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Impact of Sensing and Actuation Characteristics on Artificial Pancreas Design

A Dissertation submitted in partial satisfaction
of the requirements for the degree of

Doctor of Philosophy

in

Chemical Engineering

by

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Impact of Sensing and Actuation Characteristics on Artificial Pancreas Design

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by

Lauren Maria Huyett

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For my grandmother, Ruth Daniels.

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Abstract

Impact of Sensing and Actuation Characteristics

on Artificial Pancreas Design

by

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Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by the body's inability to produce insulin, leading to chronically high blood glucose (BG) concentrations. T1DM is treated by frequent self-administration of insulin based on BG measurements; however, there is a fine line between too little and too much insulin, and an overdose can lead to a dangerous drop in BG. The artificial pancreas (AP), consisting of a glucose sensor, an insulin pump, and a feedback control algorithm, will replace self-treatment by automatically calculating and delivering insulin dosages based on continuous glucose measurements. Many iterations of the AP utilize commercially available subcutaneous (SC) insulin pumps and glucose sensors, but these devices introduce physiological limitations that make control difficult.

In this work, we present a clinical evaluation of an AP that uses SC devices, as well as an investigation of the intraperitoneal (IP) space as an alternative site for insulin delivery and glucose sensing to improve AP performance. Our results show that glucose sensors placed in the IP space have a lower time constant than SC sensors, allowing the controller to respond more quickly to BG disturbances. Similarly, insulin

delivered through the IP space has faster pharmacokinetic and pharmacodynamic characteristics than SC insulin. Based on models of the sensing and actuation dynamics, a proportional-integral-derivative control algorithm with anti-reset windup protection was designed for the IP-IP route and evaluated on 10 simulated T1DM subjects. Using the IP-IP route led to a more robust controller that provided excellent control during the simulation studies. Our results support the development of a fully implantable AP that will operate within the IP space to safely and effectively control BG levels.

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Chapter 1

Introduction¹

Type 1 diabetes mellitus (T1DM) is a disease that requires intensive self-treatment. A small miscalculation or wrong decision can lead to both immediate and long-term health problems. Technological advancements have greatly improved the way that T1DM is treated. Even so, this disease is an ideal candidate for an automated treatment solution, and in fact efforts have been in place to develop one for over 30 years [2]. Continuous insulin infusion pumps and glucose sensors are commercially available, but the loop must remain open until a suitable controller is designed. The development of automated control for T1DM will increase the quality of life of those with the disease by reducing the burden of self-treatment, as well as by providing improved health outcomes. The objective of this dissertation is to investigate the characteristics of glucose sensing and insulin action through different routes, as well as the impact that they have on the development of safe, effective closed-loop control for T1DM.

¹Some content from this chapter is published in F. J. Doyle III, L. M. Huyett, J. B. Lee, H. C. Zisser, and E. Dassau, "Closed-loop artificial pancreas systems: engineering the algorithms," *Diabetes Care*, vol. 37, pp. 1191-7, 2014. [1]

1.1 Type 1 Diabetes Mellitus

As of 2010, an estimated 1 in every 300 people under the age of 18 in the United States has T1DM [3]. This disease is characterized by the autoimmune destruction of pancreatic beta cells. The cause of this destruction is unknown, but it is hypothesized to involve both genetic and environmental factors [3, 4].

The pancreas is charged with regulating the blood glucose concentration (BG) within the body. The regulation process is depicted in Figure 1.1. Cells receive much of their energy by processing glucose, which is absorbed into the blood stream through the digestion of carbohydrate-containing food. The pancreas then controls the uptake of glucose from the blood stream into tissue cells and the liver to maintain BG homeostasis by secreting insulin, glucagon, and other hormones. In response to elevated levels of glucose in the blood, the pancreas produces insulin to stimulate the uptake of glucose into muscle and fat cells to be used for energy. Glucose is also stored in the liver as glycogen. In response to low levels of glucose in the blood, the pancreas produces glucagon, which stimulates the conversion of the stored glycogen to glucose. This process can be viewed as a closed-loop control system, where the pancreas acts together with the liver to control the BG within the body [4].

1.1.1 Pathophysiology

When the beta cells are destroyed, the pancreas can no longer produce insulin, which disrupts the feedback loop by removing one of the manipulated variables [6]. The inability to produce insulin leads to chronically high glucose concentrations in the blood ($BG > 180$ mg/dL), known as hyperglycemia. Glucose is toxic to the vasculature at high concentrations. Common long-term complications of hyperglycemia

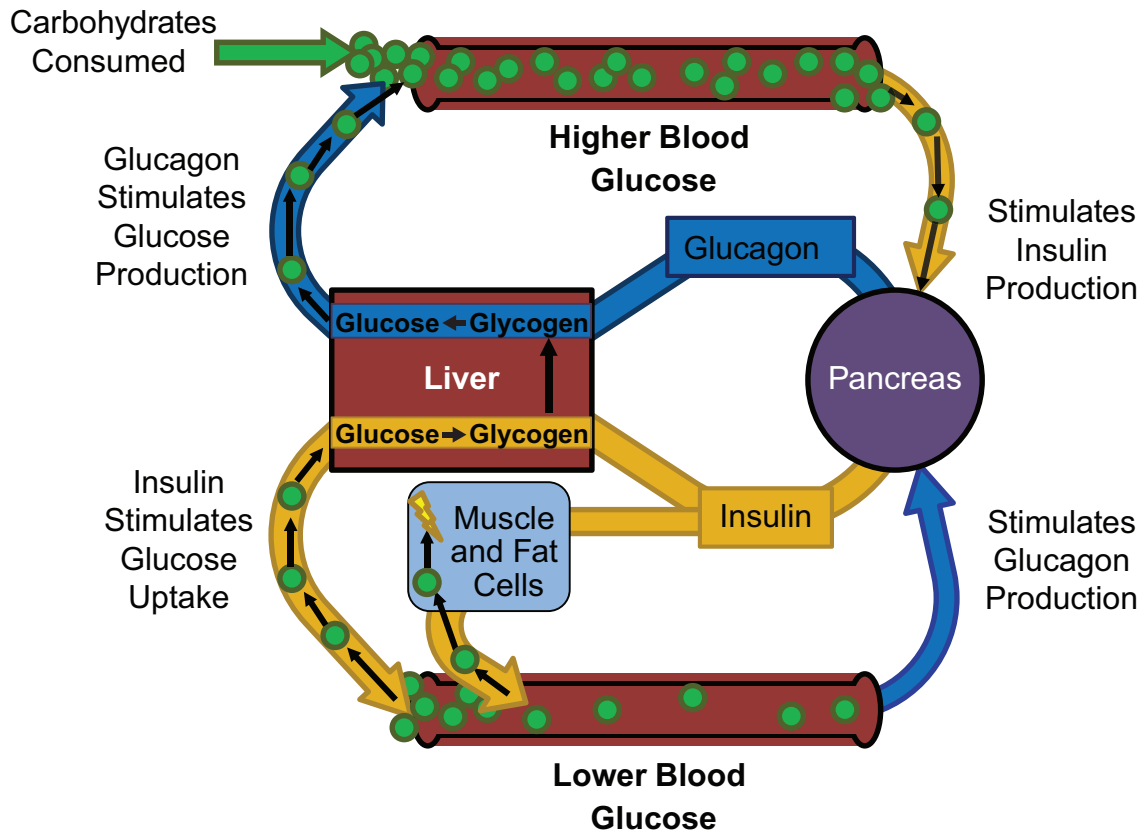


Figure 1.1: Schematic of glucose homeostasis maintained by the pancreas and the liver. In response to elevated levels of glucose in the blood, the pancreas produces insulin to stimulate the uptake of glucose into muscle and fat cells to be used for energy. Glucose is also stored in the liver as glycogen. In response to low levels of glucose in the blood, the pancreas produces glucagon, which stimulates the conversion of glycogen to glucose. Figure adapted from [4] and [5].

include nephropathy, retinopathy, neuropathy, and cardiovascular disease [4].

In addition to the long-term complications related to chronic hyperglycemia, untreated T1DM leads to diabetic ketoacidosis (DKA) in the short-term. This complication begins when the glucose uptake by cells decreases, while the breakdown of glycogen and other non-carbohydrate molecules occurs, leading to an excess of glucose within the bloodstream. At the same time, lipids are broken down to form ketones, which can provide energy to cells as a replacement for glucose. The kidneys begin to remove the excess glucose and ketones from the blood, causing water and electrolytes to be secreted as well. The resulting dehydration leads to increased urination and thirst, which are both common symptoms of undiagnosed T1DM. This process ultimately leads to reduced arterial blood pressure and brain blood flow, while the blood becomes more acidic due to elevated ketone levels. If left unimpeded, the result of DKA is impaired brain function, coma, and death [4, 6].

1.1.2 Treating Type 1 Diabetes Mellitus

Before insulin was isolated in the early 1920s, there was no way to successfully treat T1DM [4]. Once the commercial production of insulin began, it was used successfully by people with T1DM to replace the role of their absent beta cells. While this treatment with exogenous insulin allowed people with T1DM to survive, much improvement in the treatment process was still needed to achieve better long-term patient outcomes. A key event in this process of improvement was the landmark study by the Diabetes Control and Complications Trial Research Group, which showed that intensive insulin treatment reduces the severity and delays the onset of long-term complications of T1DM [7].

While intensive insulin therapy can reduce the long-term complications of hyperglycemia, it also increases the risk of hypoglycemia, or a BG that is too low

(BG < 70 mg/dL). Hypoglycemia can occur if an overdose of exogenous insulin is delivered. Other potential causes are exercise or malnourishment. When the glucose concentration becomes too low, the sympathetic nervous system is triggered. The resulting symptoms include increased heart rate, trembling, nervousness, sweating, and anxiety. In addition, severe hypoglycemia deprives the brain of glucose, leading to headache, confusion, dizziness, slurred speech, convulsions, coma, and death [4, 6].

The goal of T1DM treatment is to minimize hyperglycemia, while avoiding hypoglycemia, through the delivery of exogenous insulin. The desired range for preprandial glucose is 80-130 mg/dL, with a peak postprandial glucose less than 180 mg/dL. Additionally, it is recommended that the glycated hemoglobin (HbA1c), a measure used to indicate BG levels over the past few months, be maintained lower than 7.0% [8]. Successful treatment is accomplished by using a combination of tools and techniques to monitor the BG and adjust insulin delivery according to those measurements, as well as in anticipation of meals and other daily-life events that affect glycemia.

1.2 Technology and Diabetes Treatment

1.2.1 Insulin Delivery

To effectively treat T1DM, exogenous insulin must be delivered on a daily basis. Insulin is needed both at a low background level, known as basal insulin, as well as in larger doses in response to meals or to correct a high BG. While the most desired method for the delivery of chronic medication is the oral route, taking an insulin pill currently is not an option due to low bioavailability through this route [9]. In fact,

for decades the only option for insulin delivery was through subcutaneous injections with a syringe [10]. Over time, insulin delivery regimes have grown more refined in an attempt to exert finer glycemic control.

The two regimens for insulin delivery used most often today were both introduced in the 1970s. The first is multiple daily subcutaneous injections (MDI) of insulin, which includes doses for basal insulin and doses for meals [11]. MDI was improved by the development of insulin pens in the 1980s, which allowed for more convenient and comfortable injections [12]. However, people with T1DM find that injections can be inconvenient, complex, lacking in precision, and difficult to use in conjunction with variation in day-to-day activities [13]. Additionally, injections must use combinations of slow- and fast-acting insulin to meet both the basal and prandial insulin requirements [13].

The second insulin delivery method used today is continuous subcutaneous insulin infusion (CSII) using a miniature pump. The pump delivers insulin via a cannula that is inserted subcutaneously [10]. Insulin pumps use only fast-acting insulin. They meet basal insulin requirements by delivering small amounts of insulin (called microboluses) every five minutes. They can also be commanded to deliver larger boluses to meet insulin requirements for meals and correction doses. CSII has become much more advanced over the years, with the development of pumps that can be programmed to fine-tune and customize basal insulin delivery and allow easy calculations for meal and correction boluses [13].

CSII has been associated with improved glycemic control, decreased hypoglycemia, and better quality of life [14–16]. Still, there are several disadvantages of this delivery route. Using CSII means that the patient is attached to an external device, which may be inconvenient in daily life. Additionally, it is recommended to change the infusion set every three days to reduce problems with site irritation

and irregularity in insulin delivery caused by blocked catheters, insulin leakage, or cannula dislodgement [17]. A failure of the infusion set can lead to hyperglycemia, and potentially DKA if the problem is not detected in time.

The subcutaneous route of insulin administration is not ideal for many reasons. This route is nonphysiological and results in peripheral hyperinsulinemia [18]. The pharmacokinetic and pharmacodynamic characteristics of insulin delivered through CSII cause delays between delivery and effect, and the insulin can remain active for as long as 4-6 hours following injection. In addition, inter- and inpatient variabilities in insulin sensitivity and absorption through the subcutaneous route can cause inconsistent pharmacokinetic and pharmacodynamic properties [19]. For these reasons, the development of alternative insulin delivery routes is an important and active area of research. One such alternate route that has shown promise in overcoming the disadvantages of the subcutaneous route is delivery through the intraperitoneal space. The use of intraperitoneal insulin delivery is discussed more in Chapters 4 and 5 of this dissertation.

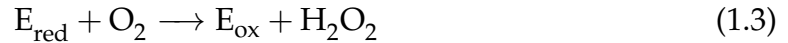
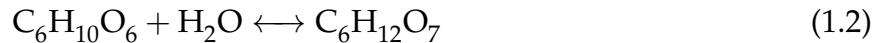
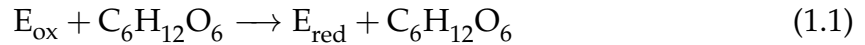
1.2.2 Glucose Measurement

Accurate BG measurement is essential for safe and successful treatment of T1DM. The current standard of care for BG measurement is the capillary blood test [20]. A lancet is used to prick the fingertip to release a small drop of capillary blood, which is placed onto a test strip in a handheld glucose meter. This method requires active work by the user and is somewhat painful, meaning that it can be expected to be performed at most once every few hours, and only while the patient is awake. In fact, a conventional approach to glucose monitoring will result in only three to four measurements per day [21]. These measurements create a discrete picture of the BG over time, but often miss important trends.

The development of glucose sensors that operate *in vivo* to provide a continuous estimation of the BG has allowed patients to observe the continuous trajectory of their BG over time. The first continuous glucose monitor (CGM) was approved for use in the United States in 1999 [22]. This device, produced by MiniMed (later bought by Medtronic in 2001), did not display BG readings in real-time; rather, the data were downloaded and analyzed retrospectively by the user's doctor after the 3 day period of wear [23]. CGM technology has advanced greatly since then, with devices today providing patients with a real-time readout of their BG over 6 or 7 days of continuous wear. These sensors are worn on the skin, with a transcutaneous sensing element inserted into the subcutaneous space [24].

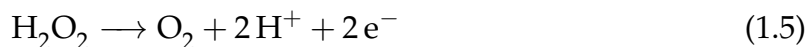
Methods of Glucose Detection

The CGMs currently available in the United States operate through the electrochemical detection of glucose using the enzyme glucose oxidase [24]. The following series of reactions is of interest to the detection of glucose [23]:



In these reactions, E_{red} and E_{ox} are the reduced and oxidized forms of the enzyme, respectively. The fourth step represents the optional inclusion of a mediator to react directly with the enzyme, with M_{ox} being the oxidized mediator and M_{red} being the reduced mediator. Examples of mediators are ferrocene or Os(III). The glucose concentration can be inferred either by measuring the production of hydrogen peroxide

or the production of the reduced mediator (if in use) [23]. The hydrogen peroxide concentration or the reduced mediator concentration is measured amperometrically by inducing its oxidation at a suitable electrode. This process is described by the following reactions:



To make the measurement, a constant voltage is applied across the working and reference electrode to make the reaction thermodynamically favorable.

The two continuous glucose monitors on the market today (Dexcom G4 Platinum and G5 Mobile, Dexcom, San Diego, California and the Medtronic Enlite, Medtronic Diabetes, Northridge, California) utilize the detection of hydrogen peroxide, with no additional mediator used. A schematic diagram of an electrochemical sensor using this method is shown in Figure 1.2. As the hydrogen peroxide is oxidized, an electrical current is produced in proportion to the number of molecules that have reacted. In order for this reaction scheme to be useful, the electrical current produced must be directly proportional to the concentration of glucose in the range of interest (approximately 30-360 mg/dL of glucose). The best way to ensure this linearity is to design the sensor so the mass transport of glucose to the enzyme layer of the electrode is the rate limiting step [23, 25].

The CGM sensor is designed with a series of selective membranes to limit the production rate of hydrogen peroxide by the diffusion of glucose. The outer layer allows a higher flux of oxygen than glucose. This membrane creates an excess of oxygen within the enzyme layer, ensuring that the rate of production of hydrogen peroxide will not be limited by the concentration of oxygen. This diffusion-limiting step is

needed because in the interstitial fluid (ISF) where the sensor is placed, oxygen is usually found in concentrations that are an order of magnitude smaller than glucose concentrations. The next layer of the electrode is the enzyme layer, which contains immobilized glucose oxidase. Excess enzyme is included so the glucose molecules react as soon as they reach the enzyme layer. The hydrogen peroxide produced by the reaction diffuses through the interference layer into the electrode layer. The interference layer is a selective membrane that is included to prevent other species that could be oxidized at the electrode from passing through. The hydrogen peroxide reacts immediately upon arrival at the surface of the working electrode to produce a current in proportion to the number of molecules oxidized. Since the process is designed to be limited by the diffusion of glucose, the current produced will be linear in glucose concentration [23].

To be used for *in vivo* glucose measurements, the sensing element must be inserted transcutaneously so that one end sits in the subcutaneous space, while the other end connects to the transmitter that is placed on the outside of the body. The sensor measures the electrical current produced in reaction to the ISF. This current is calibrated to the BG [23]. Both the Dexcom and the Medtronic sensors require calibration with a fingerstick measurement every 12 h throughout the sensor wear period, because the relationship between the glucose concentration and the resulting electrical current changes over time [23, 24]. While the sensor directly measures the glucose concentration in the ISF, this measurement is used as an estimation of the BG. The transmitter sends a value to the receiver at a frequent time interval (usually every five minutes) [23].

