$$

where S_b and D_b are basal insulin secretion and degradation respectively.

Endogenous Glucose Production

EGP, Endogenous Glucose Production, and its full description has been made earlier [22] and covers a direct glucose signal as well as a delayed and expected insulin signal. I_{po} $(pmol/kg)$ is the level of insulin in the portal vein and I_d $(pmol/L)$ is a delayed insulin signal which has two compartments described by the last two equations. The extrapolated EGP at zero insulin and glucose is denoted by k_{p1} $(mg/kg/min)$, and the liver glucose effectiveness is expressed by k_{p2} (min^{-1}). The parameter controlling the amplitude of the insulin action on the liver is given by k_{p3} $(mg/kg/minperpmol/l)$ and corresponding parameter for portal insulin is given by k_{p4} $(mg/kg/min/(pmol/kg))$. k_i (min^{-1}) describes the rate of delay between insulin signal and insulin action.

$$EGP(t) = k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot I_d(t) - k_{p4} \cdot I_{po}(t), \qquad EGP(0) = EGP_b \tag{2.15}$$

$$\frac{dI_1(t)}{dt} = -k_i \cdot (I_1(t) - I(t)), \qquad I_1(0) = I_b \tag{2.16}$$

$$\frac{dI_d(t)}{dt} = -k_i \cdot (I_d(t) - I_1(t)), \qquad I_d = I_b \tag{2.17}$$

At the basal steady-state, the following is expressed,

$$k_{p1} = EGP_b + k_{p2} \cdot G_{pb} + k_{p3} \cdot I_b + k_{p4} \cdot I_{pob} \tag{2.18}$$

Glucose rate of Appearance

This physiological model describing the appearance of glucose is based on earlier work [23]. This model describes how the glucose is first taken up in the stomach and then travels further to the intestines. Q_{sto} (mg) is the glucose mass in the stomach, where Q_{sto1} and Q_{sto2} represents glucose masses in solid and liquid state respectively. Q_{gut} is the glucose mass in the intestine. The rate of grinding is represented by k_{gri} min^{-1}, the rate of gastric emptying is denoted by $k_{empt}(Q_{sto})$ (min^{-1}). The rate of constant intestinal absorption is represented by k_{abs} (min^{-1}), the fraction of intestinal absorption that would occur in plasma is f, the amount of in-taken glucose is represented by D (mg), BW is the subjects body weight and Ra $(mg/kg/min)$ is the rate at which glucose

appears in plasma.

$$Q_{sto} = Q_{sto1}(t) + Q_{sto2}(t), \qquad Q_{sto}(0) = 0 \quad (2.19)$$

$$\frac{dQ_{sto1}(t)}{dt} = -k_{gri} \cdot Q_{sto1}(t) + D \cdot d(t), \qquad Q_{sto1} = 0 \quad (2.20)$$

$$\frac{dQ_{sto2}(t)}{dt} = -k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) + k_{gri} \cdot Q_{sto1}(t), \qquad Q_{sto2} = 0 \quad (2.21)$$

$$\frac{dQ_{gut}(t)}{dt} = -k_{ab} \cdot Q_{gut}(t) + k_{empt}(Q_{sto}) \cdot Q_{sto2}(t), \qquad Q_{gut} = 0 \quad (2.22)$$

$$Ra(t) = \frac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW} \qquad RA(0) = 0 \quad (2.23)$$

Glucose Utilization

This part of the model was built [1] by combining literature results [24–27]. The utilization is divided into two compartments, one for insulin-dependent and insulin-independent glucose utilization respectively. The insulin-independent uptake takes place in the brain and erythrocytes and is here denoted by U_{ii}, whilst the insulin-dependent uptake, U_{id}, takes place in a remote compartment and is described as a non-linearly dependency on the glucose in the tissues [26, 27]. Here, $V_m(X(t))$ and $K_m(X(t))$, is the maximum rate and Michaelis constant (concentration when the rate is half of the maximum rate) respectively.

$$U_{ii}(t) = F_{cns} \quad (2.24)$$

$$U_{id}(t) = \frac{V_m(X(t)) \cdot G_t(t)}{K_m(X(t)) + G_t(t)} \quad (2.25)$$

$$V_m(X(t)) = V_{m0} + V_{mx} \cdot X(t) \quad (2.26)$$

$$K_m(X(t)) = K_{m0} + K_{mx} \cdot X(t) \quad (2.27)$$

$$\frac{dX(t)}{dt} = -p_{2u} \cdot X(t) + p_{2u} \cdot [I(t) - I(b)], \qquad X(0) = 0 \quad (2.28)$$

$$U(t) = U_{ii}(t) + U_{id}(t) \quad (2.29)$$

At the basal steady-state, the following is hold

$$G_{tb} = \frac{F_{cns} - EGP_b + k_1 \cdot G_{pb}}{k_2} \quad (2.30)$$

$$U_b = EGP_b = F_{cns} + \frac{V_{m0} \cdot G_{tb}}{K_{m0} + G_{tb}} \quad (2.31)$$

$$V_{m0} = \frac{(EGP_b - F_{cns}) \cdot (k_{m0} + G_{tb})}{G_{tb}} \quad (2.32)$$

Insulin Secretion

This part of the model is based on earlier work regarding pancreatic insulin secretion [28, 29]. γ (min^{-1}) is the transfer rate between the portal vein and liver, the pancreatic response to rate of change in glucose levels is denoted as K $(pmol/kgpermg/dl)$, insulin secretion delay in response to glucose signal is represented by α (min^{-1}), pancreatic responsivity to glucose is given by β $(pmol/kg/minpermg/dl)$, the threshold of glucose

for which the β-cells will start producing new insulin is given by h (mg/dl)

$$S(t) = \gamma \cdot I_{po}(t) \tag{2.33}$$

$$\frac{dI_{po}(t)}{dt} = -\gamma \cdot I_{po}(t) + S_{po}(t) \tag{2.34}$$

$$S_{po}(t) = \left\{ \begin{array}{ll} Y(t) + K \cdot \frac{dG(t)}{dt} + S_b & \text{for } \frac{dG(t)}{dt} > 0 \\ Y(t) + S_b & \text{for } \frac{dG(t)}{dt} < 0 \end{array} \right\} \tag{2.35}$$

$$\frac{dY(t)}{dt} = \left\{ \begin{array}{ll} -\alpha \cdot [Y(t) - \beta \cdot (G(t) - h)] & \text{if } \beta \cdot (G(t) - h) \geqslant -S_b \\ -\alpha \cdot Y(t) - \alpha \cdot S_b & \text{if } \beta \cdot (G(t) - h) < -S_b \end{array} \right\} \tag{2.36}$$

Glucose Renal Excretion
When glucose levels in plasma exceeds a certain threshold, the liver will excrete glucose given the expressions below. The glomerular filtration rate and the renal threshold for glucose is given by k_{e1} (min^{-1}) and k_{e2} (mg/dl) respectively.

$$E(t) = \left\{ \begin{array}{ll} K_{e1} \cdot [G_p(t) - k_{e2}] & \text{if } G_p(t) > k_{e2} \\ 0 & \text{if } G_p(t) \leq k_{e2} \end{array} \right\} \tag{2.37}$$

