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By

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Dedication

This work is dedicated to my parents Brigitte and Martin Zedelmaier who were teaching me the most valuable lessons in life and always supported me during my educational journey. Special thanks to my love Emily Quagliariello who was always standing by me in my hard times during this work.
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Nomenclature

B  absorption rate constant
C  inertial resistance matrix
C_2 inertial loss coefficient
d  adipose cell diameter
D_{1,2} diffusion coefficient of species 1 into species 2
G  mass flow rate
J  diffusion flux due to concentration gradients
L  length scale pressure loss equation
M  momentum source/sink term
p  pressure
r  radial coordinate
R  viscous resistance matrix
R_v viscous resistance
S  species source/sink term
t  time
v  velocity vectors
\|v\| magnitude of velocity
v_m  mean velocity
v_r radial velocity
v_x x-direction velocity
v_y y-direction velocity
v_z z-direction velocity
x  x-direction coordinate
y  y-direction coordinate
Y  species mass fraction
z  z-direction coordinate

Greek symbols
\alpha  permeability
\varepsilon  porosity
\rho  density
\mu  dynamic viscosity
ABSTRACT

NUMERICAL SIMULATION OF INSULIN DEPOT FORMATION AND ABSORPTION IN SUBCUTANEOUS TISSUE MODELED AS A HOMOGENEOUS ANISOTROPIC POROUS MEDIA

By
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Master of Science in Mechanical Engineering

In this study, a numerical model of the insulin depot formation and absorption in the subcutaneous adipose tissue is developed using the commercial Computational Fluid Dynamics (CFD) software ANSYS Fluent. A better understanding of these mechanisms can be helpful in the development of new devices and cannula geometries as well as predicting the concentration of insulin in the blood. The injection method considered in this simulation is by the use of an insulin pump using a rapid acting U100 insulin analogue. The depot formation is analyzed running Bolus injections ranging from 5-15 units of insulin corresponding to 50-150μl. The insulin is injected into the subcutaneous tissue in the abdominal region. The main composition of the subcutaneous tissue is blood vessels and adipose cells surrounded by interstitial fluid. The tissue is modeled as a fluid saturated porous media. An anisotropic approach to define the tissue permeability is studied by varying the value of the porosity in parallel and perpendicular direction having an impact on the viscous resistance to the flow. Following recent experimental findings this configuration results in a disk shaped insulin depot. To be able to run the simulation over longer timeframes the depot formation model has been extended implementing the
process of absorption of insulin from the depot. The developed model is then used to analyze the formation of the insulin depot in the tissue when using different flow rates and cannula geometries. It was observed that changes in the diameter of the cannula have insignificant impact on the formation of the depot. Increasing the insulin flow rate results in a slightly flatter depot shape. The addition of multiple holes in the wall of the cannula, as well as using an array of cannulas, can alter the shape of the depot. When increasing the distance of the circumferential holes to the cannula tip or between the cannulas in the array, several separate insulin depots can be obtained improving the diffusion of insulin in the tissue. The numerical model is an effective option to evaluate new cannula designs prior to the manufacturing and testing of prototypes, which are rather time consuming and expensive.
CHAPTER 1: INTRODUCTION

1.1 Blood Glucose Regulation

The metabolism in the human body is managed by a feedback process involving several hormones including the endocrine hormones insulin and glucagon. The endocrine system consists of glands, such as the pancreas which is located in the abdomen, that send hormones over the circulatory system to other organs to trigger certain processes. The main task of the anabolic hormone insulin is to control blood glucose levels and manage the storage of energy in the fat cells, liver and skeletal muscles (Figure 1). The stored energy can then be released by a separate process triggered by glucagon and adrenalin.

![Fig. 1 Normal regulation of blood glucose in human body [1]](image-url)
When food is digested in the human body it is broken down into its basic components such as carbohydrates, fats, proteins, and vitamins. Carbohydrates, in the form of glucose, are responsible for providing energy to the body, especially to the muscles and the brain. During digestion, glucose molecules pass through the walls of the intestines and enter the bloodstream, where it is supplied to the rest of the body. When there is a rise in the blood glucose levels in the human body, the beta cells, that can be found in the islets of Langerhans [2], release the hormone insulin signaling the liver to convert glucose from the blood into glycogen and store it. Furthermore, insulin in combination with GLUT4 transporters (Glucose transporter type 4) enable glucose to diffuse from the bloodstream through cell walls such as the adipose cells and striated cells (muscle cells) to lower the blood glucose levels. Glucose and glycogen are stored in cells and the liver and can be released again when energy is needed which is indicated by a drop in blood glucose levels. This process, which is opposing the effects of insulin, is mainly triggered by the catabolic peptide hormone glucagon, produced in the alpha cells of the pancreas, and the stress hormone adrenalin, produced in the adrenal gland. In case of a malfunction in this feedback process such as the failure to produce insulin, the blood glucose levels cannot be regulated which can cause major damage in the body and be lethal in severe cases if left untreated. This malfunction in the regulation of the blood glucose levels is known as diabetes.
Diabetes

1.2 Diabetes

Diabetes is a disease that is currently ranked the 7th leading cause of death in the United States [3]. In the year 2010, the number of deaths in the United States with diabetes listed as direct cause was 234,051 [4]. The National Diabetes Statistic Report for 2014 shows that 2.9 million of the US population has some form of diabetes, which accounts for 9.2% of the population [4]. Diabetes is a disease characterized by high levels of glucose in the blood. The cause of these high levels can be a malfunction in the natural production of insulin by the body as well as a disability of the cells to utilize insulin. In both cases, instead of being transported to the cells to create energy, the glucose remains in the bloodstream leading to elevated critical levels of blood glucose known as hyperglycemia. This condition can lead to nervous system damage in the feet and legs causing infections, and further lead to amputation. It can also lead to blindness due to blood sugar blocking the tiny blood vessels in the eyes causing decreased oxygen supply to the eye. Elevated glucose levels also effects kidney function as the kidneys constantly try to filter out the excess glucose causing their functionality to deteriorate and can ultimately end in kidney failure and death.

Based on the main causes of diabetes, it can be categorized in two types known as Type 1 and Type 2. Diabetes Type 2 is a non-insulin dependent form of diabetes accounting for 90% of all cases in adults [2], which most commonly develops during adulthood and is therefore also known as adult-onset diabetes. With this form of diabetes, the pancreas is able to produce insulin but the cells are not able to manage it properly by not allowing it to enter, causing the glucose to remain in the bloodstream. The development of Type 2 diabetes can take several years where patients go from slightly elevated blood glucose levels to becoming insulin resistant. At some point, the pancreas is no longer able to produce sufficient amounts of insulin to meet the rising needs leading to hyperglycemia if left untreated. Among the factors that promote the risk of developing Type 2 diabetes are obesity, poor eating habits and inactive lifestyle. As these factors tend to increase in today's society, it is expected that the number of Type 2 diabetes will also increase. Diabetes Type 1 is an autoimmune disease where the body’s immune system mistakenly destroys the beta cells in the pancreas that are responsible for the production of insulin. This form of diabetes usually develops in early ages and is therefore known as juvenile-onset diabetes. When the ability of the body to produce insulin is completely eliminated, the patient is depending on externally injected insulin in form of an synthesized insulin analogue.
1.3 Insulin Analogues

In 1922, Banting and Best were the first to extract insulin from an adult beef pancreas, without toxic impurities, and tests on fully diabetic dogs showed it was able to prolong their life quite significantly [6]. Further isolation by Collip resulted in a sterile and potent extract, which was safe to be administered to diabetic adults. Since this discovery by Banting and Best, researchers were able to synthesize insulin and give it variable action profiles by providing it with add-ons using recombinant DNA technology. These synthesized insulin analogs act in the same way as natural human insulin when absorbed from the subcutaneous tissue into the blood flow. Currently, there are several formulations of insulin grouped into long acting insulin for basal administration which has a flat and long acting profile, and rapid acting insulin for Bolus administration with a rapidly attained peak in action [8]. To achieve these properties, the fact that has been used that only low molecular weight insulin is able to penetrate the capillary walls [8].

To obtain long acting insulin such as insulin glargin, amino acids are added to make it more soluble in low pH environment and less soluble in physiological pH of 7.4 [9]. In order to make the molecules more stable at acidic levels, asparagine is replaced by glycine. The solution is formulated at a pH of 4.0 where is it fully soluble in water. When injected in the body having a pH of 7.4, it forms microcrystals of hexameric insulin. The breakdown of these crystals into dimeric and monomeric molecules delays the absorption providing only small amounts of insulin over a long time period. For intermediate Insulin such as NHP (Neutral Protamine Hagedorn), microcrystals are formed by the use of zinc in presence of protamine a basic poly-arginine peptide [10]. Depending on the use of peptides, different sizes of microcrystals can be obtained having an impact on the profile and duration of action. Rapid acting insulin such as insulin lispro is very similar to natural human insulin where only the location of lysine and proline in the molecule are interchanged [11]. This minor manipulation results in a weakening effect of the insulin to form hexamers. In its initial state insulin lispro contains only monomeric insulin resulting in a rapid action onset and shorter duration of activity. While in conventional insulin therapy by the use of syringe, a combination of slow and fast acting insulin injections is needed, in insulin pump therapy only rapid acting insulin is used as the basal rate can be administered continuously in very low doses.
1.4 Insulin Pump Therapy

Insulin pump therapy is also known as continuous subcutaneous insulin infusion (CSII) [5]. It can replace the traditional syringe and needle injection and consists of a short cannula or needle inserted into the skin, which is attached to a pump by the use of a thin tube (Figure 2). The pump itself contains a small reservoir of insulin, which can be refilled or it can use a prefilled interchangeable insulin cartridge. Although a steel needle may be easier to insert, it cannot remain in the tissue as long as a Teflon cannula, which can be utilized for about 3 days.