The Abbott FreeStyle Libre is a new type of glucose sensor that is available in Europe, but not yet in the United States. This sensor is designed to replace fingerstick measurements in determining insulin doses. The sensor can be worn for 14 days

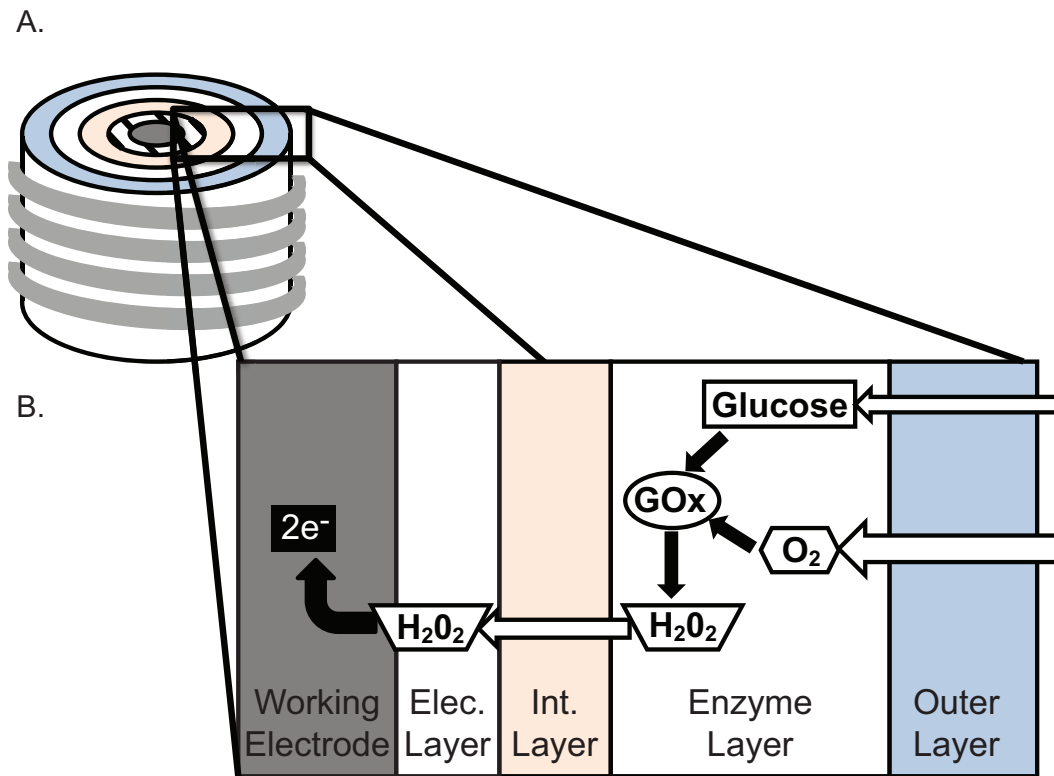


Figure 1.2: Schematic representation of a sensing element that could be used in a CGM. (A) Cross section of the electrode. (B) Layers of the glucose sensing electrode. Figure adapted from [23] and [25].

and is factory-calibrated, meaning that no fingerstick measurements are required throughout the entire device wear period. However, this sensor is not yet a CGM. Rather than continuously transmitting measurements to a monitor for a real-time readout, the sensor provides the measurement only when the meter is used to scan the sensor. Upon scanning, the most recent measurement, plus a history of up to 8 h, is provided [26]. In the future, this sensor may become available as a true factory-calibrated CGM.

The FreeStyle Libre operates through Wired Enzyme™ technology, which was previously used in the FreeStyle Navigator CGM [26, 27]. This technology uses the detection of a mediator, rather than hydrogen peroxide, to measure the glucose concentration. To prevent the mediator from diffusing out of the sensor, it is bound within a redox active gel, which contains the glucose oxidase and the Os-based mediator attached by anchors to a polymeric backbone film enzyme. This sensing mechanism provides a more stable response over the lifetime of the sensor than hydrogen peroxide-based sensors. Additionally, the use of the mediator removes the dependence on the oxygen concentration, so the system of selective membranes to orchestrate a higher concentration of oxygen is no longer necessary. Since oxygen is no longer a key component for glucose detection, the glucose measurement will not be affected by fluctuations in oxygen concentration in the *in vivo* environment. Lastly, the potential that needs to be applied to the working electrode to drive the reaction is much smaller than what is needed for hydrogen peroxide sensors (40 mV versus 500-700 mV). Using this smaller potential removes the possibility of interference from other electroactive compounds, such as acetaminophen [23, 26]. The feasibility of a factory calibration was enabled by advances in the sensor manufacturing process that ensure consistent and reproducible sensor production [27, 28].

An emerging type of CGM operates without using glucose oxidase or any other

electrochemical reaction. Instead, it detects glucose using a fluorescent indicator. The sensor consists of a hydrogel containing the fluorescent indicator, an LED to excite the indicator, and photodiodes to measure the fluorescence intensity. Glucose binds with the indicator in a reversible reaction that prevents fluorescence quenching, thus increasing the fluorescence in proportion to the glucose concentration. The fluorescent sensor in development by Senseonics (Germantown, MA) is designed to be fully implantable within the subcutaneous space, meaning there is no transcutaneous component. The implanted sensor uses an antenna to communicate with the transmitter placed on the skin above the sensor site [29]. Data from a clinical study show that the implanted sensor is able to measure glucose for at least 90 days, which is a significant improvement over the 6, 7, or 14 day wear period of other sensors [30]. The Senseonics Eversense CGM System has recently received the CE mark for adjunctive use and will be commercialized beginning in Sweden [31].

Subcutaneous Glucose Sensing Characteristics

Subcutaneous CGMs are advantageous for many reasons: they require little patient effort, capture trends that would be missed by capillary glucose measurements, continue working even while the patient is asleep, and are painless apart from the initial insertion. The disadvantages are that the sensors need to be calibrated by capillary glucose measurement every 12 h, pressure on the sensor site during sleep can cause the signal to drop, and measurements may not be accurate or may lag behind the true BG [32, 33]. Despite these drawbacks, CGMs have been shown to improve treatment for adults and children with T1DM, especially when combined with pump therapy [34–36].

Understanding the glucose measurement process and potential errors associated with it is important to ensuring that these sensors have a positive impact on patient

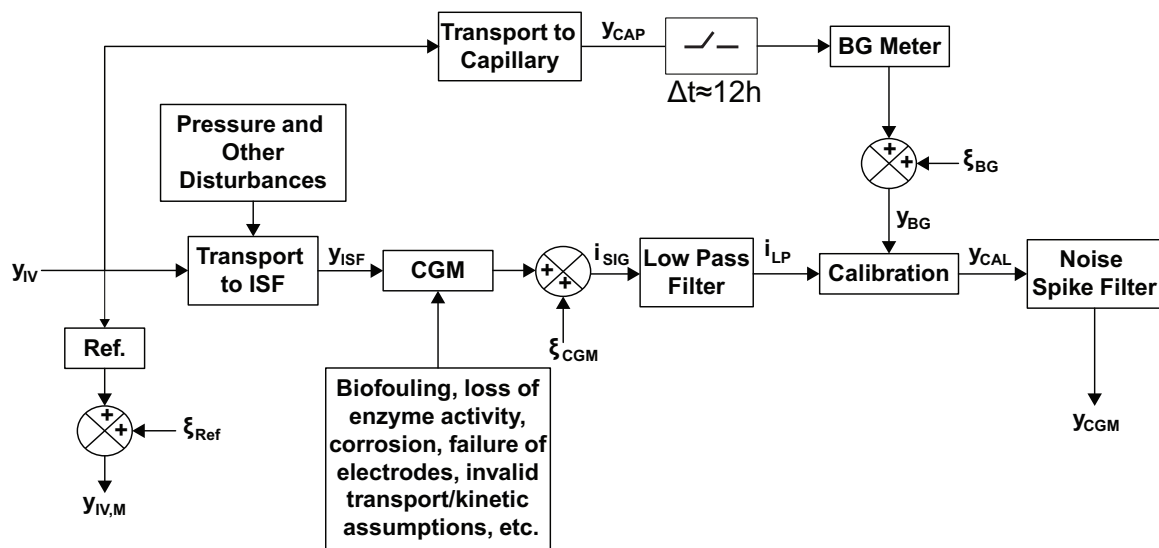


Figure 1.3: Block diagram demonstrating factors that contribute to CGM error. The input is IV glucose concentration, and the output is the CGM glucose measurement. Glucose is transported from the blood to the ISF, where it is then detected by the sensing mechanism. Calibration is used to convert the measurement from electrical current to glucose concentration. The transport process from the blood to the ISF, as well as other factors such as biofouling and encapsulation, induce a lag into the measurement.

care. Since the sensor is acting *in vivo*, there are many sources of error that can affect the measurement [23, 37]. The block diagram in Figure 1.3 depicts the measurement process from the intravenous (IV) glucose concentration to the measured CGM value. Glucose must be transported from the blood to the ISF, which adds a diffusion lag [38]. Pressure on the sensor site can affect the volume of the ISF, acting as a disturbance to the transport process [33, 39]. The ISF concentration is measured by the CGM, which produces an electrical current (i_{sig}) that is designed to be linear in glucose concentration. Various factors such as biofouling, corrosion, and invalid kinetic assumptions can affect the accuracy of the measurement. Random signal noise (ξ_{CGM}) is present as well.

The electrical current is processed with filters as designed by the manufacturer. The signal is then operated upon by the calibration function to produce a signal in concentration units. The calibration function receives capillary BG updates periodically (approximately every 12 h). The capillary glucose measurements are used to fit a linear relationship between electrical current and glucose concentration, although the exact method used is typically proprietary information of the manufacturer [23]. Any error in the capillary measurement will potentially lead to an incorrect calibration, which will create a persistent error in the CGM measurement. Finally, the calibrated glucose signal may be filtered by a noise spike filter to remove unrealistically large changes in concentration. The CGM measurement thus produced is often compared to a measurement of the IV BG by a standard reference instrument, which can also have a small error.

The error present in the glucose measurement process can be dangerous to the patient if it is significant enough to cause incorrect treatment. Conversely, small errors in the measurement are not important and will result in the same overall treatment. The performance characteristics of various CGMs as observed in clinical

Table 1.1: Performance characteristics of various CGMs over time. Source of reference measurement is listed as YSI (venous blood with YSI glucose analyzer), GS (venous blood with GlucoScout), VB (venous blood), or SMBG (capillary blood measurement).

Mfgr.	Model	Ref.	Year	N	Comp.	MARD (%)	CEG A (%)	CEG A+B (%)
Dexcom	G4 Platinum	[40]	2015	72	YSI	13	81	98
		[41]	2015	51	YSI	9	92.4	99.5
		[42]	2015	24	YSI	13.6	79.9	94.9
		[43]	2014	24	GS	10.8	84.5	99.6
		[44]	2014	38	SMBG	13.9		
	[45]	2013	72	YSI	13	79		
	Seven Plus	[45]	2013	53	YSI	16	73	
		[46]	2013	6	GS	16.5	76.2	98.9
	Seven	[47]	2009	72	YSI	16.7	70.4	97.9
		[48]	2009	14	YSI	16.8	72	94.8
	STS	[49]	2008	14	YSI	21.2	55.4	100
Medtronic	Enlite	[42]	2015	24	YSI	16.6	72.3	92.3
		[50]	2014	90	YSI	14.71	81.3	98.6
		[43]	2014	24	GS	17.9	69.1	98.9
		[44]	2014	38	SMBG	17.8		
	Guardian	[46]	2013	6	GS	20.3	63.7	96.9
		[49]	2008	14	YSI	15.2	76.3	97.5
Abbott	FreeStyle Libre	[27]	2015	72	YSI	12		
	Freestyle Navigator II	[51]	2015	57	SMBG	14.2		
	Navigator	[43]	2014	24	GS	12.3	84.2	98.4
		[46]	2013	6	GS	11.8	80.6	98.9
		[48]	2009	14	YSI	16.1	77.5	93.2
[49]	2008	14	YSI	15.3	76.3	99.7		
Senseonics	Senseonics	[30]	2015	24	VB	11.4	87	99.5

studies are displayed in Table 1.1. The table includes the number of subjects (N) involved in each study. The accuracy is presented as the mean absolute relative difference (MARD) between the sensor measurement and the reference measurement. Another measure of accuracy is given by the Clarke Error Grid (CEG), which is used to determine the clinical implications of the CGM error [52]. The CGM measurements are plotted against the corresponding reference measurements on a graph that is divided into five zones: A, where the glucose sensor measurement was within 20% of the reference; B, where the error was greater than 20% of the reference, but the treatment determined from the glucose sensor and reference would have been the same; C, where unnecessary treatment would have been given that could have led to dangerous hyperglycemia or hypoglycemia; D, where dangerous hyperglycemia or hypoglycemia would have gone undetected; and E, where the treatment given would have been the opposite of the required treatment [52]. According to one source, the percentage of points in the A and B zones should be higher than 98% to be acceptable [23]. The table reports both the percentage of points in the CEG A zone and the acceptable A+B zones.

The improved control quality resulting from increased CGM accuracy can be analyzed as a return on investment. Once the glucose sensor reaches a certain level of accuracy, increasing it any further will no longer lead to improved control. Much research has been done to investigate and characterize CGM error, with the goal of using this knowledge to improve the sensor or design filtering and processing techniques to reduce the error [38, 40, 53–59]. While CGMs are not currently approved for nonadjunctive use in the United States, it is anticipated that they will eventually be approved for use in treatment decisions once accuracy standards are established [20]. A major concern with the use of subcutaneous glucose sensors is the measurement lag introduced by diffusion between the blood and the ISF. Placing the sensor

in a different location may reduce this lag, thereby making the sensor more accurate and reliable [38]. The characterization and impact of sensor lag are discussed more in Chapters 3 and 4 of this dissertation.

1.3 Closed-Loop Control for Type 1 Diabetes Mellitus

1.3.1 Motivation

Even with the current standards of treatment and technology available, the risk of premature death for people with T1DM is two times that of the average person without it [4]. One study found that the number of participants who reach the recommended HbA1c level of $<7.0\%$ was less than 15% [60]. Data from 16,061 participants in the T1D Exchange clinical registry showed that the mean HbA1c was 8.2%, with an average of 9.2% in 19-year-olds. Of 2,561 participants who responded to the questionnaire, 6% listed that they experienced a seizure or loss of consciousness due to hypoglycemia within the past 3 months [61]. A separate analysis of the 13,316 participants in the T1D Exchange aged younger than 20 years showed that only 21% of participants met the HbA1c criteria for their age group [62].

While physicians can advise patients on how to best use their prescribed insulin, the onus of most treatment decisions falls on the patient. The degree to which treatment is successful depends greatly on the amount of effort the patient (or patient's guardian) is willing and/or able to exert. The patient must take over the role of the pancreatic beta cells by frequently monitoring the BG and calculating the appropriate insulin dose to avoid both hyperglycemia and hypoglycemia. This process is made difficult by the myriad factors that affect insulin sensitivity and BG [63]. Since hypoglycemia has severe and immediate health effects, many patients become fearful of

their BG going low and are therefore more willing to spend time in hyperglycemia, especially since the consequences are less severe on short time scales [64]. The requisite constant self-monitoring can cause psychological disorders as well. For example, people with T1DM are more likely to develop depression [65]. An algorithm that automatically controls the BG of people with T1DM by connecting a CGM and insulin pump in a feedback loop would lessen the burden of treatment while improving the quality of control that can be achieved.

1.3.2 Design and Implementation

The components required for closed-loop control of BG are a CGM, an insulin pump, and a control algorithm, with appropriate communication between the three. This combination of devices is often referred to as an artificial pancreas (AP). Beyond the inclusion of these three essential components, there are many different choices that can be made to design a specific AP implementation. The block diagram in Figure 1.4 depicts the design choices that have been made in AP development. The major components are discussed in the sections below.

Control Target

The control target is a necessary specification for an AP design. The desired BG can be set as either a range, as in [66] or a setpoint, as in [67], depending on the controller design [1]. The target can also be fixed or time-varying. For example, some controller designs raise the target to a more conservative value overnight to prevent hypoglycemia [68]. In [67], the controller target is raised from 120 mg/dL to 160 mg/dL upon announcement of exercise. On the other hand, some designs use the same target throughout the entire operation, as in [69].

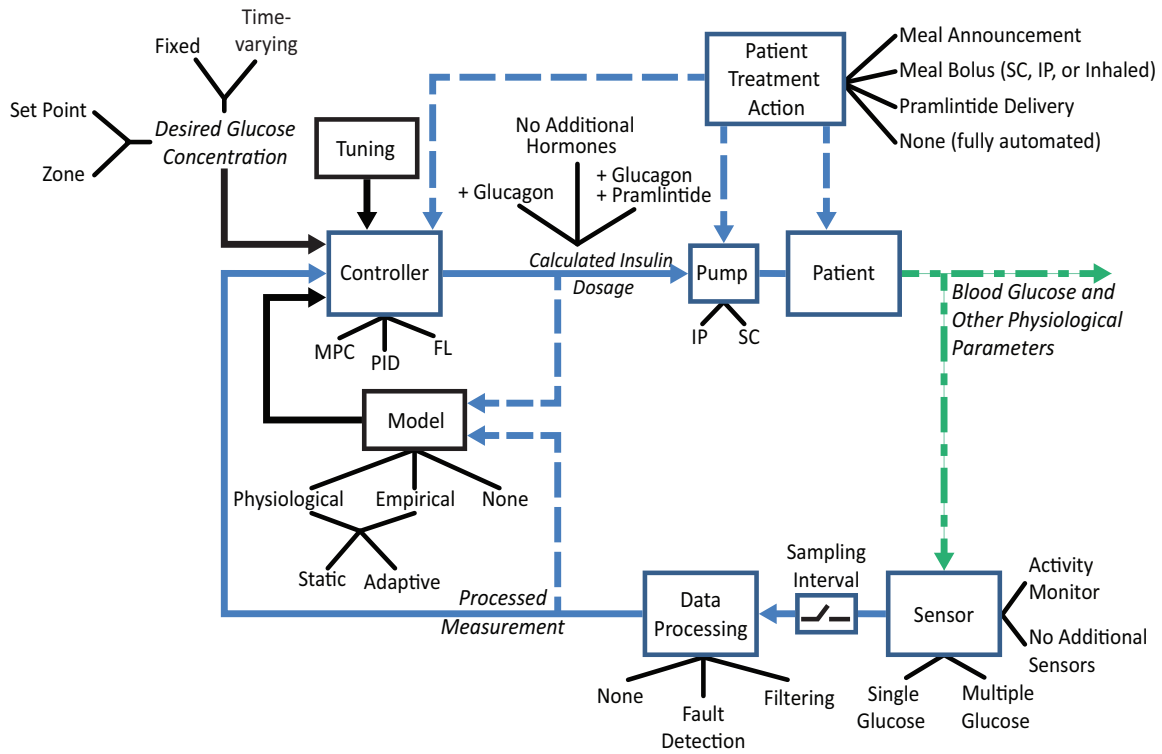


Figure 1.4: Block diagram demonstrating the design choices available for the artificial pancreas. A specific artificial pancreas configuration is created by selecting options for each of the major elements shown in the figure. Solid lines demonstrate connections that are always present and dashed lines represent connections that may be present in only some configurations. The tuning, model, and desired glucose concentration are all part of the controller, as signified by the black arrows. The green dash-dot line distinguishes physiological states or properties from measured or digital signals. Black lines are used to indicate predetermined features of a block, and blue lines indicate signals or actions conducted during closed-loop operation. Reprinted with permission from [1].