2.1.1 Encapsulation

To include encapsulation, glucose and insulin diffusion over the membrane was implemented. Here a mathematical model previously described [30] was used,

$$C_{x_1} = C_{x_2} - (C_{x_2} - C_{x_{1_0}}) \cdot e^{-\lambda \cdot t} \tag{2.38}$$

where C_{x_1} is either glucose or insulin concentration in the compartment, C_{x_2} the concentration outside the compartment and $C_{x_{1_0}}$ the starting concentration in the compartment when C_{x_2} is subject to a change. This equation was applied for both glucose and insulin diffusion across the membrane.
The models equations are differentials and describes the rate of change of the entities, therefore the above equation had to be derived to get the rate of change of the concentration,

$$\frac{dC_{x_1}}{dt} = \frac{dC_{x_2}}{dt} - (\frac{dC_{x_2}}{dt} - \lambda \cdot C_{x_2} + \lambda \cdot C_{x_{1_0}}) \cdot e^{-\lambda \cdot t} \tag{2.39}$$

The equations that had to be modified in the original model included equations 2.35 and 2.36 which are now expressed as,

$$S_{po}(t) = \left\{ \begin{array}{ll} \frac{dI_{cap}(t)}{dt} - (\frac{dI_{cap}}{dt} - \lambda_{ins} \cdot I_{cap}(t) + \cdot \lambda_{ins} I_{pb}) \cdot e^{-\lambda_{ins} \cdot t} + K \cdot \frac{dG(t)}{dt} + S_b & \text{for } \frac{dG(t)}{dt} > 0 \\ \frac{dI_{cap}(t)}{dt} - (\frac{dI_{cap}}{dt} - \lambda_{ins} \cdot I_{cap}(t) + \cdot \lambda_{ins} I_{pb}) \cdot e^{-\lambda_{ins} \cdot t} + S_b & \text{for } \frac{dG(t)}{dt} < 0 \end{array} \right\}$$

$$\frac{dY(t)}{dt} = \left\{ \begin{array}{ll} -\alpha \cdot [Y(t) - \beta \cdot (G_{cap}(t) - h)] & \text{if } \beta \cdot (G_{cap}(t) - h) \geqslant -S_b \\ -\alpha \cdot Y(t) - \alpha \cdot S_b & \text{if } \beta \cdot (G_{cap}(t) - h) < -S_b \end{array} \right\}$$

where I_{cap} is insulin in the capsule, G_{cap} is glucose in the capsule and λ_{ins} is the diffusion constant for insulin.
The glucose diffusion over the capsule membrane was then expressed as,

$$\frac{dG_{cap}}{dt} = \frac{dG(t)}{dt} - (\frac{dG(t)}{dt} - \lambda_{glu} \cdot G(t) + \lambda_{glu} \cdot G_{pb}) \cdot e^{-\lambda_{glu} \cdot t}$$

where λ_{guc} is the diffusion constant for glucose.

This altered model simulates encapsulation of a normal subjects pancreatic islets and therefore places the encapsulation device where the pancreas would be. Possible transplantation sites of these devices is the peritoneal cavity, the omentum or muscle tissue etc. For model simplicity, the device has been placed as a pancreas substitute.

2.1.2 Model parameters

This section shows a table of the parameters and their values used in the model [1]. The normal value column displays the values used in the model for a subject with normal metabolism and the T2DM value column displays the values used in the model for subjects with T2DM metabolism.

TABLE 2.1: Parameters used in the model [1]. Where the normal value column and T2DM column represents the parameters used in the model for subjects with normal and T2DM metabolism.

Process	**Parameter**	**Normal**	**T2DM**	**Unit**
Glucose Kinetics	V_g	1.88	1.49	dl/kg
	k_1	0.065	0.042	min^{-1}
	k_2	0.079	0.071	min^{-1}
Insulin Kinetics	V_I	0.05	0.04	L/kg
	m_1	0.190	0.379	min^{-1}
	m_2	0.484	0.673	min^{-1}
	m_4	0.194	0.269	min^{-1}
	m_5	0.0304	0.0526	$min \cdot kg/pmol$
	m_6	0.6471	0.8118	*dimensionless*
	HE_b	0.6	0.6	*dimensionless*
Rate of Appearance	k_{max}	0.0558	0.0465	min^{-1}
	k_{min}	0.0080	0.0076	min^{-1}
	k_{abs}	0.057	0.023	min^{-1}
	k_{gri}	0.0558	0.0465	min^{-1}
	f	0.90	0.90	*dimensionless*
	a	0.00013	0.00006	mg^{-1}
	b	0.82	0.68	*dimensionless*
	c	0.00236	0.00023	mg^{-1}
	d	0.010	0.09	*dimensionless*
Endogenous Production	k_{p1}	2.70	3.09	$mg/kg/min$
	k_{p2}	0.0021	0.0007	min^{-1}
	k_{p3}	0.009	0.005	$mg/kg/min$ per $pmol/L$
	k_{p4}	0.0618	0.0786	$mg/kg/min$ per $pmol/kg$
	k_i	0.0079	0.0066	min^{-1}
Utilization	F_{cns}	1	1	$mg/kg/min$
	V_{m0}	2.50	4.65	$mg/kg/min$
	V_{mx}	0.047	0.034	$mg/kg/min$ per $pmol/L$
	K_{m0}	225.59	466.21	mg/kg
	p_{2u}	0.0331	0.0840	min^{-1}
Secretion	K	2.30	0.99	$pmol/kg$ per mg/dL
	α	0.050	0.013	min^{-1}
	β	0.11	0.05	$pmol/kg/min$ per mg/dL
	γ	0.5	0.5	min^{-1}
Renal Excretion	k_{e1}	0.0005	0.0007	min^{-1}
	k_{e2}	339	269	mg/kg

2.2 Encapsulation devices

This section will go trough the three types of devices, in more detail, that have been used to model encapsulation.
The Beta-Air device has the shape of a disc with two compartments containing islets and an oxygen central module which supplies oxygen through an exterior pump [14]. The possibility of constantly supplying the encapsulated islets with oxygen makes it possible for more dense packing with less risk of hypoxia and necrosis of centrally located cells, which is illustrated in Figure 1.2. In a study done on minipigs [14] a seeding density of 4,160 $\pm$ 380 IEQ/cm^2 was used with promising islet graft survival. The device had the external dimensions of 68 mm and 18 mm for diameter and height respectively. The islet modules were 0.060 cm thick and had a diameter of 4.9 cm (capacity of 75,000 IEQ / module, with 4,000 IEQ/cm^2), which gives a volume of 2.26 mL(1.13 mL per islet module).
The second type of Beta-Air device has a elliptical disc form [14] and has the external dimensions of major diameter 11, minor diameter 7 and height 1.8 (cm). This device is described of being able to carry 500,000 IEQ. If using the same packing density as the above mentioned device, then this transcribes into 62.5 cm^2 per islet module and a major and minor axis of 5.59 and 3.56 (cm) respectively. If having the same height of the modules as before then the volume becomes 7.5 ml (3.75 ml/module).
The diffusion constants used for these two devices were taken from literature [14], and were 1.69 x 10^{-6} cm^2/sec and 1.11 x 10^{-7} cm^2/sec for glucose and insulin respectively.

The third device used in the model is the ViaCyte device Encaptra, which also uses a macroencapsulation set up but with the shape of a flat sheet. An illustrion of this device can be seen in Figure 1.3. Encaptra has a width of 3 cm, length of 8 cm and a volume of 250 μL [18], which gives the height 0.0104 cm. One of these devices will not be enough to carry a sufficient amount of IEQ. Since it is stated that their 20 μL device is able to carry 2,500 human IEQ (email correspondence) and if directly translated to the 250 μL device will equal a capacity of 31,250 IEQ. In order to have this device being comparable to the Beta-Air device, five devices where used in the simulations to be able to hold the 150,000 IEQ. ViaCyte has not given any information on the diffusion constants for glucose and insulin of their membrane, so the constants stated in the Beta-Air case is used in the simulations.

