PATIENT-SPECIFIC CONTROLLER FOR AN IMPLANTABLE ARTIFICIAL PANCREAS

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Declaration

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

Ho Yick Wai Yvonne Audrey

4 Jan 2016

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Contents

Summary

Diabetes if untreated results in prolonged hyperglycaemia which can lead to diabetic retinopathy, neuropathy and nephropathy. Treatment for diabetes include oral medication and insulin therapy. The risk associated with insulin therapy is hypoglycaemia. Diabetics monitor their blood glucose levels using capillary blood glucose monitors or Continuous Glucose Monitoring Systems (CGMS).

The aim of the artificial pancreas is to improve the quality of diabetics' lives. An electromechanical artificial pancreas essentially consists of a glucose sensor, drug delivery system and a controller. An issue with subcutaneous glucose sensing and insulin delivery are the time lags between venous and interstitial fluid glucose concentrations. An implantable artificial pancreas employing intravenous glucose monitoring and insulin delivery more closely mimics pancreatic insulin secretions to the portal vein.

Model Predictive Control (MPC) can be extended for hypoglycaemia avoidance and to take various constraints into account. Parameters of models used have inter-patient variance hence patient specific models are preferred. Patient parameters can change over time with physiological changes. An artificial pancreas system that adaptively tunes the patient specific controller is proposed.

The artificial pancreas is to be implanted in the ilium and the device has to fit the space and encapsulate the controller and the insulin delivery system. Automatic insulin dosage is handled by a low-power microcontroller, with wireless communication for data logging. As an implantable glucose sensor is planned to be used in the artificial pancreas, two fluid flow connections integrating intravenous glucose sensing and insulin delivery were investigated

and compared.

Scalable micropump units were designed to reduce flow rate such that larger micropumps, which are more easily available, can be used for insulin delivery. The microchannels divert part of the flow from the pump back to the reservoir and the amount diverted depends on the cross-sectional area of the channel. The insulin delivery subsystem consisting of micropump, microchannel and insulin reservoir were tested under various reservoir fill levels and various pump settings to map pump controller inputs of voltage and frequency to insulin delivery rates. Pump to pump variation was also characterized.

Optimization in MPC can be solved using gradient-based methods or search heuristics. Gradient methods are established and efficient but suffer from local minima traps, while search heuristics can be used for non-convex problems. A hybrid optimization scheme comprising of Primal-Dual-Interior-Point (PDIP) and a modified Ant System search heuristic is used for MPC. The Ant algorithm is used when PDIP fails to converge. Simulation of the optimization scheme showed promising results.

In vivo experiment on a porcine model was conducted with an implantable artificial pancreas prototype which included the scalable micropumps and MPC with PDIP optimization embedded on a microcontroller. Normoglycaemia was reached in 100 minutes of peak glucose levels.

Patient specific parameters of the Minimal Model were estimated using CGMS glucose readings from 11 free-living patients. The data was first pre-processed to extract the monotonically decreasing sections. Nonlinear least squares was then performed to obtain the parameters. This process was also applied to glucose readings from virtual patients.

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List of Abbreviations

AP ..... Artificial Pancreas

ASIC ..... Application-Specific Integrated Circuit

BG ..... Blood Glucose

CSII ..... Continuous Subcutaneous Insulin Infusion

FPGA ..... Field Programmable Gate Array

IDMM ..... Insulin Dependent Diabetes (Type 1 diabetes)

ISF ..... Interstitial Fluid

IVGTT ..... Intravenous Insulin Tolerance Test

MDI ..... Multiple Daily Injections

MPC ..... Model Predictive Control

NIDMM ..... Non-insulin Dependent Diabetes (Type 2 diabetes)

NLLS ..... Nonlinear Least Squares

PCB ..... Printed Circuit Board

PID ..... Proportional-Integrative-Derivative (control)

sc-sc ..... Subcutaneous glucose sensing and insulin delivery

Chapter 1

Introduction

The artificial pancreas aims to improve the quality of life of diabetics by automatically regulating blood glucose levels. This thesis presents my research and development of the mechanism and control of an implantable artificial pancreas.

The objective is to develop a prototype implantable artificial pancreas with intravenous insulin delivery. This includes design of the insulin delivery system, the implementation of the closed-loop controller, development of optimization schemes for dosage and parameter estimation of the mathematical model used.

1.1 Diabetes Mellitus

Diabetes Mellitus is a chronic disease that is characterized by persistent hyperglycaemia i.e. elevated blood glucose levels. There are an estimated 347 million people with diabetes in 2014 [4], about 9% of the global adult population (18 years and above) [5].

Diabetes is classified into Type 1, Type 2 and gestational diabetes; and while other forms exist, they are rare [4]. The two main types of diabetes, Type 1 and Type 2 diabetes, account for almost all the diabetes cases. In the diabetic population, about 10% have Type 1 while around 90% have Type 2 diabetes [4]. Gestational diabetes affects a proportion of pregnancies and may cause complications but is not chronic. Type 1 diabetics are unable to produce their own insulin and have to depend on exogenous insulin. Type 2 diabetes is a result of insulin resistance where glucose storing cells do not utilize insulin as efficiently. Double diabetes patients are Type 1 diabetics who develop insulin resistance of Type 2 diabetes [6].

The result of diabetes is elevated blood glucose, which when left untreated can lead to retinal problems, and lower-extremity diseases, in particular peripheral vascular disease (PVD) and peripheral neuropathy. Complications from diabetes are the leading cause of non-accident amputations.

1.1.1 Diabetes Therapy

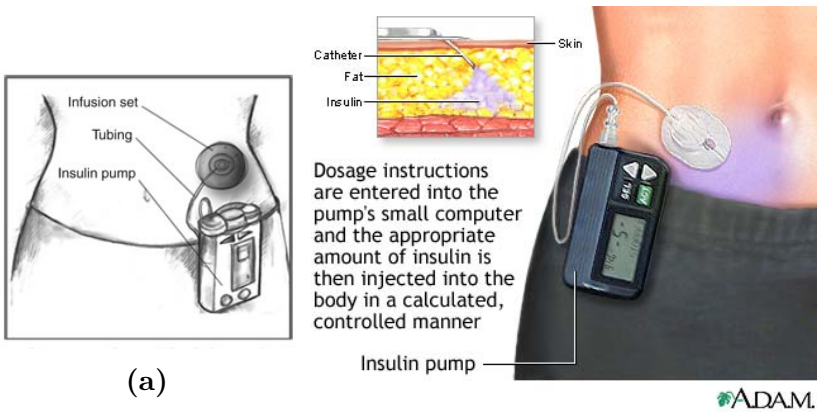
Therapy for diabetes includes oral medication and administration of exogenous insulin, depending on the type of diabetes and severity. Type 2 diabetics are prescribed oral medication which suppresses endogenous glucose production in the liver (e.g. Metformin), stimulate the pancreas to release more insulin, increase the cells sensitivity to insulin or a mixture of the above [7]. For more severe Type 2 cases and for almost all Type 1 diabetics, exogenous insulin is required.

Insulin is delivered via subcutaneous injections or the more recently introduced subcutaneous insulin pumps. The insulin dose and type of insulin (rapid acting or slow acting) is prescribed by the clinician and the patient

can make some adjustments according to the amount of carbohydrates eaten or their measured blood glucose levels. The slow acting insulin is given as a basal dose, while the fast acting insulin is a bolus, taken 15 minutes before a meal.

Currently, the most common outpatient administration of insulin therapy is through self-administered subcutaneous injections. This is also referred to as Multiple Daily Injections (MDI). The injection sites are usually at the abdomen, sometimes on the upper thigh or buttocks.

Infusion pumps systems that deliver insulin subcutaneously are also available in the market and are referred to as Continuous Subcutaneous Insulin Infusion (CSII) systems. These pumps are connected to an insulin reservoir and to a catheter which is taped into place after subcutaneous insertion around the abdominal area (Figure 1.1).



(a) **(b)**

Figure 1.1: Continuous subcutaneous insulin delivery (a) Parts of the CSII system and where they are usually worn (b) Delivery is in the subcutaneous layer, just below the epidermis.
(a) Source: NIDC. Available from http://diabetes.niddk.nih.gov/dm/pubs/insulin/ [Accessed 23 April 2015] (b) Source: National Institute of Health (NIH) Available from http://www.nlm.nih.gov/medlineplus/ency/imagepages/18035.htm [Accessed 23 April 2015]

Sudden death from hypoglycaemia is a known risk of insulin therapy and

is a source of fear for patients and their caregivers. While hypoglycaemia during waking hours can be quickly identified by the patient (sweats, feeling faint) and rectified with glucose intake, prolonged hypoglycaemic excursions while asleep have resulted in 'death-in-bed' syndrome.

1.1.2 Blood Glucose Measurement and Monitoring

Diabetics have to monitor their blood glucose levels regularly. The terms "blood glucose" and "plasma glucose" are commonly used interchangeably although the quantity of interest is glucose concentration in blood plasma. There are two main types of blood glucose measuring methods for diabetics to use at home - blood glucose monitors and Continuous Glucose Monitoring Systems. The sensors used in these two systems are enzymatic electrochemical sensors, based on the principle of catalytic glucose oxidation.

Most diabetics currently measure their blood glucose with capillary blood glucose meters, for example, Roche Accu-chek (Fig 1.2 or One Touch UltraMini (http://www.onetouch.com/). The finger is pricked with a lancet to collect a drop of blood which is placed on a disposable sensor strip, which is then inserted into the glucose monitor to read. This is usually done up to several times a day for Type 1 patients and less frequently for Type 2 patients [8]. Haemoglobin A1c (hbA1C) levels are also used to monitor patients' blood glucose control, however this is done during regular check-ups and requires laboratory analysis.

Wearable glucose sensors became commercially available around 2004, with several companies such as Medtronic, Dexcom Inc producing and selling sensor systems. The sensor system includes a wireless transmitter which communicates with a small handheld pager-sized device, sending glucose

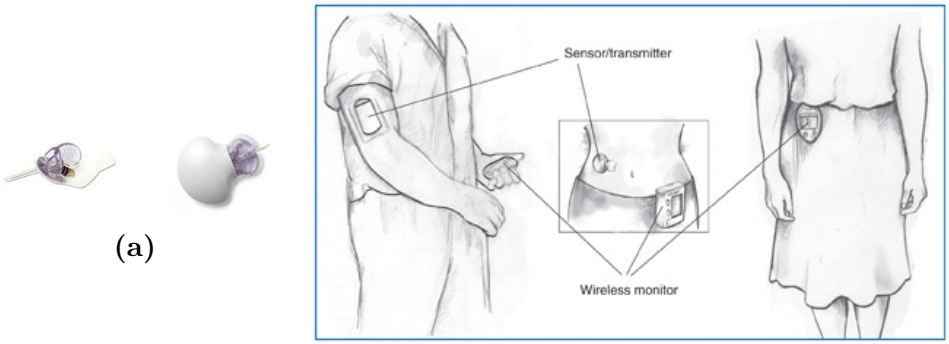
Figure 1.2: Capillary blood glucose monitor (Roche Accu-chek Active) with disposable sensor strips and fingerprick device holding lancets. Source: Roche Available from http://www.roche.com/pages/downloads /photosel/071002/html/detail_4.html [Accessed 23 April 2015]

readings every few minutes (usually between 5 and 15 mins) and hence are commonly referred to Continuous Glucose Monitoring Systems (CGMS) (Figure 1.3). The frequent glucose level reporting enables diabetics to closely monitor their glucose levels and take action quickly in case of glucose excursions.

These disposable glucose sensors are worn externally, on the abdomen or upper arm, and the sensor is inserted into the subcutaneous via a catheter, measuring glucose levels in the interstitial fluid (ISF). Although the sensor insertion is relatively painless, each disposable sensor is expensive and also requires change every 3 to 7 days. CGMS also does not remove the need for finger prick blood testing on the monitors, as these are used to calibrate the CGMS every day.

1.2 Artificial Pancreas

The artificial pancreas would function in a similar way to the biological pancreas for maintaining blood glucose homeostasis by automatically delivering



(a) **(b)**

Figure 1.3: Continuous glucose monitoring sensor and system (a) Glucose sensor, and sensor with attached transmitter Medtronic sof-sensor (Medtronic MiniMed, Inc.); (b) The glucose sensor is worn on the upper arm or abdomen and transmits readings to the pager sized monitor wirelessly. (a) Source: Online. Image by Doug Kanter. Available from http://dougkanter.wordpress.com/2011/06/16/my-treatment-the-hardware/ [Accessed 23 April 2015] (b) Source: National Diabetes Information Clearinghouse (NDIC). Available from http://diabetes.niddk.nih.gov/dm/pubs/glucosemonitor/index.aspx [Accessed 23 April 2015]

appropriate amounts of hormones like insulin and glucagon in response to current blood glucose levels. This improves diabetes therapy in several ways —automatic drug delivery lessens the worry about appropriate insulin dosage for the day's meals and activities, reduces hypoglycaemic excursions and, in some cases, also treat hypoglycaemia with glucose or glucagon.

Several types of artificial pancreas are being developed using various approaches —bioengineered, gene therapy and electromechanical. The bioengineering approach (also known as bio-artificial pancreas) involves implanting an islet sheet —encapsulated alpha and beta cells (islets of Langerhans) in a layer of bioengineered tissue —into the body. In gene therapy, genes are injected, for example, such that cells in the intestine or the duodenum would react to glucose levels and reproduce and release insulin that was injected with the gene. An electromechanical artificial pancreas essentially

comprises of glucose sensor, pumps to deliver exogenous drugs and an embedded controller to calculate the required doses. Some groups refer to it as a "robo-pancreas" [9] or "bionic pancreas" [10].

The solution for diabetes via the artificial pancreas is a wide area of research. Multiple approaches are still being considered and under active research and development and researchers in various fields contribute to advancement of diabetes therapy in their own areas of expertise. Recent advances of computer, sensor and actuator technologies enable the construction of a robust clinical viable electromechanical implantable device in the not too distant future. This electromechanical engineering approach to the artificial pancreas will be the focus of this thesis.

Two artificial pancreases, Biostator and Nikkiso STG-22, were developed in 1970s and used intravenous glucose sensing and intravenous insulin delivery. Due to their size, their usage was confined to within the hospital. Advances in Microelectromechanical systems (MEMS) technology have resulted in devices small enough for wearable and implantable artificial pancreases [11].

Most of the current clinical trials for the artificial pancreas and closed-loop control algorithms are mainly using subcutaneous sensing and subcutaneous insulin delivery, based on state-of-the-art technology available that have obtained approval by governmental regulatory boards. As regulatory time for medical equipment is long, this incremental approach minimizes regulatory risk. This also improves likelihood of patient acceptance of new technology. The aim of the Artificial Pancreas Project (APP) spearheaded by the Juvenile Diabetes Research Foundation (JDRF) is to minimise the time for an artificial pancreas to be available to patients. The subcutaneous route seems to be the most pragmatic solution for now [12].

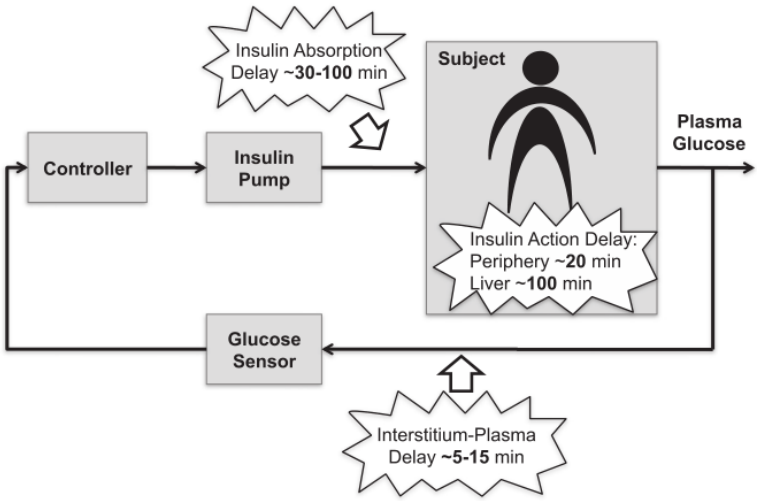


Figure 1.4: Artificial Pancreas closed loop delays in subcutaneous sensing and delivery [1]

A key issue with subcutaneous sensing or delivery is the time lag. ISF glucose concentrations trend with plasma glucose, but with a 5 to 15 minute lag [13]. In addition, insulin delivered through the subcutaneous layer takes 30 to 100 minutes to be absorbed [1]. Another issue is that these devices are worn externally, which limits some activities where the sensor or pump can be dislodged.

An implanted artificial pancreas with venous delivery of insulin mimics the pancreas which secretes insulin into the portal vein. This area is still under research and current issues include bio-compatibility of the implant materials and clotting at the site of vascular insertion [12, 14]. A suitable site of implantation of a device is the ilium, a hollow space in the pelvis; and the device outlet to be attached to the illiac vein (portal vein), which is close to the pancreas. This would allow the drug delivery to mimic pancreatic secretions into the blood stream.

1.3 Patient Specific Controllers

The glucose sensing and drug delivery components of the artificial pancreas are linked by the controller. Several closed-loop control schemes are available and the most commonly used ones are Proportional-Integral-Derivative (PID) and Model Predictive Control (MPC) [15]. There are various metrics for control objectives - for example to bring blood glucose to a target level, to keep it in a zone, or the total time in euglycaemic range.

MPC is a promising control scheme as it can be extended for hypoglycemia avoidance and can also take into account controller constraints [16]. In MPC, the future states of the system are predicted by a known model of the dynamic process of the system and used to find the optimal input. Parameters of the models can have great inter-patient variance, hence the model should be patient specific for better accuracy.

Patient physiology and corresponding mathematical model parameters are liable to change over time due to increased insulin resistance, and other metabolic, health and lifestyle changes. With a rich amount of data that can be collected, the MPC controller can be updated with the more recent parameters. Clinicians can also better monitor the disease by analysing long term trends in patient parameters. We propose an artificial pancreas system that adaptively tunes and calibrates the model as more data is collected from the CGMS.

The overview of the proposed system is shown in Figure 1.5. Initial model parameters used may be obtained from a smaller sample set. The parameters can later be adaptively tuned and calibrated at regular intervals to improve model parameter estimates. CGMS are comparatively less invasive to Intravenous or Oral Glucose Tolerance Tests (IVGTT, OGTT) and can

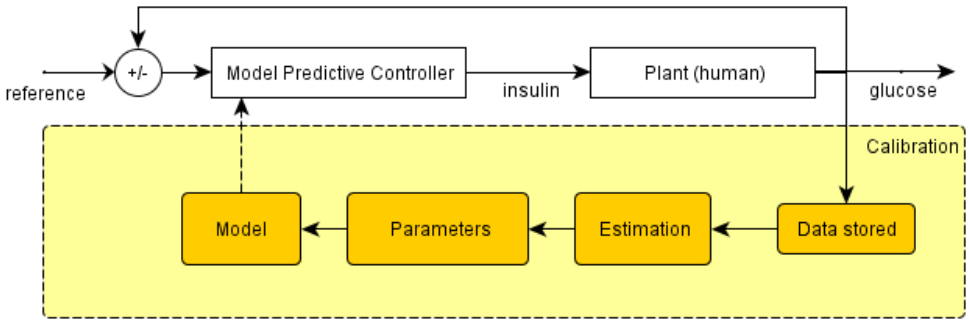


Figure 1.5: Overview of artificial pancreas system with adaptive recalibration of model parameters

provide frequently sampled blood glucose values of 5 minute intervals. Over a longer time frame, drifts in parameters due to physiological changes can also be tracked by regular calibration.

1.4 Objective and Scope

Our objective is to research, develop and experiment a prototype implantable artificial pancreas which delivers insulin intravenously. The scope of this thesis includes designing and fabricating the drug delivery mechanism, and also the development and implementation of the closed-loop controller. Development of the controller include obtaining parameters of the mathematical model used and the optimization schemes for optimal dosage.

An implantable artificial pancreas can improve the quality of life of diabetes sufferers in many ways. Firstly, automated drug delivery will remove the stress related to self-administered dosing. Secondly, although wearable devices are small and generally unobtrusive, they will still inhibit certain activities like swimming or anything that may dislodge the pump or sensor, unlike for the case of an implanted device. Most importantly, intravenous

sensing and delivery can improve therapy as it removes the lags between glucose and insulin concentrations in the blood and ISF.

The insulin delivery system required a new design of fluid flow connections between output, pump and reservoir. Investigation into the pumping characteristics across pumps and over reservoir fill levels was done. An in vivo experiment was conducted to assess the viability of an implantable artificial pancreas.

MPC was chosen as the control scheme with MPC parameters (N_p and N_c) for optimal blood glucose regulation. N_p is the prediction horizon, which is how long into the (predicted) future to track the effects of the control output. The control horizon N_c is how long into the future the control outputs vector is. As the interior point method, commonly used to solve optimization problems, did not always converge, a hybrid optimization scheme was developed that applied a modified Ant System heuristic in the case.

The mathematical model used in MPC representing the body's glucose-insulin over time has several model parameters to be determined. These parameters vary from person to person and can change over time. Patient specific parameters for the model used in the MPC was obtained from a virtual patient. The viability of obtaining patient parameters from free-living actual patients was also studied.

1.5 Thesis Organization

The rest of the thesis is organized as follows :

- In Chapter Two, glucose metabolism in humans and diabetes pathology

is described in greater detail;

- Chapter Three presents a literature review of current artificial pancreas state of the art, mathematical models of glucose-insulin interactions, control schemes for blood glucose regulation and various optimization methods;
- The design and development of an implantable artificial pancreas are presented in Chapter Four;
- An optimization algorithm based on Ant Systems is proposed in Chapter Five;
- Experimental results of the implantable artificial pancreas using the Model Predictive Control described in the preceding two chapters are reported in Chapter Six;
- In Chapter Seven, parameter estimation from glucose readings of free-living patients is presented; and
- Artificial pancreas with patient specific control is discussed and concluded in chapter eight.

Chapter 2

Glucose Metabolism and Diabetes

2.1 Glucose and its utilization

Glucose is the primary source of energy for the human body. It is also commonly known as dextrose and is a monosaccharide i.e. a simple sugar and has a chemical formula of $C_6H_{12}O_6$. It is obtained from carbohydrates ingested and then broken down into simpler sugars in the small intestine, where it leaves through the walls of the small intestine, aided by glucose transporter GLUT2, into the bloodstream.