Control Algorithm

Automatic control is a field that has been well-developed within the chemical process industry [70]. The same algorithms that are applied to regulate the flow from a tank or the concentration of product leaving a reactor can be successfully applied to regulate the BG in the human body. The most frequently used control algorithms for AP applications are model predictive control (MPC) and proportional-integral-derivative control (PID), although other strategies such as proportional-derivative control, fuzzy logic, and empirical algorithms have also been applied [1].

MPC is an advanced control method that utilizes a process model to predict the future trajectory of the system based on past measurements and inputs [70]. While an MPC controller can be designed to track a single setpoint value, it can also be designed to keep the controlled variable within a desired zone. The latter approach is ideal for application in T1DM, since there is no clear choice for a specific setpoint value [71]. This approach, known as zone model predictive control (ZMPC), has been applied successfully in several clinical studies [66, 72, 73].

The plots in Figure 1.5 demonstrate two ZMPC scenarios. At each time step, the controller predicts the measured output P steps into the future, while calculating the necessary input for each of the next M steps to achieve the control objective. The objective is to minimize a cost function that weights the output error and the input energy based on their relative importance for the system. The first calculated input step is then implemented, after which the next measurement is received and the process repeats [70].

When using ZMPC, action is taken only if the measured variable is predicted to leave the desired zone. For example, in the first panel of Figure 1.5, the controlled variable is predicted to remain within the desired zone, so the output from the con-

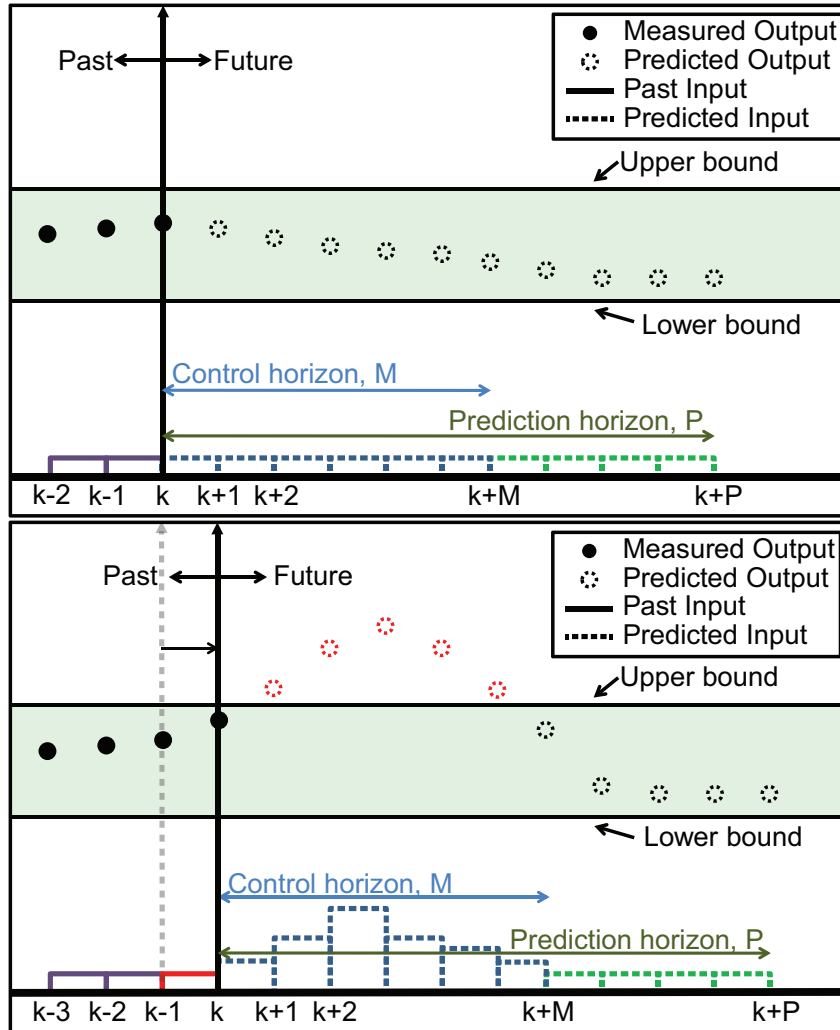


Figure 1.5: Schematic representation of zone model predictive control. At a given time-point, the controller chooses the next M inputs in order to minimize the cost function, which includes excursions from the desired zone for the next P predicted output values. The first input is then implemented, and the process is repeated at the next time-point.

troller will be the nominal value of the manipulated variable. In the second panel, the measured value is predicted to leave the desired zone, so the necessary inputs over the next M steps required to return to the zone are calculated. An additional feature of MPC is the ability to directly incorporate constraints into the optimization process. For example, the ZMPC controller is designed to incorporate both physiological and safety constraints [68, 71, 74, 75]. More information about the ZMPC controller is presented in Chapter 2.

PID controllers first became commercially available in the 1930s. This type of controller includes three modes that are added together to produce the final controller action. The proportional mode produces controller action in proportion to the error (defined as the difference between the measurement and the setpoint). The integral mode eliminates persistent error between the measurement and the setpoint by acting in proportion to the integral of the error over time. Lastly, the derivative mode contributes to the controller action in proportion to the rate of change of the error [70]. PID control has been applied in several AP designs in clinical studies [67, 76–81]. This type of controller is explored more in Chapters 4 and 5 of this dissertation.

Once the controller type has been selected, it must be tuned to meet the safety and performance requirements of the system. Additionally, predictive controllers require the selection of a process model [70]. The tuning of the control algorithm determines how aggressively it will react to BG deviations from the desired value. While the specifics of the tuning procedure depend on the type of controller being used, typically the parameters are selected using a combination of process modeling and simulation studies [82–84]. The controller output and resulting glucose measurements may be used to update the controller or model parameters through adaptation, as demonstrated in run-to-run approaches and adaptive learning schemes [85–89].

The control algorithm generates an output for insulin delivery and may also cal-

culate glucagon, pramlintide, and/or additional glucoregulatory hormone delivery. The controller output is calculated at discrete times determined by the controller action interval. This interval has typically been selected as between 5 and 15 minutes [1].

Actuation

Following the computation of the desired controller action, this signal must be communicated to the actuator. In nearly all clinical evaluations of the AP thus far, the actuator has been a subcutaneous insulin pump. A limited number of trials have used an intraperitoneal insulin pump to take advantage of the faster insulin pharmacokinetic and pharmacodynamic properties of this route [90, 91]. A majority of systems have used insulin alone as the manipulated variable, but some implementations have added glucagon or pramlintide as a second input [88, 92–96]. The addition of glucagon allows the controller to have a mechanism of raising the BG in the case of current or impending hypoglycemia [97].

Sensing

All AP implementations require at least one CGM. Typically, commercially available subcutaneous enzymatic CGMs are used. While including more than one glucose sensor would make the system more robust, this approach would not be accepted by patients due to the limited space on the body for sensor placement [1]. Other types of sensors may be included to provide additional inputs to the controller. For example, an activity sensor that measures heart rate and accelerometry data may be included to detect exercise or determine whether the user is sleeping [98]. All sensor signals need to be processed and filtered before being communicated to the control algorithm in order to prevent undesired controller action based on sen-

sor noise or erroneous measurements. After receiving the updated measurements, the control cycle repeats at the next sample time [1].

User Interaction

Ideally, the AP would be fully automated, with no input required from the user. However, due to the realities of physiological limitations in the speed of insulin action, user input or action may be required to achieve satisfactory control. The most frequently encountered type of user action is the meal announcement. The user is required to enter an estimate of the meal carbohydrate content prior to consuming the meal. This announcement is a type of feedforward action that triggers an immediate insulin bolus based on the insulin to carbohydrate ratio. However, including user action introduces human error into the control loop. Over- or underestimation of the meal size could lead to suboptimal performance and safety risks [1]. Additional options for user interaction include the announcement of exercise, as in [99].

Safety Systems

While the AP is designed to result in better health outcomes for people with T1DM, there are safety risks involved that need to be considered in the design. The most prominent risk is hypoglycemia due to over-delivery of insulin. Most AP designs include an algorithm to limit the commanded insulin dosage based on the glucose and insulin history. The two most commonly used algorithms are Insulin On Board (IOB) [100] and Insulin Feedback (IFB) [101]. Both of these methods use the insulin delivery history to adjust the current insulin dose to account for how much active insulin is already in the blood. An AP may also include an independent safety system to detect and alert the user to impending hypoglycemia. An example of this type of safety system is the Health Monitoring System, which alerts the user to pre-

dicted hypoglycemia and recommends the consumption of 16 g CHO to prevent or mitigate the episode [72, 102].

1.3.3 Recent Progress in Clinical Evaluation

To date, there have been 99 published clinical evaluations of AP devices. A full bibliography of these studies is included in Appendix A. As shown in Figure 1.6, the number of studies published per year has been increasing steadily since 2004, with the peak reached in 2014. The clinical protocols used to evaluate AP designs have varied greatly, making it difficult to compare results across different studies. Varying factors include the number, type, and size of meals, whether meals are announced, the presence of physical activity, the level of supervision, the setting, the length of time spent in closed-loop, and the age and number of subjects [1].

The fifteen² studies that were published in 2015 are summarized in Table 1.2. Of these fifteen studies, nine took place in the outpatient environment, whether at a diabetes camp [67, 96], in a house/hotel/outpatient suite [66, 103, 104], or at home [81, 92, 105, 106]. The other studies simulated daily-life conditions as closely as possible to ensure a realistic evaluation of the system. In recent years, the difference between inpatient and outpatient evaluation has become difficult to delineate, as studies outside the clinic can still involve significant supervision by study staff. The transition space between inpatient studies to fully unsupervised outpatient studies is truly a spectrum, with each study falling somewhere in between the two extremes.

A new trend observed in 2015 is the inclusion of meal announcement in all but one of the twelve studies that included closed-loop meals [66, 67, 69, 73, 81, 94, 103, 105–108]. Most studies used the subjects' usual parameters to calculate either a full or par-

²The study in [69] was published online in 2015 and so is included in this discussion, although the print publication year is 2016.

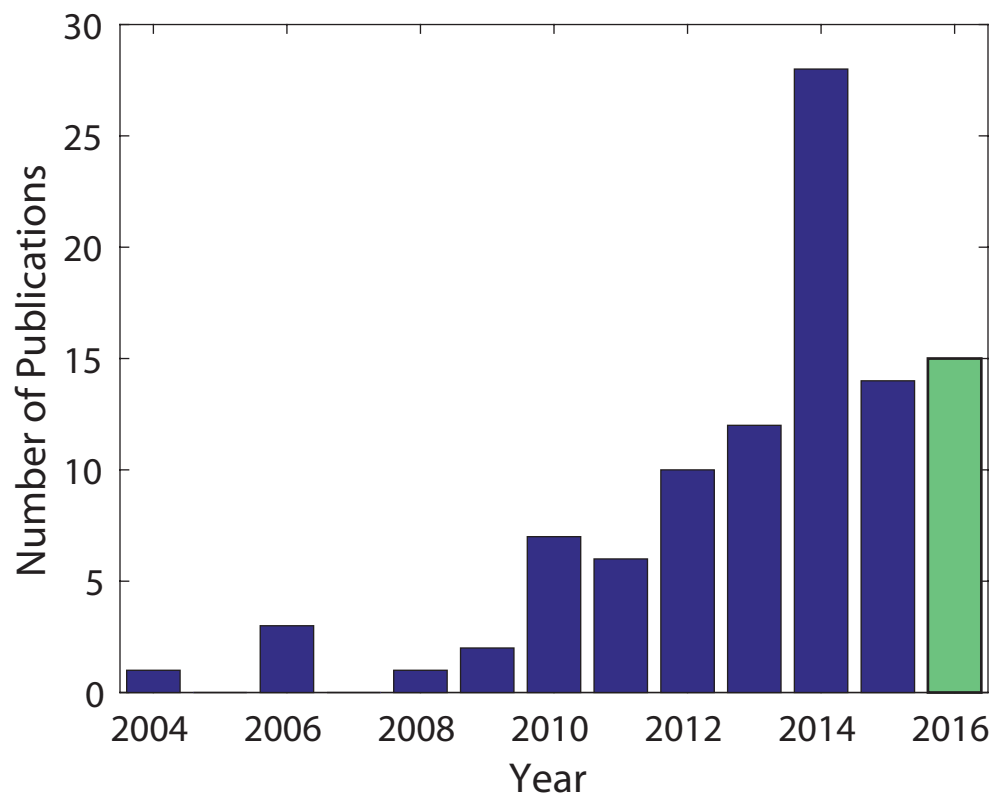


Figure 1.6: Number of artificial pancreas clinical trials published per year from 2004-2016.

Table 1.2: Summary of artificial pancreas clinical trials published in 2015.

Ref.	Glucagon	Setting	Bolus Type	Exercise During CL	Controller	Device Platform
[105]	No	Home	Full	Variable	MPC	Android Phone
[81]	No	Home	Full	Variable	PID+IFB	Android Phone
[106]	No	Home	Full	Variable	MPC	Android Phone
[92]	Yes vs. No	Home	No CL Meals	None	MPC	Computer
[96]	Yes vs. No	Camp	No CL Meals	None	MPC	Tablet Computer
[67]	No	Camp	Full	Basketball, Soccer, Football, Running, etc.	PID+IFB	Pump
[103]	No	Hotel	Full	None	MPC	Android Phone
[104]	No	House, Hotel	No CL Meals	None	Other	Android Phone
[66]	No	House, Hotel, Outpatient Suite	Full (Adjusted or Usual I:C)	Treadmill, Stationary Bicycle, etc.	MPC	Tablet Computer
[107]	No	Clinic	Full or Partial (100% or 75%)	Stationary Bicycle	MPC	N/A
[108]	No	Clinic	Full	None	MPC	Computer
[73]	No	Clinic	Partial: Inhaled Insulin	Stationary Bicycle	MPC	Computer
[94]	Yes vs. No	Clinic	Full or Partial (70-100%)	Treadmill	MPC	Computer
[69]	No	Clinic	Full and Partial and None	None	Other	Low-power Miniaturized Chip
[109]	No	Clinic	None	Stationary Bicycle	FL	Computer

tial premeal bolus; however, some included novel approaches. In Zisser, et al. [73], a partial priming bolus of fast-acting inhaled insulin equivalent to 4U of subcutaneous insulin was delivered prior to each meal, with no carbohydrate estimate necessary. In Dassau, et al. [66], an algorithmic adjustment was made using open-loop data to improve the basal pattern and insulin-to-carbohydrate ratio, with the controller evaluated using the initial versus the adapted parameters. Lastly, Mauseth, et al. [109] presented a study designed to push their fuzzy logic AP system to its limits. Their challenges included unannounced exercise followed by an unannounced meal and a large, high-fat unannounced meal (120 g carbohydrate). Testing the controller with these extreme but realistic challenges revealed valuable information that was used to improve the controller design.

Three of the fifteen studies used glucagon as a second hormone delivered by the AP. Two evaluated outpatient overnight control [92, 96], while the other provided 24 h control in clinic [94]. The 24 h study did not find significant differences between the glycemic control provided by a single or dual hormone AP; however, the study was short and conducted in the inpatient setting. An AP system incorporating glucagon remains a promising area of research during the transition into longer, unsupervised outpatient studies.

Ten of the studies published in 2015 used model predictive control (MPC) [66, 73, 92, 94, 96, 103, 105–108]. Other controllers used were fuzzy logic [109], proportional-integral-derivative plus insulin feedback (PID+IFB) [67, 81], and empirical or model-based controllers [69, 104]. Five of the studies hosted their algorithm on an Android phone [81, 103–106], one directly on the pump [67], one on a miniaturized low-power microchip [69], two on tablet computers [66, 96], and five on computers [73, 92, 94, 108, 109].

Exercise is a part of daily life for most people, so the AP will certainly need to

handle this challenge. For this reason, it has become almost standard to include exercise activities during closed-loop. The studies in 2015 included many types of exercise, including using a treadmill [66, 94], using a stationary bicycle [66, 73, 107, 109], playing sports (basketball, soccer, football, running) [67], or following subjects' typical exercise routine [81, 106].

Overall, the year 2015 in clinical AP research represents the transition period from inpatient to outpatient studies. New territory is being crossed as researchers learn of the unique and perhaps unanticipated challenges that must be met to incorporate the AP into a person's daily routine. Included in this process is the transition from laptop computers to more portable devices. Studies moving into the fully outpatient environment inevitably become less controlled than supervised inpatient studies, while at the same time providing a better picture of the work that still needs to be done to make the AP a viable product for patients. Studying the protocol details and results of these publications will allow the research community to learn valuable lessons as they plan their next round of studies and move toward the goal of an AP to improve care for people with T1DM.

The studies that have been published as of May 2016³ are presented in Table 1.3. The trends observed in 2015 have continued. All of the studies took place in an outpatient environment except for those in [95, 111, 112], which took place in the clinic to meet their purposes of rigorously comparing different meal bolus strategies or studying the effects of liraglutide or pramlintide injections. Exercise was included in all but three studies, and most were conducted on a smart phone or custom integrated device.

³The studies presented in [110] and [69] are not included in this table because they were published online ahead of print in 2014 and 2015, respectively, although the print publication dates are 2016.

Table 1.3: Summary of artificial pancreas clinical trials published in 2016.

Ref.	Glucagon	Setting	Bolus Type	Exercise During CL	Controller	Device Platform
[113]	No	Home	Full	Usual Routine	Empirical Control-to-Range	Android Phone
[114]	No	Home	Full	Usual Routine	MPC	Nexus 5 Phone
[115]	No	Home	Full	Usual Routine	MPC	Nexus 4 Phone
[116]	Yes	Home	None	Usual Routine	PID	Custom Integrated Device
[80]	No	Protected Home	Full	Variable	PID+IFB	Android Phone
[117]	No	Camp	Unknown	Moderate to High Intensity	MPC	Android Phone
[118]	No	Camp	No CL Meals	None	PID+IFB	Android Phone
[119]	Yes	Camp	Partial	Usual Routine	MPC	iPhone 4S
[99]	No	Hotel	Full	Usual Routine	PID+IFB	Pump
[120]	Yes vs. No	Outpatient	Full or Simplified	Usual Routine	MPC	Tablet Computer
[111]	No	Clinic	None	None	PID+IFB	Unknown
[112]	No	Clinic	None	None	PID+IFB	Laptop Computer
[95]	Yes	Clinic	Full or Partial or None	Walking	MPC	Computer

1.3.4 Challenges and Future Directions

The AP system must be able to handle frequent disturbances to the BG that are part of daily life. Important challenges include meals and physical activity, both of which result in rapid changes in the BG. Nearly all of the AP designs developed so far have utilized subcutaneous glucose measurements paired with subcutaneous insulin delivery. A significant disadvantage of this route is that it depends on molecular transport between the blood and ISF. The delays associated with this route culminate in approximately 90 minutes between when insulin is delivered and when its effects on the subcutaneous glucose concentration are seen [121]. Such a large delay makes compensation for meal disturbances difficult, so many researchers have added a prandial insulin bolus or meal announcement to their control scheme [1, 122]. While this approach may result in better control, it is not ideal because the system is not fully automated and human action is added to the control loop. For this reason, an important future direction for AP development is the investigation of alternate insulin delivery and glucose sensing sites. As discussed in the following section, this dissertation is focused on characterizing these alternate insulin delivery and glucose sensing sites and evaluating their use in the AP.