2.3 Optimization

In order to find the optimal parameters of the Beta-Air device an optimization program was constructed in MATLAB. The program uses the in-built function *fmincon* which

finds the minimum of a problem specified by,

$$\min_x f(x) \; such \; that = \left\{ \begin{array}{ll} c(x) & \leq 0 \\ ceq(x) & = 0 \\ A \cdot x & \leq b \\ Aeq \cdot x & = beq \\ lb \leq x \leq ub & \end{array} \right\} \tag{2.40}$$

where $c(x)$ is the nonlinear inequality constraint, $ceq(x)$ is the nonlinear equality constraint, A is a matrix of linear constraints, b is the vector specifying the linear constraint values, Aeq is the matrix of linear equality constraints, beq is the vector holding the values of the linear equality constraints, lb and ub specifies a upper and lower bounds for the result x.
In the case of the Beta-Air device, the diameter and height was set to vary between 0.03 and 20 (cm). The mean human islet has a diameter of about 150 μm and rarely exceeds 500 μm. To be able to house a majority of islet sizes, the diameter and height had the restriction not to be smaller than 300 μm. The upper limit was set to 20 cm for height and diameter to have a realistic sized device for implantation. The volume was always kept constant at 2.26 mL during the optimization to assure the volume needed to house the islet cells were used. The equations below are the linear and nonlinear constraints expressing the above mentioned,

$$0.03 \leq D, H \leq 20 \tag{2.41}$$

$$2\pi \cdot \left(\frac{D}{2}\right)^2 \cdot H = 2.26 \tag{2.42}$$

where D and H is the diameter and height (cm) respectively.
For this setup the linear constraints can then be expressed as,

$$A = \begin{pmatrix} 1 & 0 \\ -1 & 0 \\ 0 & 1 \\ 0 & -1 \end{pmatrix} \tag{2.43}$$

$$b = \begin{pmatrix} 20 \\ -0.05 \\ 20 \\ -0.05 \end{pmatrix} \tag{2.44}$$

$$A \cdot x \leq b \tag{2.45}$$

and the nonlinear constraint as,

$$ceq = 2\pi \cdot \left(\frac{D}{2}\right)^2 \cdot H - 2.26 = 0 \tag{2.46}$$

The optimization was then run until completion, with restrictions to not exceed 10,000 iterations and have a termination tolerance of $1.0 \cdot 10^{-13}$.

2.4 Graphical interface

To make the model implemented in this thesis more easily available to future research projects a graphical interface was constructed in MATLAB. This interface was based on earlier work [19].
In this interface the user can simulate one meal of chosen amount of glucose, at specific time, and choose between Beta-Air and ViaCyte encapsulation techniques. The dimensions of the chosen device can be altered, as well as its diffusion constants for both glucose and insulin. Other parameters that can be changed are basal glucose level, basal insulin, basal glucose production, body weight, peripheral and hepatic insulin sensitivity, static and dynamic β-cell responsivity. When run, a figure will show the glucose and insulin levels compared to a normal case without encapsulation. The interface is illustrated in Figure 2.2.

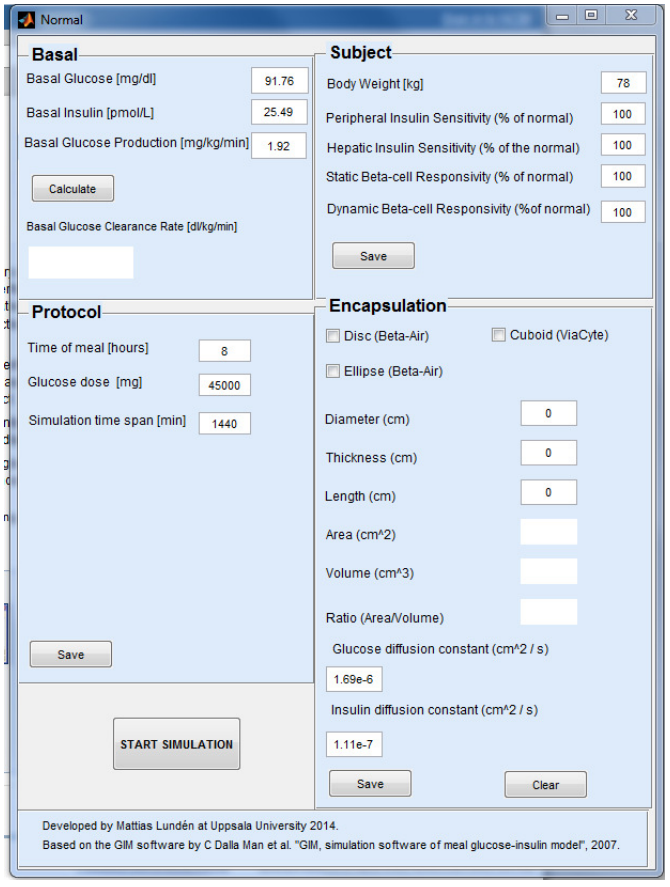

FIGURE 2.2: Figure showing the main window of the graphical interface. Here the user can simulate the model with their own specified parameter values and have the results displayed.

Chapter 3

Results

3.1 Model simulation

The model implemented and explained in Chapter 2 was run for the Beta-Air and ViaCyte devices and the results are displayed below. The parameter values used in all simulations are the ones presented in the normal value column in Table 2.1, unless mentioned otherwise.

3.1.1 Beta-Air disc

The results from running the model with the Beta-Air disc device can be seen in Figure 3.1. The simulation was made with the current dimensions of the device and included a meal of 25 g at one hour. It was found that the encapsulation would have significant impact on the glucose control. The peak glucose values are elevated compared to the normal case (6.73 compared to 6.37 mmol/L) and takes longer time to reach basal values (about 13 min) due to the delay in insulin response. Another important observation is that the glucose levels drop down below the basal levels more in the encapsulated case, lowest peak at 4.68 mmol/L (basal 5.09 mmol/L) due to insulin delay. The AUC values for both glucose and insulin was used for evaluating the differences. The AUC for glucose shows a 1.5-fold increase and AUC for insulin is decreased by 3 %, when compared to the normal case. All the AUC values are stated in Table 3.1.

3.1.2 Beta-Air ellipse

The results from running the model with the hypothetical ellipse shaped Beta-Air device can be seen in Figure 3.2. The same simulation protocol was used as for the Beta-Air disc device. As can be seen when comparing these two Beta-Air devices, the curves are the same and so are the AUC values, which can be observed in Table 3.1.