![Insulin pump with tube and cannula and glucose sensor (Medtronic)](image)

Fig. 2 Insulin pump with tube and cannula and glucose sensor (Medtronic)

The cannula is inserted into the tissue by the help of a needle located inside the cannula to puncture the skin. Once the cannula is in place the needle can be removed. The length of the cannula is based on the thickness of the subcutaneous tissue of each patient and is typically ranging from 6 to 12mm. In case the cannula chosen is too long, it may penetrate the muscle fascia leading to discomfort for the patient and a potentially less efficient insulin absorption. On the other hand, if the cannula is too short, the bolus injections might be painful for the patient as the upper layer of the skin contains more
nerve ends. The insulin used in pump therapy is a rapid acting insulin analogue, which is delivered by the pump continuously in very small amounts. The insulin concentration in externally delivered insulin is measured in units per milliliter. For the use in insulin pumps a concentration of 100 units/ml is used, which means that an amount of 100 units (100U) of insulin corresponds to 1ml of the solution. Modern insulin pumps are able to deliver very small amounts in the range of 0.1 to 0.025 units per hour. They can be combined with continuous glucose monitoring systems measuring the glucose level in the interstitial fluid and transferring this data to the pump which is then able to calculate and suggest adaptations of the insulin rates based on this data. The benefit of insulin pump therapy over traditional injections containing long acting insulin is the high adjustability of doses leading to a better glycemic control. Furthermore extended release insulin used in traditional injection has a long period of action, which can lead to induced hypoglycemia brought on by high physical activity of the patient, leading to a lower need of insulin for this period of time. By using insulin pump therapy, this can be prevented due to the high adjustability by reducing injection rate when needed. Insulin pumps are working with two different injection rates named basal and bolus rates. The basal rate is continuously delivered over day and night time and needs to be programmed individually for the patients needs. It can be split up in different time increments allowing delivery at different rates based on the time of the day and the according need of the patient at this time. Finding the appropriate rates for each patient requires close monitoring over the first days or weeks of insulin pump therapy and furthermore need to be adjusted regularly as the patient’s needs might change over the years. The bolus delivery is an additional insulin injection on top of the basal delivery to be able to level carbohydrate intake such as for meals. The bolus rate is typically delivered in one dose over a short period of time but can also be programmed over an extended period of time. The required dose depends on the intake of carbohydrates and can be calculated by the patient or is based on the suggestion of the pumps automatic calculation when entering a desired blood glucose range and the amount of carbohydrate intake.
1.4 Subcutaneous Adipose Tissue

When treating diabetes type 1 by the use of insulin pump therapy, insulin is injected into the deeper layers of the skin, which are known as the subcutaneous tissue. The human skin consists of several distinct layers running parallel to the outer surface (Figure 3). The outermost layer is the epidermis followed by the dermis right underneath it. Beneath the dermis is the hypodermis, which is also known as the subcutaneous tissue (from Latin subcutis: “beneath skin”) [12]. Even though the hypodermis is not considered part of the skin, it connects the skin to the bones and muscle structure underneath and enables the skin to move more freely while also supplying it with blood vessels and nerves. The subcutaneous adipose tissue in the abdominal region consists mainly of adipose cells grouped together by a fibrous collagen matrix and surrounded by interstitial fluid and blood vessels. Underneath the subcutaneous tissue lies the deep fascia, a fibrous connective tissue separating the hypodermis from the muscles. Arteries pass through the deep fascia and form branches known as the first, second and third plexus. The branches of the first plexus are reaching into the subcutaneous tissue forming a capillary network that spreads between the fat cells. The blood vessels of the first plexus are in general larger than the ones of the second and third plexus spreading into the dermis, which makes the absorption of drugs from the subcutaneous tissue very effective.

![Fig. 3 Tissue layers](image)
One purpose of the adipose subcutaneous tissue is to store fat, however, there are certain areas of the body where fat is stored more preferably. This leads to a high variability of the thickness of the subcutaneous layer between different body regions and furthermore between patients depending on their body fat percentage. This variability is reflected in the variation of the fat cell diameters ranging from about 60μm in a lean patient to over 150μm in an obese patient. The mean fat cell diameter in the adipose subcutaneous tissue of a non-obese patient is observed to be around 80μm [13]. The part of the body where the subcutaneous layer is the thickest due to the high amount of fat cells is the abdominal region with a mean thickness of about 13.9mm in men and 19.0mm in women [14]. The thickness in that region makes it the preferred injection site for inulin delivery since it makes it easier to target exactly that layer by the use of a needle or a cannula even for self-treatment.
2.1 Computational Fluid Dynamics

Computational Fluid Dynamics (CFD) is widely used in analyzing fluid flow and heat transfer by means of computer aided simulation and is applied in many disciplines such as aerodynamics, hydrodynamics, turbo machinery, internal combustions etc. At first CFD was mainly used in the aerospace industry but with the availability of affordable high performance computers and more user-friendly interfaces it quickly spread to other areas. Even though CFD is not meant to completely replace the experimental approach, it can give timely insights to problems prior to experimental testing which greatly reduces lead time and costs. It also enables simulation in areas where experiments are not possible such as in hazardous environments or large-scale problems.

Most commercial CFD codes such as ANSYS Fluent used in this study are structured into three main categories: the pre-processor, the solver and the post processor [15]. The pre-processor is the first step in a CFD simulation, which includes the description of the flow problem such as geometry, fluid properties, physical phenomena and boundary conditions. The area of interest, the computational domain, is meshed into a grid used by the solver to calculate the solution at each node inside the cells. The finer the mesh of the computational domain the better the accuracy of the solution however, this also results in more extensive simulation time. The solver in most CFD codes is using the finite volume method integrating the governing equations over the control volumes. The complex governing equations such as momentum and energy equation are discretized to obtain a system of solvable algebraic equations. These algebraic equations are solved by iterative methods solving for a set of parameters and inputting them into the other equations to find the additional parameters. A scheme of such an iterative method, called the SIMPLE method, is used in this simulation and explained in more detail in the following chapters. When the solution is calculated, the results can be visualized by the use of the post-processor by plotting the variables in vector and contour plots, tracking of particle paths or animation of transient results.
2.2 Workstation Cluster for Parallel Computation

Some simulations such as transient cases over long periods of time with small step sizes or calculations on meshes with millions of nodes, can take up a lot of calculation time, which slows down the process of development or research. To be able to run calculation extensive simulations in a reasonable amount of time, they can be run in parallel on several cores, processors or even on a cluster of workstations. The cluster that has been set up for this study consists of six HP Z230 workstations with Intel XEON 3.4 GHz processors.

Fig. 4: Workstation cluster for parallel calculations
Each of these processors has 4 cores, which gives the cluster a total amount of 24 cores. The workstations are equipped with random-access memory (RAM) between 8-16GB each. To enable the communication between the computers a message-passing interface (MPI) needs to be installed and the workstations have to be connected to each other using a switch. For this specific cluster, tests have revealed, that it is necessary to use a gigabit switch to ensure the best possible performance when transferring data between the computers. When running ANSYS Fluent in parallel on several workstations the program needs to be installed in the same manner on all of the devices. One of the computers is dedicated to be the host where Fluent is started and operated by the user over the user interface. By the usage of a text file containing the hostname of all the machines in the cluster, the host is getting the information for the sub nodes. On these sub nodes, Fluent will run in the background completing the dedicated packages assigned by the host. The workstations of this cluster are gathered in a stack and would require 6 monitors, keyboards and mouse devices to operate them. To have a clean, easy to use configuration, a Keyboard-Video-Mouse switch (KVM) is used. It connects all 6 computers to one monitor, keyboard and mouse. By the push of a button it is possible to switch back and forth between the computers. Performance tests executed on a two dimensional simulation revealed that the parallel simulation running on the cluster with 24 cores showed a higher performance by a factor of 2.8 when compared to serial calculation running on a single computer. This performance increase is saves critical simulation time especially when running cases that would take up to a week in serial calculation. Performance tests comparing the results for the 3D case have not been possible since the simulation cannot be run on a single machine due to RAM limitations. When the simulation is executed on the cluster this high RAM demand can be distributed on the workstations in the cluster.
3.1 Problem Description

In this study the flow of insulin in the subcutaneous tissue is investigated. As previously described in chapter 1, the subcutaneous tissue consists of different compartments such as the blood vessels, the adipose cells and the interstitium which itself can be divided into the extracellular matrix and the interstitial fluid [16]. Describing each of these components in a model would be extremely complex and even with the availability of high performance computers it would result in a vast amount of calculation time. In order to avoid an overly complicated model, a simplified macroscopic model using a porous media approach has been chosen for this simulation. The subcutaneous tissue has therefore been divided into two regions being the vascular region (blood vessels) including the adipose cells and the extravascular region including the interstitial fluid surrounding the vessels and cells (Figure 6). This approach is resulting in a tissue model represented by a fluid saturated porous media.