1.4 Thesis Overview

In this dissertation, the development of the AP is explored, with a specific focus on the role of the glucose sensing and insulin delivery route in determining overall controller performance. Chapter 2 presents the application of the state-of-the-art ZMPC+HMS AP in adolescents. During the trial there were significant challenges to the controller, including twice-daily mild to moderate exercise and free-choice

announced meals.

Since subcutaneous CGMs measure glucose concentration within the ISF, they introduce an undesirable diffusion lag to the measurement process. We hypothesized that placing the sensor in the intraperitoneal space would decrease the diffusion lag. In Chapter 3, experimental data is used to quantify the diffusion lag experienced by subcutaneous and intraperitoneal sensors placed in non-diabetic swine. Additionally, the effect of long-term sensor implantation is explored.

In Chapter 4, the lag estimation from Chapter 3 is used to explore the impact of glucose sensor dynamics on the AP. The error caused by various amounts of sensor lag is quantified using retrospective analysis of clinical data. Robust performance and stability analysis, as well as simulation studies, are used to quantify the effect of sensor lag on the AP controller performance.

Current implementations of the AP are limited by the properties of subcutaneous glucose sensors and insulin pumps. Chapter 5 outlines the process used to design a robust PID controller for use in a fully implantable AP that is designed to work with intraperitoneal devices. Data from the sensor lag studies, as well as from previous studies of intraperitoneal insulin pharmacokinetic and pharmacodynamic properties, inform the design of the controller.

Chapter 6 provides a summary of the conclusions made in this dissertation. The future directions of the work described here are also outlined.

Chapter 2

Outpatient Evaluation of Artificial Pancreas with Exercise in Adolescents¹

2.1 Introduction

As discussed in Chapter 1, advances in medical device technology have enabled vast improvements in the way that type 1 diabetes mellitus (T1DM) is treated. For example, the use of continuous glucose monitors (CGMs) provides patients with a wealth of information about their blood glucose concentration (BG), its history, and its real-time trends, allowing them to make more informed adjustments to their insulin therapy. Improvements in CGM technology have increased the accuracy of these devices, with the prediction that they will soon be approved for non-adjunctive use in the United States [20]. In addition to CGMs, rapid-acting insulins and programmable pumps for continuous subcutaneous insulin infusion (CSII) have also shown promise in allowing patients to exert finer control over their BG; however, successful imple-

¹ Portions of this chapter were submitted for publication in the journal *Pediatric Diabetes* on 13 May 2016 [123]. This study is registered on clinicaltrials.gov with clinical trial registration number NCT02506764.

mentation of CSII and CGMs requires time, effort, and ongoing education on the part of patients and their families [124]. The development of a closed-loop artificial pancreas (AP) device to regulate the BG by adjusting insulin delivery in real-time based on feedback from a CGM will automate the treatment process, removing much of the daily patient effort and active decision-making that are a part of manual treatment [1]. While AP devices have been shown to be safe and effective in the inpatient environment [66, 72, 78, 125–129], a great challenge remains in determining their safety and feasibility in a free-living outpatient environment [81, 96, 105, 106, 130–136].

Model predictive control (MPC) is an advanced control strategy that has been widely implemented in the chemical industry for controlling complex processes with input and output constraints [70, 137, 138]. This control strategy is promising for use in the AP, especially due to its ability to directly incorporate physiological constraints (i.e., cannot remove insulin from the body), its capacity to handle delays in insulin action, and its customizability in designing the objective function to optimize insulin delivery according to clinical needs [71, 72]. The state-of-the-art Zone Model Predictive Control (ZMPC) AP algorithm developed at UCSB and Harvard University uses a model to predict the future BG trajectory and calculate the optimal insulin dose needed to maintain the BG trajectory within a desired zone, rather than at a specific set point [71, 74, 75]. When the BG is predicted to be within the desired zone, the controller delivers the usual basal insulin dose to minimize excessive controller action in response to small changes in glucose, such as may occur with noise in CGM measurements. When the predicted BG trajectory includes excursions from the zone, the controller modulates the insulin dose up or down to deliver the optimal dose to produce safe and effective glucose control as calculated by the objective function. The Health Monitoring System (HMS) provides an additional safety layer, independent of the controller, to predict and alert the user to impending hypoglycemia [72, 102].

The ZMPC algorithm has performed well in several controlled inpatient and research suite evaluations in adults with T1DM [66, 72, 73]. For this controller to be tested in the outpatient setting, a portable platform is required. To this end, the ZMPC+HMS algorithms were integrated into the Diabetes Assistant (DiAs) platform from the University of Virginia (UVA), hosted on an Android smartphone [139]. The DiAs system has undergone extensive clinical testing to demonstrate its safety and feasibility for use in the outpatient setting [139]. The remaining components of the AP system are a Dexcom G4P Share CGM (San Diego, CA) and a Roche Accu-Chek Spirit Combo pump (Mannheim, Germany), as shown in Figure 2.1. The devices communicate wirelessly via BluetoothTM, eliminating the need for hard-wired connections. The data is automatically transferred by the DiAs platform to a secured server to allow the subject's status to be monitored remotely.



Figure 2.1: Components of the ZMPC+HMS/DiAs system. The ZMPC+HMS algorithms are hosted on the DiAs platform, which runs on medical Android on a Nexus 5 phone. The DiAs platform communicates with the Roche Accu-Chek insulin pump and the Dexcom G4P CGM via Bluetooth. The DiAs platform also communicates with the DiAs Web Monitoring site by 3G or internet connection.

While the feasibility of the AP with ZMPC+HMS has been demonstrated in the adult population in controlled inpatient or research suite settings, it has neither been evaluated in children or adolescents, nor in highly ambulatory settings with frequent exercise [66, 72]. Satisfactory glucose control in adolescents and children with T1DM is notoriously difficult to achieve, with T1D Exchange data showing that approximately 80% of adolescents have hemoglobin A1c (HbA1c) values above the American Diabetes Association target of 7.5% (58 mmol/mol)[61, 62]. This trend is particularly concerning for older adolescents, who saw an average HbA1c of 9.0% (75 mmol/mol) in the 13-17 year-old age group [61]. Adolescents experience both physiological challenges due to changes in insulin sensitivity related to puberty [140–143] and psychosocial barriers presenting as missed meal boluses, less frequent self-monitoring of blood glucose (SMBG) testing, and difficulty following a fixed plan or regimen [144]. Significantly elevated insulin resistance in pubertal teenagers presents a challenge to model-based controllers, as the parameters for this population may differ from those modeled for adults with T1DM. Additional challenges to AP systems in this age group include school-based sports and more frequently missed meal boluses.

The purpose of this study was to determine the feasibility of the AP with ZMPC+HMS in adolescents with T1DM engaging in supervised, free-living conditions with twice-daily mild to moderate intensity exercise. This study represents the first evaluation of the ZMPC+HMS algorithms in the adolescent population. Additionally, this study is the first evaluation of the ZMPC+HMS algorithms in the transitional hotel environment with frequent repeated exercise, thus bridging between the inpatient and unsupervised outpatient settings.

2.2 Research Design and Methods

2.2.1 ZMPC+HMS/DiAs System

The integration of the ZMPC+HMS algorithms with the DiAs platform and devices comprises a portable automated glucose management system (see Figure 2.1). The ZMPC algorithm automatically regulates the insulin dose based on the glucose level as determined by current and historical CGM measurements, predicted glucose trends, historical insulin delivery, and patient-specific information. The model used by the controller to predict future glucose concentrations is personalized using the subject's total daily insulin dose (TDI). The algorithm is designed to drive the BG to a target zone. During the day (06:00-22:00) the target zone is 80-140 mg/dL and during the night (24:00-04:00) the target zone is 90-140 mg/dL, with smooth, two hour transitions in between the two. As long as the BG is predicted to remain in the target zone, the controller delivers the subject's usual basal rate. A previous iteration of the ZMPC algorithm is described in detail in [68]. Additional features that modify the objective function to enhance performance in correcting hyperglycemia, while also reducing the risk of hypoglycemia, are presented in [74, 75].

The HMS provides an additional safety layer outside of the ZMPC algorithm by analyzing CGM data and trends to detect impending hypoglycemia [102]. This system produces an audio-visual alarm when the CGM is predicted to cross the 65 mg/dL threshold within 15 min. The user is prompted to perform a SMBG measurement and to treat with oral carbohydrates (CHO), thus preventing or mitigating the impending hypoglycemic episode.

The ZMPC+HMS/DiAs system is programmed at the start of the study with the subject's TDI, as well as the insulin to CHO ratio (CR), correction factor (CF), and

basal rate profiles. Meal announcements are made through the DiAs interface to trigger a bolus. The bolus size is computed using the preprogrammed CR and CF profiles based on the meal size estimate and a SMBG measurement. If the SMBG at the time of the meal is <120 mg/dL or if no SMBG is entered, the bolus size is 80% of the value computed using the CR. If the SMBG at the time of the meal is >120 mg/dL, the bolus size is 100% of the value computed using the CR. Lastly, if the SMBG is >150 mg/dL, the full meal bolus is accompanied by a correction bolus to 150 mg/dL calculated using the CF. The correction bolus is added only if there has not been another meal bolus with a correction bolus within the past two hours.

The insulin dose calculated by the controller is subject to safety constraints. At each five-minute interval, the insulin dose is limited to be less than 1 U (excluding meal/correction boluses). During the period of 22:00 to 04:00, the insulin infusion is constrained to be less than 1.8 times the basal rate. Lastly, the Insulin on Board (IOB) algorithm prevents over-delivery of insulin by taking into account the insulin infusion history over the past eight hours [75, 100].

2.2.2 Study Design

The primary objective of this study was to determine safe and feasible operation of the ZMPC+HMS/DiAs system in adolescents with T1DM engaging in free-living conditions with twice-daily unannounced mild to moderate intensity exercise. Ten subjects were recruited for the study (5 subjects each at Stanford University (SU) and the Barbara Davis Center (BDC)). Subjects resided in a hotel setting for three days, where they slept overnight and engaged in mild to moderate intensity exercise at least twice daily, with clinical staff in attendance at all times. Subjects chose the size, content, and timing of their meals to emulate free-living conditions, with no restriction on meal size. The study protocol was approved by the Stanford University

Institutional Review Board and the Colorado Multiple Institutional Review Board.

The inclusion criteria for the study were: clinical diagnosis of T1DM, daily insulin therapy for at least 12 months, aged 10 to 19 years, insulin pump use for at least 3 months with current use of a downloadable pump, TDI requirement >0.4 U/kg/day over the preceding two weeks, and ability to speak and understand English. Additional criteria for female participants were: use of acceptable method of contraception if sexually active and a negative urine pregnancy test for subjects who have entered menarche. Informed consent was obtained from subjects and/or parents and the assent form signed by the subject if <18 years. Study exclusion criteria were diabetic ketoacidosis (DKA) in the past month, history of seizure or loss of consciousness in the last 6 months, or any medical disorder that would affect the completion of the protocol.

2.2.3 Study Preparation

The Dexcom G4P Share CGM was inserted during a screening visit at least 72 h prior to the hotel admission. Subjects continued with their usual sensor-augmented pump therapy (SAP) during the period between CGM insertion and the beginning of the CLC phase. The data from this period were analyzed to determine the subjects' usual glycemic control. Upon arrival for the CLC phase, subjects removed their own pumps and inserted a new infusion set for use with the study pump. After programming the pump and DiAs system with the subjects' information and establishing communication between the study devices, CLC was commenced.

2.2.4 Daily Study Procedures

A full timeline of events at each site is shown in Figure 2.2. The daily procedures for the trial proceeded as follows: subjects ate breakfast at the hotel, then left for supervised sessions of physical activity in the morning and afternoon. Exercise was not announced to the system. The physical activity sessions included a variety of mild to moderate intensity exercise of variable duration lasting at least 30 min. The exercise sessions included activities such as soccer, basketball, tennis, ultimate FrisbeeTM, walking, and bicycling. Lunch was provided during the afternoon between physical activity sessions. Dinner was consumed in the evening, followed by additional activities such as playing pool, completing schoolwork, and watching movies. CLC continued for three full days (72 h). Throughout the study, subjects made their own food choices and decided their own meal size announcement. At least three meals were consumed per day, with no restrictions on food selection. Subjects were also free to choose the type and intensity of physical activity.

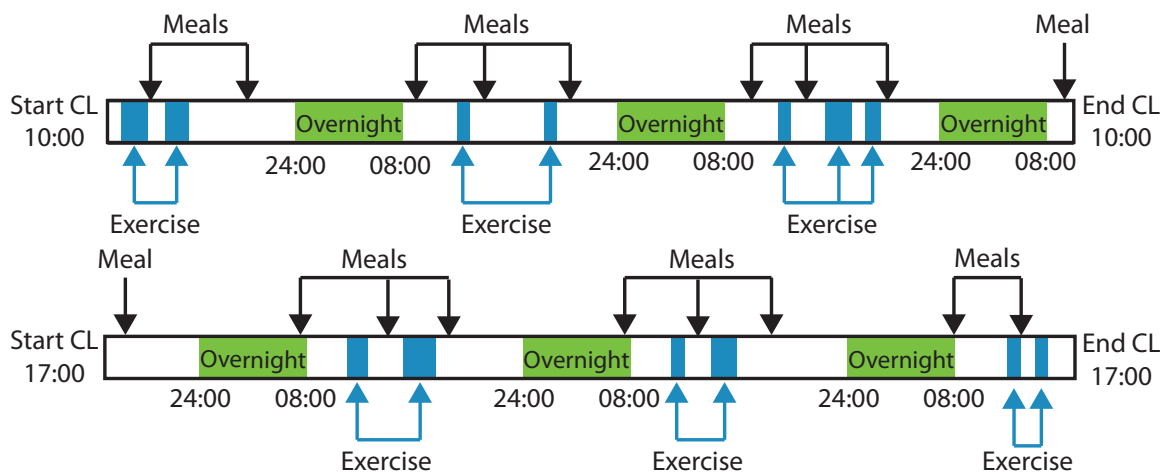


Figure 2.2: Timeline of the 72 h protocol at each clinical site. The timeline indicates timing of meals, exercise, and overnight periods. The top panel shows the timeline for SU, and the bottom panel shows the timeline for BDC.

Participants were provided with a meter for fingerstick SMBG measurements and test strips. SMBG measurements were required at a minimum of 5 times daily (before meals, prior to and after exercise and at bedtime) throughout the study. An additional SMBG check was done by study staff at 03:00. CGMs were calibrated as per the manufacturer's instructions (at least twice daily), and any time there was a calibration request from the CGM itself, provided that the SMBG was between 40-400 mg/dL and the CGM indicated a low rate of change by displaying a horizontal arrow. The CGM was also calibrated if the error compared to SMBG was >20%.

2.2.5 Safety and Remote Monitoring

At least one clinical staff member was present at all times to supervise use of the system during the day and night. Monitoring was performed by visually observing the subjects or by checking the remote monitoring website to view the current status of all subjects. Subjects were asked to respond to HMS alerts by taking a SMBG measurement. The HMS alert prompted the user to enter the SMBG and to indicate whether treatment was given. In the case that $\text{SMBG} > 70 \text{ mg/dL}$, the subject was prompted to treat with oral CHO, but the treatment was not required. In the case that $\text{SMBG} < 70 \text{ mg/dL}$ or the subject was symptomatic, the subject was given oral CHO and the SMBG check and treatment process was repeated every 15 min until $\text{SMBG} > 70 \text{ mg/dL}$ and/or the subject was no longer symptomatic.

2.2.6 Statistical Methods

The primary outcome of this study was the feasibility of the system in this cohort and setting. Feasibility was defined as proper functioning of the system for at least 75% of the total study time. Secondary outcomes included percentage of time

spent in various glycemic ranges and mean CGM (as described in the recommendations published in [145]). The secondary outcomes were evaluated using CGM values from the entire CLC period. The data are presented as either mean±standard deviation (SD) or median (interquartile range (IQR)), depending on the determined distribution. Comparison between the CLC and SAP data was done using either a paired sample Student’s t test for normally distributed data, or the Wilcoxon signed rank test for non-normal data. Normality was determined using the Shapiro-Wilk goodness-of-fit test. The statistical analysis was performed using Matlab 2015b.

2.3 Results

Ten adolescents (11-17 years, 5M/5F) completed 3 days of CLC in a hotel setting, resulting in 30 person-days of CLC. Subject information is shown in Table 2.1. Data from 95±14 h of SAP immediately prior to CLC are included to provide a comparison to the subjects’ glycemic control with their usual therapy.

Table 2.1: Subject demographics for the study (N=10).

Characteristic	
Age, years, mean ± SD (range)	15.3 ± 1.8 (11.9-17.7)
Gender, n (%)	
Female	5 (50)
Male	5 (50)
Race and ethnicity, n	
White	9
Native Hawaiian or Pacific Islander	1
Weight, kg, mean ± SD (range)	58.4 ± 13.9 (37.4-85.2)
Body mass index, kg/m ² , mean ± SD (range)	21.5 ± 3.6 (15.6-26.9)
Hemoglobin A1c,	
%, mean ± SD (range)	8.1 ± 1.3 (6.8-11.2)
mmol/mol, mean ± SD (range)	65 ± 14 (51-99)
Duration of diabetes, years, mean ± SD (range)	5.1 ± 2.3 (2.3-9.6)
Total daily dose (U/day, mean ± SD (range)	48.8 ± 18.2 (26.8-86.1)

2.3.1 System Performance

The system demonstrated feasibility in this cohort, with CLC active for $95.0 \pm 1.1\%$ of the intended study time, or $97.3 \pm 1.7\%$ of the time when excluding the two hours of disconnection resulting from CGM change required in 6 of the 10 subjects. The primary cause of time spent out of CLC was disruption in the Bluetooth connection between the devices. The system was safe in this cohort, with no episodes of DKA or severe hypoglycemia resulting in seizure or coma. All system safety alerts for hypoglycemia and hyperglycemia performed as expected. In one subject (referred to as subject 4), the controller did not perform as intended due to a technical issue with the integration of the DiAs and ZMPC systems. Due to a timing anomaly the controller did not exploit CGM feedback properly for approximately 60% of the study duration. During this time the controller was not able to respond as designed to increasing or decreasing CGM trends. Instead, basal insulin delivery was commanded. The issue was not detected until the data analysis stage of the study, and did not affect safety during the trial. The subject's data was included in the analysis on an intention-to-treat basis for the feasibility and glucose control endpoints; however, the subject is delineated from the others during discussions of controller performance.