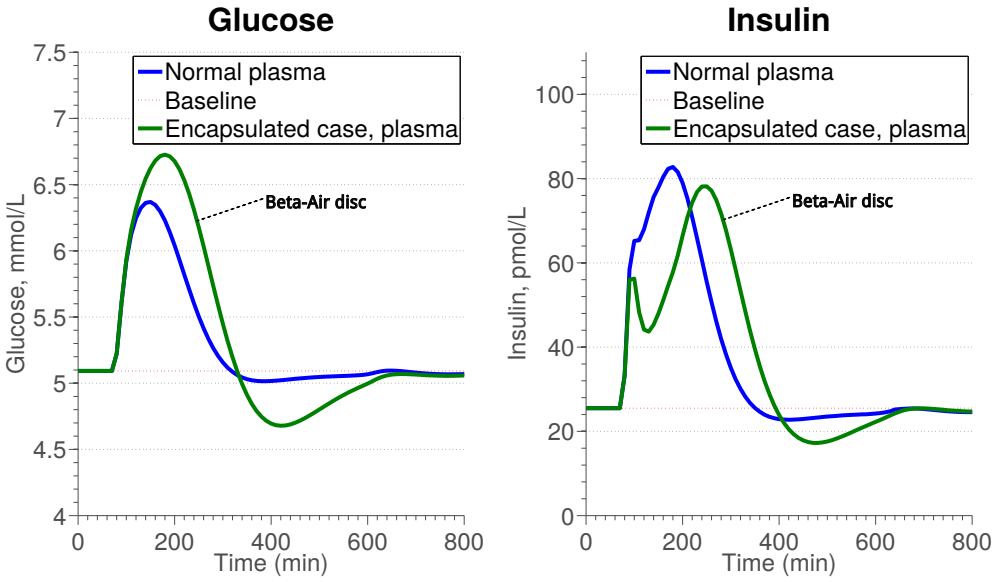

FIGURE 3.1: Simulation of a 25 g glucose meal with current Beta-Air dimensions in green compared with the normal case in blue, the baseline values are illustrated by red dotted lines. To the left is the glucose levels and to the right is the insulin levels over time respectively. The encapsulated case shows elevated glucose levels (1.5-fold AUC increase compared with the normal case) and delay in insulin secretion.

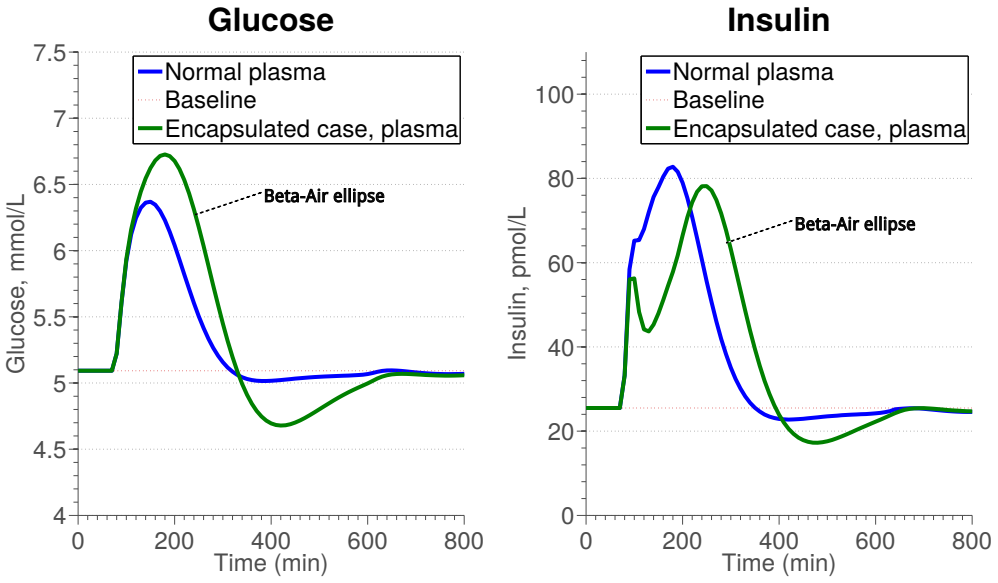

FIGURE 3.2: Simulation of a 25 g glucose meal with the hypothetical ellipse Beta-Air device in green compared with the normal case in blue, the baseline values are illustrated by red dotted lines. To the left is the glucose levels and to the right is the insulin levels over time respectively. The encapsulated case shows elevated glucose levels (1.5-fold AUC increase compared with the normal case) and delay in insulin secretion.

3.1.3 ViaCyte

The results from running the model with the ViaCyte device can be seen in Figure 3.3 using the set up described in section 2.2. The simulation settings were the same as before, a 25 g meal at time one hour. The Encaptra device mimics and almost completely overlaps the normal case. The AUC values are stated in Table 3.1.

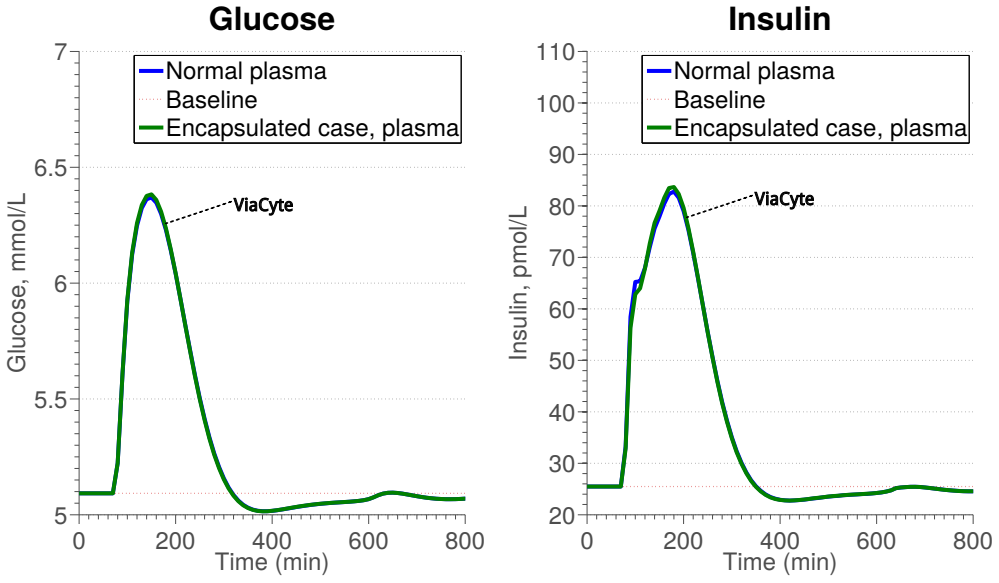

FIGURE 3.3: Simulation of a 25 g glucose meal with the ViaCyte Encaptra device having the dimensions described in Section 2.2. The resulting glucose and insulin levels are in green, the normal case in blue and the baseline is represented by the red dotted line. The encapsulated set up almost mimics the normal case.

3.2 Optimization

The optimization program implemented and described in section 2.3 was run for only the Beta-Air device, since the ViaCyte device already had an optimal performance. The AUC for glucose was used as minimization target to find the optimal values of the diameter and height of the device. The optimal values found were 6.93 and 0.0300 (cm) for diameter and height respectively (giving a surface-area-to-volume ratio of 33.3 compared to 16.7 when using the current device) and simulations shows a 1.2-fold increase of glucose AUC compared with the normal case, which is an improvement from the current device. Figure 3.4 shows a run of the model with optimized device and using the same meal settings as in the previous section and Table 3.1 shows the corresponding AUC values.