The use of a porous media approach is widely spread in many different engineering disciplines such as analyzing thermal insulation, packed bed heat exchangers, catalytic reactors, ground water flow and oil reservoirs. In the field of biomedical engineering the use of a porous media approach is also common practice since most human tissues and organs can be modeled as such. Much research has been done on the delivery of drugs to the brain using microfluidic or biodegradable drug delivery devices and a porous media approach to model the brain tissue [17, 18]. Other studies used the approach to analyze the use of micro needle arrays for transdermal drug delivery [19] or the fluid backflow along the outer surface of a needle during injection [20]. Besides analyzing fluid flow the porous media approach has also been used for biomedical heat transfer such as analyzing the thermal interaction between tissue and vasculature, which is of great importance during hyperthermia treatment of tumors and cancerous cells [21]. One of the main advantages when compared to other models is the use of fewer assumptions when using a porous media approach [22, 23]. Even though many human tissues can assumed to be homogeneous certain properties such as the resistance to flow within the tissue might be anisotropic, which means that a direction dependent permeability can be observed [23, 24, 25]. The permeability is one of the main characterizations of porous media and is a measure of the flow conductivity. Another main characteristic is the porosity, which is the ratio between the void space and the total volume of the media. Based on the wide use of the porous media approach in the biomedical engineering field for various sorts of human tissues it is expected that this approach will give fast and reasonable results when applied to model the subcutis in order to analyze the flow of externally injected insulin.
While many numerical and quantitative studies have been conducted on the absorption process and insulin plasma appearance by the use of simplified compartment models [26,27,28,8], little research has been done on the development of the insulin depot itself. Few studies implemented the shape of the depot into their models [29,30] based on the assumption of a spherical depot formation. In 2013 Leuenberger Jockel et al. conducted experiments on porcine tissue to examine the formation of the insulin depot in the subcutaneous tissue [31]. In the experimental setup dyed insulin was injected into a slab of porcine tissue, which was shock frozen in liquid nitrogen immediately after the injection. By the use of a cryomicrotome thin slices have been cut from the frozen sample (Figure 5 A) and the insulin appearance has been documented by taking a digital image. Using image software the information from the slices has then been used to reconstruct a three-dimensional image of the depot (Figure 5 B). The experiments revealed that the depot is taking a disk shape rather than a spherical shape due to the formation of channels in the parallel direction in the tissue (Figure 5 C). Leuenberger Jockel et al. concluded that these channels are forming only in that direction due to the fact that the tissue is composed of layers of adipose cells parallel to the skin surface, which are bound by a collagen matrix. Even though the opening process of the channels in the tissue needs further investigation and also shows great local and interpatient variability the recent experimental findings are taken into account in this numerical model in order to obtain a model that is simulating the processes of depot formation in the tissue as precisely as possible. The model is set up in the Computational Fluid Dynamics (CFD) Software ANSYS Fluent allowing high flexibility in terms of the physical properties used in the simulation as well as in the cannula geometries under consideration.

Fig. 5: A: Porcine tissue slice, B: 3D insulin depot, C: channel formation in the tissue [31]
3.2 Tissue and Insulin Properties:

To obtain realistic results when simulating the insulin depot formation by the use of a porous media approach, it is important to model the physical properties of the subcutaneous tissue as accurately as possible. The composition of the tissue is complex and random in nature with respect to cell size and local permeability etc., therefore several simplifications have been used in this simulation. As previously described a homogeneous anisotropic porous media approach has been chosen to model the tissue, consisting of a solid matrix consisting of the vascular region and the adipose cells and an interconnected void the extravascular region [22]. Interstitial fluid occupies the void space with a void fraction of $\varepsilon=0.2$ [19]. The interstitial fluid or interstitium is bathing the cells of the human body and is taking the void space between the cells. It consists of the interstitial water and its solutes such as glucose, hormones and neurotransmitters. Its function in the body is the transport of nutrients and waste products between the cells and the capillaries [32]. A mean value of 80$\mu$m has been used for the adipose cell size [13]. The interstitial fluid has a density of 1000kg/m$^3$ [33]. The viscosity of the interstitial fluid having a value of 0.0035kg/m-s [34] is slightly higher than the one of water measured at 20°C being 0.01kg/m-s. When running cases with a viscosity of 0.0035kg/m-s and 0.001kg/m-s no differences in the formation of the depot was observed but a much faster convergence was achieved when using the value of 0.001kg/m-s. For simplicity reasons the viscosity of water at 20°C has therefore been used in this simulation for the interstitial fluid. The properties of insulin have been assumed to be the same as of water. Since the insulin in the pump is stored at room temperature the properties have been evaluated at a temperature of 20°C. Even though the dynamic viscosity of water is changing with temperature ($\mu_{w,20^\circ C}=0.0010$kg/m-s, $\mu_{w,28.5^\circ C}=0.0008$kg/m-s), only insignificant differences in the depot formation could be observed when simulating cases using the properties of water at an average value of 28.5°C ranging between room temperature of 20°C and the body temperature of 37°C. Therefore the warming of the insulin to body temperature after injection has been neglected at this point of time. A list of the properties used for the tissue model and the insulin can be found below.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness subcutaneous tissue</td>
<td>13.9</td>
<td>mm</td>
</tr>
<tr>
<td>Porosity subcutaneous tissue</td>
<td>0.2</td>
<td>-</td>
</tr>
<tr>
<td>Diameter adipose cells</td>
<td>80</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>Density interstitial fluid</td>
<td>1000</td>
<td>kg/m$^3$</td>
</tr>
<tr>
<td>Viscosity interstitial fluid (water at 20°C)</td>
<td>0.001</td>
<td>kg/m-s</td>
</tr>
<tr>
<td>Density of insulin (water at 20°C)</td>
<td>998.2</td>
<td>kg/m$^3$</td>
</tr>
<tr>
<td>Viscosity of insulin (water at 20°C)</td>
<td>0.001</td>
<td>kg/m-s</td>
</tr>
</tbody>
</table>

Table 1: Properties for subcutaneous tissue and insulin used in the numerical model
3.3 Computational Domain

The geometry under consideration for this simulation consists of two parts, the tissue and the cannula. In order to evaluate the formation of the depot in the tissue by the use of a standard cannula a basic model has been set up as a 2D axisymmetric simulation (Figure 6). The 2D model is saving calculation time due to the drastically reduced number of grid nodes when compared to a 3D model. Only the tip of the cannula has been modeled since the flow at low velocities is quickly developing resulting in a very short entry length in the cannula. The top boundary of the cannula has been set up as a velocity inlet and the cannula and tissue are connected by the use of an interface. The channel in the tissue formed by the cannula as well as the top and the bottom of the domain have been defined as a wall assuming no flow through the fascia which is laying underneath the subcutaneous tissue. Since the tissue is not limited to a width of 20mm the right side of the domain has been defined as a pressure outlet.

Fig. 6: 2D axisymmetric and 3D 1/4 symmetry model of the tissue and the cannula
To be able to run cases that are non-axisymmetric such as using cannulas with holes in the wall an additional 3-dimensional model has been created using the same dimensions as in the 2D model. The cannula geometries under consideration are all symmetric and therefore only \( \frac{1}{4} \) of the cylinder had to be modeled using the symmetry properties of the solver. Based on measurements on the subcutaneous tissue in the abdominal region [14], the tissue has been modeled as a cylindrical slab representing only the subcutaneous layer without the overlaying skin layers with a thickness of 13.9mm and a radius of 20mm. For the basic case used in the development of this model a cannula with inner diameter of 0.381mm and outer diameter of 0.5588mm has been used. The length has been chosen to be 9mm, which results in an injection depth into the subcutaneous layer of 6.8mm since the skin layers lying above the subcutaneous tissue such as the dermis and epidermis have a combined thickness of 2.2mm [14]. Several cannula geometries have been tested for their influence on the depot formation once the general model has been developed such as circumferential holes in the wall of the cannula or an array of four cannulas (Figure 7).

Fig. 7: A: Standard cannula, B: cannula with circumferential holes, C: array of cannulas
3.4 Governing Equations

3.4.1 General Flow

The tissue model has been set up as a porous media where the flow is governed by the basic continuity equation including a sink term when absorption is implemented into the model and momentum equations including a momentum sink term to account for the porous media, which is restricting the flow. For the 2D model the continuity equation (Eqn.1) and the momentum equations in radial (Eqn.2) and axial (Eqn.3) direction are taking the following form:

\[
\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x} (\rho v_x) + \frac{\partial}{\partial r} (\rho v_r) + \frac{\rho v_r}{r} = S_l \tag{1}
\]

\[
\frac{\partial}{\partial t} (\rho v_r) + \frac{1}{r} \frac{\partial}{\partial x} (r \rho v_x v_r) + \frac{1}{r} \frac{\partial}{\partial r} (r \rho v_r v_r) = -\frac{\partial p}{\partial r} + \frac{1}{r} \frac{\partial}{\partial x} \left[ r \mu \left( \frac{\partial v_r}{\partial x} + \frac{\partial v_x}{\partial r} \right) \right] + \frac{1}{r} \frac{\partial}{\partial r} \left[ r \mu \left( 2 \frac{\partial v_r}{\partial r} - \frac{2}{3} \left( \frac{\partial v_x}{\partial x} + \frac{\partial v_r}{\partial r} \right) \right) \right] - 2 \frac{\mu v_r}{r^2} + \frac{2 \mu}{3} \frac{v_x}{r} + \frac{v_r}{r} + M_r \tag{2}
\]

\[
\frac{\partial}{\partial t} (\rho v_x) + \frac{1}{r} \frac{\partial}{\partial x} (r \rho v_x v_x) + \frac{1}{r} \frac{\partial}{\partial r} (r \rho v_r v_x) = -\frac{\partial p}{\partial x} + \frac{1}{r} \frac{\partial}{\partial x} \left[ r \mu \left( 2 \frac{\partial v_x}{\partial x} - \frac{2}{3} \left( \frac{\partial v_x}{\partial x} + \frac{\partial v_r}{\partial r} \right) \right) \right] + \frac{1}{r} \frac{\partial}{\partial r} \left[ r \mu \left( \frac{\partial v_x}{\partial r} + \frac{\partial v_r}{\partial x} \right) \right] + M_x \tag{3}
\]