Through glycolosis, pyruvate (pyruvic acid) is formed and energy released. In aerobic respiration (requiring oxygen), the pyruvate enters the mitochondria and through the citric acid cycle (Krebs cycle) is oxidised to finally form carbon dioxide and water (Figure 2.1). The simplified overall reaction is $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + H_2O + heat$. Pyruvate is reduced to lactate in anaerobic (oxygen not present) conditions in a process referred to as fermen-

tation. Lactate can be oxidised to pyruvate or be used in gluconeogenesis to form glucose.

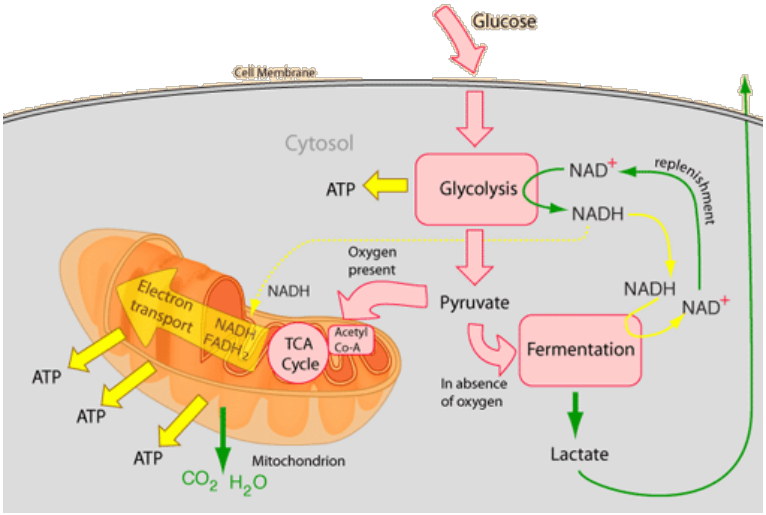


Figure 2.1: Aerobic respiration in cells. Glucose undergoes glycolysis, forming pyruvate which is further oxidised in the cell, releasing carbon dioxide, water and energy
Source: Hyperphysics, Georgia State University. Image by: C.R. Nave, 2012. Available from http://hyperphysics.phy-astr.gsu.edu/hbase/biology/celres.html [Accessed 24 Feb 2015]

Glycogen is polysaccharide form of glucose and its chemical formula is given as $(C_6H_{12}O_6)_n$. It is synthesised from glucose monomers in an endergonic process (energy consuming), forming a branched polymer. Triglycerides are another form of stored glucose, from the esterification of fatty acids and glycerol; and is stored in adipose tissue. Fatty acids are the main source of fuel to the heart muscle. Glycogen together with triglycerides are the body's primary storage of energy. While fatty acids require oxygen to form glucose, the degradation of glycogen releasing usable glucose monomers (also called glycogenolysis) is an anerobic process.

The utilization, clearance and also the endogenous production of glucose is regulated by two pancreatic hormones - insulin and glucagon. The liver and adipose tissues utilizes the greatest percentage of glucose and store it in the

form of glycogen and triglycerides, and these processes are insulin mediated (Figure 2.2). When blood glucose levels are low, glucagon triggers the liver to convert glycogen to glucose and signals for the breakdown of triglycerides to fatty acids and glucose. Glycogen is stored in the muscles and the liver; and insulin is required to stimulate glycogen synthesis. Glycogen stored in the liver is readily mobilised to free glucose and transported to the bloodstream to fuel other organs and cells [17]. The liver contains up to 10% by weight of glycogen and absorbs over half of blood glucose. When blood glucose is low, the pancreas secretes glucagon which triggers glycogenolysis, cleaving glycogen branches and resulting in free glucose to be transported in the bloodstream. Glycogenolysis and gluconeogenesis (formation of glucose from other products) are also triggered by the hormone epinephrine. The liver is the site of endogenous glucose production and is also responsible for the 'dawn effect' where blood glucose rises before breakfast is consumed. The liver is key to glucose homoeostasis. After a meal, insulin signals the liver to start glycogenesis, clearing more than half of the glucose from the bloodstream and storing it as glycogen [17]. Insulin is then broken down in the liver and cleared. The liver also uses other hormones to sense blood glucose levels and trigger either glycogen synthesis or glycogen degradation to release free glucose. When blood glucose is low, glucagon from the pancreas triggers the degradation of glycogen (glycogenolysis) to release glucose back into the bloodstream. This regulation is important for brain function. Epinephrine (adrenalin) also triggers glycogen breakdown in a fight-or-flight response. The liver also regulates lipid metabolism, esterifying fatty acids to triglycerides to be stored in adipose tissue or breaking down fatty acids to ketones.

The brain's primary fuel source is glucose and it requires a continuous

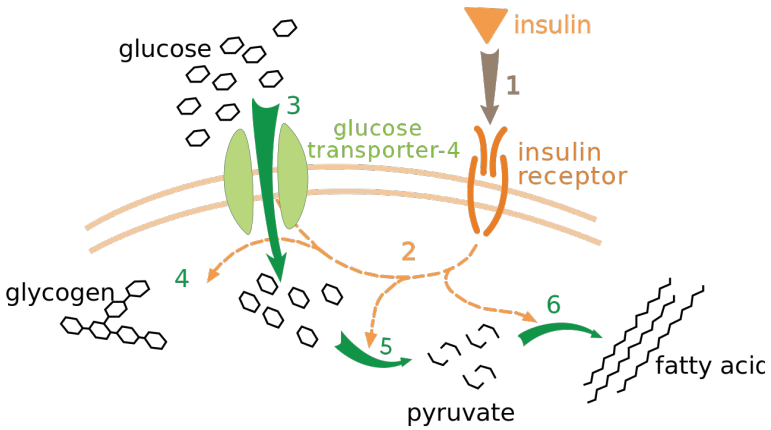


Figure 2.2: Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1), which starts many protein activation cascades (2). These include translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and triglyceride (6).
Source: Wikipedia. Caption and image credit : "Insulin glucose metabolism ZP" by XcepticZP (2007). Available from http://en.wikipedia.org/wiki/Insulin [Accessed 24 Feb 2015]

supply of glucose for normal function, consuming about 120mg glucose daily [17]. Although it does have a small store of glycogen to use during hypoglycemia [18], low blood sugar is linked to poor decision making, dizziness and fainting and prolonged severe hypoglycaemia can lead to coma and death.

The kidneys also utilize glucose as fuel in kidney cellular respiration in the process of re-absorbing minerals in the blood. The kidneys tubular cells filter glucose from the blood and absorb it to prevent it being excreted out. However when glucose tubular transporters become saturated, the glucose is excreted in the urine —an indication of high blood glucose levels.

Muscles use glycogen as a local immediate supply of glucose. The glycogen is stored in muscles in an insulin dependent process. This glycogen is unable to be used as fuel for other organs as muscles lack an enzyme for

conversion of glycogen to free glucose. These glycogen stores are depleted through exercise. Muscles also obtain glucose without insulin mediation from GLUT1 glucose transporters.

There are several glucose transporters in humans, named GLUT1 to GLUT12. It was found that at basal blood glucose levels, most of the glucose uptake was independent of insulin. In elevated blood glucose levels however, most of the glucose uptake is from insulin mediated processes [19].

From the time of carbohydrate ingestion, it takes gut 15 minutes to break down the glucose and release it to the bloodstream. There the glucose gets transported to various parts of the body and is moved out of the bloodstream into muscles and adipose tissue, hence there is a lag between glucose concentration peaks and troughs in the blood stream and the periphery.

Blood glucose concentrations are given in mg/dl or $mmol/l$. The molecular weight of glucose is 180, hence a value in $mmol/l$ is multiplied by 18 to get the equivalent glucose concentration in mg/dl. For diagnostic purposes, the plasma glucose concentration is obtained from venous blood, as opposed to arterial or capillary blood.

2.2 Insulin

Insulin is a hormone produced in the pancreas, in particular the beta-cells in the islets of Langerhans. Insulin triggers glycogen synthesis in the liver and skeletal muscles. It also triggers the esterification of fatty acids in adipose tissue where triglycerides are stored.

The secretion of insulin is governed by the amount of the glucose in the

bloodstream in a negative feedback control loop. When blood glucose levels reach normal or lower, insulin secretion halts. Other hormones like norepinephrine (noradrenaline) can suppress insulin secretion. The insulin is secreted in pulses with a period of 3 to 6 minutes, and the oscillating secretion is currently linked to the downregulation of insulin receptors on cells and insulin resistance [20, 21]. Insulin secreted enters the portal vein and into the bloodstream for use in the liver, muscles and adipose tissue, and its presence triggers other biochemical processes in the body.

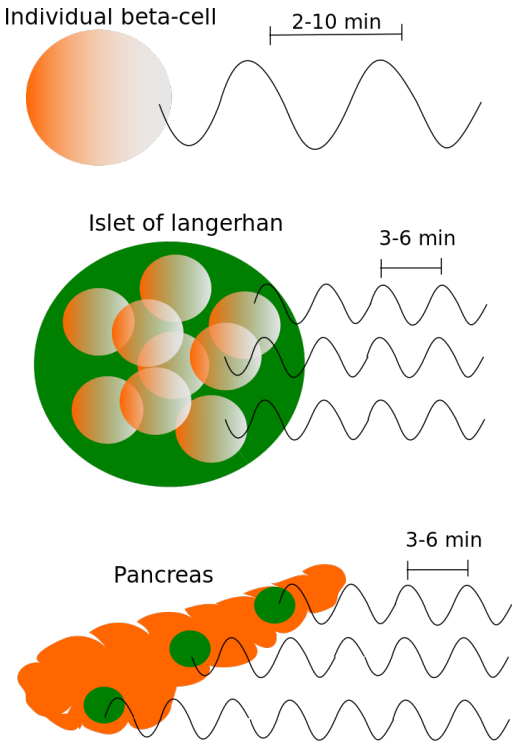


Figure 2.3: Pulsatile secretion of insulin. Each beta cell has an oscillation period of 3-10 minutes. The islets of Langerhans a period of 3 to 6 minutes and the secretion is synchronised such that the pancreas secretes insulin at the same frequency [21].
Image credit : Häggström, Mikael. "Medical gallery of Mikael Häggström 2014". Last retrieved 22 Feb 2015 http://en.wikipedia.org/wiki/Insulin_oscillation

In 1922, insulin extracted from ox-calf pancreas and successfully treated Type 1 diabetics who were in comatose from ketoacidosis [22]. In 1960s, biosynthetic insulin based on recombinant DNA started production and is

now widely used in insulin therapy; examples include Humulin and Novolin. In 1990s and 2000s, insulin analogues were introduced, e.g. insulin lispro and insulin aspart. Insulin analogues are also known as "insulin receptor ligands". These insulin analogues mimic human insulin effects on glucose regulation.

Fast acting insulin are used during mealtimes to immediately act on blood glucose increases from carbohydrate ingestion. Long acting insulin is active up to 24 hours in the body and mimics the effect of endogenous basal insulin. Some insulin are sold as a combination of slow and fast acting, eg Novolog Mix 70/30. Most diabetics administer their prescribed insulin subcutaneously through injections.

Endogenous insulin has a half life of 4-6 minutes and is estimated to be degraded within 1 hour from its release. After the cell has used insulin to absorb glucose, it can either return the insulin molecule to circulation or degrade it. The liver and kidneys are primary sites for insulin clearance.

Besides secreting insulin, the pancreas also produces glucagon. Glucagon is a peptide hormone produced by the α-cells of the pancreas. Glucagon triggers the liver to convert glycogen stored into glucose, releasing glucose back into the bloodstream.

2.3 Diabetes

The World Health Organization (WHO) diagnoses diabetes as either a) fasting plasma glucose level more than $7.0 mmol/l$, b) plasma glucose more than $11.1 mmol/l$ two hours after a $75g$ oral glucose load as in a glucose tolerance test, c) showing symptoms of hyperglycaemia and casual plasma

glucose more than 11.1$mmol/l$ (200mg/dl) or d) glycated haemoglobin (HbA1C) more than 48$mmol/mol$ ($\leq$ 6.5 DCCT %) [23]. The American Diabetic Association (ADA) uses a similar criteria for diagnosis [24].

Type 1 diabetes occurs when an autoimmune dysfunction kills beta-cells in the pancreas, disabling endogenous insulin production. It is also known as Juvenile diabetes and previously referred to as insulin dependent Diabetes (IDDM). It is usually diagnosed at a young age and patients require insulin to manage the disease.

Type 2 diabetes is also known as Adult-onset diabetes and was previously referred to as non-insulin dependent diabetes (NIDDM). Type 2 patients have functioning pancreases and have endogenous insulin. Type 2 diabetes is caused by insulin resistance —where the efficiency of insulin is reduced and cells do not use insulin as effectively. As Type 1 and Type 2 have different causes, there are diabetics who have double diabetes —Type 1 patients without endogenous insulin production who also develop insulin resistance later on in life.

The effect of diabetes regardless of type is the same —hyperglycaemia. Prolonged hyperglycaemia leads to blood vessel damage which is the cause of diabetic retinopathy, neuropathy and nephropathy. Retinal blood vessel damage can lead to vision loss and blindness. Nerve damage from microvascular complications show up as numbness, altered pain sensation, skin damage, foot ulcers and other diseases of the extremities which may lead to lower limb amputations [25]. Persistent hyperglycaemia also damages the capillaries in the kidney glomeruli which leads to fluid filtration dysfunction and other effects of kidney failure.

On the other hand, insulin therapy which is mismanaged can result in overly

low blood sugar. Hypoglycaemia can lead to reduced glucose availability to the brain [26] and may result in coma and death. This is especially significant at night when the patient is sleeping and unaware of blood glucose levels.

Exercise which results in muscle contractions can aid in blood regulation [27] which is important for diabetics. Muscles express GLUT1 and GLUT4 glucose transporters and GLUT4 is responsible for a larger portion of the glucose uptake in muscles. Insulin triggers the movement of GLUT4 from intracellular vesicles to the plasma membrane to absorb glucose. Besides insulin, muscle contractions also increase the expression of GLUT4, resulting in glucose uptake in muscles without insulin [27]. For diabetics, insulin independent glucose uptake through exercise can play a part in blood sugar management.

Chapter 3

Literature Review

This chapter presents the prior work on Artificial Pancreas development including current clinical trials, development and research direction. The literature related to control schemes and physiological models are reviewed.

3.1 Artificial Pancreas State of the Art

The discovery and use of insulin in the 1920s gave hope to diabetics for treatment. Since then, better understanding of human metabolism, disease pathology, together with insulin development and electronics technology enable automatic regulation of blood glucose. Research into the electromechanical Artificial Pancreas (AP) started in the 1960s; and in the 1970s, the two artificial pancreas became commercially available for hospital inpatient use - the Biostator [28] and the Nikkiso STG-22 which was still used even in 2009 [29]. These used intravenous blood for glucose sensing and closed-loop regulation with intravenous insulin delivery. The control algorithm for the Biostator was similar to a PID [30]. These artificial pancreases were meant for in-patient use and were too large and heavy for ambulatory use.

Biostator required blood to be drawn from the forearm for sensing and insulin delivered via the forearm; and was used for short-term inpatient care. The review paper by Cobelli, Renard and Kovatchev [1] give a historical perspective to the development of the artificial pancreas technology, an overview of current sensor and insulin delivery systems, and their limitations. The paper also presents an overview of control schemes and requirements for the AP, including low level control, automatic dosage and adaptive systems. Another paper by Cobelli et al. [15] tracks the historical development and current literature of glucose-insulin models, modelling methodology and control schemes. These papers though comprehensive have a greater emphasis on subcutaneous sensing and insulin delivery for Type 1 patients. They are useful to understand current research direction of international consortiums and provide a good introduction to thee technology and algorithms. [16] is a brief overview of the current state of AP research direction, modeling and control schemes for the hardware and automatic dosage algorithms. In [31], Hovorka presents the research direction of various groups working on closed loop control and artificial pancreas, and their various prototypes and clinical studies (as of 2008).

Several clinical trials have been reported in recent years, marking milestones closer to a commercially available artificial pancreas. The AP in these trails mostly use the subcutaneous sensing and subcutaneous insulin delivery (sc-sc) routes (Figure 3.1). Bock et al. [32], a group from Medtronic, a glucose sensor and insulin pump manufacturer, in collaboration with the JDRF, published results in 2015 of a feasibility study of an sc-sc AP. 8 patients used the Medtronic AP for 7 days, 2 days of in-patient training followed by 5 days of usage, in outpatient normal life setting. The control algorithm used was a PID with meal announcements, and PID parameters

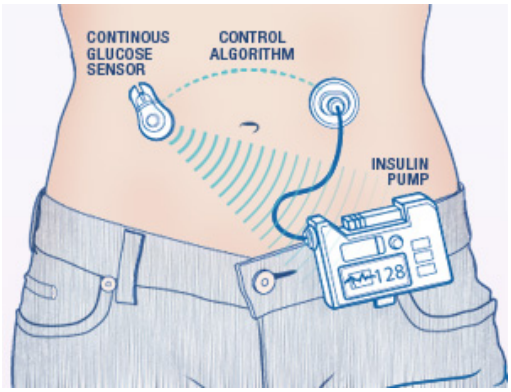


Figure 3.1: Artificial Pancreas with subcutaneous glucose sensor and subcutaneous insulin delivery. Source: Online from Mayo Clinic. Available from http://www.mayo.edu/research/labs/artificial-pancreas/overview [Accessed 27 Apr 2015]

were personalised for each patient.

Several groups in collaboration worked on Diabetes Assistant, DiAs, which uses a smartphone for the artificial pancreas control and user interface platform. The pilot study [33] was conducted in Montepellier and Padova with two Type 1 diabetics and showed feasibility of the system. Follow up proof of concept was conducted and results published in [34] and [35], which reported reduction of time in hypoglycaemia with closed-loop control compared to open-loop pump infusion therapy. This was conducted with 20 Type 1 diabetic adults, across 4 centres in Europe and USA. The patients tested the AP over 2 days in an outpatient free-living situation, though monitored by healthcare professionals remotely. The AP used the sc-sc routes using sensors and pumps from Dexcom. Closed loop control calculations were done on a smartphone (Sony Corp) using the MPC algorithm published by Toffanin el al. in [36].

Similarly another group of collaborators have conducted clinical trials for an sc-sc AP in Cambridge, UK. After several pilot studies [37], a recent

clinical trial in 2014 [38], was conducted with adolescents and children with Type 1 diabetes in free-living conditions and unmonitored by healthcare professionals. Subcutaneous CGMS (Freestyle Navigator, Abott) and insulin pumps (Dana R, Diabecare) were used which communicated wireless with the control algorithm software on a laptop. The software, named the Florence control system [39], uses MPC with the mathematical model published by Hovorka [40, 41].

A clinical trial reported by Breton et al. [42] in 2012 used a control to range (CTR) strategy to maintain normoglycaemia. The participants were adults and adolescents with type 1 diabetes, using subcutaneous sensors and pumps. Closed loop regulation during meals and exercise was included in the study which was conducted for 12 to 14 hours overnight. Fully automatic closed loop control was done in this trial, with the control algorithm software on a laptop. Two types of control-to-range strategies were used, the more aggressive one used MPC to maintain normoglycaemia in a tighter target range.

While most of the trials study single drug delivery, the "Bionic Pancreas" [10, 43] studied glucagon administration in addition to insulin for an artificial pancreas. Such a device would need two or more pumps or a switching mechanism for drug delivery. The control algorithm used is described in [44](Supplementary material) and based on earlier work [45]; and computation was done on an iPhone 4s (Apple Inc), communicating wirelessly with the glucose sensor (Dexcom Inc) and two pumps (Tandem Diabetes Care Inc). MPC with an autoregressive-moving-average model with exogenous inputs (ARMAX) was used for insulin dose calculation, with meal announcements to trigger partial bolus insulin. PID was used for automatic glucagon dosage which only got triggered if blood glucose falls

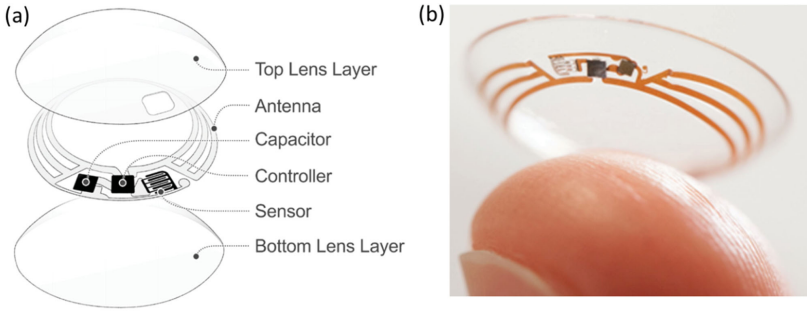


Figure 3.2:
Google's contact lens which can sense glucose levels in tears.(a) Schematic of contact lens (b) Contact lens, jointly developed by Google and Novartis Source: [46], which was obtained from Google's Press Release, "What is Google doing with a smart contact lens?", Jan 2015

below a certain value.

3.1.1 Blood Glucose Measurement

Research into glucose sensors have been ongoing for over fifty years. Sensors reported in literature operate on various sensing principles including electrochemical and optical methods. Glucose is measured from the interstitial fluid (ISF), capillary blood or venous blood; other body-fluids such as tears [46] (Figure 3.2) and saliva [47] can also be used. While intravenous measurements are done in the hospital, outpatient glucose testing mostly uses capillary blood. In 2004, CGMS measuring glucose from the ISF became commercially available and have been gaining users.

Regardless of the principle of sensing, glucose sensors can be non-invasive, minimally invasive or invasive. Non-invasive sensors usually sense glucose optically employing transdermal methods or use other body-fluids to measure glucose. Minimally invasive sensors do not require a foreign object to be lodged in the body, as ISF is drawn to the dermis by various methods like

sonophoresis, skin blister technique or microneedles. Invasive sensors are designed to be placed in the subcutaneous, peritoneal or intravenously, for continuous glucose monitoring. An overview of the various sensing methods and invasiveness is given in [48].