2.3.2 Glucose control

The glycemic control characteristics during CLC and SAP are summarized in Table 2.2 and Figure 2.3. Overall, subjects spent $71 \pm 10\%$ of time in the desired range of 70-180 mg/dL. The CLC period showed a significant improvement over the subjects' usual therapy, where only $57 \pm 16\%$ of time was spent in the 70-180 mg/dL range ($p=0.012$). Additionally, time in the tight control range of 80-140 mg/dL was significantly higher during the CLC session, with 47% (39%, 53%) of time in range

during CLC, as compared to 30% (21%, 42%) during SAP (p=0.002). In general, CLC provided a tighter distribution of CGM values, with a narrower vertical band on the cumulative histogram (Figure 2.4).

Table 2.2: Comparison of glycemic control during daytime and overnight for CLC versus SAP therapy.

	CLC	SAP	p-value
Day and Night			
Mean CGM (mg/dL)	150 ± 19	173 ± 31	0.042*
SD CGM (mg/dL)	58 ± 13	95 ± 14	0.23
COV CGM (%)	39 ± 5	38 ± 8	0.87
% of Time			
70-180 mg/dL	71 ± 10	57 ± 16	0.012*
80-140 mg/dL	47 (39, 53)	30 (21, 42)	0.002*
>180 mg/dL	26 ± 11	39 ± 18	0.033*
>250 mg/dL	8 ± 6.9	16 ± 14	0.088
>300 mg/dL	3.5 ± 3.9	7 ± 7.6	0.22
<70 mg/dL	2.5 ± 1.8	4.2 ± 3.1	0.13
<60 mg/dL	0.68 ± 0.63	1.9 ± 1.8	0.076
<50 mg/dL	0.13 ± 0.26	0.44 ± 0.5	0.125
Overnight (00:00-07:00)			
Mean CGM (mg/dL)	154 ± 30	157 ± 45	0.832
SD CGM (mg/dL)	45 ± 16	46 ± 19	0.91
COV CGM (%)	29 ± 8	30 ± 9	0.88
% of Time			
70-180 mg/dL	71 ± 22.5	67 ± 23	0.713
80-140 mg/dL	46 ± 26	34 ± 17	0.18
>180 mg/dL	29 ± 23	27 ± 28	0.902
>250 mg/dL	6 ± 7.1	11 ± 18	0.456
>300 mg/dL	2.2 ± 3.8	4.2 ± 7.1	0.448
<70 mg/dL	0 (0, 0.6)	1.1 (0, 14)	0.078
<60 mg/dL	0 (0, 0.2)	0.1 (0, 7.6)	0.156
<50 mg/dL	0 (0, 0)	0 (0, 1.5)	0.25

The proportion of time that each subject spent with CGM>180 mg/dL and CGM<70 mg/dL during CLC and SAP is indicated by the points plotted in Figure 2.5. The contour lines on the plot represent the percentage of time with CGM in the range of 70-180 mg/dL. Ideal control is represented by the lower left corner of

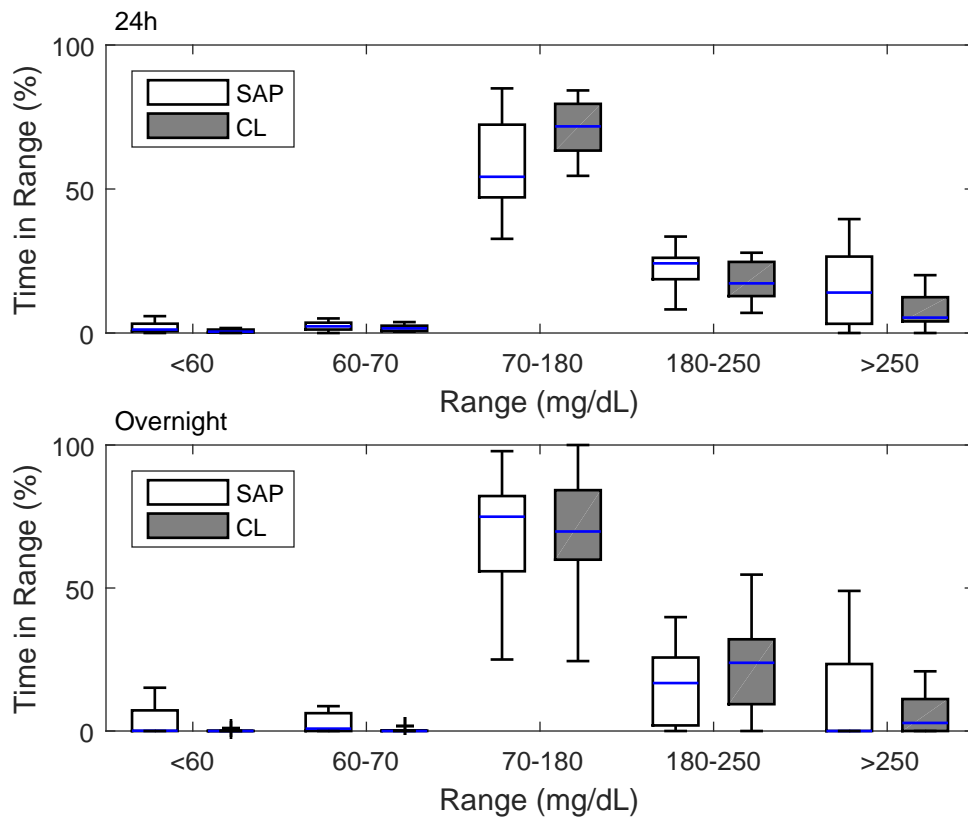


Figure 2.3: Box and whisker plot showing the percentage of time with CGM in various ranges for SAP and CLC. The horizontal blue lines indicate the medians, the box represents the IQR, and the thin vertical lines represent the range. Outliers are shown as plus symbols.

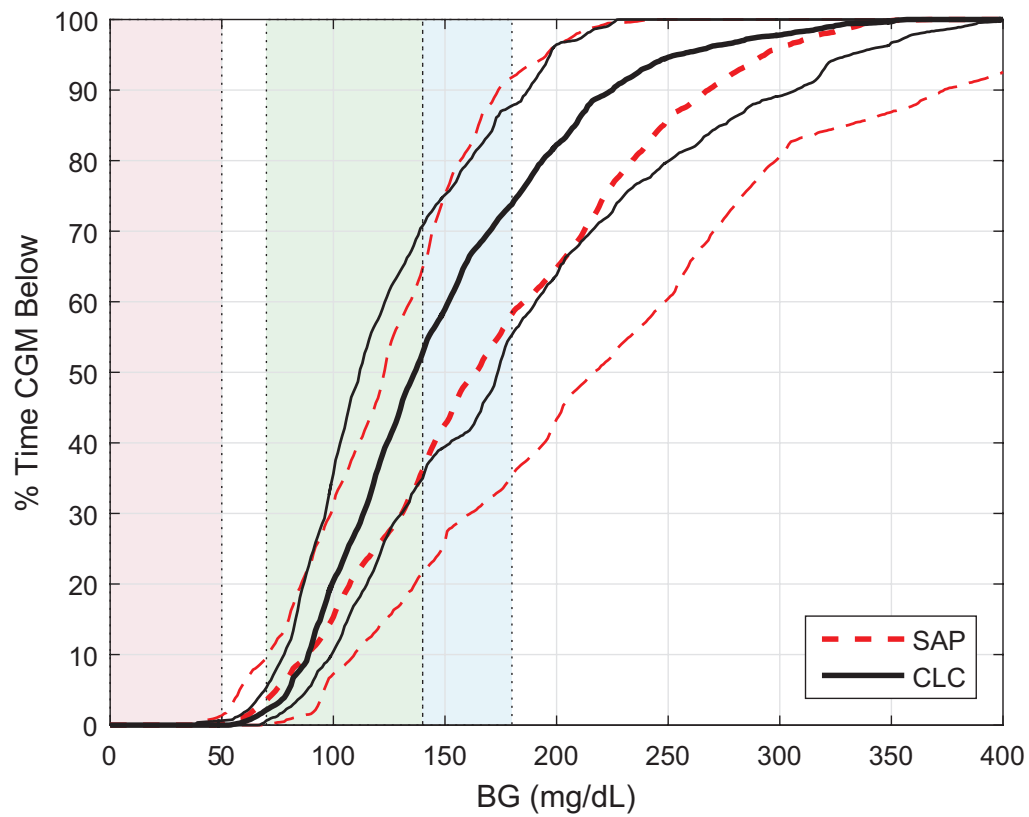


Figure 2.4: Cumulative histogram of CGM values for all 10 subjects during SAP and CLC. The thick line represents the average, and the thin lines represent the minimum and maximum values. The red, green, and blue shaded areas show <50 mg/dL, 70-140 mg/dL, and 140-180 mg/dL, respectively.

the plot, with improvements in control demonstrated by movement toward this ideal corner. The subjects showed a migration toward the lower-left corner during CLC, with an overall narrower distribution on the plot demonstrating consistent control between subjects. The SAP results are scattered across the upper and right portions of the plot, demonstrating wide variability in quality of control during usual therapy.

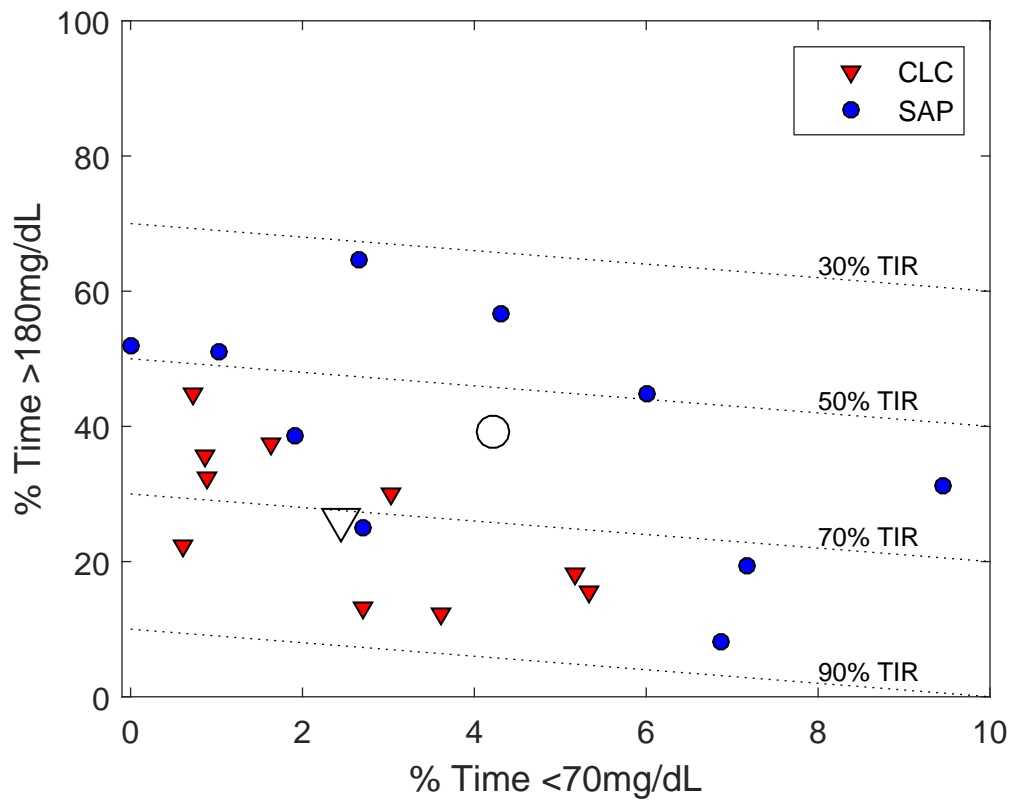


Figure 2.5: Plot of percent time >180 mg/dL versus percent time <70 mg/dL for each subject. The symbols indicate CLC (red triangles) or SAP therapy (blue circles). The parallel dotted lines show contours of percentage time in range (TIR, 70-180 mg/dL). The large unfilled triangle and circle indicate the mean for CLC and SAP, respectively.

The mean sensor glucose during closed-loop was 151 ± 19 mg/dL. This result was significantly lower than the SAP value of 173 ± 31 mg/dL ($p=0.042$). Excluding subject 4, subjects who had a high mean glucose (>168 mg/dL) during SAP saw a decrease to

a lower value during CLC, along with an increase in the percent time in range (Figure 2.6A). For other subjects, the mean glucose remained steady, while the percentage of time in hypoglycemia remained similar or decreased (Figure 2.6B).

The median CGM traces for 24 h glycemic control for CLC and SAP are shown in Figure 2.7. The distribution of announced meals and snacks during CLC is shown in the lower panel of the figure (meal information was not recorded during SAP). The dinner meals at the Stanford site were consumed late in the evening (19:49, 20:53, and 20:11), which contributed to the hyperglycemia in the beginning of the overnight period experienced by some subjects. Individual glucose and insulin traces for each subject are shown in Appendix B.

2.3.3 Hypoglycemia

Time spent with CGM <70 mg/dL was $2.5 \pm 1.8\%$ during CLC. While this is lower than the SAP value of $4.2 \pm 3.1\%$ of time, the difference was not significant. Overnight (00:00-07:00), time <70 mg/dL during CLC was reduced to 0% (0%, 0.6%). The amount of time spent in hypoglycemia as defined by various thresholds during CLC and SAP is shown in Figure 2.8. Information about the number and duration of hypoglycemic episodes during CLC (defined as a CGM excursion below the specified threshold for >10 min as recommended in [145]) is shown in Table 2.3. Overall, there were 1.3 (0.58, 2.0) episodes per subject per day <70 mg/dL and 0.33 (0.0, 0.5) episodes per subject per day <60 mg/dL. The HMS provided 1.8 (1.3, 3.5) alarms per subject per day warning of impending hypoglycemia. These alerts allowed subjects to take a carbohydrate treatment before the hypoglycemic event had started, thereby preventing or shortening the impending hypoglycemic event.

Three subjects each experienced a single event where the CGM measured below 50 mg/dL. These events lasted 4, 24, and 25 min, respectively. They were preceded

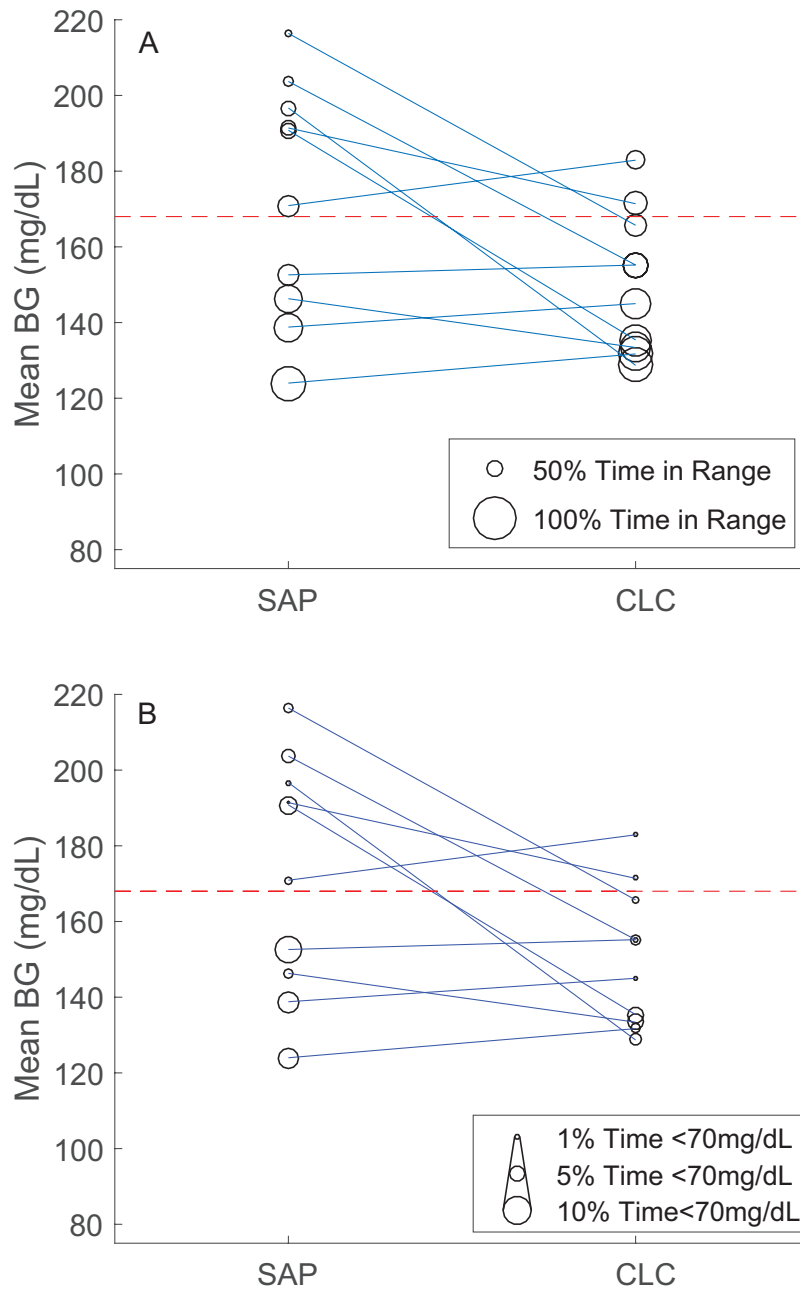


Figure 2.6: Mean CGM for each subject during SAP and during CLC. The line connecting icons represents the same subject. (A) The size of the circle icon indicates the percentage of time spent in range (70-180 mg/dL). (B) The size of the circle icon indicates the percentage of time spent below 70 mg/dL. The dashed red line represents a mean BG of 168 mg/dL, which corresponds to an HbA1c of 7.5% (58 mmol/mol) [146]

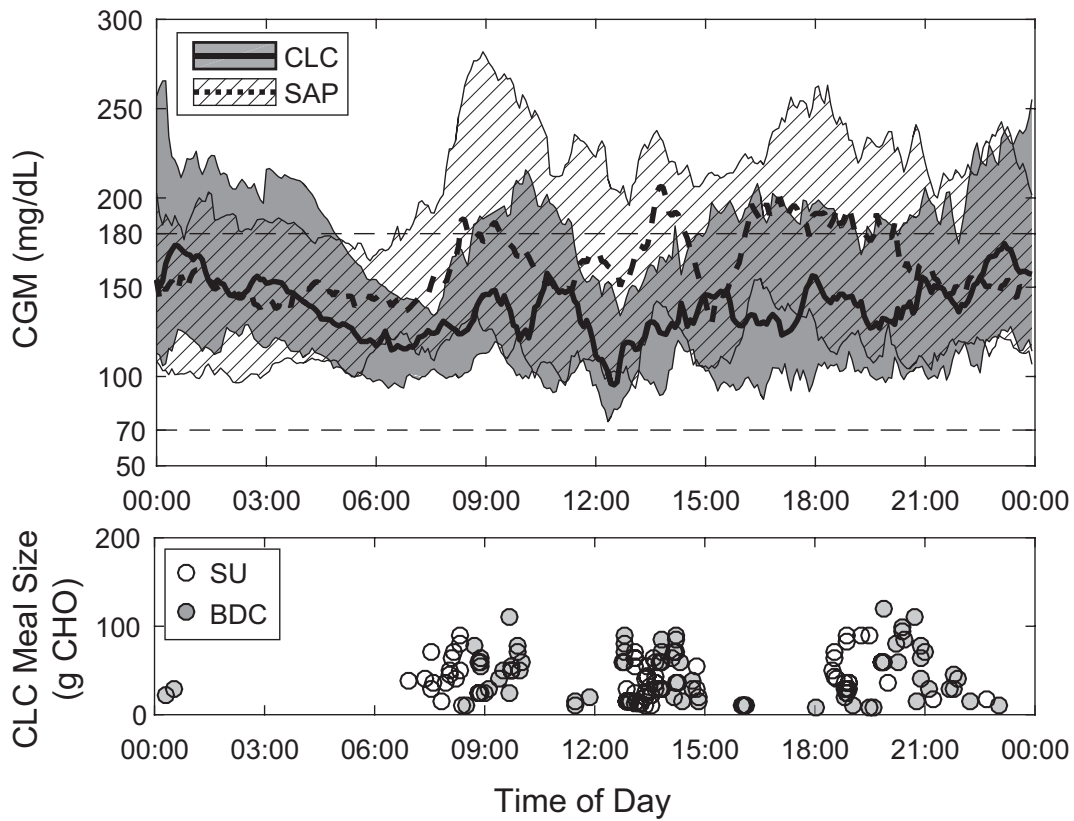


Figure 2.7: CGM over 24 h during the closed-loop study during SAP and CLC periods. The solid and dashed lines show the median CGM value for 10 subjects during CLC and SAP, respectively, while the shaded regions show the IQR. The lower panel shows the time and size of announced meals during CLC.