In the event that the geometry under consideration is non axisymmetric, such as it is the case with circumferential holes in the cannula a 2D simulation is not applicable. The continuity equation (Eqn.4) and the momentum equations in x-, y- and z-direction (Eqn. 5-7) are shown below:

\[
\frac{\partial \rho}{\partial t} + \frac{\partial \rho v_x}{\partial x} + \frac{\partial \rho v_y}{\partial y} + \frac{\partial \rho v_z}{\partial z} = S_l \tag{4}
\]

\[
\rho \left( \frac{\partial v_x}{\partial t} + v_x \frac{\partial v_x}{\partial x} + v_y \frac{\partial v_x}{\partial y} + v_z \frac{\partial v_x}{\partial z} \right) = -\frac{\partial p}{\partial x} + \mu \left( \frac{\partial^2 v_x}{\partial x^2} + \frac{\partial^2 v_x}{\partial y^2} + \frac{\partial^2 v_x}{\partial z^2} \right) + \rho M_x \tag{5}
\]
\[ \rho \left( \frac{\partial v_y}{\partial t} + v_x \frac{\partial v_y}{\partial x} + v_y \frac{\partial v_y}{\partial y} + v_z \frac{\partial v_y}{\partial z} \right) = -\frac{\partial p}{\partial y} + \mu \left( \frac{\partial^2 v_y}{\partial x^2} + \frac{\partial^2 v_y}{\partial y^2} + \frac{\partial^2 v_y}{\partial z^2} \right) + \rho M_y \]  

(6)

\[ \rho \left( \frac{\partial v_z}{\partial t} + v_x \frac{\partial v_z}{\partial x} + v_y \frac{\partial v_z}{\partial y} + v_z \frac{\partial v_z}{\partial z} \right) = -\frac{\partial p}{\partial z} + \mu \left( \frac{\partial^2 v_z}{\partial x^2} + \frac{\partial^2 v_z}{\partial y^2} + \frac{\partial^2 v_z}{\partial z^2} \right) + \rho M_z \]  

(7)

The approach to model porous media used in ANSYS Fluent is based on the studies on flow through packed beds by Ergun in 1952 [35]. He was able to establish a connection between pressure drop and kinetic and viscous energy losses (Eqn. 8) where the first term in the equation is the loss due to viscous losses and the second term due to inertial or kinetic losses.

\[ \frac{|\Delta p|}{L} = 150 \left( 1 - \varepsilon \right)^2 \frac{\mu v_m}{d^2} + 1.75 \left( \frac{1 - \varepsilon}{\varepsilon^3} \right) \frac{G v_m}{d} \]  

(8)

In ANSYS Fluent these loss terms are occurring as a sink term in the momentum equation (Eqn. 9).

\[ M_i = - \left( \sum_{j=1}^{3} R_{ij} \mu v_j + \sum_{j=1}^{3} C_{ij} \frac{1}{2} \rho |v| v_j \right) \]  

(9)

For a simple homogeneous media the matrices \( R \) and \( C \) reduce to diagonal matrices containing the terms \( 1/\alpha \) and \( C_2 \) on the diagonals and the sink term equation can therefore be expressed using those terms (Eqn. 10).

\[ M_i = - \left( \frac{\mu}{\alpha} v_i + C_2 \frac{1}{2} \rho |v| v_i \right) \]  

(10)
When considering the two terms of this equation separately it can be seen that the first term represents Darcy’s law for laminar flow. The second term is only relevant for cases with high velocities where \( C_2 \) acts as a correction factor taking into account the inertial losses in the porous media. To derive the input for the porous media in ANSYS Fluent the two loss terms can be compared to the Ergun equation (Eqn. 8) and the permeability \( \alpha \) in terms of the viscous resistance \( R_v \) equal to \( 1/\alpha \) (Eqn. 11) and the inertial loss coefficient \( C_2 \) (Eqn. 12) can be derived which are the input parameters in ANSYS Fluent.

\[
R_v = \frac{1}{\alpha} = \frac{150(1-\varepsilon)^2}{d^2\varepsilon^3}
\]  

(11)

\[
C_2 = \frac{3.5(1-\varepsilon)}{d\varepsilon^3}
\]

(12)

For cases with low flow rates the pressure drop is proportional to the velocity and the inertial loss coefficient can be considered to be negligible since it is approximately proportional to the square of the velocity. Therefore the Ergun equation reduces to the Blake-Kozeny equation for laminar flow (Eqn. 13), which results in the viscous resistance being the only input parameter for the porous media sink term in the momentum equations (Eqn. 2-3 and Eqn. 5-7).

\[
|\Delta p| = \frac{150\mu(1-\varepsilon)^2}{d^2\varepsilon^3} \nu_m
\]

(13)

Based on the experimental findings of channels forming in the parallel direction with respect to the skin surface (Figure 8) the goal was to develop a model with lower resistance to the flow in parallel direction. Using the fact that the formation of channels in one direction is also changing the porosity and therefore the permeability in the same direction, different values of viscous resistances can be achieved by varying the value of porosity. This can be clearly seen from the viscous resistance equation (Eqn. 11) with porosity to the power of three in the numerator giving smaller values for the viscous resistance with rising values of porosity.
3.4.2 Species Transport

The transport of one species within another is governed by the laws of diffusion. In ANSYS Fluent the species transport equation (Eqn. 14) calculates the change of the mass fraction of N-1 species in each cell and therefore the concentration of each species in the cell as the remaining unknown species can be easily obtained when all other mass fractions are known.

\[
\frac{\partial}{\partial t} (\rho Y_i) + \nabla (\rho \bar{v} Y_i) = -\nabla J_i + S_i \tag{14}
\]

In this study insulin is diffusing into the interstitial fluid surrounding the adipose cells. Therefore the total number of species is N=2 and the N-1=1 species that needs to be calculated is insulin. The diffusion flux J (Eqn. 15) due to concentration gradients is calculated based on the diffusion coefficient \(D=5.6E-10 \text{ m}^2/\text{s}\) which has been obtained from the literature \([36]\) and the mass fraction \(Y\).

\[
\bar{J}_i = -\rho D_{1,2} \nabla Y_i \tag{15}
\]
3.4.3 Absorption

To be able to use the model to evaluate the effect of cannula geometry on depot formation and absorption, the simulation needs to run over larger timeframes, up to several hours, and absorption added as a sink term in the species transport equation starts to play a significant role. Therefore it needs to be implemented into the model. The absorption of insulin is based on the local concentration in the tissue and is non-uniform throughout the domain. As previously described, there are many formulations of insulin analogues available categorized into slow, medium, fast and rapid acting insulin based on the timely manner they can be absorbed into the bloodstream. This study focuses only on rapid acting insulin used in insulin pumps therefore an absorption rate $B$ of 0.00039333/s has been used [36]. Due to the variation of concentrations of insulin in the tissue ranging from mass fractions of one to zero, it is not possible to specify a constant sink term that is valid throughout the domain. For every cell in the domain, the mass fraction of insulin needs to be obtained and based on that the absorption of insulin from this specific cell can be calculated by use of the absorption rate constant $B$. This has been achieved by implementing a User Defined Function (UDF) in lieu of the insulin sink term in ANSYS Fluent (APPENDIX A) which is looping over all cells in the domain at every time step calculating an individual amount of insulin absorption (Eqn. 16). The mass sink term for the species insulin has to appear in the continuity equation (Eqn. 1 and Eqn. 4) in order to achieve mass conservation.

$$S_i = -Y_i B \rho_i$$  (16)
3.5 Fluent Solver Setup

The solution of a flow problem and the corresponding governing equations is depending on how the solver is setup in Fluent. Some of the settings used in this simulation are described in the following section.

The simulation in ANSYS Fluent can be setup using single precision or double precision. Solving the solution with double precision means that the numbers used in the solution have twice as many decimal places when compared to single precision. This of course means the double precision number takes up more memory and makes the simulation much slower. Due to the higher precision the solution tends to be more accurate especially in simulations where small relative differences are significant. The simulation of insulin in the tissue is mainly governed by diffusion with the absence of high velocities and it showed that the use of double precision, even though more time extensive, showed much better accuracy and faster convergence when compared to single precision. The simulation time, which was quit extensive using the double precision solver in serial mode was greatly reduced when setting up the cluster and running the simulation in parallel mode. When setting up the simulation it has to be determined which solver is used. It can be selected between pressure-based and density-based solver. In general it can be said that the pressure-based solver has been developed for low velocity incompressible flows while the density based solver gives better results in compressible flow at higher MACH numbers. In the pressure-based solver used in this simulation the pressure field is obtained by solving a pressure correction equation. The mixing and the transport of species without reaction are calculated by solving for the convection diffusion equation, which gives the local mass fraction of the species. As heat transfer does not play a role the diffusion coefficient is not a function of temperature and the diffusion flux can be solved by the use of the constant dilute approximation, which considers only Fickian diffusion.