Electrochemical sensors based on enzymatic reaction are the most common sensors available commercially for home and outpatient use. Most, if not all, CGMS systems and the capillary blood glucose test strips (finger prick type) are based on these reactions. A review of enzymatic sensors can be found in [49]. Research is also ongoing in the field of non-enzymatic glucose sensors, which oxidises glucose in the sensor instead of depending on an enzyme to trigger the reaction. Non-enzymatic glucose sensors are reviewed in [50] which also compares the advantages and disadvantages of both enzymatic and non-enzymatic sensors.

Sensor systems can also be single use, short term use or long term use. Capillary blood glucose monitor strips on which the enzymatic reaction takes place are single use, while the monitor strip reader lasts a few years. Sensors in CGMS are used for 3-7 days before needing to be replaced. Enzymatic sensors that were implanted for one year in the subcutaneous layer have been reported in literature but not available in commercial systems [51]. Similarly, a fluorescent hydrogel fibre sensor was implanted subcutaneously for 140 days, and the sensor still under research [52, 53].

As glucose from blood takes time to be transported to the other physiological compartments., there is a time lag between venous blood glucose readings and measurements taken from ISF or other body fluids like sweat or tears. A sensor which measures from venous blood would not be affected by the transport time lag and hence be better for real-time regulation, however these are currently being used in hospital and ICU settings and are also not

implantable [54]. Subcutaneous CGMS use a variety of methods to mitigate the lag including daily calibration with capillary glucose and predictive modeling [55].

While the official diagnosis of diabetes uses venous blood glucose levels, capillary blood glucose is used for outpatient self-monitoring due to correlation with venous blood glucose and ease of testing. Capillary blood glucose is usually taken from the fingers, however alternate sites are used too, like the palm, thigh or forearm. However there are differences between capillary glucose among various sites, e.g. between the finger and the thigh, especially in the post-prandial state and after exercise [56].

As CGMS systems are set to be part of the AP, several groups have sought to model the dynamics between ISF and plasma glucose concentrations. Rebrin and Steil [57] validate a previously proposed two-comparment mathematical model of gluocose transport dyanamics. Fachinetti et al. [58] attempt to reconstruct plasma glucose by deconvolution of CGMS readings. Basu et al. [59] used tracers to characterize the transport lag time between ISF and plasma. A more comprehensive review of the various studies prior to 2009 and also a introduction to the issues with subcutaneous sensors is presented in [60].

Glucose sensor accuracy is often reported using the Clarke Error Grid or the newer Consensus Error Grid [61]. Error grid analysis is not without its shortcomings, but while its clinical adequacy is being debated [62, 63], error grids are still used widely. Both the American Diabetic Association (ADA) standard [8] and ISO 15197 specifications in vitro glucose monitoring systems are based on error grid analysis.

3.1.2 Insulin Delivery

In the human body, the pancreas secretes insulin into the portal vein for transportation to organs and cells. Exogenous insulin can enter the bloodstream by diffusion from the subcutaneous or peritoneal areas, through the lungs when inhaled, via the digestive tract or by direct injection into veins. The bioavailability and efficiency of insulin absorption differ across the various routes, and some modes are more susceptible to variations due to patient weight and lifestyle. There are several modes of insulin delivery, the most common being manual needle injections and electromechanical pumps connected to needles or catheters. Aerosol insulin for inhalation [64] is commercially available, although in the past, products were discontinued due to poor sales. Other methods include glucose sensitive membranes [65] which respond to glucose levels and increase pore size or increase swelling proportional to glucose concentration, thus increasing insulin delivered.

Insulin secreted from the pancreas enters the portal vein and into the bloodstream and intravenous delivery is not associated with the infusion lags from the subcutaneous route. While the Biostator and Nikkoso STG-22 employ intravenous delivery, neither are implantable devices. Implantable peritoneal insulin pumps have been studied in the 1990s although it is used by very few patients and currently only the MIP 2007C (Minimed) is available commercially. Feasibility of closed loop control with implanted pumps in the peritoneal was reported by Renard et al. [66] in 2010. A PID control algorithm was used together with a patient activated pre-meal insulin bolus. Renard also compared subcutaneous, peritoneal and intravenous insulin delivery and the various issues for each route in [12]; and provides historical development for context.

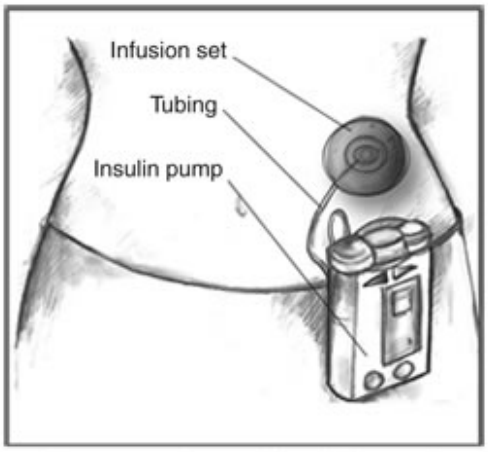


Figure 3.3: Externally worn Continuous Subcutaneous Insulin Infusion (CSII) system
Source: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), USA. Available from http://www.niddk.nih.gov/health-information/health-topics/Diabetes/alternative-devices-taking-insulin/Pages/index.aspx [Accessed 24 Feb 2015]

A review of the various micropump technologies was published by Laser and Santiago [67] in 2004 and introduces piezoelectric, osmotic and peristaltic micropumps suitable for drug delivery. Costs and patient acceptability contribute to the commercial availability of insulin delivery systems. While CSII systems have been available since the 1970s, they were the size of a backpack. Current insulin pumps are much smaller and wearable under clothing (Figure 3.3).

3.2 Control Schemes for Blood Glucose Regulation

In recent years, two closed-loop control schemes have dominated the blood glucose regulation literature, although there are other control schemes looked into. Several review papers on control schemes for the artificial pancreas

have been published over the years [68, 15, 1, 31] present an overview of the various control schemes and also serve as an introduction to the various control algorithms, presented in the context blood glucose regulation.

Parker et al. in 2001 [69] reviews several control algorithms and introduces an MPC in a state space formulation, with state estimation using a Kalman filter; and presents a solution for unconstrained MPC. The authors focused on intravenous glucose control. However in the 15 years since the work was published, subcutaneous glucose sensors have since become commercially available with good patient acceptance and the AP direction trended to the subcutaneous route.

Hovorka's 2008 review paper [31] summarizes the results of various closed-loop regulation studies published in literature, covering several kinds of closed-loop control algorithms and various modes of sensing and delivery. The issues surrounding glucose sensing such as hardware limitations, delays and variability are discussed. Also mentioned are the various performance metrics used to report such as time-in-target, average errors reporting (J-value, MAGE) and error grids.

Before the availability of continuous infusion insulin pumps, open-loop and rule based control strategies were proposed. Insulin doses had to be self-administered and injected with needles, hence insulin infusion could not be done too often. In such control strategies the glucose-insulin model need not be known. In the 1980s and 1990s, semi-closed loop control was proposed based on 3-hourly glucose readings and insulin injections [70, 71, 72]

While PID and MPC are two popular control schemes for blood glucose regulation, rule based control can simplify computation greatly. Type 1 diabetics currently inject insulin to cover for basal insulin, and administer

bolus insulin to regulate blood glucose after meals. Basal insulin is calculated based on weight, while the bolus dose amounts depends on the amount of carbohydrates consumed. However, constant basal infusion does not take into account the circadian variation of metabolism. In [73], Wang et al. adapted the basal glucose infusion (for Type 1 diabetics) every 30 minutes based on glucose readings and rate of change of glucose. This can partition the control, so that glucose fluctuations just after the meal can be regulated by other schemes, but a simple rule based one maintain homoeostasis outside of meal time.

PID control is a well established control scheme extensively used in many systems. Designing a PID controller for the artificial pancreas does not require a mathematical model of metabolism. One workaround for the physiological delays due to subcutaneous infusion and time for insulin action that Weinzimer and colleagues [74] employed together with a PID controller was to add feedforward control through meal announcement to trigger the bolus. Marchetti et al. [75] also used feedforward in tandem with PID and PD feedback control, using a switching strategy based on glucose levels and a time varying setpoint.

MPC [76] is an advanced process control method introduced in the 1980s and increasingly used in industrial applications. It has been gaining popularity for use in blood glucose regulation as it performs well, is able to handle output constraints and though computationally intensive compared to simpler algorithms, can be handled by most modern controllers. Many research groups proposed MPC-based control schemes, the major difference being the models used for prediction.

Toffanin et al. propose a linear MPC scheme, updating the model in [77] (used in the AP@home trial), which was based on Meal Simulation model

(later to become the UVa/Padova simulator) [2]. The 13 state model was linearised about the operating state and the controller included constraints for insulin input and insulin bolus inputs.

Magni et al. [78] used MPC with an auto-regression with exogenous input (ARX) model for Type 1 patients. The parameters of the ARX model are updated everyday (run to run tuning) in the simulated time. The experimenters also varied insulin sensitivity for part of the experiment, linearly increasing and decreasing values within 1 week. The authors find that updating the tuning parameters is key for control performance, more so than MPC parameters (prediction and control horizons) used.

Lynch and Bequette proposed an MPC controller for Type 1 diabetes using subcutaneous glucose [79]. Bergman Minimal Model was used for the MPC, linearised about the initial conditions. The meal was modelled as a disturbance and added to the glucose values (in the state space equation). The states are plasma glucose, periphery glucose and plasma insulin. The delays due to subcutaneous glucose sensing was included as the fourth state variable. Only plasma glucose could be measured, hence the states were estimated using a Kalman Filter. The meal disturbances tested were based on models proposed by Fisher [70] and Lehmann and Deutsch [80] models. The controller was tested in simulation using the Sorensen model.

A nonlinear MPC controller was used in [41]. Hovorka et al. do not linearise the model [40] about the operating point. The Marquadt algorithm was used in the cost function optimization to find the insulin input. Bayesian method was used to estimate the parameters in the model.

In [81] published in 1998 by Trajanoski et al., MPC using nonlinear autoregressive moving average model with exogenous inputs (NARMAX)

to regulate glucose for Type 1 patient's hypoglycaemia and small meals. The MPC was turned off for one hour after a normal sized meal, using a steady infusion instead for postprandial regulation. The controller tested on simulations using the model from [82].

Parker et al. [83] present an MPC with soft output constraints. Two implementations of soft output constraints are presented. The first, asymmetric objective function assigns different penalty weights for hyperglycaemia and hypoglycaemia. The second implementation is prioritised objectives where objectives are assigned a priority and boolean variable to track if the objective is met. Constraints to the problem can include meeting a number of priorities. The authors report that prioritised objectives are mathematically and computationally complex and do not perform as well as asymmetric objective function, however they can be be extended to a MIMO problem. This approach is presented again in Dua et al. [84] with a different model for MPC and more details on the matrices and MPC parameters used.

Robust control methods [85] which seeks to minimize bounded disturbances are also used for blood glucose regulation. Parker et al. [86] implemented a H-infinity controller and compared its performance with MPC. The authors found that the robust controller performed well for patient variability, however MPC was better with tracking the setpoint with lower under- and overshoot. Kovacs et al. [87] used robust H-infinity controller and tested it in simulation with worse case large meal disturbance and sensor noise; actual patient data was also used to study patient variability effects on the controller.

Currently, most models and controllers only consider insulin as the control output. There are recent investigations about using glucagon or glucose as part of the control scheme by El-Khatib and associates [45, 88] and Castle

and associates [89]. Glucagon is a hormone which triggers the production of glucose in the body. The use of glucagon is to prevent occurrences of hypoglycaemia which is more dangerous than hyperglycaemia, especially when hypoglycaemia occurs during sleep and the patient is unaware of it. Glucagon has also been found to complement insulin and increase insulin effectiveness. In the closed loop control study in [88], MPC was used to compute insulin and a PD controller was used to compute glucagon needed.

3.2.1 Optimization Methods

In MPC, the predicted future values of the system are used to find the set of optimal control inputs. Several optimization methods are available and can generally be divided into gradient methods and heuristic methods.

The solution for the linear MPC optimization with constraints can be re-written as a primal-dual convex quadratic programming problem and can be solved using gradient methods, active set or interior point methods. The Levenberg-Marquadt algorithm [90, 91] is one of the most commonly used gradient descent methods and is the default method in Matlab's `qp` function for quadratic programming and the `curve_fit` function in the SciPy's optimization package used in Python. The algorithm is a combination of Gauss-Newton and gradient descent (trust region) methods. Its algorithmic parameter gets updated every iteration and at large values it behaves like a gradient descent; and at small values it behaves like the Gauss-Newton method. Another widely used optimization algorithm is the Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm. It is a quasi-Newton method which can be extended to deal with constraints in the optimization problem. Nocedal and Wright [91] cover these and several other numerical optimization methods.

One of the limitations of gradient descent methods is that it may converge on local optima. Several workarounds exist to mitigate this, such as running the optimization with multiple initial points. In some cases, there is no solution for the primal-dual problem due to stringent constraints. The problem may also not be a convex optimization problem. Heuristic methods, which are stochastic and biologically inspired, can be employed to find the optimum. Methods include Ant Colony System [92] and other Swarm Intelligence Methods [93], Genetic Algorithms [94] and Artificial Immune Systems [95].

Ant System is an optimization meta-heuristic developed by Dorigo et al. [92] which is inspired by the way groups of ants are able to find the shortest route from the food source to the ant colony. It was first presented as a method to solve combinatorial optimization problems such as the Travelling Salesman Problem. Ant Systems has been used to estimate parameters for a linear model [96].

The algorithm can be described as follows. At each cycle, each of the m artificial ants traverse a path travelling through n cities. The distance between city i and city j is d_{ij}. The ant is constrained such that it cannot visit a city more than once during a cycle. At the end of the cycle, the total distance travelled by each ant, L_k, is calculated.

The transition probability between cities i and j for k-th ant is

$$p_{ij}^{k}(t) = \frac{[\tau_{ij}(t)]^{\alpha}.[1/d_{ij}]^{\beta}}{\sum[\tau_{ik}(t)]^{\alpha}.[1/d_{ik}]^{\beta}} \tag{3.1}$$

where τ_{ij} is the intensity of the pheromone trail left on the path between i and j. α and β are tuning parameters to control the relative importance of pheromone trail versus distance.

After all m ants have completed the tour, the trail intensity is updated by

$$\tau_{ij}(t+n) = \rho.\tau_{ij}(t) + \Delta\tau_{ij} \tag{3.2}$$

where ρ is related to the evaporation rate of the trail.

The trail deposited between i, j is

$$\Delta\tau_{ij} = \sum_{k=1}^{m} \Delta\tau_{ij}^{k} \tag{3.3}$$

where

$$\Delta\tau_{ij}^{k} \propto 1/L_k$$

As the Ant System optimization is a search heuristic, it can be used, with little modification, to find the optimal control output vector that minimizes an objective function. The algorithm is relatively easy to implement and it is possible to build in constraints to the control output. Another bio-inspired heuristic based on artificial immune systems [95] was also considered, however it was better suited for other optimization problems such as pattern recognition and was more difficult to adapt to optimization for MPC.

3.3 Mathematical Models and Modeling of Glucose-Insulin System

Human metabolic models have been studied for over 50 years and is still an ongoing area of research. New methods of tracers, sensors and the availability of data from large clinical trials in recent years have contributed to the refinement of the models. The human glucose-insulin models proposed

vary widely in complexity, number of compartments modelled and the number of parameters needed. Simpler models can be used when there is insufficient data to estimate parameters of a more complex model; and they can also be used in low computing power applications. Models can be employed in controller synthesis or as a virtual patient simulation test bed. A comprehensive review of mathematical models of human metabolism and historical development can be found in Cobelli et al. [15].

The model proposed by Sorensen [97] in 1985 is 19th order and models the glucose uptake by various individual organs of the body instead of lumping them together. Due to its complexity it may not be possible to obtain the physiological parameters for an individual in a minimally-invasive way. However it presents the metabolic interaction of various organs and compartments, the knowledge of which researchers can use when developing simpler models.

The computer simulation program AIDA (Automated Insulin Dosage Advisor) [98] is used for patient and clinical staff education and is available as a free software download or online. Users can select various individual Type 1 diabetes patient parameters and see what the blood glucose profile will look like with a change in diet or insulin therapy. AIDA uses the glucose-insulin interaction model by Lehmann and Deutsch [80] (1992). The model has three compartments - plasma glucose, plasma insulin and active insulin (which is insulin used for glycemic control). It consists of 4 differential equations and 12 auxilliary equations. The model takes into account the delays from a subcutaneous insulin injection. The meal input to the model is the glucose equivalent of carbohydrates ingested orally.

The UVa/Padova simulator uses the meal simulation glucose-insulin model proposed by Dalla Man et al. [2] in 2007, which is also implemented in the

simulation software GIM [3]. It is a four compartment model of glucose in plasma and rapidly equilibrating tissues, glucose in slowly equilibrating tissues, insulin in plasma and insulin in the liver. The model reflects knowledge gained about hepatic glucose production and muscle glucose utilization which was obtained by new tracer experimental procedures. In 2008, the JDRF (Juvenile Diabetes Research Foundation) approved the use of this model to replace animal experiments in pre-clinical testing for closed-loop controller design. The updated model was published in 2014 [99] and included the effects of glucagon and refinement of insulin kinetics, taking into account increased insulin sensitivity during hypoglycaemia (Figure 3.4).

The model [2] consists of 13 differential equations and 26 parameters that need to be determined. The meal is modelled as glucose ingested orally. The model was developed using clinical data from 204 healthy and Type 2 diabetes patients. Averaged values of healthy and Type 2 patient parameters were reported. In the GIM software, modifications were made to include a Type 1 patient simulator, where subcutaneous insulin infusion replaced endogenous insulin. The software also includes open loop and PID algorithms for simulation.

The model proposed by Hovorka in 2002 [40] is also used in the MPC controllers. The model used consists of 10 equations and has 12 parameters that were estimated for each patient using tracers. The glucose intake was administered intravenously.

The Minimal Model proposed by Bergman et al. [100, 101] has a minimal number of parameters that need to be estimated. The model has three differential equations and five parameters. The model was developed using an intravenous glucose tolerance test (IVGTT) with healthy humans and non-diabetics. Since its publication, this model has been widely used and

modified for various applications.

One major limitations of most models in the literature is that the glucose rate of uptake during exercise is not modelled. Breton proposed a model [102] based on Bergman's minimal model, modifying the glucose flux and adding in increased energy consumption, relating it to heart rate, and changes to insulin action. Dalla Man et al. modified their model in GIM by using the method Breton proposed of relating heart rate to energy consumption and ran simulations for Type 1 diabetes [103]. Roy and Parker proposed a model with exercise effects, also based on Bergman's minimal model [104]. The model includes glucose uptake and production induced by exercise.

Another limitation is that a meal is often modelled as a one time glucose intake. The actual duration of the meal and the glycaemic indices and absorption of the various kinds of food into glucose are not taken into account [105].

Most of the models published do not model circadian changes in metabolism, and many authors do acknowledge such limitation. A study on the diurnal changes of glucose and insulin reported lower hepatic glucose and increased insulin sensitivity in the morning compared to evening [106].

3.3.1 Parameter estimation

Two common methods for parameter estimation are Least Squares and Bayesian method. More details about least squares and Bayesian estimation for physiological models can be found in [107].

Most physiological models are non-linear in the parameters, hence nonlinear least squares methods are used. The parameters for the models in [2] and the Bergman minimal model [100] use a non-linear least squares method.

Numerical methods such as Levenberg-Marquadt [90], which is a gradient method, can be used to iteratively solve for the parameters. Gradient methods suffer from minima traps, and an alternative are search methods using nature inspired heuristics and stochastic algorithms to find parameters.

Bayesian methods can also be employed for system identification although a priori knowledge of the distribution of the unknown parameters are needed. Finding the a posteriori probability is also mathematically challenging. Bayesian parameter estimation was used to identify parameters used in non-linear MPC for Type 1 diabetes in the study done by Hovorka [41].

Most of the parameter estimation done is in the clinical setting with controlled glucose intake. There are few studies in literature which estimate patient parameters based on glucose data from free-living situation. This is probably due to high variability in the signal.

Eren-Oruklu et al. [108] estimated parameters using glucose sensor readings from hospitalised and free-living patients in a paper published in 2009. The authors also updated the model parameters after each sampling instant, using weighted recursive least squares with a forgetting factor. The model used was an autoregressive-moving-average (ARMA) model and the objective of the study was to develop glucose prediction models.

In [109], Gillis et al. used data from three ambulatory patients to adaptively update the model used in MPC to compensate for mismatch and for the lack of meal information. The Bergman Minimal Model [100] was used, and a fixed set of parameters was employed for all patients. Readings from the patients was used to update one of the parameters, p_1. The authors also studied adapting the meal disturbance term for each patient, instead of p_1.