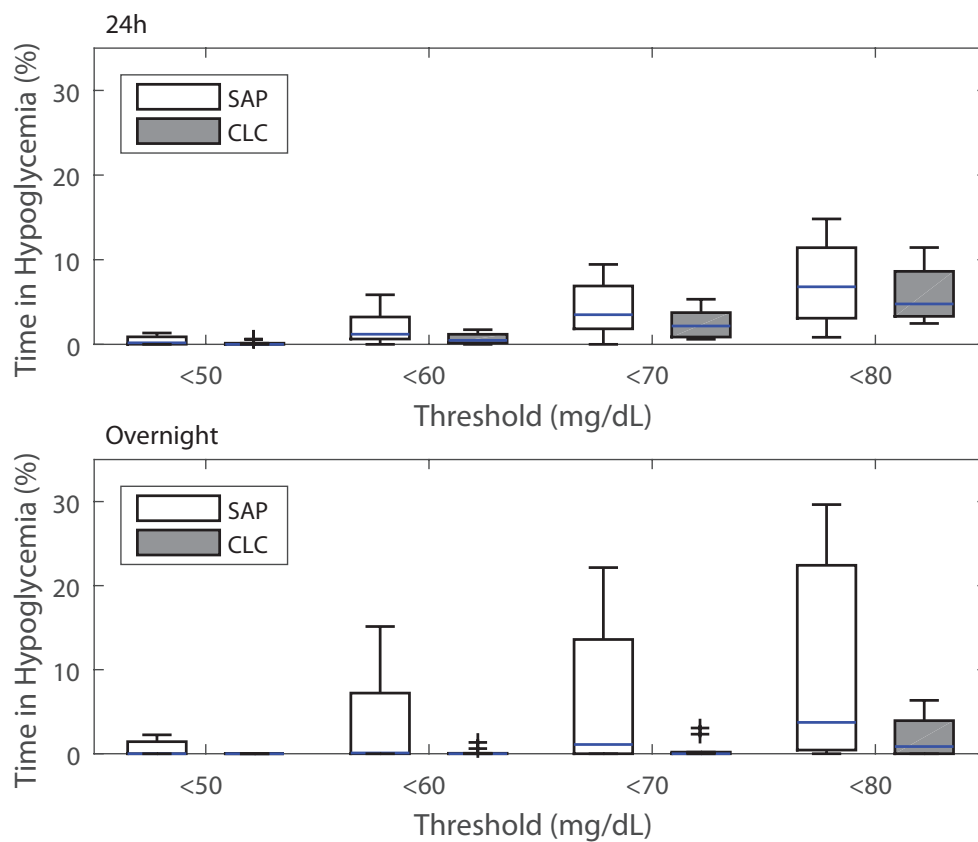


Figure 2.8: Box and whisker plot showing the percentage of time in hypoglycemia for various thresholds for SAP and CLC. The horizontal blue lines indicate the medians, the box represents the IQR, and the thin vertical lines represent the range. Outliers are shown as plus symbols.

Table 2.3: Number of hypoglycemic events lasting more than 10 min by CGM per subject per day. Episodes are broken down during overall 24 h control, during and 30 min after exercise, and during the overnight period, shown as median (IQR).

Threshold	<50 mg/dL	<60 mg/dL	<70 mg/dL
Total episodes	2	11	36
Per subject per day			
Overall	0 (0, 0.08)	0.33 (0, 0.5)	1.33 (0.58, 2)
Exercise (+30 min)	0 (0, 0)	0.17 (0, 0.42)	0.5 (0.33, 1)
Overnight (00:00-06:00)	0 (0, 0)	0 (0, 0)	0 (0, 0.08)
Number of exercise sessions with episode per subject (of 6 or 7)	0 (0, 0)	0.5 (0, 1.3)	1.5 (1, 3)

by 124, 72, and 48 min of pump suspension, which started when the CGMs were 133 mg/dL, 168 mg/dL, and 110 mg/dL. The second event occurred during exercise, although the CGM was already at 87 mg/dL when exercise began. Alerts from the HMS and corresponding CHO treatments, as well as the controller-directed suspension of insulin delivery, allowed subjects to recover quickly from these episodes, with no adverse events. Each of these events occurred in the time period 2-4 h after a meal, indicating that the meal bolus could have contributed to the event.

2.3.4 Insulin

The average TDI during CLC was 47 ± 18 U/day (0.81 ± 0.23 U/kg/day). This amount was not significantly different from the usual TDI values of 49 ± 18 U/day (0.82 ± 0.17 U/kg/day) ($p=0.52$). Still, the percentage of time spent in hyperglycemia (>180 mg/dL) decreased from $39 \pm 18\%$ of time during SAP to $26 \pm 11\%$ of time during CLC ($p=0.03$). The ZMPC+HMS system was able to significantly reduce the amount of time spent in hyperglycemia without significantly increasing the TDI or increasing time spent in hypoglycemia.

2.3.5 Carbohydrate Consumption

Meal choice throughout the study was determined by the subjects, with no restrictions. The average amount of CHO estimated for meals per day was 208 ± 32 g for female subjects ($n=5$, mean weight 56 kg) and 259 ± 60 g for male subjects ($n=5$, mean weight 61 kg). Meal size estimation and announcement were performed by subjects. A standard schedule of three daily meals was followed, with opportunities for snacks as desired.

2.3.6 Exercise

Subjects engaged in 2-3 daily sessions of mild to moderate intensity exercise lasting at least 30 min each. This frequency and duration of exercise was intended to challenge the system, since there was no announcement to the controller of exercise or pre-exercise preparation, such as lowering or suspending basal insulin delivery. Additionally, the exercise took place following large breakfast or lunch meals, when the IOB could be high (estimated IOB at start of exercise was 2.0 U (0.54 U, 4.1 U)).

Since there was no exercise announcement or activity measurement in this study, the only way for the controller to react to an exercise event was through feedback from the CGM (i.e., if the CGM is decreasing quickly or approaching hypoglycemia). In Figure 2.9, the final CGM is plotted versus the minimum rate of change during each exercise session, with the size of the icon indicating the duration of any associated controller-directed pump suspension. There are three ways a pump suspension can be associated with an exercise period: (1) the pump suspension began during the exercise period, (2) the pump suspension began before the exercise period and lasted at least 30 min after the start of the exercise period, or (3) the pump suspension began within 30 min of the end of the exercise period. An indication of desired controller

performance is a pump suspension when the CGM is low at the end of exercise, especially if the CGM is also dropping quickly. Additionally, the pump should not be suspended (or should suspend for only a short period), if the CGM is high and/or if the CGM was steady or increasing.

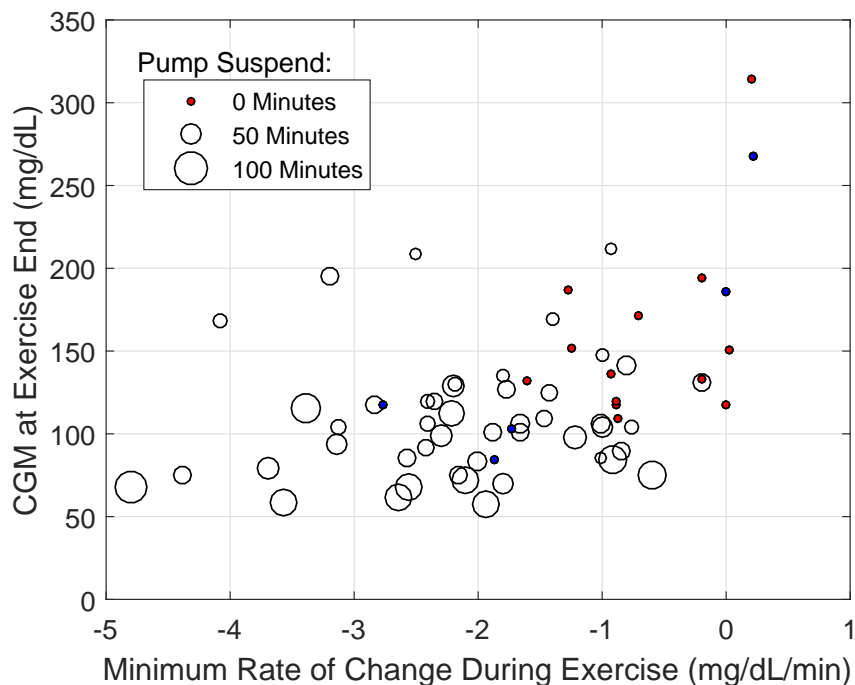


Figure 2.9: CGM at exercise end versus minimum rate of change during exercise for each exercise period for each subject. The size of the icon indicates the length of pump suspension associated with that exercise period, in minutes. Exercise periods with no pump suspension are filled red. Exercise periods with no pump suspension for the subject where the controller was not functioning as intended are filled blue.

As shown in Figure 2.9, the controller performed as desired during exercise in this study. Excluding subject 4, there were pump suspensions associated with all exercise periods ending with CGM below 108 mg/dL, regardless of the rate of change. If the CGM during exercise was dropping any faster than -0.9 mg/dL/min, then there were pump suspensions for all exercise periods ending with CGM below 131 mg/dL. If the CGM during exercise was dropping at a rate that was any faster than -1.6 mg/dL,

there were pump suspensions for all exercise periods, regardless of the final CGM. Lastly, the pump did not suspend for each exercise period where CGM was dropping no less than -0.9 mg/dL/min and ending CGM was greater than 150 mg/dL. Including subject 4, there were three instances where a pump suspension would have been desired but did not occur. These results are summarized in Table 2.4. As a result of the ZMPC+HMS action during exercise, only 1.5 (1, 3) exercise sessions per subject (of a total 6 or 7 exercise sessions) resulted in a hypoglycemic event with CGM <70 mg/dL.

Table 2.4: Number of exercise periods with pump suspensions out of total exercise periods for various ranges of minimum rate of change (ROC_{min}) and CGM at exercise end (CGM_{end}). The asterisk indicates cases where there would have been 100% pump suspension excluding subject 4.

CGM_{end} (mg/dL)	ROC_{min} (mg/dL/min)				
	< -2.5	-2.5 to -1.6	-1.6 to -0.9	-0.9 to 0	> 0
>150	2/2	1/1	2/4	0/3	0/3
131-150	N/A	1/1	1/3	1/2	N/A
108-131	2/3*	6/6	2/2	1/5	N/A
90-108	2/2	6/7*	3/3	1/1	N/A
<90	7/7	5/6*	2/2	2/2	N/A

2.4 Discussion

In this chapter, we present the first evaluation of ZMPC+HMS in the adolescent population. This study showed that the use of this system is feasible in this population. Even in the face of challenges such as large free-choice meals, twice-daily mild to moderate unannounced exercise, and ambulatory conditions in the outpatient environment, the controller was able to achieve $71 \pm 10\%$ time in range, which is an improvement over the subjects' typical control ($57 \pm 16\%$ time in range). This im-

provement was made without increasing the amount of time spent in hypoglycemia or increasing the TDI.

The glycemic control in this study is comparable to that observed in other day-and-night studies of CLC for adolescents. For example, Tauschmann, et al. [115] showed a median (IQR) of 72% (59%, 77%) of time spent with glucose level between 70-180 mg/dL, as compared to our study, which had 72% (64%, 79%) time in range. Similarly, Ly et al. [67] reported a mean of 70% time spent in range. While the protocols and controller designs of these studies differed, the similarity of the results for insulin-only systems indicates that performance may be limited by the constraints of the slow action of subcutaneous insulin and the hormones present during adolescence that make control difficult. Additionally, these systems are not fully automated. There is work involved for the patients that can introduce error into the system, such as in meal size estimation and determination of basal, CR, and CR profiles. Innovations in AP design to reduce the need for patient interaction, including faster insulin action, may be needed to improve above the 70-75% time-in-range mark.

The pattern of hypoglycemic episodes during the postprandial period, especially visible following breakfast (Figure 2.7) suggests that some of the meal boluses could have been too large. Although the system is designed to give 80% of the total meal bolus when BG is below 120 mg/dL, there were 57 out of 161 meals that were announced with BG >120 mg/dL and therefore received the full bolus. One potential cause of postprandial hypoglycemia is a CR that is too high. An algorithmic adjustment of the insulin to carbohydrate ratio based on open-loop data as in Dassau, et al. [66] could potentially reduce postprandial hypoglycemia during CLC. Errors in the estimation of the meal size could be caused either by subjects estimating CHO for the entire meal but only consuming part of it, or overestimating the amount of CHO in the meal. Subject behavior could also be influenced by the clinician-supervised

setting, where there may be more pressure to demonstrate good control and avoid under-dosing. Several studies have investigated the use of a partial bolus based on a percentage of the total calculated bolus for the meal regardless of the SMBG, allowing the controller to deliver the rest of the required insulin on an as-needed basis using feedback from the CGM [78, 88, 147]. While Elleri, et al. [107] did not find evidence that a partial meal bolus reduced the risk of hypoglycemia, they found that it did not decrease the time spent in range. Further investigation is needed to optimize the integration of an announced meal bolus within the AP system.

There was some hyperglycemia during the overnight period in this study, especially in the first half of the night. This hyperglycemia was caused by late-night meals and snacking, as shown in the lower panel of Figure 2.7. The protocol should always be kept in mind when interpreting overnight control results calculated using a common predetermined time range (e.g. 00:00 to 07:00), especially for studies that allow varying or unusual meal and sleep schedules. Protocols that allow late-night meals or snacks will inevitably result in more overnight hyperglycemia. Overnight control in this study was conservative by design, with safety constraints in place to prevent over-delivery of insulin from 22:00 to 06:00. Using fixed start and end times for the additional safety measures at night does not allow for flexible or atypical schedules. An added announcement for sleep to start the safety constraints may reduce overnight hyperglycemia if users are awake and/or eating at atypical times. However, this extra announcement also creates additional work for the user and may lead to safety risks if the user forgets to make the announcement. The compromise between design safety and efficacy will be an important consideration as the AP moves forward.

Although this study took place in the outpatient environment, subjects were supervised at all times. Study staff were on hand to assist subjects with troubleshooting

the system, checking infusion sets and CGM sites, and responding to system alerts, although subjects were responsible for estimating meal size, entering their meal bolus, taking SMBG measurements, and interacting with the DiAs interface. The presence of the clinical team ensured that HMS and other system alarms were responded to promptly. The level of supervision in this study could have led to better results than if the subjects had been unsupervised. When using the device unsupervised in daily life, subjects may respond less quickly to alerts for hypo- or hyperglycemia or take longer to repair loss of communication between devices. Alternatively, subjects may be more vigilant during unsupervised use since they will not have the reassurance that nearby clinical staff provide. Still, the level of supervision in this study, necessary to comply with regulatory requirements, had the advantage of ensuring the best possible assessment of the ZMPC algorithm itself, with minimal time spent out of CLC and no confounding factors related to patient non-compliance.

There were some technical difficulties encountered during this study. These issues represent the primary challenge that is faced when transitioning from a highly controlled inpatient environment to a more unpredictable outpatient environment. A timing anomaly between the CGM and the DiAs system caused a malfunction in the controller for one subject, resulting in suboptimal (but still safe-by-design) performance. The potential for this issue has since been addressed in updated versions of the controller. Additionally, disruptions in the Bluetooth communication between the pump, CGM, and DiAs system resulted in some time spent out of CLC. These communication issues need to be improved as the system is prepared for more extensive outpatient use.

2.5 Conclusions and Future Work

In conclusion, the ZMPC+HMS algorithms were shown to be feasible for use in the adolescent population. Additionally, the system was able to provide improved glycemic control as compared to SAP, even in the ambulatory outpatient environment emulating real-life conditions. The controller was not informed of the twice-daily exercise sessions, but it was able to react to the decreasing CGM measurements to lower or suspend insulin delivery during or after exercise as needed. This study represents a promising step forward for the ZMPC+HMS AP system in the transition from inpatient to outpatient evaluation, as well as in expanding the user population to include adolescents as well as adults.

A follow-up study is being conducted to evaluate the system in the fully outpatient, unsupervised environment. This study will be conducted in a randomized crossover design, with a total of 10 subjects at each clinical site. Five subjects will be randomized to use CLC and five will use SAP during a two week period at home. The subjects will then cross over to the other therapy for the next two-week session. This design will provide a control group that can be used for efficacy comparisons between SAP and CLC. This study will be conducted in adults, rather than adolescents, because the system is not yet ready to be used in a fully outpatient unsupervised setting by adolescents. The study has been approved by the FDA based on supporting data from this chapter, and will be conducted in May-June 2016.

While the ZMPC+HMS algorithms are able to provide control of the BG, the use of subcutaneous insulin delivery and glucose sensing places fundamental limitations on the quality of control that can be achieved. The system is not fully automated, since users must enter an estimate for the meal carbohydrate content prior to eating. Even with this meal announcement and subsequent insulin bolus prior to the meal, there

are still postprandial BG values reaching above 300 mg/dL. Additionally, suspending the pump is not always enough to prevent hypoglycemia due to the long residence time of subcutaneously delivered insulin in the body. For these reasons, a promising area of research related to the artificial pancreas is the investigation of alternative insulin delivery and glucose sensing routes. In the next three chapters, the use of the intraperitoneal space for glucose sensing and insulin delivery for the artificial pancreas is explored.