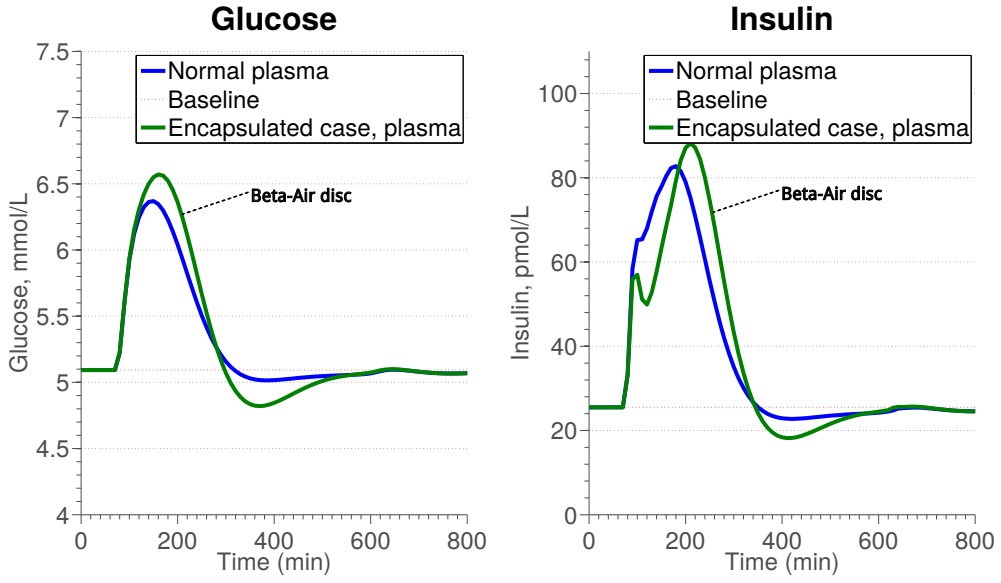

FIGURE 3.4: Simulation of the model with optimal Beta-Air device shape, compared with a normal case. The optimal Beta-Air is shown as green, normal case as blue and the basal level as red dotted line. An oral glucose meal of 25 g is taken at one hour, the glucose and insulin levels are showed to the left and right respectively. This hypothetical device shows less elevated glucose levels, compared to the current Beta-Air (1.2 against 1.5 fold increase in glucose AUC compared with normal case), and less drop under glucose basal levels also under a shorter time period.

3.3 Beta-cell responsivity

The devices used for encapsulation in the model are estimated to be able to carry 150,000, 500,000 and 150,000 IEQ for Beta-Air disc, Beta-Air ellipse and ViaCyte respectively. A healthy pancreas contains about one million islets [31] and 12,000 IEQ/kg body weight is estimated to be needed for a successful islet transplantation [10]. In all the simulations of the model, the body weight has been set to 78 kg which means that the needed amount

Setup	**Device**	**Diameter** (cm)	**Height** (cm)	**Length** (cm)	**Ratio** (cm^2/cm^3)	**Glucose** AUC	**Insulin** AUC
Normal	-	-	-	-	-	3.08×10^3	8.24×10^3
Current	Beta-Air disc	4.89	0.0600	-	16.7	4.75×10^3	8.03×10^3
	ViaCyte	3	0.0104	8	193	3.09×10^3	8.24×10^3
	Beta-Air ellipse	5.59	0.0600	3.56	16.7	4.75×10^3	8.03×10^3
Optimal	Beta-Air disc	6.93	0.0300	-	33.3	3.65×10^3	8.23×10^3
Respons-	Beta-Air disc	4.89	0.0600	-	16.7	1.35×10^4	4.81×10^3
ivity	Beta-Air ellipse	5.59	0.0600	3.56	16.7	6.93×10^3	7.17×10^3
	ViaCyte	3	0.0104	8	193	1.25×10^4	4.92×10^3

TABLE 3.1: Simulation results for the current Beta-Air and ViaCyte devices. The optimal Beta-Air is also shown as well as the normal case for comparison.

of islets is ∼900,000 IEQ. The Beta-Air disc and ViaCyte devices contains ∼17 % and the Beta-Air ellipse device contains ∼56 % of this amount. In order to take this into account in the model the parameters of static and dynamic beta-cell responsivity where set to matching percentage of normal values for each simulation. The results can be seen in Figures 3.5-3.7. Not so surprising, the simulations of the three devices indicate increased glucose levels and decreased insulin levels, especially for Beta-Air disc and ViaCyte. The corresponding AUC values are presented in Table 3.1 under responsivity.

3.4 Parameter importance for performance

This section displays the results gained from running the model with varying surface-area-to-volume ratio and glucose and insulin diffusion constants. This to evaluate their impact on the results and determine how they could be set to improve performance.

3.4.1 Surface-area-to-volume ratio

Since a higher surface-area-to-volume ratio will increase the diffusion possibilities over the membrane, it is of importance when developing encapsulation techniques. This can be observed in Table 3.1, where the optimal case has a higher ratio. To evaluate the role of this parameter the glucose-insulin model was run with varying ratio, from 10 to 200 with a step length of one. The results can be seen in Figure 3.8.

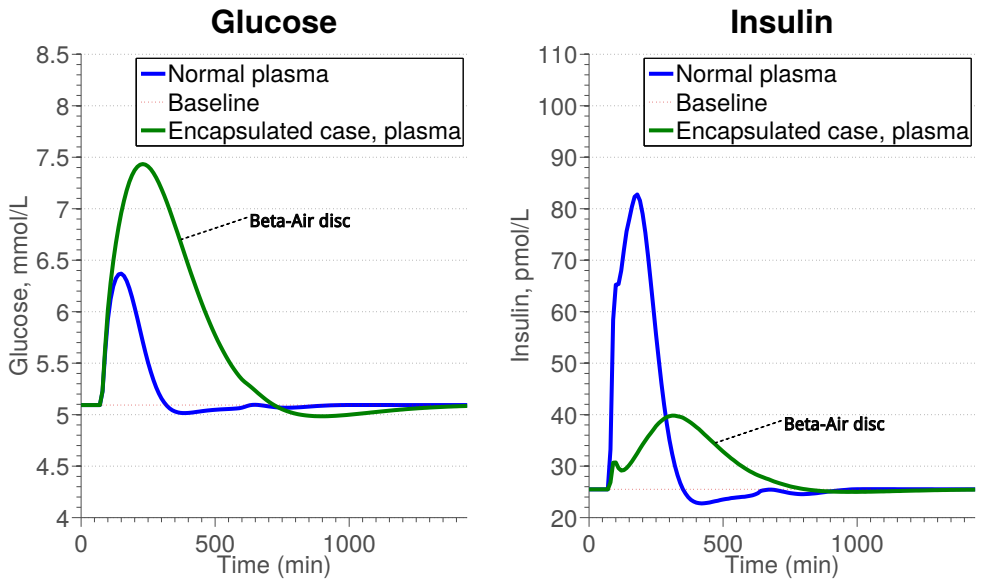

FIGURE 3.5: Simulation of a 25 g glucose meal with the Beta-Air device having the current dimensions, also taking into account the number of IEQ that the device can hold by lowering the static and dynamic Beta-Cell responsivity to 17 % out of the normal. The resulting glucose and insulin levels are in green, the normal case in blue and the baseline is represented by the red dotted line.