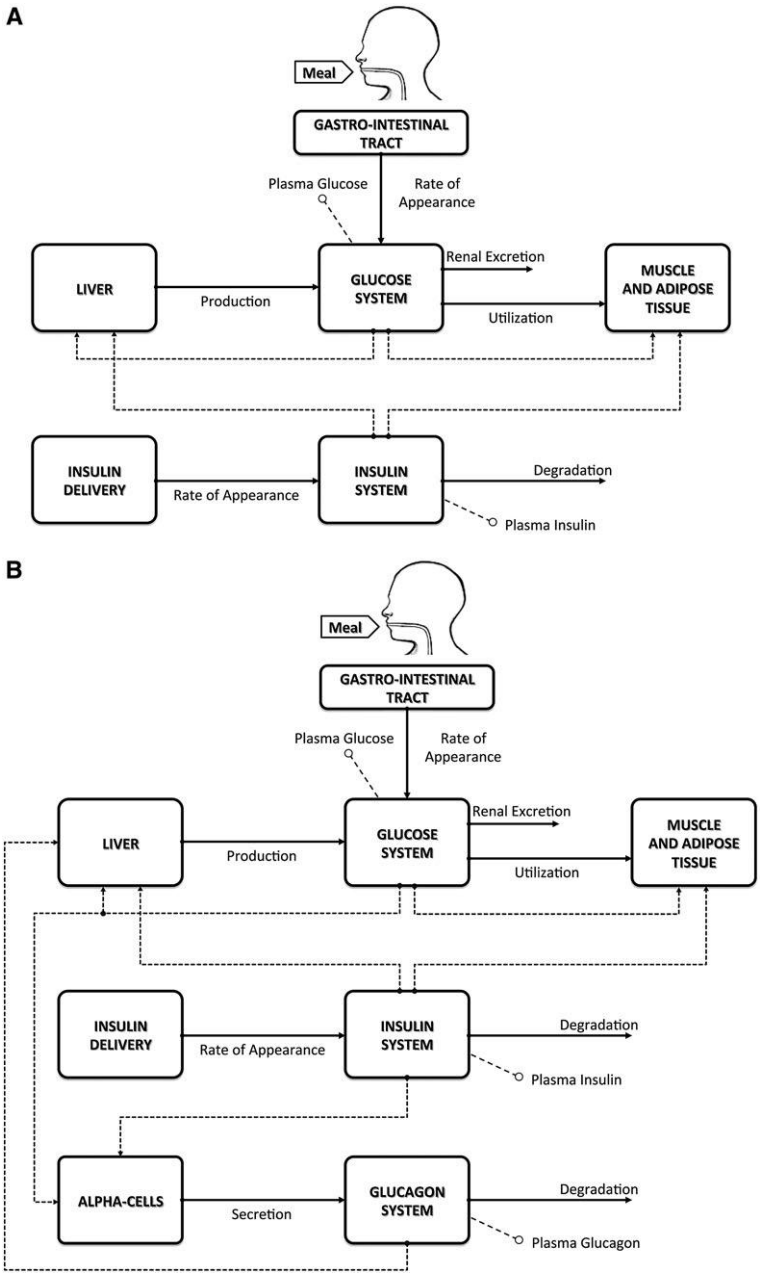


Figure 3.4: UVa/Padova Meal Simulator, proposed by Dalla Man et al. [99]: (a) Model proposed in 2007 [2], (b) Updated model [99] which include effects of glucagon and other refinements

Chapter 4

Design of an Implantable Artificial Pancreas

This chapter presents an overview of the implantable artificial pancreas and its modular components including: (a) scalable micropumps which passively reduce flow rate from the micropump enabling flow reduction of up to 20 times, (b) the insulin reservoir which minimizes the probability of air bubbles, if any, leaving the reservoir and (c) two fluidic flow connections which integrate blood glucose sensing and drug delivery.

4.1 Design Requirements

The artificial pancreas proposed is an implantable one, automatically delivering insulin and any other drugs intravenously; for use in an outpatient setting.

The device is to be used by diabetics and people who need exogenous insulin. As it is to be implanted, the device should be light and small enough to be

implanted without causing user discomfort or limit the range of movement. It should deliver insulin automatically, calculating the optimal dose for the patient based on real-time glucose values and possibly other user inputs. Insulin infusion should be continuous or near continuous and the dose to be calculated as close to real-time as possible, at least every 10 minutes. The device is meant for outpatient use and users should be able to refill their device with insulin and monitor the dosage. Data logs should be available for download to a PC or other device on a regular basis for long term disease monitoring.

The power consumption needs to be low as the device is to be implanted for many years. An implantable device has to be fabricated with materials certified safe for implantation. Parts in contact with the drugs or body fluids should also not be corroded by these fluids or leech chemicals that will affect the fluids. All components to be implanted should be sterilisable.

The low power consumption requirement plays an important part in the choice of subcomponents and systems design. Besides consuming little power, the choice of embedded electronics has to be powerful enough for computationally intensive control algorithms, e.g., MPC. Communications of the device and a computer or smartphone is needed to transfer logging data from artificial pancreas. Wireless communication signals should be able to transmit across layers of tissue, subcutaneous and dermis. While power consumption remains a likely barrier, new improvements to wireless charging may enable long term implantable smart devices.

For near real-time regulation, glucose sensing should be done every 10 minutes or less. More frequent sensing should lead closer to real-time feedback, however it would increase the device power consumption. Ideally the implantable artificial pancreas would have an embedded or internal

glucose sensor reading venous blood glucose. However currently such a sensor is not easily available, hence non-implantable non-venous blood glucose sensors have to be considered for the prototype.

The micropump chosen has to be small enough, reliable, sufficient duty cycle and have accurate and repeatable pumping over its life. It should also consume little power and be fabricated of materials that are safe for use in delivering insulin intravenously. The insulin reservoir should hold enough insulin to last for a few days and have a port for refilling. One option of topping up of insulin is via a subcutaneous port. The size of the insulin reservoir is determined by safety considerations and it should not store too much insulin in case there is a leak of the reservoir.

Two specifications apply to the hardware presented in the following sections - the size of the device and the insulin delivery rates. The artificial pancreas is to be implanted in the ilium, in a hollow cavity in the pelvic bone as in Figure 4.1. This is near the iliac vein which the pancreas secretes insulin into. The size of the device should fit inside the ilium and the hollow space is about the size of a closed fist, and should contain the embedded electronics, power supply and drug delivery subsystem.

Pancreatic insulin secretion rate is from 0 to $250mU/min$ [110, 111] which translates to 0 to $2.5\mu l/min$ delivery rate if a U-100 insulin is used. (U-100 insulin contains 100 units of insulin per ml.) Other insulin concentrations are available, though less commonly so, and can also be utilized for insulin delivery. Basal insulin infusion rates are around $10mU/min$ for adults and lower for children [112], hence the pumping system should be able to deliver infusion rates of $5mU/min$ accurately.

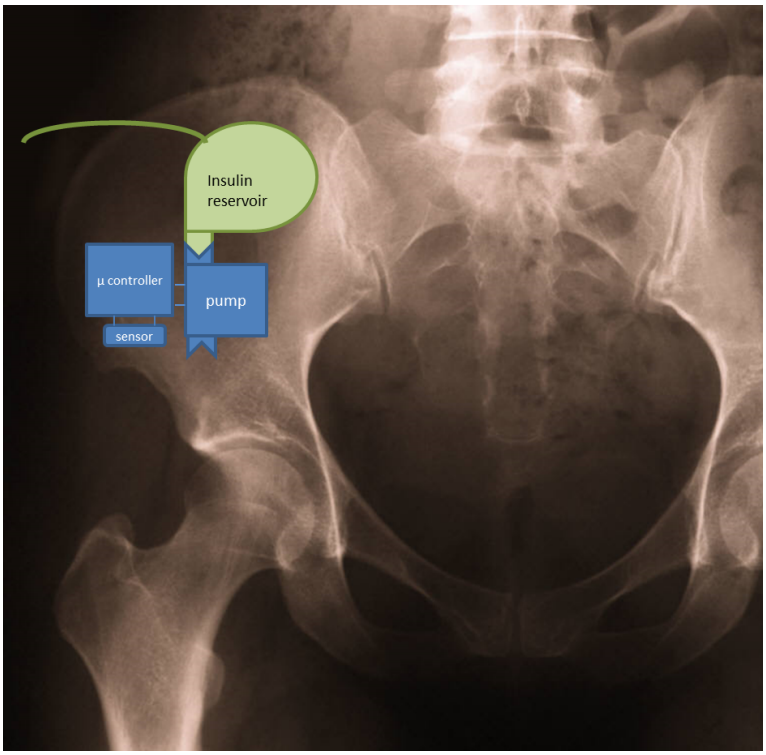


Figure 4.1: Proposed site of artificial pancreas implantation

4.2 Design Overview

The electro-mechanical artificial pancreas essentially consists of a glucose sensor and a drug delivery system with electronics on board for communication and low level control. The computer program which controls the dose can also be onboard, usually on a PCB with a microprocessor and other controllers, or it can be on a remote machine.

The measurement and drug delivery can be via subcutaneous, peritoneal or intravenous paths. An artificial pancreas that senses glucose concentrations and delivers insulin and other pancreatic hormones via the portal vein mimics the human pancreas closer than if these were done via the subcutaneous route.

The size of the implanted device is an ellipsoid or oblate spheroid, of maxi-

mum dimensions $10cm$ and $7cm$ on the major and minor axis respectively, which is roughly the size of a closed fist. The device outlet is to be attached to the iliac vein (portal vein), which is close to the pancreas. This would allow the drug delivery to mimic pancreatic secretions into the blood stream. The casing encapsulates the electronics for control and communications, internal tubing and pump, power supply and possibly medication reservoirs. The shell is made of 2 parts joined at the centre. One half contains the insulin delivery system comprising of the pump, reservoir and fluid flow connections. The other half contains the printed circuit board (PCB) and the power supplies.

Blood glucose sensing and insulin delivery will be intravenous and can be fluidically connected such that the glucose sensor can be within the device. The device's outlet tube for drug delivery is connected into the iliac vein. An inlet tube is used for refilling the reservoir via a subcutaneous port. An onboard microcontroller automatically calculates the dose based on sensed glucose concentration. Glucose levels and insulin dose are stored on the microcontroller memory until it is transferred to a remote machine (computer, smartphone etc.) wirelessly. Wireless charging of the device's internal power supply is planned for the artificial pancreas. The deployment of the artificial pancreas is illustrated in Figure 4.2. A custom PCB will have the microprocessor, wireless communications and pump controller and required electrical circuitry for the device and fit the dimensions of the device.

4.2.1 Glucose Sensing and Insulin Delivery

Currently commercially available CGMS require the glucose sensor to be changed every 3-7 days. There is ongoing research and development to

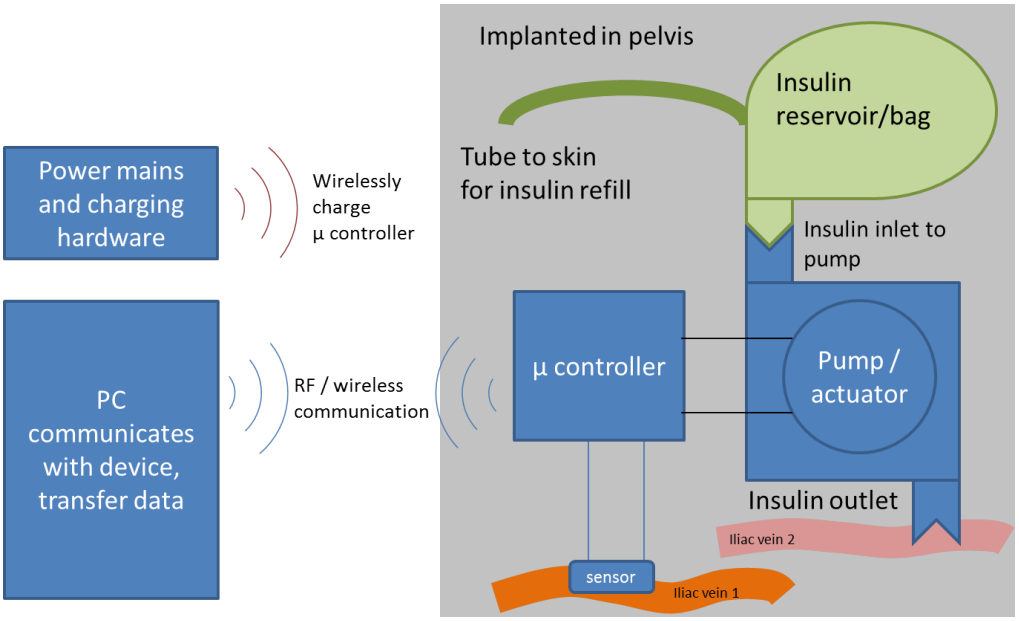


Figure 4.2: Deployment of the artificial pancreas. The device is implanted in the body, with intravenous glucose sensing and automatic drug delivery

increase sensor life, which is required for implantable sensors. Electrochemical sensors implanted for one year have been reported [51]. Injectable fluorescent sensors have also been implanted for 140 days [52].

The design for our device is for use with an implantable intravenous long term use sensor. Fluidic flow connections that integrate intravenous glucose sensing with drug delivery are presented in the next section, with such an embedded sensor in mind. However such sensors are currently not easily accessible, hence the design is modular; and the rest of the device can be used along with a subcutaneous glucose sensor.

Costs and patient acceptability contribute to the commercial availability of insulin delivery systems. While CSII systems have been available since the 1970s, they were the size of a backpack. Now with MEMs technology and the availability of micropumps, CSII are much smaller and wearable under clothing. The pump technology for micropumps include piezoelectric,

osmotic and peristaltic pumps [67].

The micropumps that were easily available were too large for the fluid rate specified by the controller. A pumping subsystem has to deliver insulin at a flow rate of $0.033ml/min$ to mimic a single injection of 30 units. A minimum flow rate of around $0.001ml/min$ is required if the delivery of $100U$ of insulin is spread uniformly over the course of the day. These numbers are indicative of the range of flow rates required of the pumping system. To achieve these low insulin infusion rates with a larger micropump, a method to reduce flow rate by mechanical means was devised — flow from the outlet of the pump was divided into two unequal flows, one of which returned back to the reservoir. The objective was to divert a larger proportion of the micropump flow back into the reservoir and hence reducing the flow rate at the artificial pancreas device outlet.

4.2.2 Electronics and Embedded Software

Electronics for the sensor and pump telemetry are required in the artificial pancreas to communicate the glucose level to both the user and the controller. The control algorithm can be either onboard or on a remote machine. An onboard controller reduces reliance on reliability of communications between implanted device and remote machine, however it will increase power consumption. The control program and electronics for other controllers and communications can be on the same PCB. Figure 4.3 shows the proposed scheme.

Closed loop control algorithms which include Proportional-Integral-Derivative (PID) control and Model Predictive Control (MPC) [15] would automatically calculate the insulin dose from the glucose sensor readings. PID and MPC

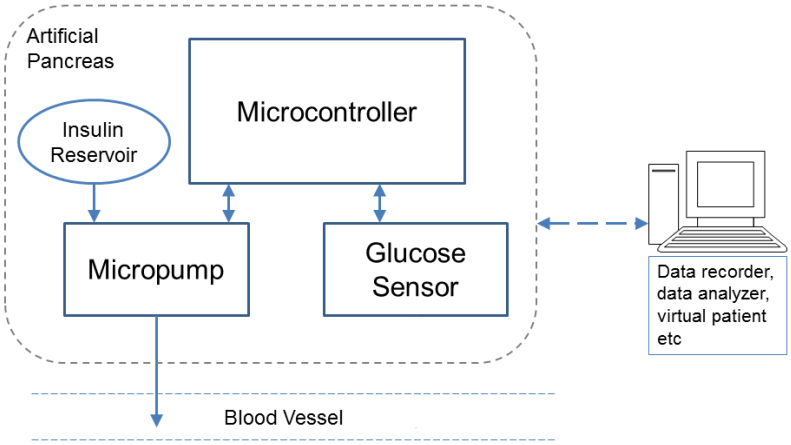


Figure 4.3: System overview of the embedded control scheme and electronics

are established control methods and are widely reported in literature for blood glucose regulation. MPC has been implemented using Application-Specific Integrated Circuit (ASIC) [113], Field-Programmable Gate Array (FPGA) [114, 115, 116] and general purpose microcontrollers [117, 118, 119].

Microcontrollers are more flexible to hardware design changes compared to ASICs; and firmware is easier to be upgraded. ASICs can be more power efficient and take up less space, however ASIC design requires expertise and are expensive for prototypes. Compared to FPGAs, MCUs are lower cost and consume much less power; in addition, other controllers can be implemented on the same chip to support other hardware modules. For our prototype, we used a microcontroller as it was the cheapest and most energy efficient solution which also suited our research focus.

The next two sections present the insulin delivery system with scalable micropumps, insulin reservoir and fluid flow connections. The microcontroller embedded systems and control algorithm is presented in Chapter 5.

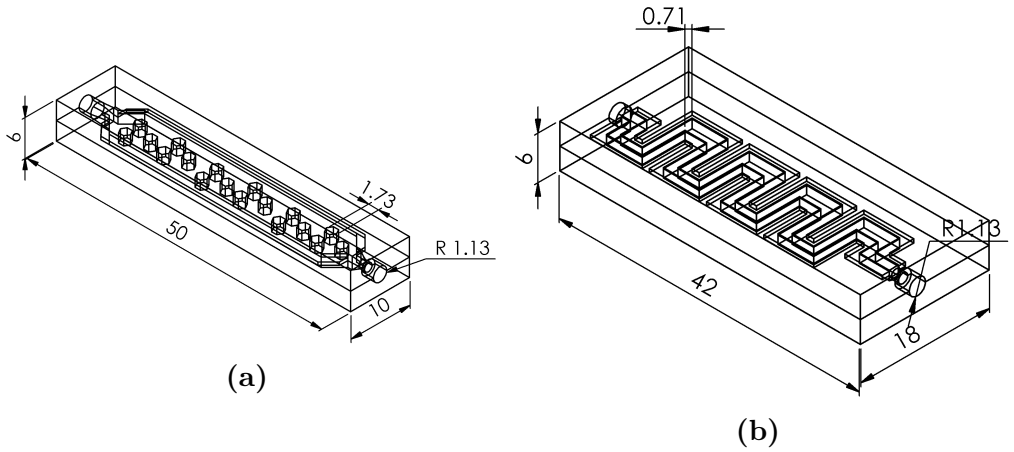


Figure 4.4: Microchannel dividers: (a) hexagonal posts design, (b) zig-zag design

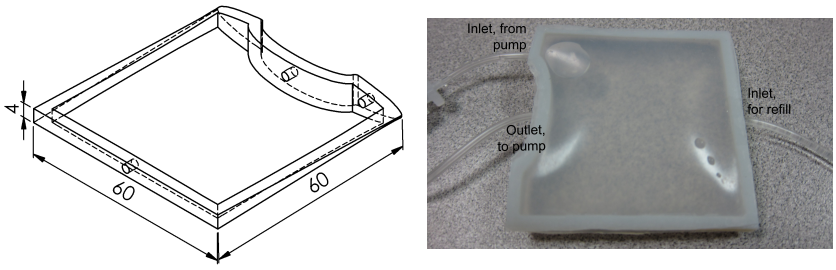
4.3 Scalable Micropump Units and Insulin Reservoir

Two microchannel designs, shown in Figure 4.4, were tested. In both designs the aim was to increase and vary the cross-sectional area of the flow thus drawing fluid into the channel. The micro-channels parts were rapid-prototyped and fabricated in two parts and then glued together. Of the two designs, the one with the hexagonal posts (Figure 4.4a) performed better at diverting a larger amount of the flow.

To ensure that blood does not flow into the device, a check valve was added to the device outlet. This also served to restrict flow via the outlet and divert more flow back into the reservoir. The inlets of the microchannel dividers have the same diameter as the tubing from the outlet of the micropump.

The reservoir module stores the insulin and has two inlets and one outlet that is connected to the micropump, as shown in Figure 4.5. One inlet to the reservoir is for refilling of insulin, which when the device is implanted

can be connected to a port near the surface of the skin. The other inlet is for insulin to re-enter the reservoir from the micropump.



(a) **(b)**

Figure 4.5: Reservoir module: (a) parts drawing, (b) reservoir with tubes attached

A design consideration was to minimize the chances of bubbles present leaving the reservoir. The reservoir module is designed such that the outlet has little probability of being at the highest point regardless of its orientation, thus reducing the chance of a bubble trapped near the reservoir outlet.

4.3.1 Experiments

Firstly, testing was done on the two micro-channels designs to determine which of the microchannel designs would reduce flow rate more. Testing was done without the reservoir, using with the amplitude and frequency input to the pump which gave the highest flow rate. It was found that the microchannel with the hexagonal posts gave a higher reduction in flow rate compared to the microchannel with the zigzag path with varying cross-sectional area. Flowrate achieved with the microchannel with hexagonal posts (Fig.4.4a) was $0.146ml/min$ on average, while the flowrate with the zig-zag design microchannel (Fig.4.4b) was $0.265ml/min$ on average. Without the microchannel flow divider, the micropump's flow rate was about $3ml/min$ at those same frequency and amplitude settings.

Next, experiments were performed to determine flow rates of the whole pumping subsystem, which consists of the insulin reservoir, microchannel flow divider, valves and the micropump. The inputs to the pump microcontroller are voltage amplitude and frequency of pumping, the combination of which would determine the flow rate of the piezoelectric pump. The objective was to evaluate the translation of the insulin dose (in mU/min) obtained from the Model Predictive Control into a voltage amplitude and frequency to be input to the pump microcontroller.

Before each experimental run, the system was primed. The system is self-priming and an initial priming to ensure no air enters the bloodstream needs to be done only once before deployment. The reservoir was filled with $20ml$ of fluid. A particular amplitude and frequency was chosen and the pump was run for a set time. After which, the weight of the fluid pumped was measured and the flow rate determined. Various frequencies were tested and repeated until the flow rate was near zero indicating depletion. The frequencies were changed randomly and not in any order. For the whole test run for one reservoir, each test frequency was repeated so that variation due to fill level could be characterized. The results are presented in Table 4.1. When the reservoir level had dropped low to around $5ml$, the flow rates which had been constant for each setting started to decrease until there is no more flow.

In the next experiment, the highest frequency, which corresponds to the highest flow rate, was run for the entire fill level of the reservoir module. The flow rate was recorded every few minutes until reservoir depleted. This gave the flow rate variation as the fill level of the insulin reservoir changed.

Testing was also done to ascertain if there was pump-to-pump variation and characterize it accordingly. It was observed that the microchannel dividers

Frequency (Hz)	Amplitude (V)	Average Flowrate (ml/min)
1	3	0.0034
2.5	3	0.0157
5	3	0.0344
7.5	3	0.0542
10	3	0.0702
15	3	0.1220
20	3	0.1425
25	3	0.1903

Table 4.1: Average flow rates for various frequencies

tended to attract bubbles that have entered the pump and diverting it back into the reservoir, thus minimising chances of bubbles exiting the device and entering the blood stream.

4.4 Fluidic Connections for Insulin Delivery

Two fluid flow connection designs which integrate the glucose sensing and insulin delivery for the system are presented in this section.

The first design presented is a bypass system which draws blood from the vein to test for glucose levels and pumps out the blood together with the insulin dose back into the vein. The device is connected via two catheters into the vein. Figure 4.6a and Figure 4.6b show the schematic of the fluid flow in the insulin delivery system. The catheters are connected to the device with luer connections.