Different methods and algorithms can be used in Fluent as a scheme to solve the discretized governing equations. The SIMPLE algorithm (Semi-Implicit Method for Pressure Linked Equations) is chosen which is a numerical solution to solve the Navier Stokes equations, which was developed by Spalding and Patankar in the early 1970s [15]. The SIMPLE algorithm is as the name indicates a fairly straightforward method but it proved very robust. The SIMPLE scheme is a pressure-based segregated algorithm, which means that the governing equations to obtain the solution variables are solved sequentially (Figure 9). The evaluation of pressure is done in a guess-and-correct fashion.
Fig. 9: Sequence of operations for SIMPLE algorithm
ANSYS Fluent uses the finite volume or control volume approach. The main step in this method is the integration of the governing equations over a control volume in order to obtain a discretized equation, which can be solved numerically. The volume integrals are then rewritten into surface integrals by the use of Gauss’s divergence theorem. By the use of differencing schemes the properties at the faces of the control volume can be approximated. The following shows the differencing schemes used in this simulation:

- Gradient: Least Squares Cell Based
- Pressure: PRESTO!
- Momentum: Second Order Upwind
- Species: Second Order Upwind

Least squared cell base is used to evaluate the gradients at the cell faces. When using higher order differencing schemes in an unstructured grid, such as when using polyhedral meshes, it is recommended to use this method over the default cell based gradients in order to get more accurate flow solutions. In order to discretize the momentum equations the pressure values on the cell faces are needed. When using standard discretization this is obtained from the cell center pressure values. When using porous media it is recommended to use the PRESTO! Scheme (PREssure STaggering Option), which gives more accurate results since the cell face pressure values are calculated using a staggered control volume about the face which is similar to the use of a staggered grid. The differencing scheme used for momentum and species equations is done by the use of the Second Order Upwind scheme. Other than central differencing the Upwind schemes are able to take the direction of the flow into account. The face values are derived based on the values of the upstream node. Therefore the scheme is very stable when convection plays a role in the simulation and has strong transportive properties. Higher order upwind schemes such as the one used in this simulation take into account more neighboring nodes and therefore reduce the discretization errors.

When solving a transient simulation not only the spatial but also the temporal discretization of the governing equations is needed as a rate of change term is added to the equation. That means every term in the equation needs to be integrated over a time step $\Delta t$. The pressure-based solver is using the implicit scheme, which is using properties at time $t + \Delta t$ to calculate the time integral. The implicit scheme is unconditionally stable but requires small time steps for accurate results since it is a first-order scheme.
3.6 Grid and Time Step Independence:

In order to obtain a grid and time step independent solution, measurements for the positive and negative depot height, as well as the outspread, have been taken and compared to the next finer grid/time step. For all simulations convergence is assumed when residuals become less than $10^{-5}$. It has been defined that grid and time step independency is realized when the error of these measurements compared to the next finer grid/time step is in the range of 0.2%. The 2D model has been simulated with meshes ranging from 14,000 to 900,000 nodes and grid independency was achieved for a mesh with 128,000 nodes. The 3D case has been setup with meshes between 450,000 and 6,000,000 nodes and grid independency was obtained using a mesh of 4,500,000 nodes. For both cases, 2D and 3D, the transient solution has been evaluated with time steps of 0.2s, 0.1s, 0.05s, 0.02 and 0.01s where the value of 0.05s showed adequate results with an error within the range of 0.2% for both cases (Figure 10).

![Graphs showing grid and time step independency for 2D and 3D simulation](image)

**Fig. 10:** Grid and time step independency for 2D and 3D simulation
CHAPTER 5: RESULTS AND DISCUSSION:

4.1 Depot Formation Simulation:

In order to obtain a realistic model for the formation of the depot in the tissue, different approaches to define the local viscous resistance have been used in the simulation, starting with an injection volume of 5U and an injection time of 25s. The shape of the depot in the tissue when using a porous media approach is depending on the viscous and inertial resistance to the flow in each direction. As discussed in the previous chapter, the resistance to the flow at very low velocities is dominated by the viscous resistance, and therefore the inertial resistance can be neglected. Based on the recent experimental results [31] it is assumed, that channels are forming in the parallel direction in the tissue. The formation of channels in one direction gives rise to a change in porosity in that particular direction having an impact on permeability and viscous resistance. Considering these aspects the tissue has been modeled as a homogeneous porous media with anisotropic permeability (Table 2). From the viscous resistance equation (Eqn. 7), it can be seen that the higher the values for the porosity the smaller becomes the viscous resistance and therefore the outspread of insulin is increasing in that direction. Different approaches with the porosity as a variable (Table 3) have been executed and compared to the experimental results.

<table>
<thead>
<tr>
<th>Porosity</th>
<th>Permeability (m²)</th>
<th>Viscous Resistance (1/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>1.99E-13</td>
<td>5.02E+12</td>
</tr>
<tr>
<td>0.2</td>
<td>5.33E-13</td>
<td>1.88E+12</td>
</tr>
<tr>
<td>0.25</td>
<td>1.19E-13</td>
<td>8.44E+11</td>
</tr>
<tr>
<td>0.3</td>
<td>2.35E-12</td>
<td>4.25E+11</td>
</tr>
<tr>
<td>0.35</td>
<td>4.33E-12</td>
<td>2.31E+11</td>
</tr>
</tbody>
</table>

Table 2: Porosity and according permeability and viscous resistance

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Perpendicular Porosity</th>
<th>Parallel Porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>CASE2</td>
<td>0.15</td>
<td>0.2</td>
</tr>
<tr>
<td>CASE3</td>
<td>0.15</td>
<td>0.25</td>
</tr>
<tr>
<td>CASE4</td>
<td>0.2</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Table 3: Simulated cases with anisotropic permeability (Case1 isotropic spherical reference)
Cases 1 to 4 are set up with a porosity value that has been kept constant throughout the domain in both directions parallel and perpendicular. Case 1 is set up as a reference with the same resistance in parallel and perpendicular direction and is subsequently showing a spherical depot formation. Cases 2 to 4 with different values of porosity in parallel and perpendicular direction are showing as expected a disk shaped depot formation rather than a spherical shape (Figure 11). For cases 1 to 4 with the porosity as a constant, it can be seen that the more the values between the two directions differ from each other the flatter the depot shape becomes since the injected insulin is preferably taking the way of the least resistance to the flow.

Fig. 11: Insulin concentration contours showing the depot formation using 5U insulin at t=25s
Cases 1 to 4 have also been run using a higher dose of 15U of insulin. The injection velocity has been kept constant resulting in an injection time of 75 seconds. Since the porosity is kept constant in these cases the depots for the higher doses are showing the same geometrical shapes as with the smaller doses (Figure 12).

![Diagram showing contours of 1% insulin concentration cases 1 to 4](image)

**Fig. 12:** Contours of 1% insulin concentration cases 1 to 4 (A: 5U/t=25s, B: 15U/t=75s)
Following the experimental results [31], the parallel outspread of the depot at higher doses above 10U is slowing down and the depot is starting to grow more into the perpendicular direction instead. This means the shape of the depot is differing between low doses and high doses taking a flatter shape for the lower doses. It is assumed that this effect arises because the channels preferably form around the tip of the cannula and become smaller further away from the needle tip. Therefore the resistance to further parallel outspread becomes higher than the resistance to penetrate deeper into the tissue. When analyzing the experimental results it can be observed that the parallel outspread does not go much further than a radius of 6mm from the needle tip even when a higher amount is injected. To implement this behavior into the model cases 5 to 8 are set up with a locally varying value for the porosity in the parallel direction while the porosity in perpendicular direction is kept constant (Table 4). This has been achieved by the use of linear and polynomial viscous resistance profiles in the parallel direction (Figure 13, 15, 17). Whereas there is a constant increase of the resistance for the linear profile with increasing distance from the cannula, the polynomial profile remains merely constant in close proximity to the cannula tip but rises when reaching a distance of 6mm from the tip. In Fluent this variable viscous resistance is implemented by the use of a UDF, which is calculating a specific local value for the viscous resistance at each point in the parallel direction (Appendix B).

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Perpendicular Porosity</th>
<th>Parallel Porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE5</td>
<td>Constant: 0.2</td>
<td>Linear: 0.35-0.2</td>
</tr>
<tr>
<td>CASE6</td>
<td>Constant: 0.2</td>
<td>Polynomial: 0.35-0.2</td>
</tr>
<tr>
<td>CASE7</td>
<td>Constant: 0.2</td>
<td>Poly/Linear: 0.35-0.2</td>
</tr>
</tbody>
</table>

Table 4: Simulated cases with varying parallel porosity

All the cases with variable viscous resistance values are run with porosity values varying from 0.35 at the needle tip to 0.2 further away from the needle. The same porosity values have been used as constants in case 4, which is therefor used as a reference to show the impact of the varying viscous resistance profiles on the shape of the depot.
At lower doses of 5U it can be seen that in case 5 with linearly increasing viscous resistance (Figure 13) the parallel outspread is already slowed down when compared to case 4. The depot for the higher dose of 15U is showing the desired reduction in outspread forming a less flat depot. Due to the constant increase of the resistance starting from the needle tip the depot at low doses becomes a more spherical shape as well, which is not desired (Figure 14).

![Linear Resistance](image1)

**Fig. 13:** Parallel viscous resistance curve using a linear function

![Contours](image2)

**Fig. 14:** Contours of 1% insulin concentration cases 4 and 5 (A: 5U/t=25s, B: 15U/t=75s)
In order to retain the flat shape at low doses a polynomial curve has been used for case 6 in order to keep the resistance low at close proximity to the cannula tip and increase it at a distance further away to slow down the outspread of higher doses without restricting the lower doses (Figure 15). The depot for low doses is therefore showing only little difference to case 4 as desired but at higher doses the outspread is reduced when compared to case 4 (Figure 16). Using this setup the resistance is keeps increasing with distance from the needle tip beyond a porosity value of 0.2, which is not realistic.