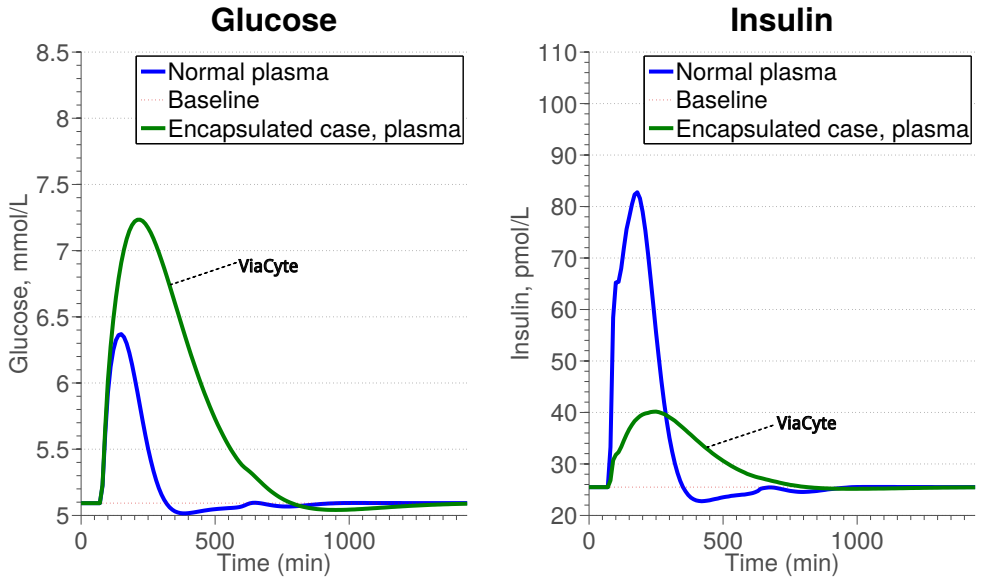

FIGURE 3.6: Simulation of a 25 g glucose meal with the ViaCyte device having the current dimensions, also taking into account the number of IEQ that the device can hold by lowering the static and dynamic Beta-Cell responsivity to 17 % out of the normal. The resulting glucose and insulin levels are in green, the normal case in blue and the baseline is represented by the red dotted line.

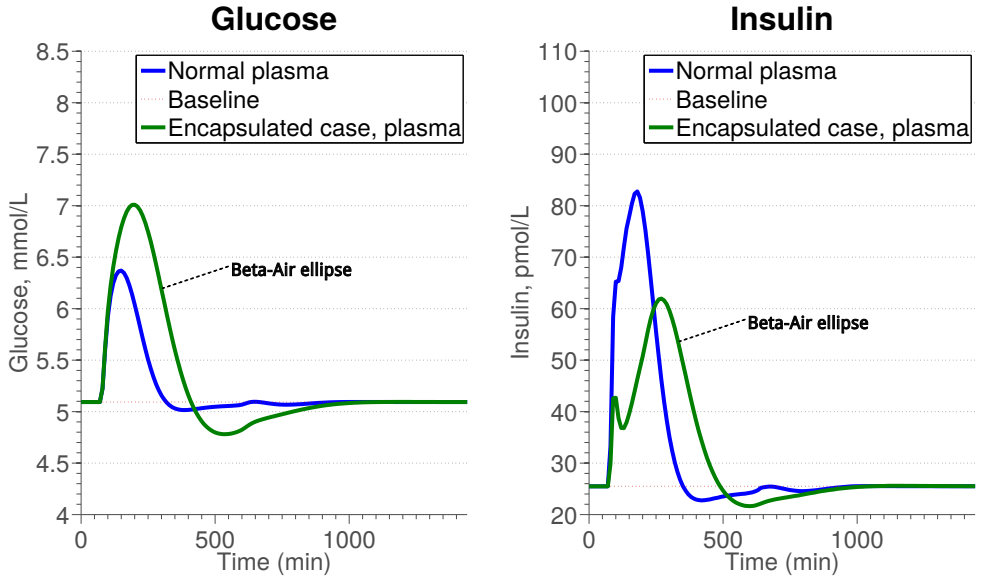

FIGURE 3.7: Simulation of a 25 g glucose meal with the Beta-Air ellipse shaped device having the current dimensions, also taking into account the number of IEQ that the device can hold by lowering the static and dynamic Beta-Cell responsivity to 56 % out of the normal. The resulting glucose and insulin levels are in green, the normal case in blue and the baseline is represented by the red dotted line.

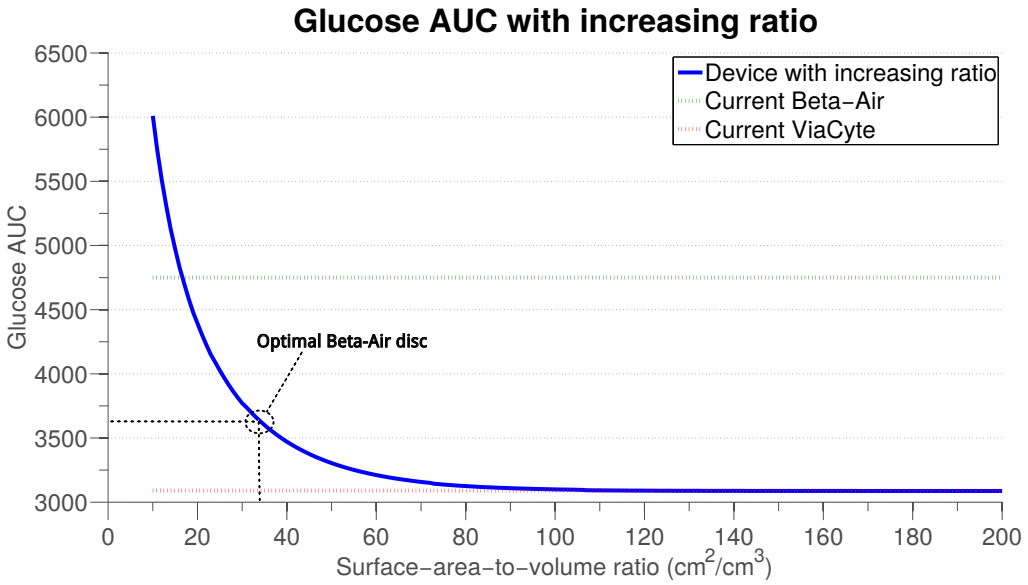

FIGURE 3.8: The model was run with varying surface-area-to-volume ratio in the span of 10-200 with a step length of one. Calculated AUC values for this stepwise increase is represented by the blue line. Beta-Air and ViaCyte are represented by the green and red dotted lines respectively.

3.4.2 Diffusion constants

The membrane properties are important in respect of what kind of molecules which are let through, but also at which rate the molecules can diffuse. In order to investigate how increasing diffusion rate would affect the outcome of the model, two approaches were used.
Firstly the glucose diffusion was set to vary from 1.69 x 10^{-6} to 1.6 x 10^{-4} cm^2/s with a step length of 1 x 10^{-6}, having the insulin diffusion constant fixed. The upper limit was set to when there was no significant decrease in glucose AUC. The current Beta-Air disc encapsulation set up was used and the results can be seen in Figure 3.9. It can be observed that the AUC decreases quite fast in the beginning but then slows down and never reaches a AUC below 4.25 x 10^3.
Secondly the insulin diffusion constant was set to vary between 1.11 x 10^{-7} and 8.5 x