First, blood is drawn into the tube, either by a micropump (Figure 4.6a) or the Venturi effect of the blood flowing through the vein (Figure 4.6b). The

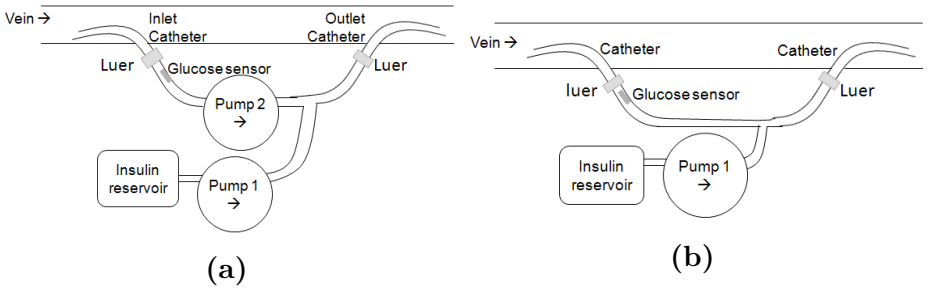


Figure 4.6: Bypass design : (a) with a pump to draw blood into device; (b) without pump to draw blood into device

blood will pass a glucose sensor embedded in the tube. With the information from the glucose sensor, the microprocessor can calculate the appropriate dosage of insulin for the patient. The pumping action will pump the blood and insulin back into the vein.

In the second design presented, the blood is pumped up a single tube to the glucose sensor and back down the same tube together with the insulin dose into the vein. Figure 4.7 shows the schematic of the fluid flow.

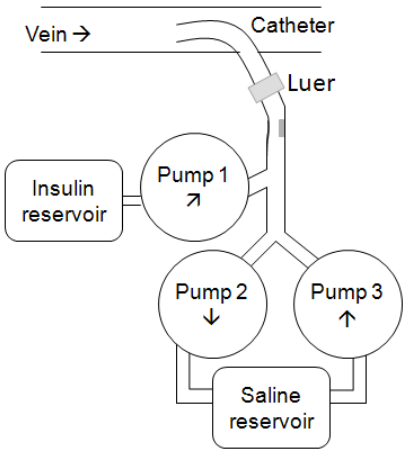


Figure 4.7: Single catheter design

This design only requires a single catheter to be inserted into the vein. The catheter is attached to the tubing system with a luer connection. Pump 2 will draw blood from the vein into the tube up to the embedded glucose sensor. The glucose sensor transmits the data to the microprocessor to

compute the insulin dosage required. Then, the insulin pump (pump 1) delivers the insulin into the tubing and in doing so, pumps some of the insulin and blood mixture in the tube back into the vein. Finally, pump 3 is run to move the rest of the insulin and blood mixture back into the iliac vein. This also effectively resets the device to its initial fluidic state. Pump 2 and pump 3 are connected to a shared saline reservoir instead of an air spring to prevent introducing air into the vein. Most micropumps available commercially are uni-directional hence the need for separate pumps to draw in fluid and discharge fluid from the system.

4.4.1 Experiments

The two fluidic connection designs and their variants were tested on the bench top using water as the fluid. The blood flow in the vein was simulated using water with colouring added, pumped by the uni-directional piezoelectric micropumps (Bartels Microtechnik mp6), through a tube of internal diameter 1.4 mm, which was about 1.5 times the outer diameter of the 22G catheter used. Uncoloured water was used in place of insulin. Tygon material tubing was used and connections between tubes were made with nylon Y-connectors.

Bypass design

In the experimental run without the pump in the bypass tube (Figure 4.6b), the coloured water entered the bypass tube via the inlet catheter due to the pressure generated by fluid flow through the vein (Figure 4.8a). The tubes were initially primed with colorless plain water. However when the insulin pump (pump 1) was turned on to pump at the same flow rate as the vein

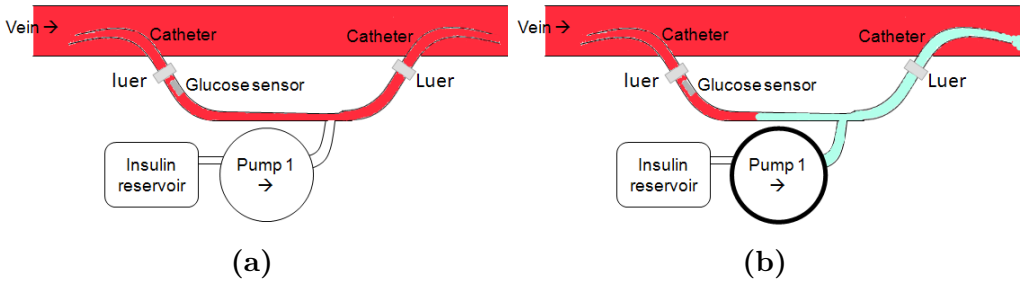


Figure 4.8: Bypass design, without pump in bypass tube: (a) when pump 1 is not running and (b) when pump 1 is run

flow rate, there was sufficient pressure to cause the colorless water to enter the bypass tube (Figure 4.8b). This displaced the fluid in the bypass tube back into the vein through the inlet catheter, which is not desirable.

With a pump along the bypass tube (Figure 4.6a), there is no issue of the backflow into the vein through the inlet. The pump along the bypass tube (pump 2) was run continuously and it drew in fluid flow from the vein at a faster rate compared to no pump in the bypass tube. When the insulin pump (pump 1) was turned on, again at the same flow rate as the flow through the vein, there was no backflow into the bypass tube. When the pump in the bypass tube was turned off while the insulin pump is pumping, there was also no backflow either as the uni-directional pump acts like a check valve for opposing flow.

Single catheter design

For the single catheter design, the operations of the pumps have to be consecutive and follow a particular sequence. First, pump 2 was run to draw coloured water into the tube to the glucose sensor. Next, the insulin pump (pump 1) was run, dispensing an amount of colorless water which displaced the some of the coloured fluid originally in the tube back into the

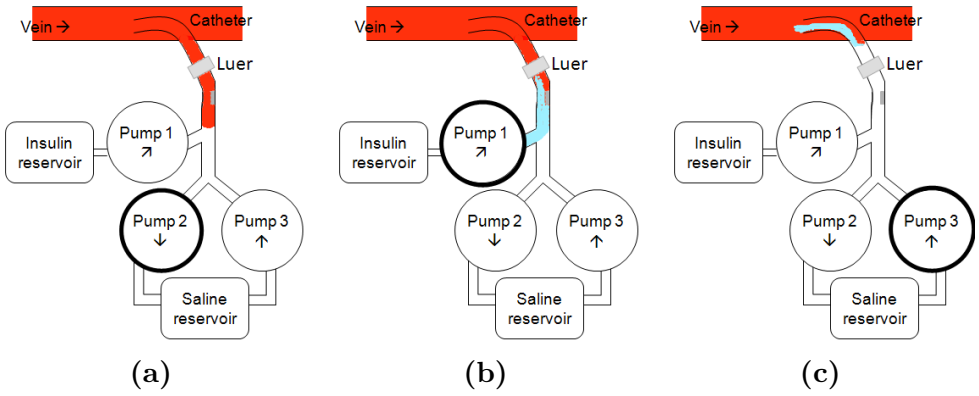


Figure 4.9: Operating cycle of single catheter design: (a) pump 2 run to draw blood in, (b) pump 1 run to dispense insulin and (c) pump 3 to discharge mixture back into vein

vein. Finally, pump 3 was run to pump out the rest of the coloured fluid and colorless fluid dispensed by the insulin pump. Figure 4.9 shows the sequence in a single operating cycle.

It is important to ensure the discharge pump, pump 3, displaces volume equivalent to the volume drawn in by pump 1 and the volume of dispensed by the insulin pump. In another experimental run, the discharge pump 3 was removed to see if a two pump system was adequate; with pump 2 to draw in fluid and the insulin pump 1 to dispense insulin and deliver all the fluid mixture back into the vein. Figure 4.10 shows the sequence of operation. It was found that it was unable to displace all blood plus fluid mixture back into the vein unless it used extra insulin from its reservoir.

The pump has only one inlet and is unable to be programmed to select a specific source if two sources are connected to the single inlet with a y-joint or multi-joint connectors. It can only use the insulin from its reservoir to displace the mixture of blood drawn in and insulin dosed back into the vein. The insulin used for this purpose would remain in the tube and can only be drawn in by pump 2 and stored. This would be a waste of insulin and

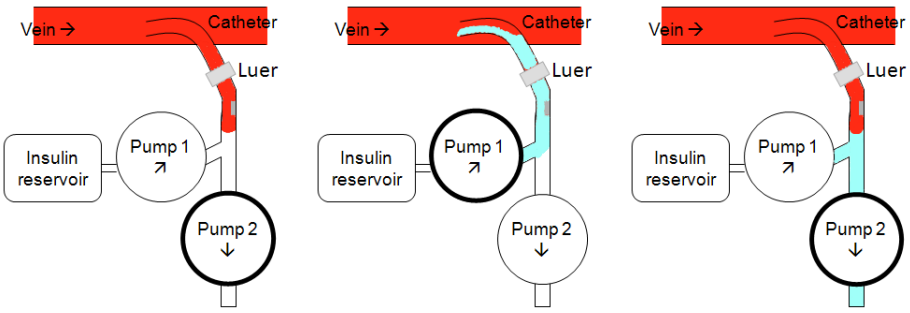


Figure 4.10: Single catheter design with discharge pump removed: (a) from initial state, run pump 2 to draw blood in, (b) correct dose of insulin dispensed, plus additional insulin to displace dose and the blood into the vein and (c) draw blood in again for the next run

increase the amount of insulin storage in the device. Discharging the extra insulin into the patient is not feasible as it may lead to hypoglycaemia. Hence, for uni-directional pumps, a three pump system is needed for the single catheter design.

4.5 Discussion and Conclusion

The experiment with the scalable micropump systems showed that diluted insulin and physical reduction of flow rate enables the use of micropumps to deliver insulin in the required range. Using a different material and changing the dimensions of the microchannel features can be done to achieve even lower flow rates and enable use with more concentrated insulin. This design opens the possibility of using relatively larger, cheaper and more easily available micropumps for the artificial pancreas, drug delivery devices and prototypes.

The micropump and associated fluidic system has been accurately delivering the amount of insulin computed by the control algorithm. We do not

observe any significant deviation. Characterization experiments have been performed to ensure accurate volume delivery across reservoir backpressure changes. For future work, measurements on the actual amount of insulin injected into the vein should be done to check if resistance due to blood flow in the vein needs to be taken into account.

Water was use to examine flow direction for the particular fluid flow connection and to observe any effects that would make it unsuitable for deployment. Non-newtonian fluids that closer resemble blood should be use in further developmental work.

Both bypass and single catheter fluidic connection designs presented have the potential to work well in an implanted artificial pancreas pending further characterization, testing and design refinements. A fluid connection design which incorporates sensing and dispensing depends on the availability of glucose sensors that meet the size and telemetry requirements. The fluidic flow design of an insulin delivery system which does not require blood to be drawn into the device for measurement was used in the artificial pancreas prototype reported in Chapter 6.

The bypass design is more robust to pump volume variations and errors compared to the single catheter design, as only the insulin pump volume needs to be accurate. However, it requires two catheter insertions into the vein. A next step in design refinement would be to add a check valve in the bypass tube which will prevent backflow.

Although the single catheter design requires only one catheter insertion, it requires three pumps and the design is less robust to the pump volume errors and variation. Further testing for reliability and the effects of repeated pump volume errors needs to be done to correctly size the amount of saline

needed.

The fluidic flow design of an insulin delivery system which does not require blood to be drawn into the device for measurement is simpler, and was used in the artificial pancreas prototype for the in vivo experiment as an implantable glucose sensor was not available to us.

Chapter 5

Model Predictive Controller using Interior Point and Ant Algorithm

This chapter presents an adaption of the Ant System for implementing the optimization routine of the Model Predictive Controller. A hybrid optimization scheme for Model Predictive Control (MPC) is also proposed, comprising both Primal-Dual Interior-Point (PDIP) method used in [120] and the search heuristic based Ant System optimization methods developed in this chapter.

5.1 Model Predictive Controller

In MPC, N_p future values of the system are predicted based on N_c future inputs into the system. The future input which gives the best predicted values is then chosen. Only the first of the N_c inputs is used and the calculation is repeated at the next time step with the actual current value

as feedback.

Consider a plant that has m inputs, q outputs and n states with the following state space representation

$$x_m(k+1) = A_m x_m(k) + B_m u(k), \tag{5.1a}$$

$$y_m(k) = C_m x_m(k), \tag{5.1b}$$

where u is the manipulated or input variable, y_m is the process output, and x_m is the state variable; A_m, B_m, and C_m have dimensions of $n_1 \times n_1$, $n_1 \times m$, and $q \times n_1$, respectively.

By defining $\Delta x_m(k) = x_m(k) - x_m(k-1)$, $\Delta u(k) = u(k) - u(k-1)$, and by defining the augmented state as $x(k) = \begin{bmatrix} \Delta x_m(k)^T & y_m(k) \end{bmatrix}^T$, the augmented state space model obtained is

$$\overbrace{\begin{bmatrix} \Delta x_m(k+1) \\ y_m(k+1) \end{bmatrix}}^{x(k+1)} = \overbrace{\begin{bmatrix} A_m & o_m^T \\ C_m A_m & I_{q\times q} \end{bmatrix}}^{A} \overbrace{\begin{bmatrix} \Delta x_m(k) \\ y_m(k) \end{bmatrix}}^{x(k)} + \underbrace{\begin{bmatrix} B_m \\ C_m B_m \end{bmatrix}}_{B} \Delta u(k), \tag{5.2a}$$

$$y(k) = \underbrace{\begin{bmatrix} o_m & I_{q\times q} \end{bmatrix}}_{C} \underbrace{\begin{bmatrix} \Delta x_m(k) \\ y_m(k) \end{bmatrix}}_{x(k)}, \tag{5.2b}$$

where o_m is a $q \times n_1$ zero matrix, and $I_{q\times q}$ is the identity matrix with dimensions of $q \times q$.

At sampling instant k_i, the future state variables are predicted for N_p samples : $x(k_i+1|k_i), x(k_i+2|k_i), ..., x(k_i+N_p|k_i)$, and the future control trajectory is described within N_c steps ($N_c \leq N_p$): $\Delta u(k_i), \Delta u(k_i+1), ..., \Delta u(k_i+N_c-1)$.

By defining

$$\Delta U = \begin{bmatrix} \Delta u(k)^T & \Delta u(k+1)^T & \cdots & \Delta u(k+N_c-1)^T \end{bmatrix}^T$$

$$Y = \begin{bmatrix} y(k+1|k)^T & y(k+2|k)^T & \cdots & y(k+N_p|k)^T \end{bmatrix}$$

where Y is the vector of the N_p predicted future values and ΔU the vector of the N_c future control inputs [121], we obtain

$$Y = Fx(k) + \Phi\Delta U \tag{5.3}$$

where

$$F = \begin{bmatrix} CA \\ CA^2 \\ \vdots \\ CA^{N_p} \end{bmatrix}^T$$

$$\Phi = \begin{bmatrix} CB & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ CA^{N_p-1}B & CA^{N_p-2}B & \cdots & CA^{N_p-N_c}B \end{bmatrix}$$

The goal is to find the optimal ΔU to minimize the difference between the predicted states Y and the set point $r(k_i) = [r_1(k_i)\ r_2(k_i) \cdots r_q(k_i)]^T$.

The cost function for this control objective is given by

$$J = (R_s - Y)^T(R_s - Y) + \Delta U^T \bar{R} \Delta U \tag{5.4}$$

where $R_s = \begin{bmatrix} I_{q\times q} & I_{q\times q} & \cdots & I_{q\times q} \end{bmatrix}^T r(k_i) = \bar{R}_s r(k_i)$, $\bar{R}$ is a block matrix with $m \times m$ blocks of $r_\omega I_{N_c \times N_c}$ ($r_\omega \geq 0$), in which r_ω is a tuning parameter.

The estimated state variable $\hat{x}_m(k)$ is derived from the plant model (5.1). At sample time k_i, with the information of $\hat{x}_m(k_i)$ replacing $x_m(k_i)$, the estimation of state variable in (5.2) is modified as

$$\hat{x}(k_i + 1) = A\hat{x}(k_i) + B\Delta u(k_i) + K_{ob}(y(k_i) - C\hat{x}(k_i)), \tag{5.5}$$

where K_{ob} is the observer gain, chosen such that the system is asymptotically stable.

5.1.1 MPC with constraints

The solution which minimizes (5.4) needs to be modified if constraints are introduced to the optimization process. The typical operational constraints are on the amplitude of the control variable U, rate of change of the control

variable ΔU, and amplitude of the outputs Y.

The constraints of the rate of change can be rewritten in a matrix inequality form

$$\begin{bmatrix} -I \\ I \end{bmatrix} \Delta U \leq \begin{bmatrix} -\Delta U^{\min} \\ \Delta U^{\max} \end{bmatrix}. \tag{5.6}$$

The amplitude of the control variable ΔU can be rewritten into the equality

$$\begin{bmatrix} -C_2 \\ C_2 \end{bmatrix} \Delta U \leq \begin{bmatrix} -U^{\min} + C_1 u(k_i - 1) \\ U^{\max} - C_1 u(k_i - 1) \end{bmatrix}. \tag{5.7}$$

Rearranging from (5.3), the constraints of the output Y can be expressed

$$\begin{bmatrix} -\Phi \\ \Phi \end{bmatrix} \Delta U \leq \begin{bmatrix} -Y^{\min} + Fx(k_i) \\ Y^{\max} - Fx(k_i) \end{bmatrix}. \tag{5.8}$$

Finally, solving the MPC with constraints is to find ΔU that minimizes the cost function in (5.4) subject to the inequality constraints in (5.6), (5.7), and (5.8). This is a quadratic programming problem with linear inequality constraints:

$$V = \frac{1}{2}\Delta U^T E \Delta U + \Delta U^T F, \tag{5.9a}$$

$$M\Delta U \leq \gamma, \tag{5.9b}$$

where E and F can be inferred from (5.4); M and γ are a matrix and a

vector reflecting the constraints from (5.6), (5.7), and (5.8). In the case that the constraints are fully imposed, M and γ have $4mN_c+2qN_p$ rows.

We present two approaches used to solve the constrained optimization - PDIP algorithm and Ant algorithm.

5.2 Optimization Methods for MPC

The optimization problem can be solved with PDIP algorithm [122] employing the predictor-corrector method [123] which is computational and resource efficient [120]. However, getting trapped in local optima is a possibility if the problem is non-convex. The Ant System can be adapted and extended to non-convex optimization problems for nonlinear MPC. Hence, a hybrid system is proposed, comprising both PDIP and the search heuristic based Ant algorithm optimization methods.

A method was proposed in [124] to determine if the primal or dual problem is infeasible. However, this required expressing the problem in a homogeneous self-dual form before finding the optimal of that program using methods like the interior point method. As the interior point optimization steps have to be done regardless in practice, an easier and less complex implementation would be to run the PDIP method and use the Ant algorithm to calculate the optimal value if the PDIP method fails to converge after a predefined number of iterations.

5.2.1 Primal-Dual Interior Point Method

Primal-Dual Interior-Point (PDIP) method is an established computationally efficient method for optimization. The Karush-Kuhn-Tucker (KKT)

conditions for the quadratic program in (5.9) can be represented as

$$\Psi(x,\lambda,s) = \begin{bmatrix} Ex + F + M^T\lambda \\ s + Mx - \gamma \\ \Lambda Se \end{bmatrix} = 0, \tag{5.10a}$$

$$\lambda, s \geq 0, \tag{5.10b}$$

where $\Lambda = diag(\lambda_1, \lambda_1, \ldots, \lambda_l)$ is the vector of Lagrange multipliers, $S = diag(s_1, s_2, \ldots, s_l)$ is the vector of the slack variables $s = \gamma - Mx, s \geq 0$; and $e = [1, 1, \ldots, 1]^T$. In this problem, x is a $n \times 1$ vector (in this particular case, x is ΔU, and $n = m \times N_c$), E is a $n \times n$ matrix, F is a $n \times 1$ vector, M is a $l \times n$ matrix, where l is the number of inequality constraints, and γ is a $l \times 1$ vector.

PDIP algorithms are path following methods that apply variants of Newton's method to (5.10a) while modifying search directions and step lengths to find the optimal solution (x^*, λ^*, s^*). The inequalities (5.10b) have to be strictly satisfied at each iteration. From the current point (x, λ, s), we can obtain the search direction $(\Delta x, \Delta\lambda, \Delta s)$ by solving

$$\Psi'(x,\lambda,s) \begin{bmatrix} \Delta x & \Delta\lambda & \Delta s \end{bmatrix}^T = -\Psi(x,\lambda,s), \tag{5.11}$$

where $\Psi' = \begin{bmatrix} E & M^T & 0 \\ M & 0 & I \\ 0 & S & \Lambda \end{bmatrix}$ is the Jacobian of Ψ. After $(\Delta x, \Delta\lambda, \Delta s)$ is obtained, the new iterate is calculated as

$$(x, \lambda, s) + \alpha(\Delta x, \Delta\lambda, \Delta s), \tag{5.12}$$

where the *step length* $\alpha \in [0, 1]$ is determined so that the condition (5.10b) holds.

However convergence can be slow when following the affine-scaling direction in (5.11) as only a small step length (i.e. $\alpha << 1$) may be obtained before the condition $(\lambda, s) > 0$ is violated. To overcome this, PDIP methods bias the direction toward the interior of the orthant $(\lambda, s) \geq 0$ and keep the components of (λ, s) away from the boundary of the orthant. Typically, the search direction is aimed to a point whose pairwise products $\lambda_i s_i$ are reduced to a lower average value. The duality measure $\mu = \frac{\lambda^T s}{l}$ is used to estimate the reduction speed of $\lambda^T s$. The search direction is then modified toward a point for which $\lambda_i s_i = \sigma\mu$, where μ is the current duality measure and $\sigma \in [0, 1]$ is termed a centering parameter.

Different strategies of choosing σ and α lead to a wide range of primal-dual interior-point methods. The method used in our implementation is based on the predictor-corrector method [122], which was proven to be efficient in practice. The details of the implementation can be found in [120].

5.2.2 Ant Algorithm for Optimization in MPC

The Ant System proposed by Dorigo et al. [92] was adapted to find the optimal sequence of control inputs for MPC that minimizes the cost function, J, in (5.4).

The discrete nature of Ant System optimization can also be applied to the insulin dosage computation. Insulin infusion rates are not required to take on continuous values. Constraints to the insulin dosage due to the physical limits of hardware and the patient are automatically done by appropriately selecting the values that each element of ΔU, ΔU_t, can take. The constraint imposed for combinatorial optimization type of problems that each node be only visited once in a tour is no longer applicable in this problem. The values that each ΔU_t takes does not need to be unique and the same value may be repeated the entire control sequence.