![Polynomial Resistance Curve](image)

**Fig. 15:** Parallel viscous resistance curve using a polynomial function

![Contours of 1% insulin concentration cases 4 and 6](image)

**Fig. 16:** Contours of 1% insulin concentration cases 4 and 6 (A: 5U/t=25s, B: 15U/t=75s)
Case 7 is a modification of case 6 implementing a constant resistance once the polynomial curve has reached a value corresponding to a porosity of 0.2 (Figure 17). This has been achieved using an “if-else” command in the Viscous Resistance UDF (Appendix B). This case is based on the assumption that there are no more channels at a certain distance from the needle tip and therefore the viscous resistance must remain at a constant value corresponding to a porosity of 0.2. The simulation shows the desired elliptical shape at low doses and a reduced outspread at high doses (Figure 18).

![Polynomial/Linear Resistance Curve](image1)

**Fig. 17:** Parallel viscous resistance curve using a polynomial function and a constant value

![Contours of 1% insulin concentration cases 4 to 7](image2)

**Fig. 18:** Contours of 1% insulin concentration cases 4 to 7 (A: 5U/t=25s, B: 15U/t=75s)
When comparing all linear and polynomial cases it can be seen that case 7 has the best overall accordance to the experimental results showing the flat and disc shape depot for low doses and a reduced outspread in the higher doses. The results for cases 4 to 7 using 5U insulin and 15U insulin are compared to the experimental results, which are plotted as 25\textsuperscript{th} and 75\textsuperscript{th} quantiles as thin lines and median as thick line (Figure 19, 20).

![Diagram](image)

**Fig. 19:** Contours of 1\% insulin concentration cases 4 to 7 using 5U at t=25s compared to experimental results (thin lines: 25\textsuperscript{th} & 75\textsuperscript{th} quantiles, thick line: median) [31]
Even though cases 5 to 7 are showing better agreement to the experimental results and implement the behavior at higher doses, the linear and polynomial functions used for the viscous resistance calculations are arbitrary and cannot be validated without further investigations in the channel formation process in the tissue. Therefore these cases will not be used in the model developed in this study at this point of time. Currently, it is not known if the channels only form around the needle tip due to the insulin injection and if they become smaller and smaller further away from the needle tip or if they exist prior to the injection and spread throughout the tissue in the parallel direction. When these factors are known the variable porosity approach developed in this study can be adopted to conduct a parametric study in order to find an adequate profile for the viscous resistance.
Case 3 with constant resistances in both directions based on a porosity of 0.15 in perpendicular direction and 0.25 in parallel direction, combining to a desired overall porosity of 0.2, is showing reasonable agreement to the experimental data (Figure 21, 22). The viscous resistance formulation is not based on arbitrary curves but on the findings that the porosity in parallel direction is higher than in perpendicular direction. Case 3 has therefore been selected as the master setup used in all further simulations.

Fig. 21: Contours of 1% insulin concentration case 3 using 5U at t=25s compared to experimental results (thin lines: 25th & 75th quantiles, thick line: median) [31]
Fig. 22: Contours of 1% insulin concentration case 3 using 15U at t=75s compared to experimental results (thin lines: 25th & 75th quantiles, thick line: median) [31]
In the following an attempt to model the random distribution of the channels in the parallel direction in the tissue is presented. For both cases 3a and 3b the porosity values of case 3 have been used. For case 3a the tissue has been divided into layers parallel to the skin surface with a thickness of 250μm, corresponding to about three times the adipose cell diameter. In a random fashion 50% of these layers have been selected to represent a channel in the tissue (Figure 23). The viscous resistance for these layers is based on a porosity of 0.25. For the remaining layers a porosity of 0.15 has been assigned, resulting in a higher viscous resistance. This setup has been implemented in ANSYS Fluent by the use of a user defined function running an “if else” statement referencing the location of the channels in the tissue (Appendix C). As expected, the resulting depot formation is showing a more random outline with a preferable outspread at the location of the channels (Figure 24).

Fig. 23: Randomly assigned channels to account for tissue variability

Fig. 24: Depot formation case 3a with variable channel distribution (A: 5U 25s, B: 15U 75s)
In case 3b the domain has also been divided into layers with the same thickness of three times the adipose cell diameter. To account for the irregular appearance of the channels in parallel direction, a random porosity has been assigned to each layer within the range of 0.15 to 0.25 (Figure 25) by the use of an “if, else if” statement (Appendix D). Similar to the results in case 3a it can be observed that the depot is showing an irregular depot outline (Figure 26). Even though both cases take into account the random appearance of the channels in the tissue, more research has to be done to be able to create a model with a proper distribution and sizing of the channels in the tissue. If these factors are known the models developed above could be a useful approach in order to obtain a more realistic depot formation model. All future calculations in this project have been run based on case 3 without taking into account the random distribution of the channels due to the better comparability when running simulations with different cannula geometries.

Fig. 25: Randomly assigned porosity values to account for tissue variability

Fig. 26: Depot formation case 3b with variable porosity distribution (A: 5U 25s, B: 15U 75s)
4.2 Absorption Simulation:

When the timeframe of the simulation is extended beyond the pure bolus injection time of 25-75s absorption is starting to play a significant role. When adding the process of absorption to the simulation and running it over several hours it is possible to obtain insulin disappearance curves. The data for the absorption curve is obtained by exporting an ASCII file including mass fraction and volume for each cell in the computational domain at various time steps during the calculation. The file name is including the time step to be able to allocate the extracted data. The ASCII files for each time step are then loaded into MATLAB by the use of an automated script (Appendix E) importing the mass fraction and volume from the files. The mass fraction and volume of a cell is then converted into the amount of insulin in the cell and all cells are added to obtain the total amount of insulin at each time step. The result is then plotted over time using the time step information in the file name. The absorption curve (Figure 27) that has been obtained running case 3 with an injected amount of 5U and an absorption rate constant of 0.00039333/s is showing good agreement to other numerical and analytical models [36] and is therefore a good validation for the developed model.

![Fig. 27: Remaining insulin in depot in % after 5U bolus injection](image)

The data obtained from the absorption model can be used for further calculations such as the estimation of the blood glucose concentration. When extending the time frame of the simulation even further and adding the basal rate injection the remaining insulin in the depot can be tracked over the course of a whole day (Figure 28). The peaks in the resulting curve are the bolus injections used to balance the increased carbohydrate intake during breakfast lunch and dinner. The injected bolus volume in this simulation has been chosen as 5U/t=25s for breakfast at 7am, 15U/t=75s for lunch at 12pm and 5U/t=25s for
dinner at 6pm. The basal rate has been kept at a constant rate of 1U/3600s between the bolus rates resulting in an injection velocity of 0.00002436m/s. A detailed documentation of the injections rates, time steps and the data exports for this simulation can be seen in Appendix F.

Fig. 28: Absorption curve for bolus and basal injection over a timeframe of 16 hours showing bolus peaks for breakfast, lunch and dinner
4.3 Impact of Cannula Geometry on Depot Formation and Diffusion

In the previous chapters a numerical model of the insulin depot formation has been developed which is used in the following to evaluate the impact of the cannula geometry on the formation of the insulin depot. Therefore several cannula geometries have been simulated using the two-dimensional and three-dimensional model (Table 5). The injection time and injected volume has been kept at 5U and 25 seconds for all simulations except case 11 in order to be able to compare the different cases. Case 3, which has been selected in the previous chapter as the master case using a standard cannula, is compared to the cases with variable cannula geometries to see if they have an impact on the formation of the depot. Case 3 has therefore been transformed into a 3D simulation in order to compare it to the non-axisymmetric simulations. The error between the 2D and the 3D setup for case 3 has been measured being below 0.2%.

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Cannula Diameter (mm)</th>
<th>Injection time (s)</th>
<th>Circumferential Holes</th>
<th>Cannulas</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE3 (2D/3D)</td>
<td>STD cannula</td>
<td>25</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>CASE10 (2D)</td>
<td>Small cannula</td>
<td>25</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>CASE11 (2D)</td>
<td>STD cannula</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>CASE12 (3D)</td>
<td>STD cannula</td>
<td>25</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>CASE13 (3D)</td>
<td>¼ STD cannula</td>
<td>25</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 5: Simulated cases in 2D and 3D with different cannula geometries

As a first step the impact of the diameter of the cannula has been investigated in case 10. Changing the diameter of the cannula from 0.381mm to 0.254mm results in an increase of the inlet velocity from 0.01754m/s to 0.1579m/s when using same injection volume and time. It was observed that the shape of the depot shows only minimal variation and case 3 and case 10 are therefore not compared in a plot. In order to get to high enough velocities, which would possibly have an impact on the shape of the depot, the cannula would have to be very thin which is not feasible. Another way of changing the velocity other than using smaller cannulas is to use shorter injection times. An injection time of 1s has been tested in case 11 resulting in an injection velocity of 0.4386m/s. The comparison to the injection time of 25 seconds showed that the depot is flatter and smaller with the faster injection time (Figure 29 A), which is due to the fact that the insulin has no time to diffuse into the tissue. This can be seen when comparing the thickness of the diffusion bands between case 3 and case 11 (Figure 30). When running the case without injection to 25s it can be seen that the depot is bigger now than the one with continuously injection over 25s since the full amount is injected in only 1
second and has more time to diffuse into the tissue. It can also be seen that the difference in viscous resistance has a higher effect on convection than it has on pure diffusion, which spreads evenly in all directions (Figure 29 B). Following this result it can be concluded that at higher injection velocities the differences in viscous resistance become more relevant and the depot after injection time is flatter.