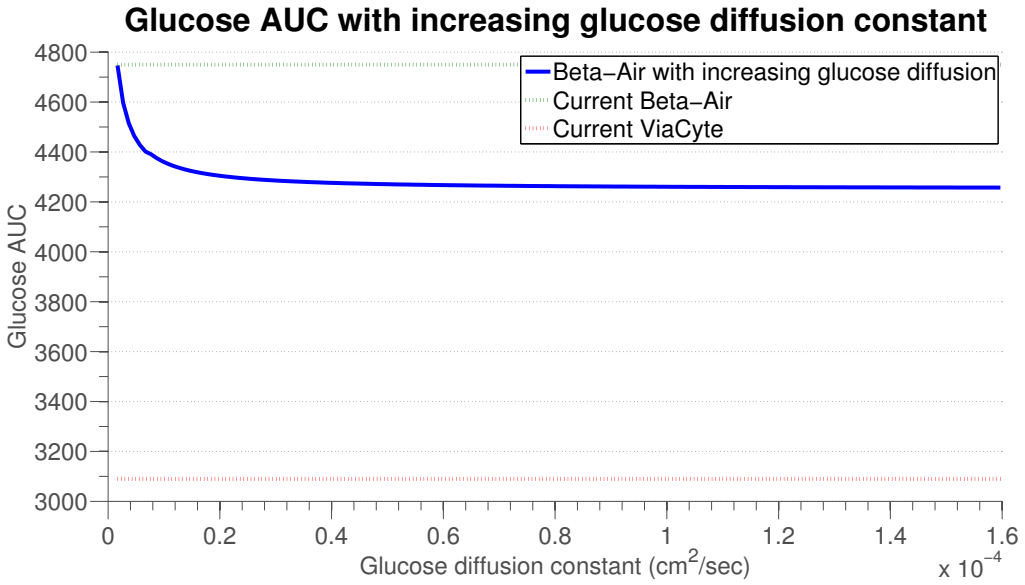

FIGURE 3.9: For the current Beta-Air device, the diffusion constant of glucose was set to vary between 1.69 x 10^{-6} and 1.6 x 10^{-4} cm^2/s with a step length of 1 x 10^{-6}. The glucose AUC was evaluated at each step and is represented by the blue line. The current ViaCyte and Beta-Air devices AUC are represented by the red and green dotted lines respectively.

10^{-6} cm^2/s with a step length of 1.5 x 10^{-7}, with the glucose diffusion constant fixed. Here the upper limit was set to when there was no longer any significant decrease in glucose AUC. As before the Beta-Air encapsulation was used in the simulations and the results can be seen in Figure 3.10. It can here be observed that an increase of the insulin diffusion constant has a larger effect on the outcome than the glucose diffusion constant, this can be explained by that glucose plasma levels is highly dependent on plasma insulin levels. Here the glucose AUC never reaches lover than 3.65 x 10^3.

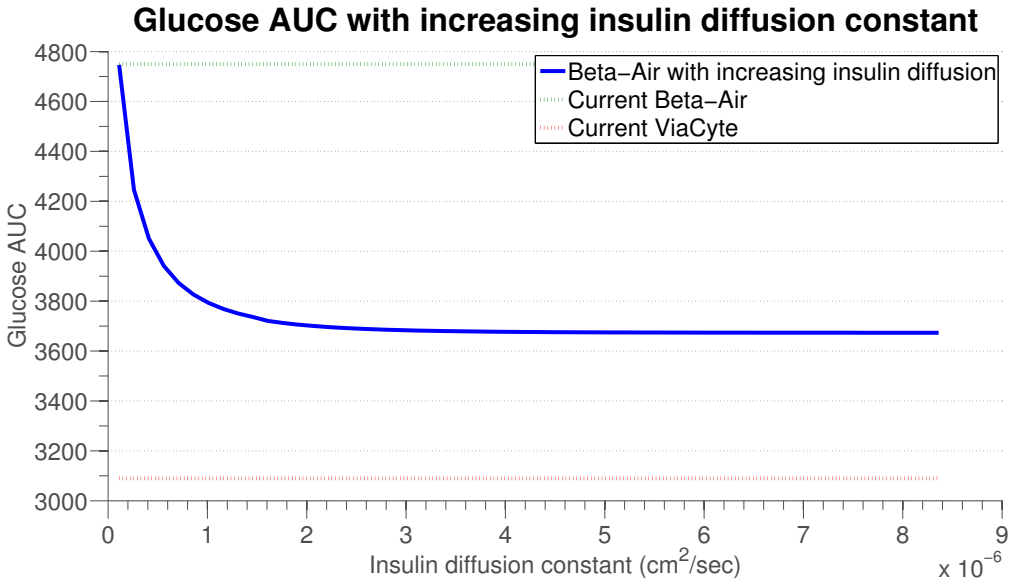

FIGURE 3.10: For the current Beta-Air device, the diffusion constant of insulin was set to vary between 1.11 x 10^{-7} and 1 x 10^{-4} cm^2/s with a step length of 4 x 10^{-7}. The glucose AUC was evaluated at each step and is represented by the blue line. The current ViaCyte and Beta-Air devices AUC are represented by the red and green dotted lines respectively.

Chapter 4

Discussion

4.1 Model

The model constructed in this project was as mentioned based on already published work [1]. This is a whole-body model which can simulate three meals during a 24 h period and the effects it has on different physiological parameters. Although it is an advanced model it has its limitations, as they mention themselves. Glucagon, which is also secreted by the islets of Langerhans (α-cells), is a counterregulatory hormone to insulin and when released will cause stored glycogen to convert into glucose. Also counterregulatory hormones such as epinephrine and growth hormone is also mentioned for implementation to improve the model. What the authors also mentions as a limitation with the current model is that it is heavily centralized around glucose. Human physiology is really complex and for example the interaction of free fatty acids with glucose and insulin is mentioned as future potential implementations.
The implementation of encapsulation to the Dalla Man et al. model, as described in section 2.1.1, is simplified in order to make the simulations feasible. First of all the diffusion of glucose and insulin is based on early work by R. E. Sparks et al. which uses a simple but convenient exponential description of the diffusion. This could be improved by using Fick's laws of diffusion which includes a concentration gradient across the membrane, which states that the membrane thickness will matter. One assumption that is made regarding the encapsulation is that vascularization of the transplanted device is as expansive as that of the islets in the pancreas. This factor depends a lot on the transplantation site and the possibility of revascularization around the device. Unsufficient vascular formation is often showed as large islet necrosis due possibly to hypoxia or other nutrient deficiency. Oxygen diffusion across the membrane and its gradient towards the most inner cells could also be added to the model.

4.2 Simulation results

From the results gained in the previous chapter it can clearly be seen that encapsulation will sure have effect on the glucose-insulin system. The results from running the model with the current Beta-Air disc and hypothetical ellipse device clearly shows elevated glucose values compared to the normal case. This is due to a longer response time and secretion of insulin as a consequence of the delayed glucose increase reaching the islets and also the diffusion of secreted insulin out from the capsule. If having chronic glucose levels over 7 mmol/L for extended periods of time, may increase the risk of having internal organ damage, a consequence of hyperglycemia.
What also can be observed is the increased dip in glucose concentration under basal glucose levels. Hypoglycemia most often occurs if having glucose levels under 4 mmol/L. Although the levels gained in the simulation never reaches below this value it is still an alarming trend since the dip is quite long lasting about 300 min (5 h). Another simulation was run with a meal of 70 g glucose to stress the model and observe the glucose dip, the results can be seen in Figure 4.1. It can clearly be seen that the glucose level drops under 4 mmol/L and for as long as 75 min (1 hour and 15 min) which gives a risk of hypoglycemia. Also the glucose peak of over 9 mmol/L is also alarming.