First, the m artificial ants are placed on the n nodes which correspond to the values the insulin infusion rate, ΔU_t, can take. Then, the next node is selected, based on p_{jt} , the probability that node j is chosen at time instant t. This is repeated for all $\Delta U_t, 1 \leq t \leq N_c$.

For each of the m ants, the predicted sequence of outputs Y based on current output y and control sequence ΔU are obtained and the cost function J is calculated. The trail values and probabilities are then updated as follows:

For the k-th ant,

$$\Delta\tau_k = \frac{J_{max} - J_k}{J_{max} - J_{min}} \tag{5.13}$$

where J_k is the cost function for the k-th ant, J_{max} and J_{min} are the maximum and minimum values of the cost function J obtained by all the

m ants in the cycle.

$$\Delta\tau_{jt} = \sum\nolimits_{k \in allowed} \Delta\tau_k \tag{5.14}$$

$k \in allowed$ if the k-th ant was at node j at time instant t.

More trail is deposited if the value of cost function J is lower when a node j is used at time instant t.

The trail is then updated by

$$\tau_{jt} = \rho\tau_{jt} + \Delta\tau_{jt} \tag{5.15}$$

Correspondingly, the probability of node j chosen at time instant t was updated before the next cycle using

$$p_{jt} = \frac{\tau_{jt}}{\sum\limits_{j=1}^{n} \tau_{jt}} \tag{5.16}$$

The process is repeated until the maximum number of allowable cycles is reached or when a stagnation point is reached such that the difference of J between cycles is below a certain threshold.

5.3 MPC-on-a-chip Implementation

The requirements of artificial pancreas are that it should be small in size and consume little energy; and the microprocessor used should have sufficient computational power to execute the required calculations in real-time. Based on these requirements, a Texas Instruments (TI) MSP430FG4618 microcontroller was chosen to implement the control algorithm. It is an ultra

low-power 16-bit RISC-architecture microcontroller which has 116KB+256B Flash ROM, 8KB RAM, and five low-power modes, optimized for extended battery life. It should be noted that the implementation can be ported to any generic RISC controller or other microcontrollers as it was developed using the standard C language [120].

Most of the calculations involve solving systems of linear equations and hence matrix operations. Since the dimensions of the matrices vary based on the application, dynamic memory-allocation was used to store matrices and intermediate values. However due to limited memory of the low power microcontrollers, built-in memory allocation routines in C, e.g. `malloc`, `realloc`, `calloc` or `free` should not be used[125]. Instead a global array was used as a buffer shared between the main function and all other sub-routines to store dynamic variables and intermediate values. For any function which requires a dynamic memory-allocation, it will be provided by the caller function as part of the global buffer through an input pointer. The caller function needs to determine the address of the buffer allocated to the called function. The size of the global array is set based on the implementation of all the functions and the size of the physical SRAM memory of the microcontroller.

5.4 Experimental Methods

5.4.1 Modified Minimal Model

The model used in our MPC controller is the Minimal Model [100, 126]. Glucose-insulin interaction is described by three differential equations and contains a minimum number of parameters to be estimated. The model was

adapted for a Type I patient by removing the endogenous insulin secretion and adding a glucose infusion term [70, 79].

The modified Minimal Model used in our work is

$$\frac{dG}{dt} = p_1(G(t) - G_b) - X(t)G(t) + D(t) \tag{5.17a}$$

$$\frac{dX}{dt} = p_2X(t) + p_3I(t) \tag{5.17b}$$

$$\frac{dI}{dt} = -nI(t) + U(t)/V_1 \tag{5.17c}$$

where G (mg/dl) is the plasma glucose concentration, I (mU/L) is the insulin concentration in plasma, X (min^{-1}) the insulin in the remote comporatment. D $(mg/dl/min)$ is the meal disturbance and $U(t)$ (mU/min) the exogenous insulin infusion rate.

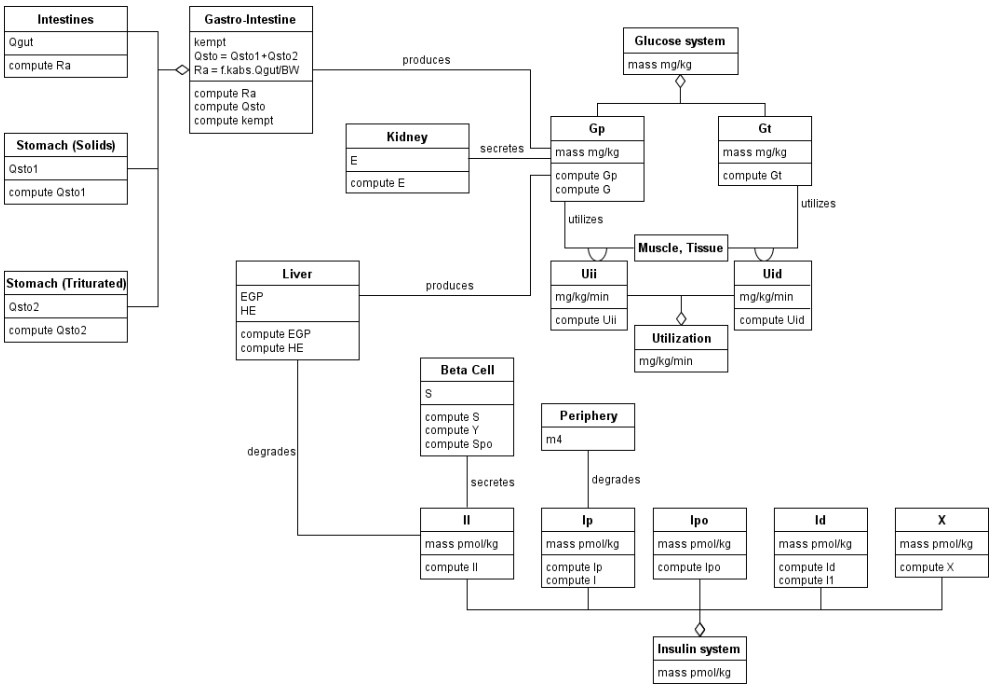
The state $x_m(k)$ is defined as $[G(k), X(k), I(k)]^T$ and the model was linearised about the steady-state values of $(G, X, I) = (G_b, 0, I_b)$. As measurements of X are physically unavailable, and those of I are inaccessible in practice, the state variable x_m is estimated using an observer.

5.4.2 UVa/Padova Simulator Virtual Patient

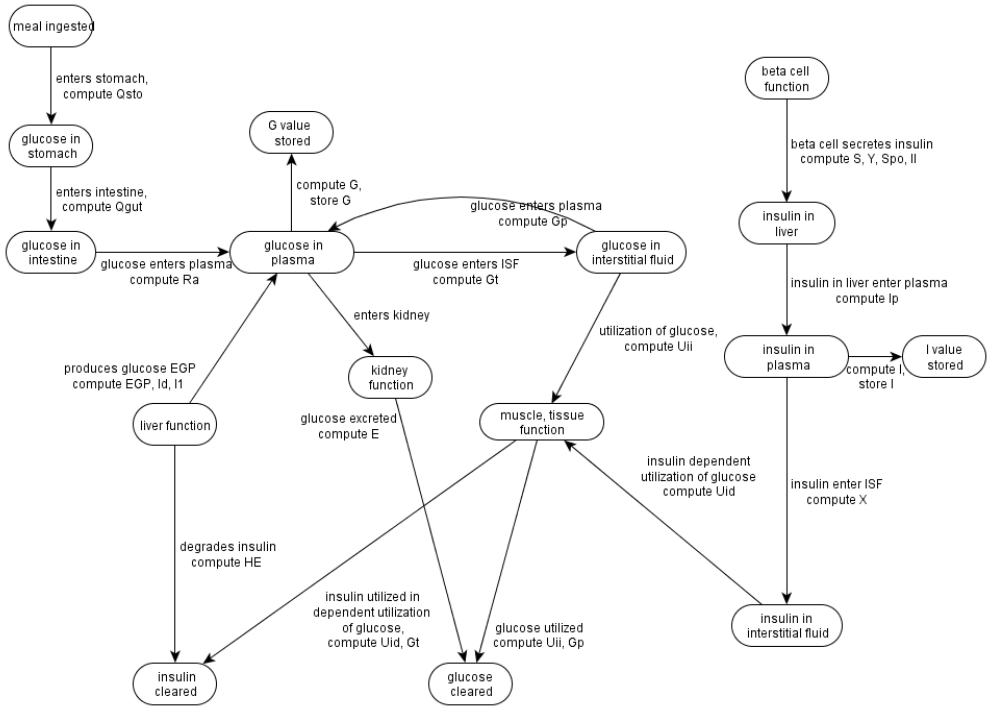
The MPC controller developed was simulated on the University of Virginia/-Padova (UVa/Padova) model [2] which is a higher order model of 13 differential equations. The patient parameters used was based on the Type 1 patient in [3] modified to use exogenous insulin provided by our MPC controller. The parameters and constants used are reported in Table 5.1. The virtual patient was implemented in MATLAB here (and using Python in Chapter 7) and the Object Modeling Technique (OMT) diagram of the implementation is shown in Fig 5.1.

Table 5.1: Model Parameters used for UVa/Padova Virtual Patient

Process	Parameter	Unit	Type 1 Patient
Body Weight	BW	kg	78
Basal Glucose Mass	G_{pb}	mg/kg	338.4
Basal Glucose	G_b	mg/dl	180
Basal Insulin Mass	I_{pb}	$pmol/kg$	1.2745
Basal Insulin	I_b	$pmol/l$	0
Glucose Rate of Appearance after Meal	k_{abs}	$min-1$	0.0568
	k_{max}	min^{-1}	0.0558
	k_{min}	min^{-1}	0.008
	f	dimensionless	0.9
	b	dimensionless	0.82
	d	dimensionless	0.01
Gluocose Kinetics	V_G	dl/kg	1.88
	k_1	min^{-1}	0.065
	k_2	min^{-1}	0.079
Glucose Renal Excretion	k_{e1}	min^{-1}	0.0005
	k_{e2}	mg/kg	339
Endogenous Glucose Production	k_{p2}	min^{-1}	0.0021
	k_{p3}	$mg/kg/min$ per $pmol/l$	0.009
	k_{p4}	$mg/kg/min$ per $pmol/kg$	0
	k_i	min^{-1}	0.0079
	EGP_b	$mg/kg/min$	2.4
Glucose Utilization	V_{mx}	$mg/kg/min$ per $pmol/l$	0.047
	k_{m0}	mg/kg	225.59
	F_{cns}	$mg/kg/min$	1
	p_{2U}	min^{-1}	0.0331
Insulin Kinetics	V_I	l/kg	0.05
	m_1	min^{-1}	0.19
	m_2	min^{-1}	0.484
	m_5	$min.kg/pmol$	0.0304
	HE_b	dimensionless	0.6



(a)



(b)

Figure 5.1: OMT diagram of the UVa/Padova virtual patient: (a) Object model diagram, (b) Dynamic model diagram.

Corresponding parameters for the Minimal Model were obtained by non-linear least squares regression on blood glucose responses of the UVa/Padova virtual patient to meals of various sizes. The parameters obtained and used in (5.17) are:

$$p_1 = 0.06204 \quad p_2 = 0.0745 \quad p_3 = 16.311 \times 10^{-5}$$

$$G_b = 180.0 \qquad I_b = 0$$

$$V_1 = 4 \qquad\quad n = 0.304,$$

and with a sampling time of 5 minutes, the parameter matrices used in the discretized state space model of (5.17) are:

$$A_m = \begin{bmatrix} 0.733 & -639.8 & -0.0183 \\ 0 & 0.689 & 0 \\ 0 & 0 & 0.219 \end{bmatrix},$$

$$B_m = \begin{bmatrix} -0.009 \\ 0.000 \\ 0.659 \end{bmatrix}, C_m = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}, D_m = \begin{bmatrix} 5 & 0 & 0 \end{bmatrix}^T.$$

A setpoint of 110mg/dl was used in our experiments. In addition, the

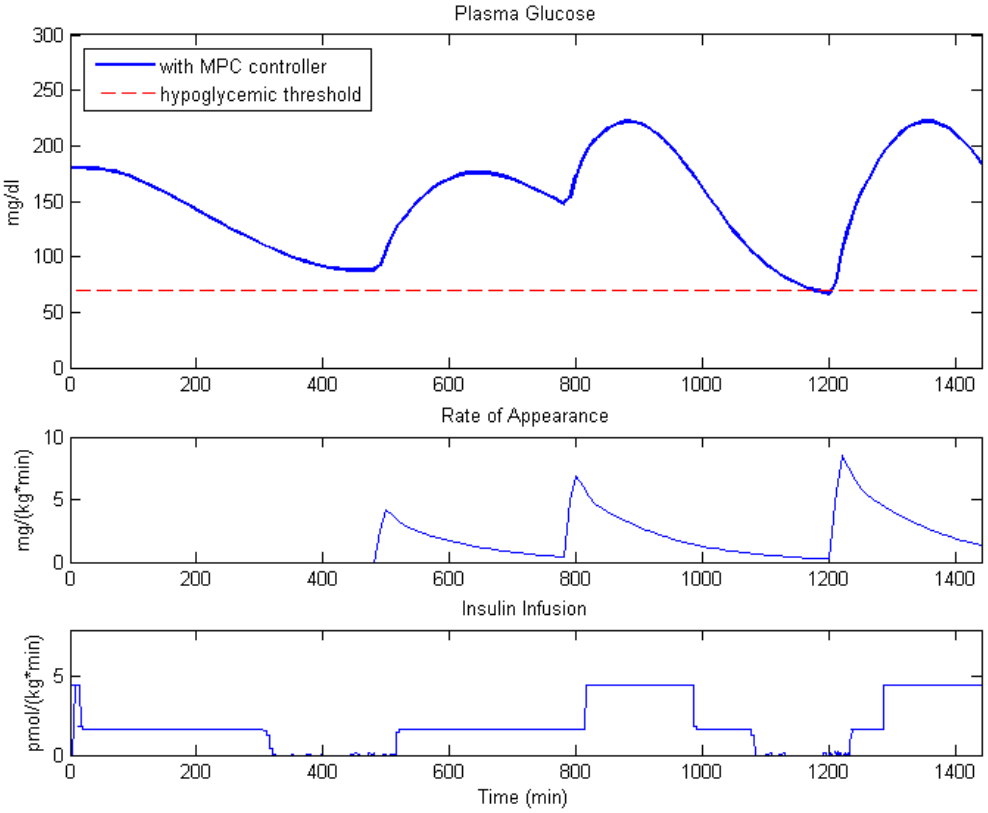


Figure 5.2: Simulation with hybrid Ant and PDIP, $N_p = 20$, $N_c = 4$, with the UVa/Padova model virtual patient. Simulation was performed using MATLAB

following constraints were also imposed:

$$0 \leq u \leq 50 \ \ mU/min, \tag{5.18a}$$

$$-50 \leq \Delta u \leq 16.7 \ \ mU/min, \tag{5.18b}$$

$$110 \leq y \leq 180 \ \ mg/dL. \tag{5.18c}$$

The first constraint refers to the range of insulin infusion rate that can possibly be enforced by a micropump. The second constraint refers to the possible changes in the insulin infusion rate. The third constraint conditions the output to avoid hypoglycaemia and extreme hyperglycaemia.

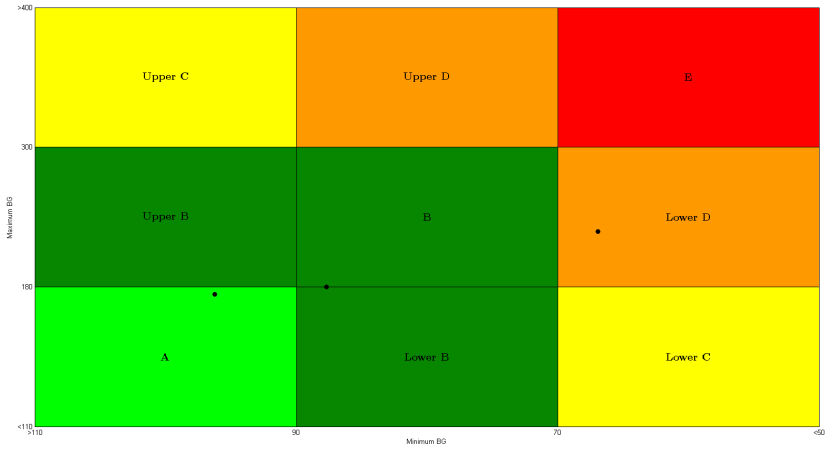


Figure 5.3: Control-Variability Grid Analysis chart (CVGA) of the results with hybrid Ant and PDIP, $N_p = 20$, $N_c = 4$

The results of the MPC controller with the UVa/Padova virtual patient are shown in Figure 5.2 and the corresponding Control Grid Variability (CVGA) chart is show in Fig 5.3. The meal sizes were $45g$, $70g$ and $90g$ and were given at 0800h, 1300h and 2000h respectively. Prediction horizons, N_p, tested were 10, 20, 50 and 100; and control horizons, N_c, tested were 2, 4, 10, 20, 50, noting that $N_c \leq N_p$. The results were compared and a prediction horizon $N_p = 20$ together with control horizon of $N_c = 4$ was found to give the best performance. The switches between PDIP and Ant algorithm optimization did not cause any spikes or discontinuity in the insulin dose.

5.5 Discussion and Conclusion

In the computer simulation PDIP and Ant algorithm for MPC optimization, normoglycemia was achieved within 60 minutes. The maximum and minimum blood glucose levels, time to reach basal level and duration of

hypoglycaemic excursions were used to evaluate performance of the artificial pancreas. Performance of both optimization methods depended largely on the choice of MPC parameters, N_p and N_c, and the same parameters may not give the same performance on both optimization methods.

The Ant algorithm optimization was used in about 5% of the 1440 simulation time steps, mostly when the blood glucose values were highly elevated. When glucose levels were near the target basal value, the PDIP method obtained the optimal input quickly, within 10 iterations.

The binary code of the MPC with hybrid optimization method on the MSP430F5438A microcontroller is 28KB, which is smaller than that of other implementations [117, 118]. Time for computation and communications during each time-step was less than 1 second on average with PDIP and 3 seconds with Ant algorithm. Even with longer prediction and control windows, the computation speed of our system is comparable with that of the other designs [117, 118, 119]. The time taken to calculate using both PDIP and Ant algorithm methods —in the case where the quadratic program is infeasible —is well within the time of 5 minutes, before the next computation of insulin is called.

This system is highly energy efficient since most of the time the processor is on standby mode with the power consumption rate of $2.1\mu A$ at $3.0V$. The power consumption rate in active mode is about $230\mu A/MHz$ at $8MHz, 3.0V$. The microcontroller takes less than $5\mu s$ to be active from standby mode.

Control Grid Variability Analysis (CVGA) [127] is a tool to compare performance of controllers for glucose-insulin systems. It has its limitation in that it reports the 97.5 and 2.5 percentile glucose values attained with the

controller but does not indicate the time in hypoglycemia, hyperglycemia or euglycemia, nor does it indicate the deviation from target values or zones. Nevertheless it is very useful for comparing various controllers and control schemes across the literature and summarizes the comparison in a single chart; and can be used to complement other performance metrics.

We have presented the design of an implantable artificial pancreas and a Model Predictive Controller on a low power chip. The method is also applicable for an external wearable artificial pancreas. The Ant System originally proposed to solve a combinatorial optimization problem was adapted for a convex optimization problem to find the optimal control input for MPC. A hybrid optimization process for MPC is proposed to select the heuristic Ant algorithm if the faster Primal-Dual Interior Point optimization method does not converge within a specific number of iterations. The hybrid selection method computes the required insulin dose well within the five minute time step between each glucose measurement. Simulation results show good performance in blood glucose regulation with our proposed method.

Chapter 6

In Vivo Experiment of the Implantable Artificial Pancreas

This chapter discusses the in vivo experiment, done in collaboration with National University Hospital (NUH) and Institute for Infocomm Research (I2R), with our implantable artificial pancreas prototype. The prototype's mechanical design is described in Chapter 4 and the control algorithm in Chapter 5.

6.1 Objective

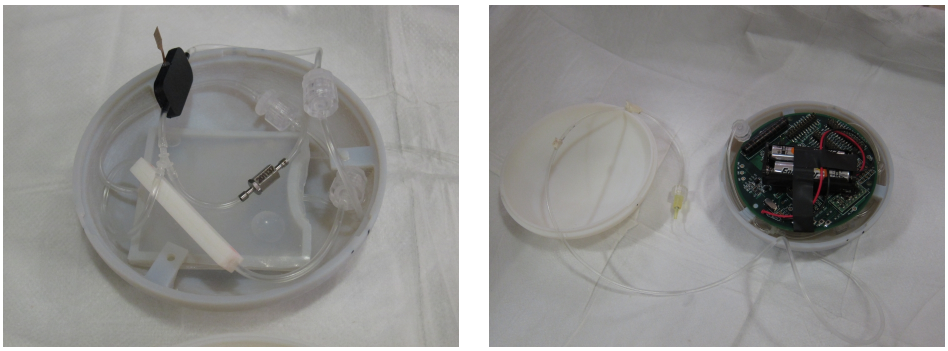
The objective of the experimental study is to establish the clinical feasibility of an implantable artificial pancreas with intravenous insulin delivery with automatic control algorithm. The experiment included testing the insulin delivery with scalable micropumps in vivo.

6.2 Implantable Artificial Pancreas Prototype

The electronics of the artificial pancreas prototype are on a custom printed circuit board (PCB). The microprocessor chosen is Texas Instruments (TI) MSP430F5438A, a 16-bit ultra-low-power RISC microcontroller with 256KB Flash and 16KB SRAM. It was chosen as it has low power consumption and adequate computational power required for quadratic programming used in control algorithm. 256KB of onboard flash would be sufficient to store up to 4 weeks data assuming each data is 30 bytes and glucose readings are recorded every 5 minutes.

On-board wireless communications (TI very-low-power RF transceiver CC1101 and a Mitsubishi chip antenna) communicated with a PC fitted with a wireless transceiver, transferring the calculated insulin doses back to the PC for logging. Ideally the CGMS would communicate with the device's embedded electronics, however the CGMS used in this prototype has proprietary communications and hence glucose readings were transferred to the device via the PC.