Fig. 29: Depot formation case 3 and case 11 (A: case 3 at 25s case11 at t=1s, B: both cases at t=25s)

Fig. 30: Diffusion bands (99-1% insulin) after injection of 5U (A: case 3 at t=25s, B: case 11 at t=1s)
When adding circumferential holes in the wall of the cannula with a distance ranging between 0.75-3mm (Table 6) to the needle tip the formation of initially two depots was observed (Figure 31). The two depots at the needle tip and at the location of the circumferential holes in the cannula are merging into one depot during injection with a distinct shape still showing the initially separate depots when the largest distance of 3mm is used. Adding circumferential holes is resulting in a less spread out depot shape in the parallel direction, which is thicker in the perpendicular direction (Figure 32). The larger the distance between the holes and the tip of the cannula the higher the depot becomes in perpendicular direction as can be seen when comparing the case with the largest distance to the case without holes in the cannula (Figure 33). Varying the distance of the holes to the needle tip the height of the depot in the tissue can be influenced. The maximum distance between the holes and the cannula tip depends on the thickness of the subcutaneous layer, which varies from patient to patient.

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Cannula Diameter (mm)</th>
<th>Distance of holes to cannula tip (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE12a</td>
<td>STD cannula</td>
<td>0.75</td>
</tr>
<tr>
<td>CASE12b</td>
<td>STD cannula</td>
<td>1.5</td>
</tr>
<tr>
<td>CASE12c</td>
<td>STD cannula</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 6: Variable parameter for case 12

Fig. 31: Section view of the depot formation at different time steps for case 12 using 4 circumferential holes with different distances to the cannula tip
Fig. 32: Depot formation varying the distance of the circumferential holes to the cannula tip

Fig. 33: Depot formation comparing case3 and case12c at t=25s (A: side view, B: top view)
A similar pattern of initially distinct depots was observed when using an array of 4 cannulas. Three simulations have been run with this setup with a distance between the cannulas ranging from 2.5-10mm (Table 7). The formation of initially 4 depots was observed that merge into one depot for the cases with smaller distance between the cannulas (Figure 34). In contrast to case 12 where the depot increased in height the results for case 13 are showing a flatter shape than when only using a single standard cannula (Figure 35). With increasing distance between the cannulas the depot becomes flatter. At some point, when increasing the distance further, the formation of 4 separate depots can be observed. These depots are flatter than the single depot using a standard cannula and have a combined larger parallel outspread in the tissue (Figure 36).

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Cannula Diameter (mm)</th>
<th>Distance between cannulas (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASE13a</td>
<td>¼ STD cannula</td>
<td>2.5</td>
</tr>
<tr>
<td>CASE13b</td>
<td>¼ STD cannula</td>
<td>5</td>
</tr>
<tr>
<td>CASE13c</td>
<td>¼ STD cannula</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 7: Variable parameter for case 13

Fig. 34: Section view of depot formation at different time steps for case 13 using an array of 4 cannulas
Fig. 35: Depot formation varying the distance between cannulas in the array

Fig. 36: Depot formation comparing case 3 and case 13c at t=25s (A: side view, B: top view)
To evaluate if the different designs of the cannula have any impact on the absorption of insulin, the absolute volume of the depot has been measured. Therefore, the volumes of all cells containing an insulin concentration of more than or equal to 1% have been measured after the injection of 25 seconds. With increasing volume of the depot, the interface between the insulin and the interstitial fluid is increasing, which is improving the diffusion of insulin into the tissue. The cases 12 and 13, which are showing the greatest variability in the shape of the depot have been compared to case 3 using a standard cannula (Figure 37). It can be seen that for both cases 12 and 13 the depot shows a larger absolute volume when compared to case 3. It can be observed, that the biggest increase can be achieved when obtaining separate insulin depots such as in case 12c and 13c. The increased interface in these cases results in a much-improved diffusion of the insulin into the tissue. When specifically considering case 13c with an absolute volume of 0.0969ml it can be seen that the initially injected volume of 0.05ml insulin has almost doubled due to the improved diffusion into the tissue.

Fig. 37: Absolute volumes of the depot (insulin concentration >=1%) using circumferential holes in the cannula (case 12) and an array of cannulas (case 13) compared to a standard cannula (case 3)
CHAPTER 5: CONCLUSION

The usage of numerical models to simulate fluid flow in the human body is essential in the development of new biomedical devices since experimentation and collection of data involving the human body is typically rather difficult. The following conclusions were drawn in the development of the numerical model for the insulin depot formation in the subcutaneous tissue and the use of the developed model to evaluate the impact of flow rate and cannula geometry on the insulin depot formation:

1. Using the same viscous resistance in all direction results in a spherical depot.

2. Using different porosity values in the calculation of the viscous resistance for the parallel and perpendicular direction results in a disk-shaped depot formation. The more the porosity values in parallel and perpendicular direction vary from each other the flatter the depot becomes. This approach takes into account the anisotropic permeability of the tissue.

3. Using a variable value for the viscous resistance in parallel direction, which is remaining merely constant in proximity of the cannula tip and increasing further away, allows to account for the limited outspread at higher injection volumes.

4. A more realistic depot model considering the variable composition of the tissue can be obtained by randomly distributing the channels or the porosity in the numerical model.

5. The process of absorption needs to be implemented into the numerical model when running the simulation over longer time frames of several minutes or hours.

6. Changes of the diameter of the cannula within reasonable range showed no impact on the depot formation.

7. Increasing the mass flow rate results in a slightly flatter depot shape.

8. When using holes in the wall of the cannula or an array of cannulas the formation of several separate insulin depots can be observed.

9. When using an array of 4 cannulas the absolute volume of the insulin depot could be increased by up to 25% when compared to a single standard cannula, resulting in a larger interface between insulin and interstitial fluid and improving the diffusion of insulin into the tissue.

Further experiments have to be conducted to investigate the channel formation process in the tissue into more detail in order to validate a precise viscous resistance profile in the tissue.
REFERENCES


[35] Ergun S. Fluid flow through packed columns, Chemical Engineering Progress 48/2 (1952) 89-94

APPENDIX A

User Defined Function for variable insulin sink term

#include "udf.h"

DEFINE_SOURCE(insulin_sink,c,t,dS,eqn)
{
    real sink;
    if(C_YI(c,t,0)>0)
    {
        /* sink term definition */
        sink = -(C_YI(c,t,0) * 0.00039333 * 998.2 * 0.2);

        /* derivative of sink term */
        dS[eqn] = 0;
    }
    else
    {
        sink = dS[eqn] = 0;
    }

    return sink;
}
APPENDIX B

User Defined Function for polynomial/linear viscous resistance profile

#include "udf.h"

DEFINE_PROFILE(parvisrespoly,t,i)
{
    real x[ND_ND];
    cell_t c;

    begin_c_loop(c,t)
    {
        C_CENTROID(x,c,t);

        if (x[1] <= 0.008)
        { /* polynomial viscous resistance profile */
            F_PROFILE(c,t,i) = ((1e23)*((x[1])*(x[1])*(x[1])*(x[1])*(x[1]))-((1e18)*((x[1])*(x[1])*(x[1])*(x[1])))-((8e18)*((x[1])*(x[1])*(x[1]))+((4e16)*((x[1])*(x[1])))-((3e13)*(x[1]))+2e11;
        }
        else /* constant viscous resistance */
        { F_PROFILE(c,t,i) = 1.88e12;
        }

    }
    end_c_loop(c,t)
}
APPENDIX C

User Defined Function for variable channel distribution

#include "udf.h"

DEFINE_PROFILE(RvChannels,t,i)
{
    real x[ND_ND];
    real a;
    cell_t c;

    begin_c_loop(c,t)
    {
        C_CENTROID(x,c,t);
        if (((x[0] > -0.0045) && (x[0] < -0.00425))
            || ((x[0] > -0.00425) && (x[0] < -0.004))
            || ((x[0] > -0.0035) && (x[0] < -0.00325))
            || ((x[0] > -0.00275) && (x[0] < -0.0025))
            || ((x[0] > -0.0025) && (x[0] < -0.00225))
            || ((x[0] > -0.002) && (x[0] < -0.00175))
            || ((x[0] > -0.00175) && (x[0] < -0.0015))
            || ((x[0] > -0.00125) && (x[0] < -0.001))
            || ((x[0] > -0.00075) && (x[0] < -0.0005))
            || ((x[0] > -0.0005) && (x[0] < -0.00025))
            || ((x[0] > 0.00025) && (x[0] < 0.0005))
            || ((x[0] > 0.0005) && (x[0] < 0.00075))
            || ((x[0] > 0.01) && (x[0] < 0.00125))
            || ((x[0] > 0.00175) && (x[0] < 0.002))
            || ((x[0] > 0.002) && (x[0] < 0.00225))
            || ((x[0] > 0.00275) && (x[0] < 0.003))
            || ((x[0] > 0.00325) && (x[0] < 0.0035))
            || ((x[0] > 0.00375) && (x[0] < 0.004))
            || ((x[0] > 0.004) && (x[0] < 0.00425))
            || ((x[0] > 0.00475) && (x[0] < 0.005)))
            a = 8.44e11;
        else
            a = 5.02e12;
        F_PROFILE(c,t,i) = a;
    }
    end_c_loop(c,t)
}
APPENDIX D

User Defined Function for variable porosity distribution

#include "udf.h"