2.6 Acknowledgments

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Chapter 3

Modeling Glucose Sensor Dynamics¹

3.1 Introduction

An important factor in diabetes treatment is the ability to measure blood glucose concentration (BG) accurately in real-time. As discussed in Chapter 1, the development of continuous glucose monitors (CGMs) has greatly improved the ability of people with diabetes to be aware of their glycemic status beyond the few isolated capillary measurements that used to be the norm [21]. However, the decision on where to place the sensor in the body is not easily made. The first application of CGM was done in the intravenous space. These sensors provided fast and accurate BG measurements, but were not feasible for use outside of a hospital and came with unacceptable safety risks [2, 149]. The selection of a CGM site requires a balance between proximity to the vasculature and the level of invasiveness required.

The placement of a CGM in the subcutaneous (SC) space has been adopted

¹ Portions of this chapter are published in D. R. Burnett, L. M. Huyett, H. C. Zisser, F. J. Doyle III, and B. D. Mensh, "Glucose sensing in the peritoneal space offers faster kinetics than sensing in the subcutaneous space," *Diabetes*, vol. 63, pp. 2498-505, 2014 [38], and L. M. Huyett, R. Mittal, H. C. Zisser, E. S. Luxon, A. Yee, E. Dassau, F. J. Doyle III, and D. R. Burnett, "Preliminary evaluation of a long-term intraperitoneal glucose sensor with flushing mechanism," *Journal of Diabetes Science and Technology*, 2016 [148].

for commercial application. This placement meets the requirements of being close enough to the vasculature to capture real-time changes in BG, while minimizing invasiveness by requiring only a small wire to be inserted under the skin [23]. Glucose enters the body through the ingestion of food. After the glucose is absorbed through digestion, it travels through the major and minor blood vessels to reach the brain, muscle cells, and other tissues. To reach individual cells, the glucose first diffuses from capillaries into the interstitial fluid (ISF), as depicted in Figure 3.1. The ISF of the SC space has been established as a minimally invasive site for a sensor to provide a continuous estimation of the BG. Commercially available glucose sensors detect the glucose once it has reached the ISF using a transcutaneous electrode or other sensing mechanism [23].

While the sensor measures the glucose concentration in the ISF, the raw sensor signal is calibrated using a measurement of the glucose concentration in the capillary blood. The gradient between the glucose concentration in the blood and the ISF at steady state has been reported as anywhere from 50% to 100%, but is difficult to establish definitively due to the lack of techniques for directly measuring the concentration of glucose in the ISF [53, 150]. However, many studies have established the accuracy of SC glucose sensors that are calibrated to BG values across a wide range of physiological BG values, making it a reasonable assumption that the concentrations are directly proportional or equal at steady state [20].

CGM in the SC space has several limitations. The sensor insertion below the skin induces an inflammatory response, leading to biofouling and tissue encapsulation [23, 151, 152]. This response limits the lifetime of the sensor to one to two weeks, after which a new sensor must be inserted. SC sensors are sensitive to external factors such as pressure on the sensor site, often induced during sleep by laying on the sensor site. Studies have shown that this pressure effect causes large and persistent

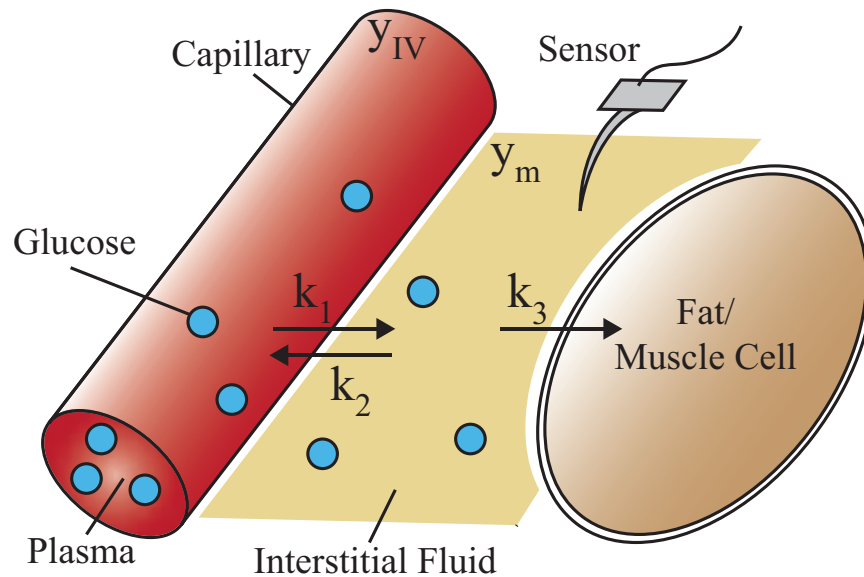


Figure 3.1: Schematic representation of the glucose transport process from the blood vessel to the ISF. This diagram is based on the model presented in [150].

inaccuracies in the measurement [33, 39]. Pressure effects on sensor measurements are problematic, given that accurate measurements are particularly important during sleep when patients are vulnerable to hypoglycemia [33, 153–162].

A limitation of SC CGM that is especially relevant to artificial pancreas (AP) applications is the dynamic lag that is introduced by sensing in the ISF. Before reaching the sensor site, glucose must diffuse from the bloodstream into the ISF. Experimental evidence has shown that SC CGM measurements appear to lag behind the BG [163–171], an effect that is exacerbated by encapsulation [172, 173]. Recent studies have found that radiolabeled glucose could be detected in the SC space with a pure delay of 5-6 minutes after IV injection [57, 58].

While the SC space has become the most popular route for diabetes applications such as glucose sensing and insulin delivery, the intraperitoneal (IP) space has long been known as an alternative. The IP space was first introduced as an alternative insulin delivery route in the 1970s [174]. Insulin delivered through the IP route has

faster pharmacokinetic and pharmacodynamic characteristics than insulin delivered through the SC route: when insulin is delivered through the SC route, the absorption peak occurs 50-60 minutes later [175], as opposed to 20-25 minutes when using the IP route [176]. The insulin is also cleared more quickly: insulin delivered through the SC route has a residence time of 6-8 hours [175], while IP insulin has a much shorter residence time of 1-2 hours [176]. Characteristics of the IP space that make it an ideal candidate for CGM location include its proximity to copious blood flow through vessels lining the peritoneal cavity [177–179], its demonstrated foreign-body tolerance in humans [180–182], and its isolation from external factors (temperature and pressure).

In this chapter, we present a direct comparison of enzymatic glucose sensors placed in the IP and SC space of anesthetized pigs. We hypothesized that a sensor placed in the IP space would respond more quickly to changes in BG than a sensor placed in the SC space of the same animal.

3.2 Research Design and Methods

3.2.1 Overview of Animal Experiments

Experiments were conducted under an IACUC-approved protocol. Multiple sensors (described below) were placed in the SC, IP, IV, and intra-arterial (IA) spaces of eight anesthetized nondiabetic juvenile female Yorkshire pigs weighing between 60 and 90 kg. After allowing several hours for sensor wetting and baseline measures, intravenous hyperglycemia challenges similar to a glucose tolerance test (IVGTT) were administered, consisting of 250 mg/kg of D50 pushed over 2 minutes intravenously by an infusion pump. Venous samples were drawn at frequent intervals post-injection

and analyzed by glucometer and YSI (YSI Inc., Yellow Springs, OH) assay. In several animals, an additional IVGTT was administered, separated from the first challenge by at least 90 minutes.

3.2.2 Sensors and Placement

The sensors used in the SC space were commercially available Dexcom Seven (DEXCOM, San Diego, CA) sensors placed in the pre-abdominal SC tissue using standard technique for sensor placement per manufacturer instructions. The sensors used in the intravenous and intra-arterial spaces were modified Dexcom Seven sensors, lengthened by attaching 30-gauge wires to the silver and platinum electrodes using conductive silver epoxy, and encapsulating these joints with epoxy to prevent shorts due to fluid intrusion. The IA and IV sensors were placed through introducers after cut-downs to the femoral or jugular vessels. The sensors used in the IP space were modified Dexcom Seven sensors, lengthened in the same manner as the IA/IV sensors and splinted to a short length of Teflon-coated coaxial wire with silicone o-rings in order to prevent the sensors from bending excessively or perforating IP tissues. IP sensors were placed in the peritoneal cavity via the Hassan technique. The signal from all sensors was captured with custom potentiostat electronics and read into LabVIEW via an analog-to-digital converter. Prior to all analyses, sensor data was smoothed using a 60-s moving average filter. Some of the data logging for experimental manipulations was done using a clock with 1-minute resolution, which could introduce a ± 30 -second error relative to the sensor board (which recorded at 1-second resolution).

3.2.3 Data Analysis: Response Time

Response characteristics for each sensor were initially quantified using two measures on each sensor waveform during the IVGTT. First, to quantify latency between rapid increases in BG and extravascular sensor measures, we calculated the time to half-maximum (from beginning of IVGTT). Second, to quantify how rapidly the extravascular measures recover toward baseline glucose levels after the bolus, we calculated the percentage by which each sensor reading returned (from its maximum) to baseline at 35 minutes post-glucose-injection.

3.2.4 Data Analysis: Compartmental Modeling

Glucose sensors placed in either the IP or SC space do not directly contact the blood; rather, they contact the ISF of the sensing space. The diffusion process between the blood and the ISF means that the concentration measured by the sensor may lag behind the BG, especially when the BG is increasing or decreasing at a high rate of change. However, it is hypothesized that the lag will be smaller for IP sensors due to the proximity to major vasculature. In order to quantify the lag from experimental data, a two-compartment model can be used to represent the glucose diffusion process. This type of two-compartment model has been used in previous studies to approximate the transport of glucose between the vascular compartment and the SC compartment [183–187]. The schematic in Figure 3.1 demonstrates the two-compartment system. The first compartment is the blood within the vessel, and the second is the ISF. Glucose diffuses between the blood vessel and the ISF, and vice versa. Glucose is also taken up from the ISF into cells.

A mass balance can be done on the ISF compartment to determine the rate of change of the glucose concentration in that compartment. The resulting first-order

model for ISF glucose concentration as a function of the glucose concentration in the major blood vessels as follows, where all time-dependent variables are measuring the deviation from steady-state:

$$\frac{dC_m(t)}{dt} = -(k_3 + k_2)C_m(t) + k_1 \frac{V_b}{V_{isf}} C_{IV}(t - \theta_S) \quad (3.1)$$

where $C_m(t)$ is the glucose concentration measured by the sensor (mg/dL), $C_{IV}(t)$ is the glucose concentration in the blood (mg/dL), k_1 , k_2 , and k_3 (min^{-1}) are the rate constants for the diffusion processes as defined in Figure 3.1, V_b and V_{isf} are the volumes of the blood and ISF, respectively, and θ_S is the time delay (min). By grouping constants together, this model can be expressed as:

$$\frac{dC_m(t)}{dt} = \frac{1}{\tau_S} (\hat{K}_S C_{IV}(t - \theta_S) - C_m(t)). \quad (3.2)$$

Here $\tau_S = \frac{1}{k_3+k_2}$ (min) and $\hat{K}_S = \frac{k_1 V_b}{(k_3+k_2) V_{isf}}$.

The glucose sensors used in this study record the measurement signal as an electrical current (nA). The glucose concentration depends linearly on the current as given in the following equations:

$$C_m(t) = a I_m(t) \quad (3.3)$$

$$C_{IV}(t) = b I_{IV}(t) \quad (3.4)$$

where a and b are constants (mg/dL)/(nA). The model in Equation (3.2) can be expressed generically as:

$$\frac{dy_m(t)}{dt} = \frac{1}{\tau_S} (K_S y_{IV}(t - \theta_S) - y_m(t)) \quad (3.5)$$

where $y_{IV}(t)$ is the model input (mg/dL or nA) and $y_m(t)$ is the model output (mg/dL or nA). If it is desired to use the uncalibrated sensor signal as the output of the model, then $K_S = \frac{1}{a}\hat{K}_S$ (nA/(mg/dL)). Similarly, if it is desired to use the uncalibrated sensor signal as the model input, then $K_S = \frac{b}{a}\hat{K}_S$. Note that a and b change between each individual enzymatic sensor, meaning that it will be difficult to validate the model parameters identified from one sensor signal on another sensor signal when using uncalibrated sensor signals. Lastly, before modeling, each sensor signal can be normalized by its maximum value. The additional ratio of $\frac{y_{IV,max}}{y_{m,max}}$ will be absorbed into the identified parameter K_S . Note that even with all these adjustments, the lag τ_S can still be identified.

Equation (3.5) can be expressed as a transfer function in the Laplace domain as follows:

$$G_S(s) = \frac{Y_m(s)}{Y_{IV}(s)} = \frac{K_S e^{-\theta_S s}}{\tau_S s + 1}. \quad (3.6)$$

The identifiable parameters in this transfer function model are the sensor time constant τ_S (min), the sensor delay θ_S (min), and the model gain K_S . Since the most challenging aspects of AP design involve time periods where the glucose is changing rapidly (after meals or during exercise), the filtering effect of the sensor dynamics is expected to have a detrimental effect on the control quality.

To determine the dynamic response characteristics of each space, the IP and SC sensor signals were modeled for each IVGTT challenge as a function of the vascular glucose concentration. The Systems Identification Toolbox in MATLAB (The MathWorks Inc., Natick, MA) was used to numerically fit the data to a first-order transfer function with time delay using least-squares regression. The time delay quantifies the amount of time it takes for the SC or IP sensor signal to begin to respond to a change in the vascular glucose. The time constant represents the amount of time it

would take for the IP or SC signal to reach 63% of the vascular glucose concentration if a step change in vascular glucose were applied.

The models were initially fit using glucometer measurements of venous blood to represent the glucose concentration in the vascular compartment ($y_{IV}(t)$), while either the IP or SC sensor signal was used for $y_m(t)$. The normalized root-mean-square error fitness value was used to quantify the goodness of fit of the model. This quantity is given by the following equation:

$$F = 100\left(1 - \frac{\|y - \hat{y}\|}{\|y - \bar{y}\|}\right) \quad (3.7)$$

where y is the experimental data (in this case, the sensor signal), \hat{y} is the output of the fitted model, \bar{y} is the mean of y , and F is the goodness of fit (%).

If more than one sensor was placed in a particular space during a challenge, the resulting model parameters were averaged. The robustness of the result was subsequently bolstered by comparing model parameters using the following additional data sources as $y_{IV}(t)$ in the model: signal from an indwelling IV sensor and signal from an indwelling IA sensor. In all cases, the parameters generated by compartmental modeling (most importantly the time constant) are a model-specific measure.

3.2.5 Data Analysis: Statistics

Thirteen IVGTT challenges in 8 animals were performed. In general, the null hypothesis for the study was that SC and IP sensor performance is equal. For each set of data in which we asked whether the null hypothesis was rejected, we carried out two statistical tests: one in which we assumed that the challenges were independent even when performed in the same animal (thus, $n=13$), and one in which we assumed that challenges performed in the same animal were completely dependent (thus,

n=8). In both cases we used the binomial test, which is an exact, non-parametric test of the significance of deviations from a theoretically expected distribution of observations into two categories. The expected distribution according to the null hypothesis is that there is a 50% chance that for a given challenge (or animal) that IP will be faster than SC, and vice-versa.

3.3 Results

Figure 3.2 shows raw sensor current data from a hyperglycemia challenge. Of note are the rapid rise and fall of the intravascular (IA and IV) sensors, and the less rapid waveforms from the extravascular (IP and SC) sensors. Figure 3.2B illustrates the response-time analysis described above, in which latency (a measure of how rapidly the tissue glucose increases after a vascular bolus) and recovery (a measure of how rapidly the tissue glucose decreases as the vascular glucose decreases over 35 minutes post-bolus) were read from each sensor curve.

Figure 3.3A compares the latency between sensors in the SC and IP spaces for the 13 IVGTT challenges (across eight animals) that were successfully carried out. On this plot, each challenge is depicted as a single point in which the IP latency (y-axis) is plotted against the SC latency (x-axis) for the same challenge. For each space, latency was calculated as the mean time to half-maximum for all sensors in that space for that challenge. SC latency was in the 4-8 minute range, consistent with the faster end of the range from prior published results (see Introduction). A diagonal line of identity is included in the plot, which illustrates that for all 13 challenges in all 8 animals, IP latency was shorter than SC latency ($p < 0.001$ for challenges, $p < 0.01$ for animals). To assess whether wetting time might influence the results, two of the 13 challenges were conducted using SC sensors that had been wetted overnight instead of for several

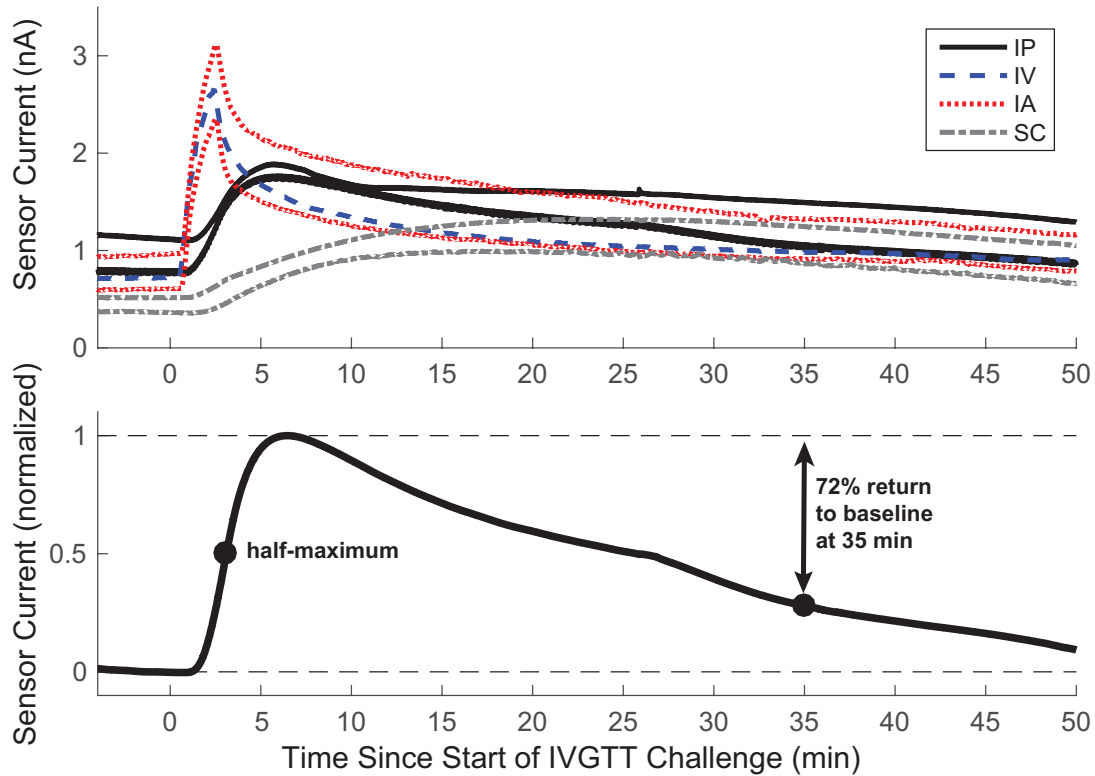


Figure 3.2: Example of experimental data used in this study. (A) Sample raw data from an intravenous glucose challenge in one pig. Unfiltered data were collected every second (1 Hz). (B) Calculation of latency (time-to-half-maximum) and recovery (percent return-to-baseline at 35 minutes) for a sample IP trace. Data are filtered using a 1-minute sliding window average. Baseline is determined by the average reading for the 3 minutes prior to onset of glucose challenge. As with baseline, the value at 35 minutes is also determined by a 3-minute average (33.5 to 36.5 minutes).

hours on the morning of the experiments. The results from these sensors were in the middle of the range of the overall results, suggesting that overnight wetting does not have a large effect on SC response times. However, because we only performed this on two sensors, we do not have the statistical power to quantify small influences.