A pump controller mounted on the PCB was connected to the micropump (Bartels mp6). A piezoelectric micropump was chosen as it was inexpensive, easy to control and easy to obtain. On its own, the flowrate was too high for continuous insulin delivery, however with the scalable micropumps and using a less concentrated insulin, the required range for insulin delivery was achieved. The pump used in the prototype was rated to last a few months, which was sufficient for the time the prototype was required to run and the time needed to characterize it. The micropump inlet was connected to the outlet of the reservoir. The outlet of the micropump was split into two flows, one delivering insulin to the vein, the other was directed back to the



(a) **(b)**

Figure 6.1: Prototype of the Artificial Pancreas Device: (a) fluidic sub-system only and (b) with PCB and pump above the fluidic sub-systems, fitted into one half of the device. The other half is for the power supply

insulin reservoir via the microchannel flow divider. The details of this are presented in Chapter 4.3. The prototype was designed to be implanted in the pelvic area and connected to the portal vein.

The power supply used in this prototype were alkaline $1.5V$ 'AA' batteries. The PCB and the insulin delivery subsystem, which includes the scalable micropump units and insulin reservoir, and the power supply were encased in a photopolymer shell (Fullcure Verogray) (Figure 6.1). The size of the implanted device was $10cm$ in diameter and $7cm$ width. The embedded program computed the insulin dosage using blood glucose readings obtained from the CGMS (Medtronic Guardian Real-time) thus enabling closed loop blood glucose regulation.

The firmware was designed for low power consumption by using state transition mechanisms and ensuring that the device could be in the lowest power consuming state most of the time. More details of the firmware and wireless hardware can be found in [128]. The states of the artficial pancreas are shown in Figure 6.2

The power consumption is the lowest in CSWor state (CPU Sleep Wake

on Radio) and it is also the state the device is mostly in. The processor of the artificial pancreas is in sleep mode while the transceiver is on Wake-On-Radio mode and wakes periodically to check for incoming base station messages. If there is no incoming message, the radio will return to sleep mode. Upon receiving a message, the transceiver generates an interrupt to wake up the microprocessor.

In CARWor state (CPU Active Wake-on-Radio), the processor of the device is activated to perform tasks including glucose sensing, MPC execution, sending signals to pump control etc. The processor and the radio are both active in the CARA state (CPU Active Radio Active), where the processor handles glucose control and insulin delivery tasks and the radio transmits the data such as glucose reading and insulin dosage to a base station for display and logging purpose.

Bulk downloading of data from the device wirelessly to the base station with the CPU idle occurs in the DL state (Download). In the CARWor state, data such as glucose readings and insulin doses are stored in the flash memory of the artificial pancreas. If the CGMS is able to communicate directly with the device, then artificial pancreas prototype will not need a PC for operations and this mode will be used to transfer data for long term record keeping.

6.3 Experimental Method and Results

Artificial Pancreas prototype using MPC with PDIP optimization was implanted after a swine pancreatectomy. Institutional guidelines for the care and use of animals have been observed, in accordance with guidelines set by the National Advisory Committee for Laboratory Animal Research

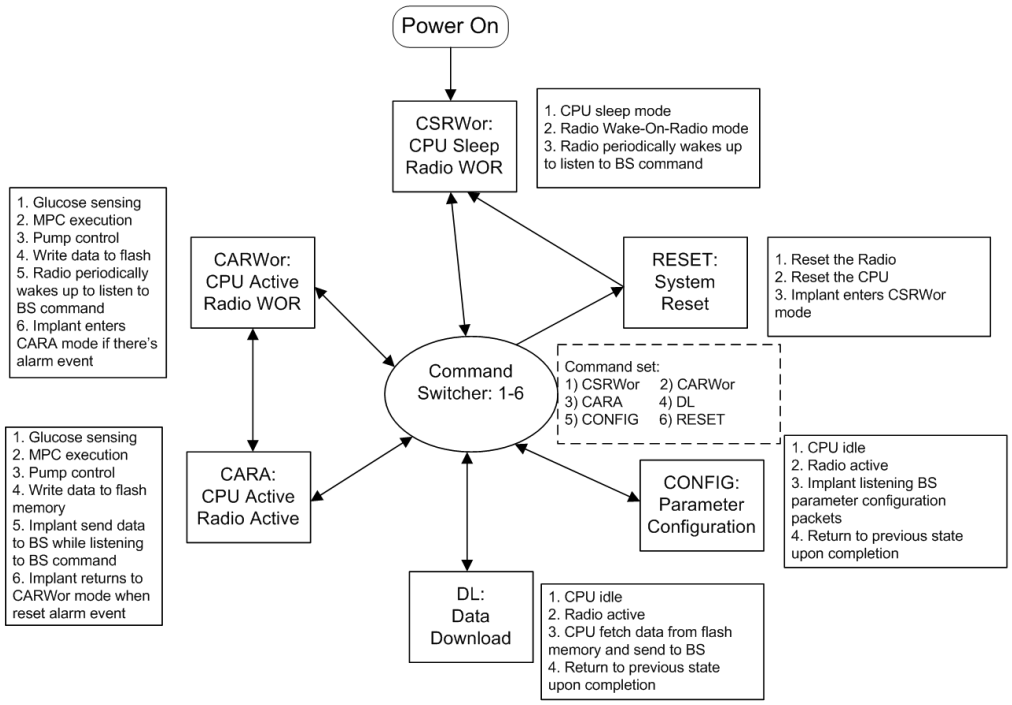


Figure 6.2: Finite State Machine of the Artificial Pancreas

(NACLAR). The animal use protocol (019/11) was approved by the Institutional Animal Care and Use Committee (IACUC), National University of Singapore (NUS).

The pig used in the experiment was a healthy female and weighed $44.75kg$. Ketamin was administered for tranquillisation. Anaesthesia was induced using thiopentone and maintained with isoflurance delivered by intubation. The pig was kept warm using portable electric blankets. Prior to the surgery, the pig fasted overnight, and Lactated Ringer's Solution (LRS) fluids were given as needed.

The artificial pancreas used is the prototype described earlier (Figure 6.1) without the proposed fluid flow connections, as an implantable glucose sensor was not available to us. The $15ml$ insulin reservoir was filled with U-100 insulin aspart (NovoRapid, Novo Nordisk) diluted with saline a

hundred times by volume. The model in the embedded MPC program was the Minimal model, using patient parameters from [79] as there was no prior metabolism data for the particular pig used in the experiment.

After the pig was anaesthetized, the CGMS glucose sensor (Guardian Real-time, Medtronic) was inserted into a peritoneal vein at the abdomen area and was calibrated with measurements drawn from a vein at the ear measured with a blood glucose meter (Roche Accu-check Active). The CGMS values were used for the MPC algorithm for closed loop glucose regulation.

Blood was drawn from the pig's ear vein before and after pancreas removal, and at the end of the experiment. 1ml blood samples from a vein at the pig's ear were also drawn at 15 minute intervals and were sent for laboratory analysis to determine plasma glucose and insulin concentration. Venous blood samples are used as they are the standard for blood glucose reporting. The CGMS reported readings every 5 minutes and were used for closed loop glucose regulation. During the pancreatectomy the pig was given $500ml$ of a 5% glucose solution intravenously for 1 hour. During this time, blood glucose had risen to hyperglycaemic levels. After the pancreas was removed, glucose infusion was halted and the artificial pancreas insulin outlet was connected via catheter to the iliac vein and automatic blood glucose regulation commenced.

The glucose and insulin levels during the experiment, obtained from laboratory analysis of drawn venous blood, are shown in Figure 6.3. Glucose levels reported by the other measurement devices, CGMS and glucose strip monitor, together with laboratory results are shown in Figure 6.4. Blood glucose levels reached a peak of $268mg/dl$ ($14.9mmol/l$) at around time t=$150min$. This was about 15 minutes after the glucose infusion was stopped and the artificial pancreas device was implanted; and about 1 hour after the

pancreas was removed. Normoglycemia was reached within 100 minutes from the peak blood glucose level.

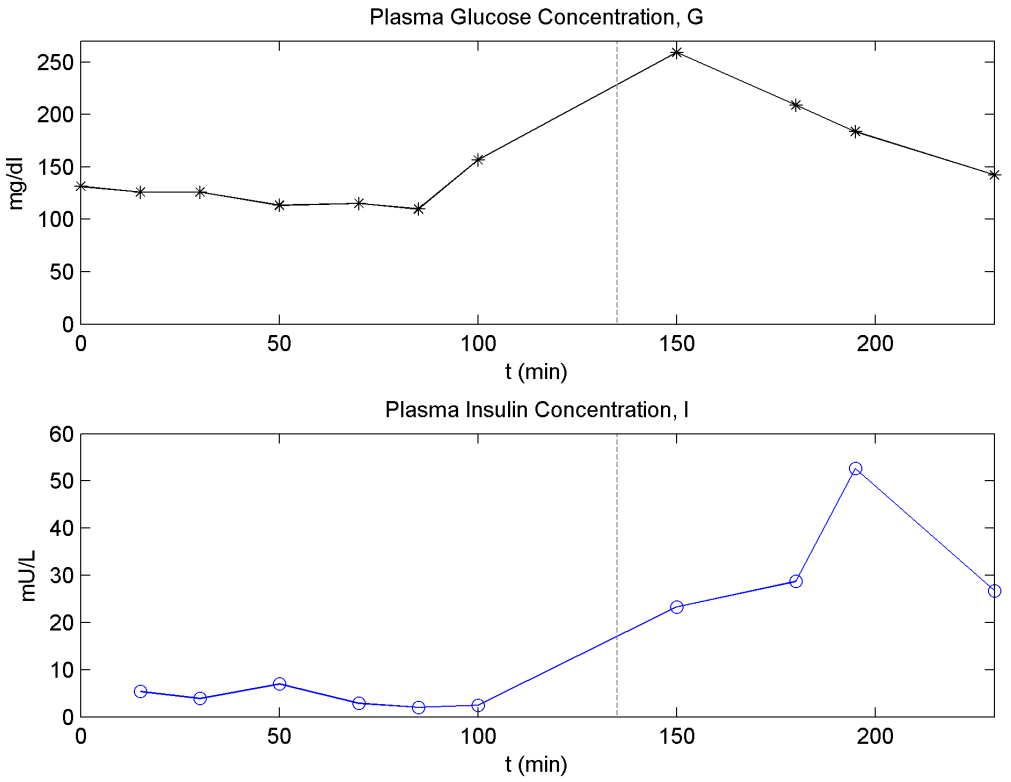


Figure 6.3: Plasma Glucose levels (asterisks) and insulin concentrations (circles) during the in vivo experiment. Pancreas was removed at time t=100 min; and the artificial pancreas was implanted and started at t=135min (vertical dashed line)

6.4 Discussion and conclusion

Peak glucose level in healthy humans is normally around 200mg/dl instead of 270mg/dl in the experiment [16]. Blood glucose levels may have reached normoglycemia sooner if the device had been implanted before the glucose infusion.

After the device was implanted, it was run for 100 minutes in accordance with the IACUC approved protocol, and it successfully lowered blood

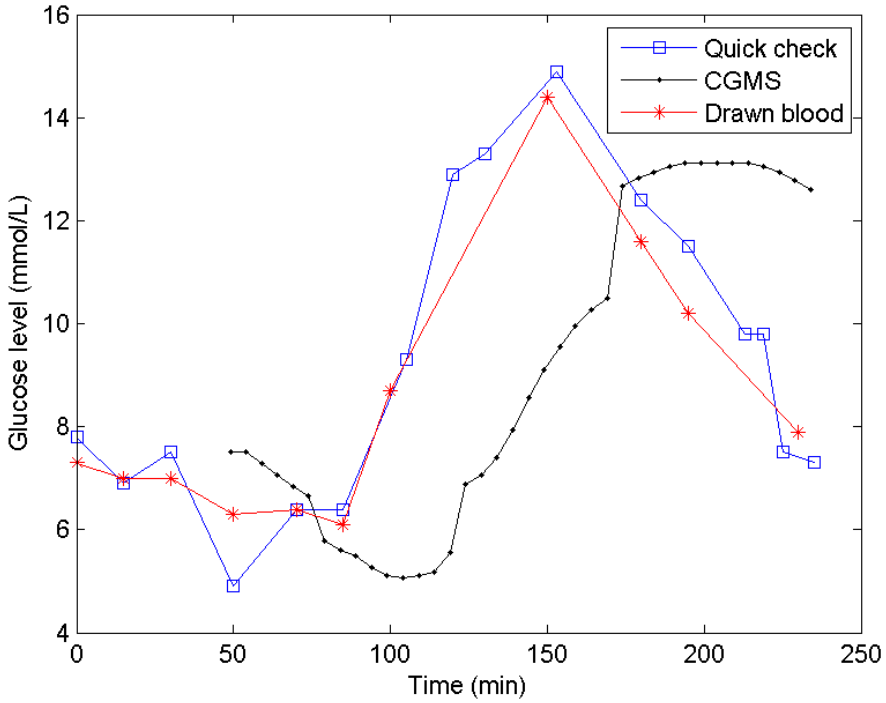


Figure 6.4: Glucose reading from the CGMS (black diamonds), glucose meter (blue squares) and laboratory analysis of drawn blood (red asterisks) during the in vivo experiment. CGMS was inserted into a peritoneal vein, drawn blood from an ear vein was used for glucose meter readings and laboratory analysis

glucose from $259mg/dl$ to $142mg/dl$. However, this was not long enough to determine if normoglycemia can be maintained and hypoglycaemia would have been avoided. In our future in vivo swine experiments, the device should run for at least 6 hours to investigate its effectiveness.

There are few implantable artificial pancreases in the literature due to the technical complexity. An implantable artificial pancreas was designed and developed and it feasibility demonstrated with an in vivo experiment on a porcine model. Future work include in vivo experiments with longer end point, pending IACUC approval, and simulation studies with virtual patients that include metabolism changes due to physical activity.

Chapter 7

Parameter Estimation for Nonlinear Mathematical Model

In this chapter, parameters are estimated for mathematical models of physiology, using glucose sensor data of free-living patients, who live their normal lifestyle of activities and meals, and are not in a clinical setting.

7.1 Introduction

Model Predictive Control (MPC) is used in our artificial pancreas used to regulate blood glucose. In MPC, a mathematical model is used to predict the system response to select for an optimal input. Accurate insulin dosage is important in preventing prolonged hyperglycaemia and more importantly hypoglcaemia, hence the model should be patient specific for better accuracy.

The model used to predict future glucose values can be based on physiology

or an auto-regressive model. Mathematical methods to obtain parameters include Nonlinear Least Squares (NLLS), Maximum Likelihood Estimation and Bayesian estimation [107]; along with methods which do not use gradient descent, e.g., Simulated Annealing, basin-hopping and Genetic Algorithms.

Data collection estimating parameters are usually obtained in a clinical setting, with controlled glucose intake. Besides plasma glucose, insulin concentrations can be obtained. When obtaining parameters in a clinical setting, a person has to stay-in for one or two days and have a controlled diet. They may be required to do this regularly, every year or so, to see if and how much parameters of the model have changed. This may decrease patient acceptance of the process. The motivation to investigate obtaining parameters from free-living patients is to minimise disruptions in patient's lives.

Several groups have studied blood glucose prediction and modeling with CGMS data in a controlled clinical setting [129, 130, 131]. Prediction of blood glucose with CGMS data from free-living patients have been studied with linear recursive models [108] and an extended Kalman Filter [132] which simultaneously updates time-varying coefficients. Studies with run-to-run tuning of MPC using ARX models [78] and a nonlinear MPC adaptively updated every control step [41] have been reported in literature.

In this chapter, individualised patient parameters for the Minimal Model [100] were obtained from 7 days of CGMS data from free-living patients who were not on controlled caloric intake. Meal times and the amount of carbohydrate consumed were also unavailable. Of the various glucose-insulin interaction models available [133], the Minimal Model was chosen for this work as its mathematical simplicity and relative accuracy makes it suitable for implementation on a low power microcontroller.

7.1.1 Minimal Model for Glucose-Insulin Dynamics

The minimal model proposed by [100] is derived from physiological system identification and contains three ordinary differential equations and six parameters to be estimated. The model was derived from the Intravenous Glucose Tolerance Test (IVGTT) and can be described mathematically as follows:

$$\frac{dG}{dt} = (-p_1 - X)G(t) + p_1 G_b \tag{7.1a}$$

$$\frac{dX}{dt} = -p_2 X(t) + p_3 I(t), \tag{7.1b}$$

$$\frac{dI}{dt} = \gamma(G(t) - h)t - nI(t) \tag{7.1c}$$

where the model parameters are described in Table 7.1. Six parameters p_1, p_2, p_3, γ, h, n are to be determined for each patient.

7.2 Experimental Methods

Patient parameters of the Minimal Model [100] were estimated using data sets of virtual patients from the UVa/Padova simulator [2] and clinical data from patients. First, data is preprocessed by extracting parts of the glucose-time data. Next, NLLS regression was performed for each data sequence to obtain model parameters. The parameters found from all the meals were then aggregated for each patient.

7.2.1 Preprocessing of Data Sequences

The Minimal Model mathematically describes glucose-insulin dynamics during an IVGTT where subjects were given an intravenous dose of glucose

Table 7.1: Bergman Minimal Model Variables and Parameters

Parameter	Unit	Description
$G(t)$	mg/dl	Plasma glucose concentration
$X(t)$	min^{-1}	Insulin variable for the remote compartment
$I(t)$	mU/l	Plasma insulin concentration
G_b	mg/dl	Basal value of plasma glucose concentration
I_b	mU/l	Basal value of plasma insulin concentration
p_1	min^{-1}	Glucose effectiveness, insulin-independent constant rate of glucose uptake
p_2	min^{-1}	Rate of clearance of active insulin in remote compartment
p_3	$min^{-2}/mU/l$	Increase in uptake ability caused by insulin
γ	$\mu U/mg.min^2$	Proportionality constant of the rate of pancreatic insulin secretion that enters the plasma
h	mg/dl	Glucose threshold for insulin secretion
n	min^{-1}	Fractional clearance of insulin

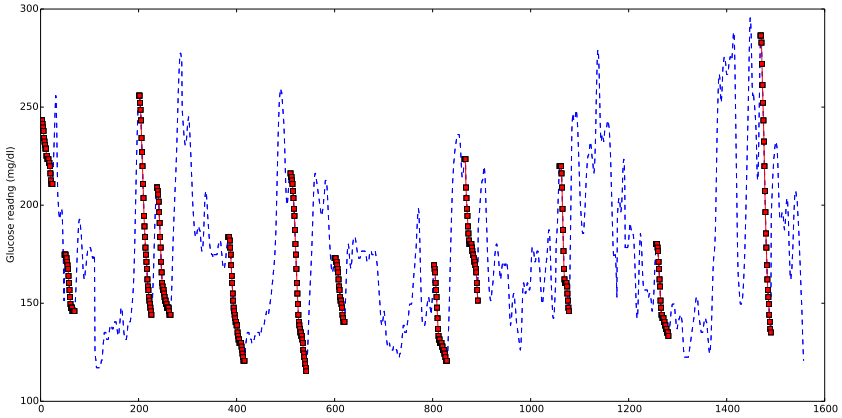


Figure 7.1: Patient glucose levels over 7 days, obtained from the CGMS. The glucose levels drops at varying rates after a meal. Occasionally, the glucose level plateaus before dropping. The dotted lines show the CGMS data collected at 5 minute intervals, the square marked solid lines indicate the data extracted for use in the parameter estimation.

at the start. Plasma glucose levels dropped exponentially immediately after the glucose was administered. CGMS data from free-living patients showed glucose levels increasing at a slower rate, often plateauing before decreasing at varying rates. To preprocess the data, the monotonically decreasing parts of the data sequence were extracted and used for the parameter estimation. Figure 7.1 shows 7 days CGMS data from a patient and the parts of the data extracted for estimation.

7.2.2 Nonlinear Least Squares

NLLS is extensively used to estimate models which are nonlinear in the parameters. It is an iterative process to approximate the minimum of a curved hyperplane.

The difference between the measured blood glucose and predicted blood

glucose at time t_j is r_j, the residual (error),

$$r = G_j - G_M(t_j, \theta)$$

where G_j is the measured glucose level at time t_j and $G_M(t_j, \theta)$ is the predicted glucose level at time t_j using the model parameters θ, a vector of p elements.

The sum of squares of the residuals, S, is given by

$$S = \sum_{j=1}^{N} r_j^2. \tag{7.2}$$

S reaches a minimum when the gradient for each parameter

$$\frac{\partial S}{\partial \theta_i} = 2 \sum_j r_j \frac{\partial r_j}{\partial \theta_i} \tag{7.3}$$

is zero.

In a nonlinear system, $\frac{\partial S}{\partial \theta} = 0$ does not have a closed solution. Each parameter θ_i can be estimated by the iterative approximation

$$\theta_i \approx \theta_i^{k+1} = \theta_i^k + \Delta\theta_i$$

where k is the iteration number and $\Delta\theta$ is the shift vector.

At each iteration, the model can be linearized by the approximation using a Taylor series expansion at θ^k

$$\begin{aligned} G_M(t_j, \theta) &\approx G_M(t_j, \theta^k) + \sum_i \frac{\partial G_M(t_j, \theta^k)}{\partial \theta_i}(\theta_i - \theta_i^k) \\ &\approx G_M(t_j, \theta^k) + \sum_i J_{ji}\theta_i^k \end{aligned} \tag{7.4}$$

where J is the Jacobian. The residual error is now

$$r_j = \Delta y_j - \sum_{s=1}^{p} J_{is} \Delta \theta_s$$

where

$$\Delta y_j = G_j - G_M(t_j, \theta^k).$$

Substituting into Equation 7.3,

$$-2 \sum_{j=1}^{N} J_{ji} (\Delta y_j - \sum_{s=1}^{m} J_{js} \Delta_s) = 0. \tag{7.5}$$

Gradient methods are usually used to find the minimum and solve (7.3) iteratively. However, the parameter estimation may not be a convex problem and the presence of local minima in a multi-dimensional problem poses a challenge. Instead of gradient methods, search methods such as Simulated Annealing and Genetic Algorithms may also be employed to find the global minimum. However such heuristic-based algorithms are usually more computationally expensive. To mitigate getting trapped in local minima and improve chances of finding the global minimum, gradient descent methods are run with multiple initial points for each data sequence to be fitted.