DEFINE_PROFILE(RvPorosity,t,i)
{
    real x[ND_ND];
    real a;
    cell_t c;

    begin_c_loop(c,t)
    {
        C_CENTROID(x,c,t);
        if (((x[0] >= -0.005) && (x[0] < -0.00475)))
            a = 1.88e12;
        else if (((x[0] >= -0.00475) && (x[0] < -0.0045)))
            a = 8.44e11;
        else if (((x[0] >= -0.0045) && (x[0] < -0.00425)))
            a = 5.02e12;
        else if (((x[0] >= -0.00425) && (x[0] < -0.004)))
            a = 8.44e11;
        else if (((x[0] >= -0.004) && (x[0] < -0.00375)))
            a = 8.44e11;
        else if (((x[0] >= -0.00375) && (x[0] < -0.0035)))
            a = 1.88e12;
        else if (((x[0] >= -0.0035) && (x[0] < -0.00325)))
            a = 5.02e12;
        else if (((x[0] >= -0.00325) && (x[0] < -0.003)))
            a = 1.88e12;
        else if (((x[0] >= -0.003) && (x[0] < -0.00275)))
            a = 8.44e11;
        else if (((x[0] >= -0.00275) && (x[0] < -0.0025)))
            a = 1.88e12;
        else if (((x[0] >= -0.0025) && (x[0] < -0.00225)))
            a = 8.44e11;
        else if (((x[0] >= -0.00225) && (x[0] < -0.002)))
            a = 5.02e12;
        else if (((x[0] >= -0.002) && (x[0] < -0.00175)))
            a = 8.44e11;
        else if (((x[0] >= -0.00175) && (x[0] < -0.0015)))
            a = 1.88e12;
        else if (((x[0] >= -0.0015) && (x[0] < -0.00125)))
            a = 8.44e11;

        cell_loop(c, i)
        {
            if (x[i] >= a) 
                \[ \text{function value} \] ...
        }
    }
}
else if (((x[0] >= -0.00125) && (x[0] < -0.001)))
a = 5.02e12;
else if (((x[0] >= -0.001) && (x[0] < -0.00075)))
a = 8.44e11;
else if (((x[0] >= -0.00075) && (x[0] < -0.0005)))
a = 1.88e12;
else if (((x[0] >= -0.0005) && (x[0] < -0.00025)))
a = 8.44e11;
else if (((x[0] >= -0.00025) && (x[0] < 0)))
a = 8.44e11;
else if (((x[0] >= 0) && (x[0] < 0.00025)))
a = 1.88e12;
else if (((x[0] >= 0.00025) && (x[0] < 0.0005)))
a = 8.44e11;
else if (((x[0] >= 0.0005) && (x[0] < 0.00075)))
a = 1.88e12;
else if (((x[0] >= 0.00075 && (x[0] < 0.001)))
a = 8.44e11;
else if (((x[0] >= 0.001) && (x[0] < 0.00125)))
a = 5.02e12;
else if (((x[0] >= 0.00125) && (x[0] < 0.0015)))
a = 8.44e11;
else if (((x[0] >= 0.0015) && (x[0] < 0.00175)))
a = 5.02e12;
else if (((x[0] >= 0.00175) && (x[0] < 0.002)))
a = 5.02e12;
else if (((x[0] >= 0.002) && (x[0] < 0.00225)))
a = 8.44e11;
else if (((x[0] >= 0.00225) && (x[0] < 0.0025)))
a = 1.88e12;
else if (((x[0] >= 0.0025) && (x[0] < 0.00275)))
a = 5.02e12;
else if (((x[0] >= 0.00275) && (x[0] < 0.003)))
a = 8.44e11;
else if (((x[0] >= 0.003) && (x[0] < 0.00325)))
a = 1.88e12;
else if (((x[0] >= 0.00325) && (x[0] < 0.0035)))
a = 1.88e12;
else if (((x[0] >= 0.0035) && (x[0] < 0.00375)))
a = 1.88e12;
else if (((x[0] >= 0.00375) && (x[0] < 0.004)))
a = 8.44e11;
else if (((x[0] >= 0.004) && (x[0] < 0.00425)))
a = 5.02e12;
else if (((x[0] >= 0.00425) && (x[0] < 0.0045)))
a = 5.02e12;
else if (((x[0] >= 0.0045) && (x[0] < 0.00475)))
a = 1.88e12;
else if (((x[0] >= 0.00475) && (x[0] < 0.005)))
a = 8.44e11;
else
a = 1.88e12;

F_PROFILE(c,t,i) = a;
}

end_c_loop(c,t)
}
APPENDIX E

MATLAB script for automated data import

% Only for 2D Simulation
% Create plot for remaining insulin in tissue
% Files have to be named: Step-xxxx
% Time steps will be selected in ascending order

clear all
clc

% Plot axis definition: Set max injected Insulin Volume (ml)
MaxVolume=0.06;
% Plot axis definition: Set max import time step (s)
MaxTimeStep=40000;

% Create Time Error
time=0;
% Create Insulin array
InsulinVolume=0;
save 'InsulinVolume';

% Creat a struct of the current directory
filelist = dir;
names = {filelist.name};
maxlen = max(cellfun(@length, names));
padname = @(s) sprintf(['%0' num2str(maxlen) 's'], s);
namesPadded = cellfun(padname, names, 'UniformOutput', false);
[~, sortOrder] = sort(namesPadded);
filelist = filelist(sortOrder);

clearvars maxlen names namesPadded padname sortOrder

% Determine the number of files in the current directory
num_file = length(filelist);
% Process file names.
% Skip first two directory names '. ' and '..'
for i = 3:1:num_file

    % Define current file name
    filename = filelist(i).name;

    % Check file for proper identification/
    if strfind(filename,'Step') > 0

    %---------------------start of subscript---------------------

        % Initialize variables
        pathname=cd;
        pathname=strcat(pathname,'\');

        % Store timestep from filename (filename has to be in seconds)
        timestep=regexp(filename,'\d+','match');
        timestep=str2double(timestep);
        timestep=(timestep/3600);
        time(end+1)=timestep;

        filename=strcat(pathname,filename);
        startRow = 2;

        % Format string for each line of text
        formatSpec = '%*44s%17f%f%^\n\r';

        % Open the text file
        fileID = fopen(filename,'r');

        % Read columns of data according to format string
        dataArray = textscan(fileID, formatSpec, 'Delimiter', '', 'WhiteSpace', '', 'EmptyValue', NaN,'HeaderLines',startRow-1, 'ReturnOnError', false);

        % Close the text file
        fclose(fileID);
% Allocate imported data to column variable names
tracer = dataArray{:, 1};
cellvolume = dataArray{:, 2};

% Clear temporary variables
clearvars filename pathname startRow formatSpec fileID dataArray ans;

% Convert cell volume of 2D axisymmetric case %
cellvolume=cellvolume*2*pi;

% Multiply cell volume and mass fraction of tracer %
m3=cellvolume.*tracer;

% Sum volum in cells and convert from m3 to ml %
Insulinml=sum(m3)*1000000;

% Apply void fraction of 0.2 and multiply by factor 2 due to symmetry %
Insulintotal=(Insulinml/100)*20;

InsulinVolume(end+1)=Insulintotal;

save('time.mat','time');
save ('InsulinVolume.mat','InsulinVolume');

clearvars -except filelist num_file InsulinVolume time MaxTimeStep MaxVolume;

end

%-----------------------------end of subscript-----------------------------

end

save('time.mat','time');
save ('InsulinVolume.mat','InsulinVolume');
% Plot absorption curve
plot(time,InsulinVolume,'LineWidth',2)
axis([0,MaxTimeStep/3600,0,MaxVolume])
grid on
legend('Rapidly-acting insulin')
xlabel('Time after subcutaneous injection (hours)','Fontsize',10')
ylabel('Insulin remaining at injection site (ml)','Fontsize',10')

clearvars filelist i num_file MaxTimeStep MaxVolume filename pathname startRow
formatSpec fileID dataArray ans;
APPENDIX F

Bolus-Basal-Bolus Simulation:

Bolus1: 7am, 5U/25s, velocity: 0.01754244m/s,
   Time step 0.05 steps 500 (25s)   Export: 20
Basa1: 7am to 12pm: 1U/3600s, velocity: 0.00002436m/s
   Time step 0.05 steps 700 (1min)  Export: 20
   Time step 0.05 steps 4800 (5 min)  Export: 100
   Time step 0.1 steps 33,000 (1hr)  Export: 500  1hr
   Time step 0.1 steps 36,000 (2hrs) Export: 500   2hrs
   Time step 0.1 steps 36,000 (3hrs) Export: 500   3hrs
   Time step 0.1 steps 36,000 (4hrs) Export: 500   4hrs
   Time step 0.1 steps 36,000 (5hrs) Export: 500   5hrs
Bolus2: 12pm, 15U/75s, velocity: 0.01754244m/s
   Time step 0.05 steps 1500 (75s)   Export: 20
Basa2: 12pm to 6pm: 1U/3600s velocity 0.00002436m/s
   Time step 0.05 steps 900 (2min)  Export: 20
   Time step 0.05 steps 3600 (5min) Export: 100
   Time step 0.1 steps 33,000 (1hr)  Export: 500   6hrs
   Time step 0.1 steps 36,000 (2hrs) Export: 500   7hrs
   Time step 0.1 steps 36,000 (3hrs) Export: 500   8hrs
   Time step 0.1 steps 36,000 (4hrs) Export: 500   9hrs
   Time step 0.1 steps 36,000 (5hrs) Export: 500  10hrs
   Time step 0.1 steps 36,000 (6hrs) Export: 500  11hrs
Bolus3: 6pm, 5U/25s, velocity: 0.01754244m/s,
   Time step 0.05 steps 500  Export: 20
Basa3: 6pm to 7am: 1U/3600s velocity 0.00002436m/s
   Time step 0.05 steps 700 (1min)  Export: 20
   Time step 0.05 steps 4800 (5min) Export: 100
   Time step 0.1 steps 33,000 (1hr)  Export: 500  12hrs
   Time step 0.1 steps 36,000 (2hrs) Export: 500  13hrs
   Time step 0.1 steps 36,000 (3hrs) Export: 500  14hrs
   Time step 0.1 steps 36,000 (4hrs) Export: 500  15hrs
   Time step 0.1 steps 36,000 (5hrs) Export: 500  16hrs