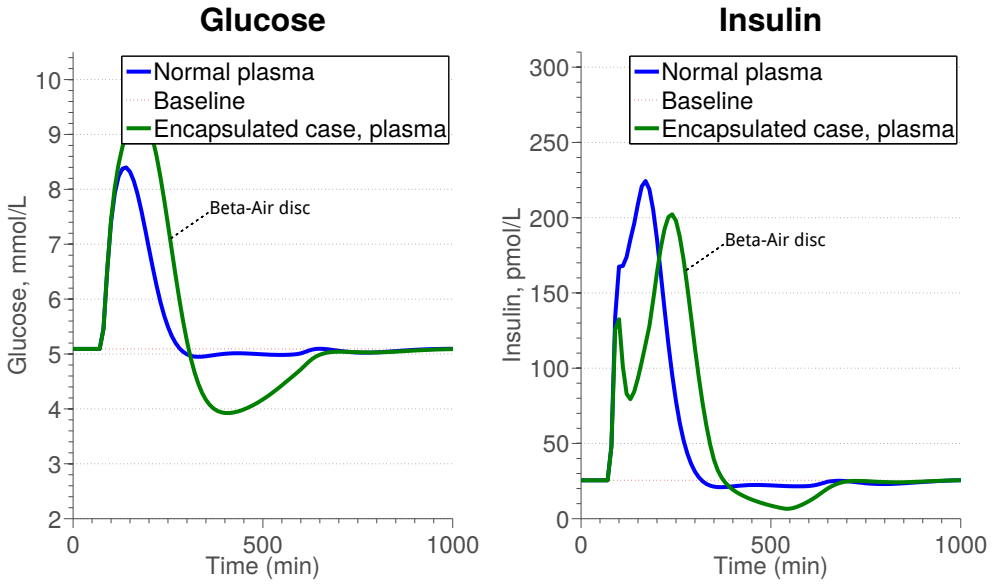

FIGURE 4.1: A simulation with the current Beta-Air disc device and a 70 g meal. Glucose levels drops below 4 mmol/L which induces risk of hypoglycemia.

The better performance of the ViaCyte device can be explained by its higher surface-area-to-volume ratio, 193 compared to 16.7. The importance of this attribute is clearly visible in section 3.4.1.

4.3 Optimization

The optimization of the Beta-Air device, Figure 3.4, improves the performance compared to the current device and shows only a 1.2 fold increase in glucose AUC compared to the normal case. This can be explained by the higher surface-area-to-volume ratio (33.3 versus 16.7) which enables diffusion to be carried out over a larger area. Also the dip under basal glucose levels is reduced to only reach about 4.8 mmol/L. Still the device can not reach the performance of the ViaCyte device. A problem with this optimized device is its size, where to transplant it successfully especially if a set of devices would be needed to achieve a insulin-independent result.

4.4 Beta-cell responsivity

When taking into account the islet packing capability of all the three devices and setting the beta-cell responsivity to correspond to the fraction of possible islets to that of needed islets, the results might reflect a more realistic outcome. As could be observed in Figures 3.5-3.7 the results showed more elevated glucose levels and delayed insulin response compared to the previous simulations.
Results gained during a clinical study with the Beta-Air disc device [17](same dimensions as the device used in these simulations) housing 2,100 IEQ/kg for a 79 kg T1DM subject (165,900 IEQ), showed the same trend as the simulation made with lower beta-cell responsivity in respects of insulin levels under glucose stimulation.
As the original model by Dalla Man et al. also offers meal simulations of a T2DM subject, it was found interesting to simulate a similar meal and compare to the results gained for the three devices with decreased beta-cell responsivity. The simulation was run with a meal of 25 g glucose and the basal glucose and insulin levels were decreased to match the normal values for comparability. The results can be seen in Figure 4.2. When comparing the beta-air ellipse (red lines) and the T2DM subject (blue lines) their trend is quite similar. This raises the question if this could result in that subjects with T1DM treated with this encapsulation technique would experience pathological features that are associated with T2DM, such as insulin resistance in peripheral tissues?

4.5 Parameter importance

From the simulations made with varying surface-area-to-volume ratio and diffusion constants, it is made very clear that these parameters are of great importance when developing a encapsulation technique.
The surface-area-to-volume ratio is what explains the great difference in simulation outcome between the beta-air devices and ViaCyte (16.7 versus 193). By increasing the ratio, which is visualized in Figure 3.8, the device will eventually come closer to the ViaCyte performance and mimic the normal case. The Beta-Air device could surely benefit from increasing its surface-area-to-volume ratio, even further than the optimal

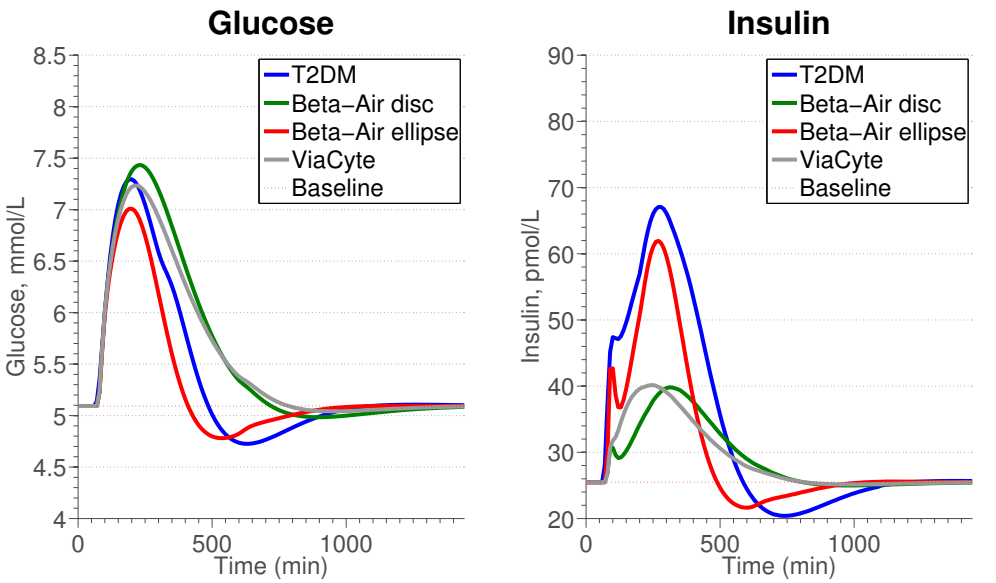

FIGURE 4.2: A simulation for the Beta-Air devices and ViaCyte device with decreased beta-cell responsivity (17 % for Beta-Air disc and Viacyte, 56 % for Beta-Air ellipse) compared with a T2DM subject. The simulation was run with a 25 g meal and the basal glucose and insulin levels were adjusted for the T2DM subject to match normal values.

case presented here, by increasing the diameter but will still have to keep the dimensions reasonable for device implantation.

The results from increasing the diffusion capability of the membrane shows that it will to some extent improve the performance, but it will not be able to reach a normal case. This factor is also very sensitive in the means of letting unwanted molecules across the membrane and interacting with the housing islets. These two parameters offers very little adjustment space and gain in comparison to the surface-area-to-volume ratio.

Chapter 5

Conclusions

This thesis has investigated the outcome of encapsulating the islets of Langerhans prior to transplantation for T1DM patients. It was found that current techniques that are under development, Beta-Air bioreactor and ViaCyte Encaptra devices, shows different capabilities of achieving the goal of insulin-independence in the treated patient. The current Beta-Air device will, according to simulations, improve and restore some insulin production but still not enough to prevent neither hyperglycemia or hypoglycemia. The ViaCyte device performed better than Beta-Air and could restore normoglycemia, but still a large number of the devices will have to be used and the oxygen supply might not be sufficient as the oxygen-supply unit provides in Beta-Air.
The parameter explaining the different outcome of the devices was the surface-area-to-volume ratio, which was also found to be the most important parameter when compared to the diffusion constants of insulin and glucose. When developing new encapsulation devices, this ratio should be considered to achieve a successful result. The graphical interface created can aid in future projects which aim at finding a more optimal device for islet transplantation in T1DM patients.

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