In this work, NLLS regression was performed using a PC, in the Spyder environment for Python. Two functions were assessed for NLLS, `lmfit` function from the lmfit package and `basinhopping` function in the scipy.optimize package.

The `lmfit` function uses the Levenberg-Marquadt algorithm to solve for the minimum. The function also allowed for constraints on the results. These were set such that the parameters found had to be physiologically possible. The function was run for each sequence with 366 random initial points.

The `basinhopping` function employs the Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm, which is a quasi-Newton method for unconstrained nonlinear optimization. As with `lmfit`, regression was run with multiple initial points, using the function default of 100.

Each data sequence would generate a set of parameters, hence the values from all data sequences were aggregated and the aggregate statistics (mean and the median) reported. Physiologically impossible parameters found, if any, were removed prior to calculating the aggregate statistics. Results showed that the RMSE using medians of the parameters found were much lower compared to those using averages, hence results in the following section are only presented using the parameter medians. Using the median also prevents outlier values from having undue influence.

7.3 Results

7.3.1 Virtual Patient Data

Parameters of the Minimal Model were estimated for two virtual patients —one normal healthy individual, and the other with Type 2 diabetes not requiring exogenous insulin. The parameters used for each virtual patient are in Table 7.2.

For each patient, 88 glucose over time data sequences were generated, with varying impulse glucose loads, simulating an oral glucose tolerance test (OGTT). The RMSE of each data sequence with the Minimal Model output using the parameters found is shown in Table 7.3.

Minimal Model parameters found for two virtual patients are in Table 7.4 using the median of all the parameters found for the patient over the 88

Table 7.2: Parameters used for the UVa/Padova simulator [2, 3] for a Normal and a Type 2 patient

Process	Parameter	Unit	Normal	Type 2
Body Weight	BW	kg	78	90.78
Basal Glucose Mass	G_{pb}	mg/kg	172.5088	244.6282
Basal Glucose	G_b	mg/dl	91.76	164.18
Basal Insulin Mass	I_{pb}	$pmol/kg$	1.2745	2.1924
Basal Insulin	I_b	$pmol/l$	25.49	54.81
Glucose Rate of Appearance after Meal	k_{abs}	min^{-1}	0.0568	0.023
	k_{max}	min^{-1}	0.0558	0.0465
	k_{min}	min^{-1}	0.008	0.0076
	f	dimensionless	0.9	0.9
	b	dimensionless	0.82	0.68
	d	dimensionless	0.01	0.09
Gluocose Kinetics	V_G	dl/kg	1.88	1.49
	k_1	min^{-1}	0.065	0.042
	k_2	min^{-1}	0.079	0.071
Glucose Renal Excretion	k_{e1}	min^{-1}	0.0005	0.0007
	k_{e2}	mg/kg	339	269
Endogenous Glucose Production	k_{p2}	min^{-1}	0.0021	0.0007
	k_{p3}	$mg/kg/min$ per $pmol/l$	0.009	0.005
	k_{p4}	$mg/kg/min$ per $pmol/kg$	0.0618	0.0786
	k_i	min^{-1}	0.0079	0.0066
	EGP_b	$mg/kg/min$	1.92	2.01
Glucose Utilization	V_{mx}	$mg/kg/min$ per $pmol/l$	0.047	0.034
	k_{m0}	mg/kg	225.59	466.21
	F_{cns}	$mg/kg/min$	1	1
	p_{2U}	min^{-1}	0.0331	0.084
Insulin Secretion	K	$pmol/kg$ per mg/dl	2.28	0.99
	α	min^{-1}	0.05	0.013
	β	$pmol/kg/min$ per mg/dl	0.11	0.05
	γ	min^{-1}	0.5	0.5
Insulin Kinetics	V_I	l/kg	0.05	0.04
	m_1	min^{-1}	0.19	0.379
	m_2	min^{-1}	0.484	0.637
	m_5	$min.kg/pmol$	0.0304	0.0526
	HE_b	dimensionless	0.6	0.6

Table 7.3: RMSE between Virtual Patient data and glucose over time of Minimal Model with parameters found

	Average RMSE		Std. Dev. of RMSE		Data Points	
	`basin hopping`	`lmfit`	`basin hopping`	`lmfit`	`basin hopping`	`lmfit`
Normal Patient	4.06	11.17	2.63	6.02	88	88
Type 2 Patient	6.12	22.198	3.07	10.12	88	88

Table 7.4: Minimal Model parameters for the two virtual patients. The median of the values found using the `lmfit` function are used.

	p_1	p_2	p_3	γ	h	n
Normal Patient	0.211	4.369	14.132	10	2.45	0.0446
T2 patient	9.23E-08	2.437	2.43	10	1.47	0.0253

data sequences, using the lmfit function.

7.3.2 Free-living Patient Data

Eight female and three male patients wore a Continuous Glucose Monitoring System (Medtronic Guardian Real-time) for two sets of 7 days. Patients were on oral medication for diabetes but were not on insulin therapy. For the first period of wearing the CGMS, they consumed carbohydrates as they normally did and recorded only their meal times. For the second set of 7 days, the patients were on a diet intervention. There was an interval of two to six weeks in between the start of the two time periods. The patients were aged between 58 and 64 years, weighed between 53.6 to 101kg and had Body Mass Indices ranging between 21 to 40. The patient demographics are

Table 7.5: Patient Demographics

ID	Age	Gender	BMI
1	61	F	34.70
2	64	M	31.30
3	60	F	21.20
4	63	M	25.50
5	63	F	34.80
6	64	F	32.50
7	64	F	26.70
8	63	F	26.50
9	58	M	40.00
10	60	F	31.40
11	63	F	24.80

given in Table 7.5. The data was provided by National University Hospital (NUH) and IRB approval has been obtained for the usage of the data.

Glucose over time data sequences for each meal were extracted for each patient as described in the previous section. Only the data from the post-diet-intervention was used. The diet intervention did not control the patients meals, but to improve dietary habits. The average RMSE of the data segments and the modelled glucose over time is shown in Table 7.6. For each patient, Minimal Model was run with the median of the parameters obtained with `lmfit`.

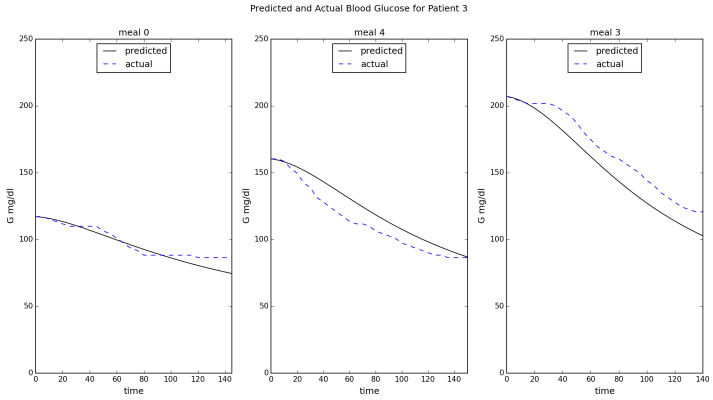
Parameters for the Minimal Model are show in Table 7.7. Parameters reported for each patient are the median of values found using the `lmfit` function on the patient's glucose sensor reading. The graphs showing the modelled glucose levels and the actual data are shown in Figure 7.2.

Table 7.6: RMSE of glucose over time, between clinical patient data and Minimal Model using parameters found

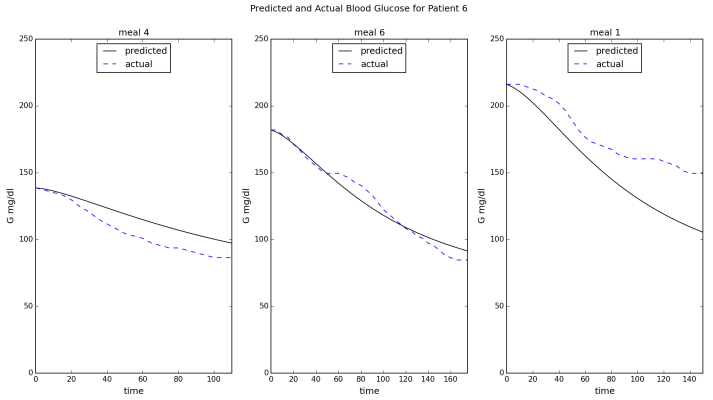
	Average RMSE		Std. Dev. of RMSE		Data Points	
Patient ID	`basin hopping`	`lmfit`	`basin hopping`	`lmfit`	`basin hopping`	`lmfit`
0	38.73	20.04	32.00	18.95	20	20
1	34.55	20.58	26.92	14.33	19	19
2	53.04	13.66	19.75	12.08	4	12
3	12.49	9.02	9.44	5.77	27	27
4	33.13	28.14	33.71	27.68	9	9
5	20.70	13.40	11.17	13.70 7	21	21
6	45.91	16.78	24.16	11.21	19	19
7	15.34	12.89	16.29	8.40	21	21
8	11.94	19.66	9.96	12.63	25	25
9	26.28	19.36	17.24	15.89	16	16
10	48.24	15.43	29.56	9.72	24	24

Table 7.7: Minimal Model parameters for the free-living patients

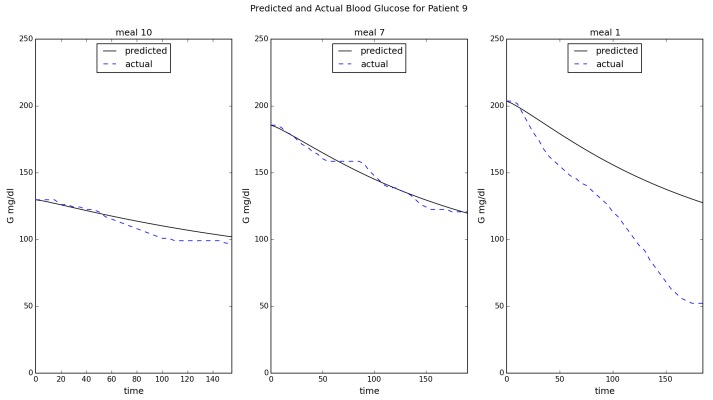
Patient ID	p_1	p_2	p_3	γ	h	n
0	0.1941	2.7997	3.1191	9.8825	0.1112	0.2175
1	0.1808	3.6119	6.0191	7.6442	0.2959	0.1752
2	0.3645	7.8029	17.5374	9.9997	2.4983	0.0876
3	0.1341	3.4467	6.5546	9.9935	0.8496	0.0557
4	0.2348	4.4345	6.0162	9.2639	1.3594	0.1034
5	0.1968	3.8011	6.3060	9.6899	0.2900	0.1025
6	0.2964	3.2241	10.1448	9.5942	0.0781	0.1091
7	0.1165	4.3301	8.3501	7.6987	1.2765	0.0875
8	0.1826	4.6620	3.3674	9.0994	0.4432	0.2773
9	0.2493	2.7562	6.1799	9.1396	0.1613	0.2038
10	0.1628	2.5898	6.9155	9.9994	0.7633	0.0498



(a)



(b)



(c)

Figure 7.2: Predicted blood glucose from Minimal Model and the actual blood glucose from typical patients. The median parameters of the NLLS regression using `lmfit` were used. (a) Patient 3, (b) Patient 6 and (c) Patient 9

7.4 Discussion and Conclusion

Differences between the modelled output and the virtual patient can be attributed to the route of glucose input. In the UVa/Padova simulator virtual patient, the glucose absorption by the gut is taken into account, the Minimal Model, however, describes an IVGTT. However the RMSE is not very large, around 5 to 10% of the basal glucose which was $92mg/dl$.

The RMSE for the free-living patient data is larger than the virtual patients. The meal of glucose of the UVa/Padova virtual patient can be considered as an impulse function or a dirac delta function at initial time, which does not hold for a free-living person. For a free-living patient, a meal may contain one carbohydrate source or a mixture of simple and complex carbohydrates, consumed together with proteins, fats and fibre, over a 10 minute to 1 hour time window. Different carbohydrates have varying time taken to be broken down into glucose. This greatly affects the glucose rate of appearance and is quite different to an IVGTT. Even though the descending glucose levels are taken when the data is pre-processed, during this time glucose may still be appearing (broken down) although at a lesser amount such that overall glucose levels are descending.

In Figure 7.2 it observed that the largest of the 3 meals shown, all starting above 200 mg/dl blood glucose, has the highest discrepancy between modelled and actual values. There is no consistent trend of the predicted values being higher or lower than the real values. It is likely that the subject consumed a large amount of carbohydrates to reach such high blood glucose levels; and the meal probably included a variety of carbohydrates and sugars which would be absorbed into the gut at different rates. The minimal model is based on only one type of input, which was glucose, and

hence, the disagreement with the model prediction. Accurately estimating meal size and predicting glucose rate of appearance in the bloodstream is a challenge for blood glucose regulation.

Circadian rhythms cause diurnal fluctuations in metabolism. Stress, changes in diet and physical activity also alter metabolism. Both the Minimal Model and UVa/Padova virtual patient were run with time-invariant parameters. Future implementations of MPC can take into consideration the time of day and the amount of physical activity.

The RMSE for the first 30 minutes of the modelled sequence is better than that for the whole sequence. As the objective of the work in this chapter is to characterize the Minimal Model, or any other model, chosen for the MPC controller. One possible course of action is for the MPC optimization objective function to have greater weightage on the earlier part of the prediction horizon, or use a shorter prediction horizon. For the real patient data, the `basin-hopping` function could not converge to a solution for several data sequences in Patient ID 2 while the `lmfit` function was able to find suitable solutions to all data sequences. If a shorter time range was used, it is possible that the `basin-hopping` function would perform better.

A framework for patient specific control that can be adaptively tuned and regularly calibrated was presented in Chapter 1 and we have shown that parameter estimation of the model for MPC using free-living patient glucose sensor reading is feasible. This method can also be used for recalibration, although more study into determining the statistical significance that parameters have changed is needed. Future work includes using more accurate yet simple models that account for exercise and circadian variations to better prevent hypoglycaemia. Methods to incorporate information regarding the meal or better ways to model and predict the meal consumed can help in

more accurate modelling and hence control of glucose levels in free-living diabetics.

Chapter 8

Conclusion and Future Work

8.1 Conclusion

The artificial pancreas employing subcutaneous sensing and delivery is progressing at a steady pace and a commercially available one looks highly possible in a few years time. However there is still much scope for work on an implantable artificial pancreas. The sensor, pumps, power and electronics have to last the lifetime of the patient or at least a few decades due to the invasiveness of the surgery required. Wireless technology for communication with electronics across the organs, muscles and tissues needs to be powerful yet consume little energy. The electronics have to meet the reliability and safety requirements for implantable devices. Further studies have to be done to assess implant sites, including the one proposed in the iliac crest which is a site where herniation can occur.

An implantable pancreas brings about challenges to the patient too, as the implantation surgery would result in downtime for recovery. Issues with the device or implantation may require additional surgery which adds to

expenses, inconvenience and pain. However no surgery is required for an external artificial pancreas, and components can be replaced or upgraded if required. However, an externally worn artificial pancreas can limit some sports and activities, care has to be taken the pump or sensor is not dislodged.

An external artificial pancreas is subject to the physiological lags due to glucose sensing and insulin delivery through the interstitial fluid. Glucose concentration at the interstitial fluid lags the glucose in the bloodstream by around 15mins. Insulin delivered subcutaneously takes over 20mins to reach the bloodstream where it can be transported to cells and organs that use it for glucose uptake, thus regulating blood glucose levels. An implanted device which senses glucose and delivers insulin venously would not be subject to these lags. Regardless if the device is external or implanted, monitoring of blood glucose and device status is still important, although this can be done in a discrete method using smart-phone alerts and other means.

One other area actively under research is power supply technology. Ideally the power supply for an implanted artificial pancreas would not require changing, be safe for implantation and able to be charged through wireless means. Power for the artificial pancreas is one key requirement and as yet, there are few suitable energy sources for the artificial pancreas. New wireless charging technology via infrared and Qi seem promising, but is not yet efficient enough and require close proximity between charger and power supply. Technology that charges the device using the patient's own body - for example, through heat or kinetic energy - should be considered also.

The fluid flow connections presented which integrate sensing and delivery are designed for implantation, assuming that a small implantable sensor

will be available in future. However the designs presented in the Chapter 4 are modular and can be easily removed from the prototype or final design without much re-design needed. An artificial pancreas which has automatic drug delivery portion implanted while using a subcutaneous sensor was used for the in vivo experiment (Chapter 6).

Scalable micropumps presented allow larger and cheaper micropumps to be used, aiding in prototyping. The microchannels will add complexity and cost to the design but it can be an interim measure before smaller micro- and nanopumps becomes more accessible.

One method to scope accuracy required of the insulin delivery system and hence the subcomponents of the system is by running simulations on various types of patients to study the effect of deviations in insulin delivery on glucose control. A control-variability grid analysis (CVGA) diagram can used to compare performance with prescribed blood glucose targets or with other blood glucose regulation systems.

MPC was implemented in a low power microcontroller using the Bergman Minimal Model with three differential equations and four states for the predictive control. The performance both in silico and in vivo are good, although the in vivo test was too short to predict if hypoglycaemia would have been avoided.

A higher order controller would require more memory and power for computation. Artificial pancreases using MPC controllers with higher order models reported in literature implement the controller on a laptop or smartphone, which are more powerful and have higher power consumption than the RISC microcontroller used in this work.

Onboard controller and external controller both have their advantages and

disadvantages. An external controller can have much higher computational capability for accurate control and also be able to have a nice user interface. Having the controller on a mobile phone or laptop would remove the need for patients to carry around an extra device to monitor the status of their artificial pancreas. However, it is dependent on the wireless connectivity between the actuator and the controller. Issues such as ensuring the device is on at all times, battery life or even the reliability of the device, are out of artificial pancreas product development control. In this work, an onboard controller is proposed in the design (Chapter 4) where automatic insulin dosage is not affected by wireless connectivity between device and the controller. The parameter estimation and recalibration computation, however, can be done on an external device.

Free-living patient data was used to estimate parameters of the model predictive controller and the same methodology can be used to recalibrate the controller to track changes in the patient's physiology. One issue is that due to the noise of the input signal and RMSE between the predicted and the actual glucose values, a study on the statistical confidence of the parameters found is warranted. Modelling inaccuracies notwithstanding, obtaining patient specific parameters using data from free-living patients still has its benefits. It is convenient for the patient and can increase acceptance of regular calibration of parameters as most clinical methods of to obtain accurate blood glucose would involve drawing blood intravenously every 15 minutes, or less, from which the glucose, insulin and other hormone levels can be obtained.

Innovative fluidic connection designs, an insulin reservoir and scalable micropumps were designed for the implantable artificial pancreas. The Ants System has been modified for use in optimizing the cost function in

MPC was used together with PDIP for a hybrid optimization scheme. The implantable artificial pancreas prototype using model predictive control law was shown to successfully lower blood glucose in vivo.

Patient specific real-time drug dosage computation can aid in the long term management of diabetes. A method of obtaining patient specific parameters of a mathematical model of glucose-insulin interaction was presented, from non-invasive method of using CGMS data of free-living patients. This also enables the possibility of adaptively re-calibrating the model parameters at regular intervals and also tracking long-term physiological changes to better manage the disease. The predicted blood glucose values using the estimated parameters do correspond with expected physiological phenomena and current understanding of metabolism and modelling limitations.

The contributions of this thesis are

- Design of fluid flow connections that integrate intravenous glucose sensing and insulin delivery,
- Design and characterization of scalable micropumps that allow the use of larger micropumps for insulin delivery requiring nano-litre doses; and also of the other parts in the insulin delivery system.
- Adaptation of the Ant System to find optimal input for MPC, to be used in a hybrid optimization scheme together with interior-point methods.
- Estimating parameters of the Bergman Minimal Model from glucose sensor readings of free-living diabetics.

8.2 Future Work

In Chapter 7 the patient specific model for a Type 2 virtual patient was presented. Patient specific controller for a Type 1 diabetic was tested in silico in Chapter 5, and the next step would be to assess how the MPC controller performs for a Type 2 patient with endogenous insulin production.

In Chapter 7, the mismatch of the predicted and actual blood glucose is due to various factors not taken into account by the model. The virtual patient used for parameter estimation will next be run with varying parameters to simulate circadian variation. Various meal disturbance profiles will be used to better simulate more realistic meals. Future work also includes using models that account for exercise and circadian variations to better prevent hypoglycaemia, for both the virtual patient simulator and the model in MPC.

The next step after obtaining patient specific parameters is to determine the statistical confidence of the parameters found, which will also inform if sufficient glucose readings were collected. This can also aid in determining how much data is needed for patient parameter estimation; and subsequently determine if patient parameters have changed with statistical significance. This however may not be a trivial task, as parameter sensitivity is not uniform. Other methods of determining with statistical confidence that parameters are to be recalibrated can be looked into.

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My Publications

Patents

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Chin-Boon Chng, Augustinus Laude, **Yvonne Ho**, Jimmy Liu, Tock Han Lim, Chee-Kong Chui, "A Robotic System for Shared Control Laser Targeting During Retinal Surgery", 11th Asian Conference on Computer Aided Surgery (ACCAS 2015), Singapore, 2015
Best Paper Award

Yvonne Ho, Binh P. Nguyen, Chee-Kong Chui, "Ant colony optimization for model predictive control for blood glucose regulation", SoICT '12: Proceedings of the Third Symposium on Information and Communication Technology, 2012

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Yvonne Ho, Chee-Kong Chui, Daniel Mok, Sumei Sun, Stephen Chang. "Fluidic Flow Connection Designs for Venous Delivery of an Artificial Pancreas", World Congress on Medical Physics and Biomedical Engineering , Beijing, China, 2012
Presented but not published

Journal Papers

Yvonne Ho, Binh P. Nguyen, Chee-Kong Chui, "Low Power Embedded Model Predictive Controller for an Implantable Artificial Pancreas using Interior Point and Ant Algorithm" (To be submitted)

Yvonne Ho, Eric Yin-Hao Khoo, Chee-Kong Chui, "Patient Specific Parameters Estimation Using Continuous Glucose Monitoring System Data Of Free Living Patients" (To be submitted)