Figure 3.3B compares the post-glucose-bolus recovery between the two sensor spaces, in a plot similar to Figure 3.3A. The average recovery for the SC space was 33%, compared to 59% for the IP space. For all challenges, the IP space showed more complete return to pre-challenge baseline glucose levels than the SC space (all points above diagonal identity line, $p < 0.001$ for challenges, $p < 0.01$ for animals). Finally, we quantified the glucose kinetics of the SC and IP spaces using compartmental modeling, in which the glucometer measurements served as an input function and the transport of glucose into the body spaces was modeled with a first-order transfer function. The glucometer measurements were used in place of the YSI measurements because the YSI data was too sparse to use as a model input. This approach yielded excellent fits to the data, as illustrated in Figure 3.4; across all challenges the mean goodness of fit was 75.6% (standard deviation (SD) 8.5%) for the IP sensor data and 83.2% (SD 8.9%) for the SC sensor data. The uncertainty of the parameters as determined from the covariance matrix was so small as to be negligible (standard deviations on the order of 1% of fitted values).

As illustrated in Figure 3.5, IP glucose kinetics during IVGTT were an average of 2.3 times faster than SC (range: 1.2 to 4.1, standard deviation: 1). The mean time constant was 5.6 (SD 2.9) minutes for the IP space and 12.4 (SD 3.6) minutes for the SC space. The difference between the SC and IP time constants was statistically significant, with the IP time constant smaller than that of SC for all 13 challenges (by paired t-test, $p < 0.001$; by binomial test $p < 0.001$ for challenges, $p < 0.01$ for animals). The mean time delays were 0.68 (SD 0.58) minutes and 1.4 (SD 0.90) minutes

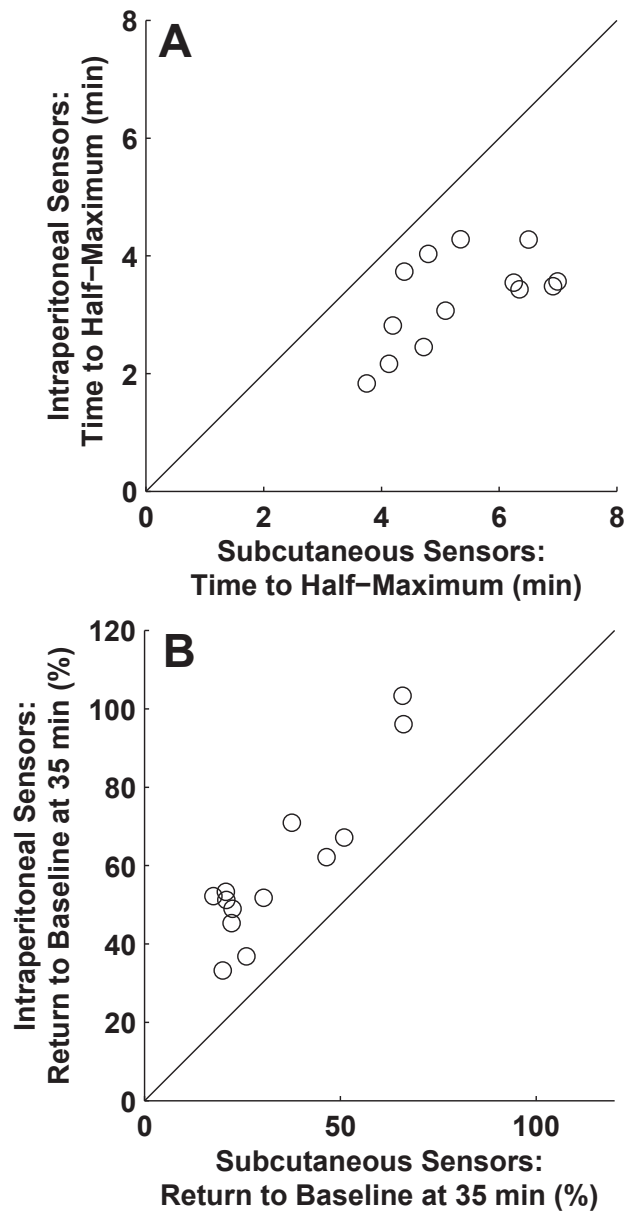


Figure 3.3: Comparison of response speed between IP and SC sensors. (A) Latency (time to half-maximum) is plotted for IP vs. SC for all 13 challenges across eight pigs. The diagonal line represents IP=SC; thus points below the line indicate IP faster than SC. (B) Recovery (Percent return to baseline at 35 minutes, see Figure 3.2B for definition) is plotted for IP vs. SC for all 13 challenges across eight pigs. The diagonal line of identity represents IP=SC; thus points above the line indicate IP sensor readings returning to baseline by a greater amount than SC sensors returned to baseline for the same IVGTT challenge.

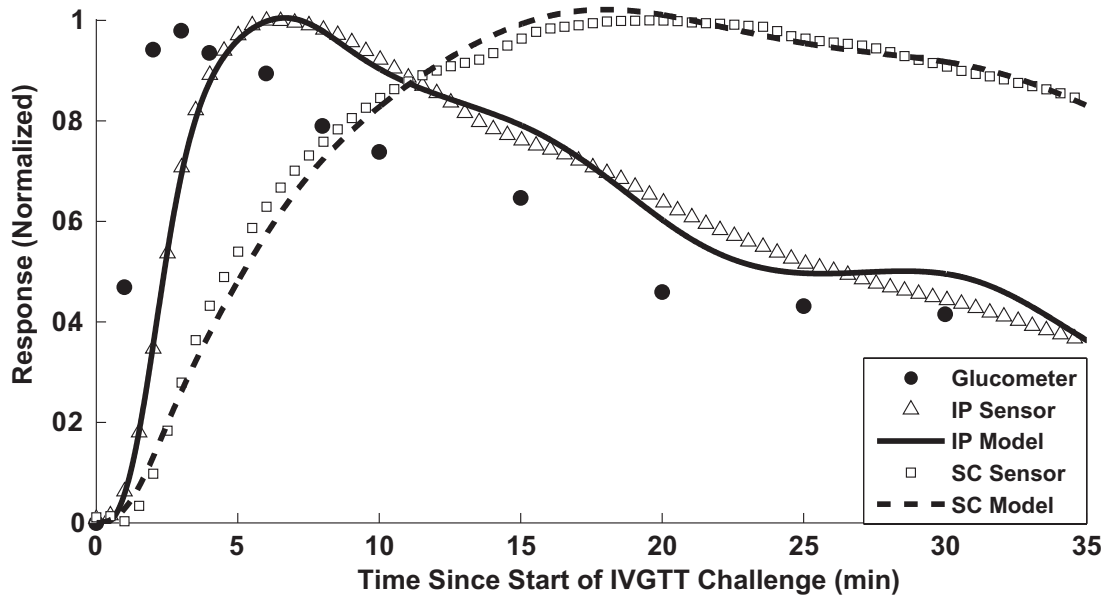


Figure 3.4: Sample of compartmental modeling fit to data. This plot shows an example of the model fitting process for a single challenge, using glucometer measurements as the input (black circles). Shown on the plot are the experimental measurements made by the IP and SC sensors (white triangles and white squares, respectively), as well as the model predicted output for each sensor (solid line and dashed line). The goodness of fit values for the IP and SC models shown were 89% and 90%, with time constants of 1.7 min. and 13.1 min., respectively.

for IP and SC sensors, respectively, although there was an estimated tolerance of 30 seconds to account for potential differences in clock synchronization. The delay for the IP sensor was significantly smaller than the SC delay (by paired t-test, $p = 0.019$). The addition of second-order dynamics did not improve the model fit.

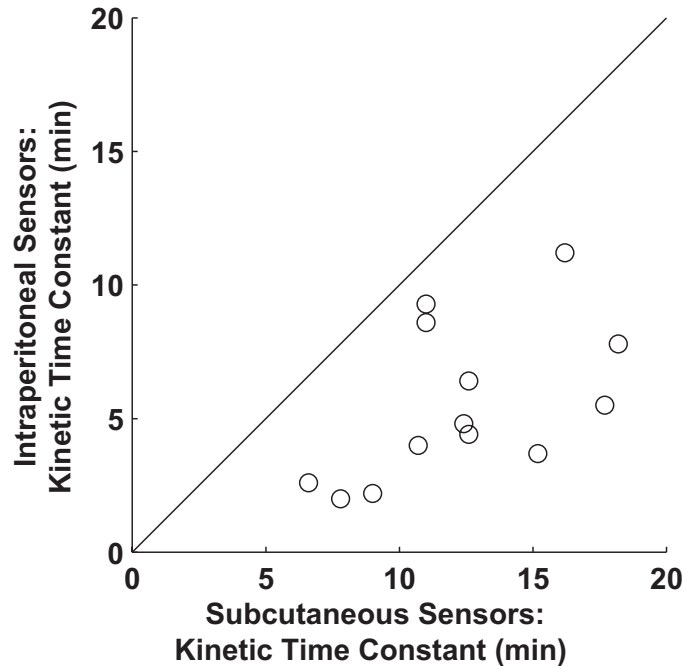


Figure 3.5: Comparison of kinetic-modeling-based response speed between IP and SC sensors for all 13 challenges. The diagonal line represents IP=SC; thus points below the line indicate IP time constants smaller (faster) than SC.

To demonstrate the robustness of the finding that IP kinetics are more than twice as fast as SC kinetics, we repeated the modeling analysis using additional sources of data to represent the vascular glucose concentration in the model ($y_{IV}(t)$ in Equation 3.5). For the challenges that had usable indwelling IA and/or IV sensors, the readings from those sensors were used as the input for modeling. Thus, the kinetics were modeled using the following three representations of the BG, unless a viable signal was not available: indwelling IV sensor, indwelling IA sensor, and glucome-

ter measurements of venous blood. Figure 3.6 demonstrates that the greater than twofold speed increase for IP over SC is independent of input-function source.

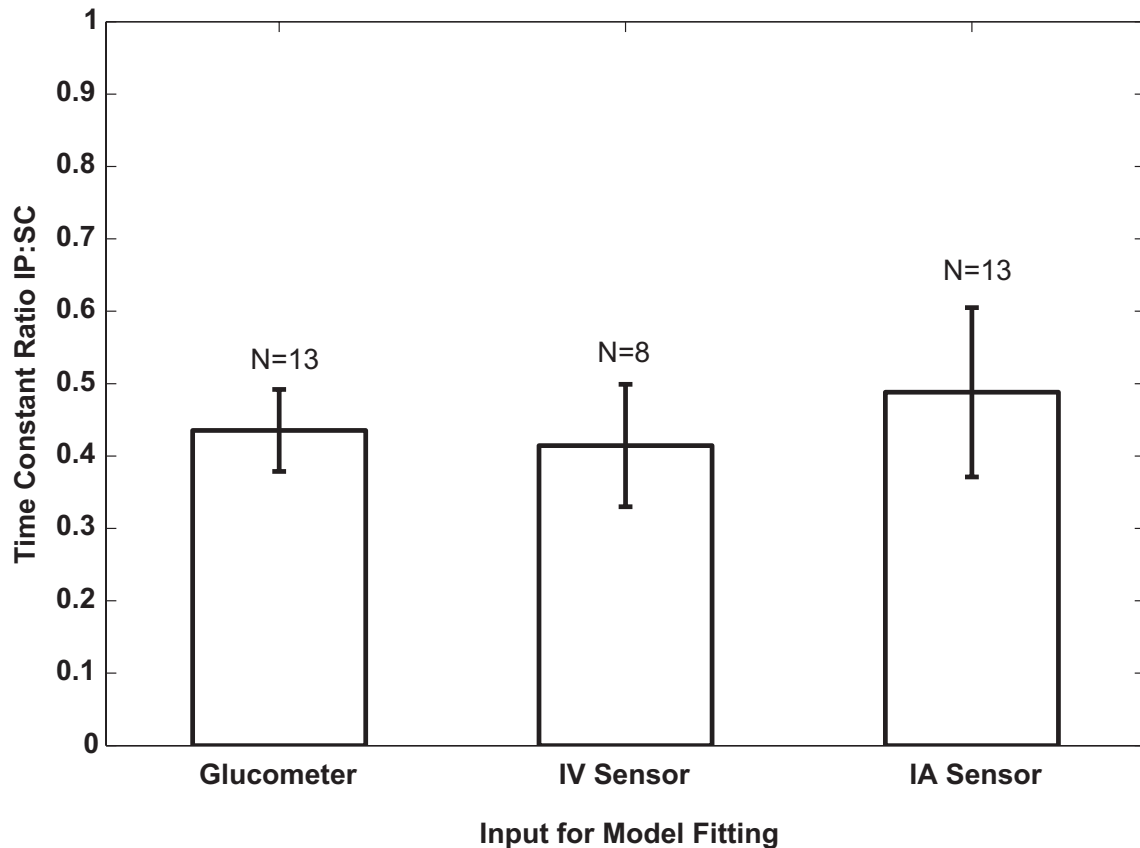


Figure 3.6: Comparison of kinetic time constants between subcutaneous and IP sensors from models fit using three different input sources for vascular glucose concentration. The average ratio is shown, with error bars indicating the standard error. The number above the bar specifies the number of challenges that had a usable signal from that particular type of input. For each type of input, the average IP time constant was less than half of the SC time constant from the same challenge.

3.4 Discussion

In summary, we show that glucose kinetics between the bloodstream and the IP space are substantially faster than between the bloodstream and the SC space,

demonstrating the suitability of the IP space for more rapidly measuring changes in BG. This improvement is likely due to the robustness of peritoneal transport, which is, for example, why this space is effectively used for dialysis in patients with renal failure.

The performance difference between sensing in the IP and SC spaces is of particular importance when considered in the context of closed-loop AP implementations. After a carbohydrate-containing meal, an ideal AP system would bring plasma glucose levels back to baseline nearly as quickly as an endogenous pancreas; however, with sensor lag in SC CGM devices and slow SC insulin pharmacokinetic and pharmacodynamic properties, there will inevitably be time spent in hyperglycemia following the meal. Reduction of delays in the feedback loop for the AP has been shown to provide quantitative improvements in controller performance [188]. In Chapter 4 of this dissertation, the mathematical model for glucose sensing kinetics developed in this study is used to inform an *in silico* evaluation of the benefits of IP sensors for closed-loop control with an AP in combination with IP insulin delivery.

As described in the introduction, the decision of where to place *in vivo* glucose sensors involves a trade-off between rapid access to plasma glucose, durability with respect to avoidance of tissue effects, and invasiveness-related complications. The IP space may optimize this trade-off, as previous work has shown that the IP space has an excellent safety profile, with no peritonitis across 63 patients over 381 patient years of implantation [180]. While the safety risk profile will not be identical, since the sensor does not deliver a hormone with growth-like properties, we do expect a sensor to have a nearly identical safety risk profile. Furthermore, unlike catheters placed in the central vasculature, which have been found to occlude in up to 36% of patients within 1-2 years [189], peritoneal dialysis catheters have been found to have a mechanical failure rate of only 0.5% over 21 months when the catheter is placed in

the true pelvis beyond the reach of the omentum [190]. In addition, while this space would have very little, if any, inherent lag, central venous catheters place patients at risk for long-term vascular complications related to catheter-related thrombosis which occurs in up to 50% of children and 66% of adults with a long-term central venous catheterization [189].

However, tissue effects are still a potential problem, particularly with catheters placed in the upper quadrants of the peritoneal cavity. Haveman also showed that in the absence of a mechanism to prevent encapsulation, 49 re-operations were required in 63 patients over 381 patient years for catheter clogging [180]. Thus, although the development of encapsulation in the IP space is much slower than in the SC space, it is still an issue that needs to be contended with, in order to realize the goal of a long-term, fully-implanted, durable AP. Additionally, although the IP space is more mechanically protected than the SC space (by virtue of being further from intrusion by objects in the environment), the IP space does experience mechanical motion and pressure fluctuations during normal activities such as breathing and peristalsis which may impact signal stability.

3.5 Long-term Sensor Evaluation

The direct comparison between SC and IP enzymatic glucose sensors presented in this chapter demonstrated that the IP sensors had a smaller dynamic lag than the SC sensors. However, in order to be used in a fully implantable AP, the IP sensor would need to maintain this same level of responsiveness over long periods of implantation on the order of one year. Tissue encapsulation is known to deteriorate the performance of long-term implantable SC continuous glucose monitors (CGMs), preventing these devices from meeting the functionality requirements for widespread

use and creating a bottleneck in AP development [23, 191]. While recent studies of implanted SC sensors have shown promising results, there is still much room for improvement, including the reduction of encapsulation-induced sensor lag [30, 152]. We present a proof-of-concept study of a novel flushing-assembly developed by our collaborators at TheraNova, LLC to routinely clean the sensor surface of an IP-placed sensor, thereby prolonging its lifetime, while also taking advantage of the smaller sensing lag in this space. Placing the sensor in the IP space allows flushing with saline that would not be possible in the restricted SC space.

Fluorescent glucose sensors were implanted in the SC or IP space of sheep. Sensors were provided by the manufacturer in a lengthened, tethered format. The IP sensors were modified with silicone tubing, flush port, Dacron cuff, and adaptors to allow flushing with saline solution. Experiments were conducted under an IACUC-approved protocol by BioSurg, Inc. (Davis, CA). After preliminary testing to optimize the flushing procedure, long-term responsiveness was evaluated with an IP sensor placed in one sheep and an SC sensor placed in a second sheep. The IP sensor was flushed weekly with saline. Glucose response challenges were performed periodically over three months by infusing 0.5 g/kg dextrose through an ear vein over 60 seconds (13 challenges over 114 d for IP, 9 challenges over 91 d for SC). The results are summarized in Figure 3.7.

The IP sensor demonstrated anomalously slow response during the first challenge (day 8) due to tissue trauma following implantation, which is known to cause inflammatory response [152]. Excluding day 8, the IP sensor maintained consistent responsiveness throughout the 114 d period, with time to half-maximum ($t_{1/2}$) between 2.7-4.7 min and time to maximum (t_{max}) between 11.6-17.2 min. Conversely, the non-flushed sensor in the SC space gradually lost responsiveness, with $t_{1/2}$ between 2.6-13.5 min and t_{max} between 9.7-72 min. By 91 d following implantation, the

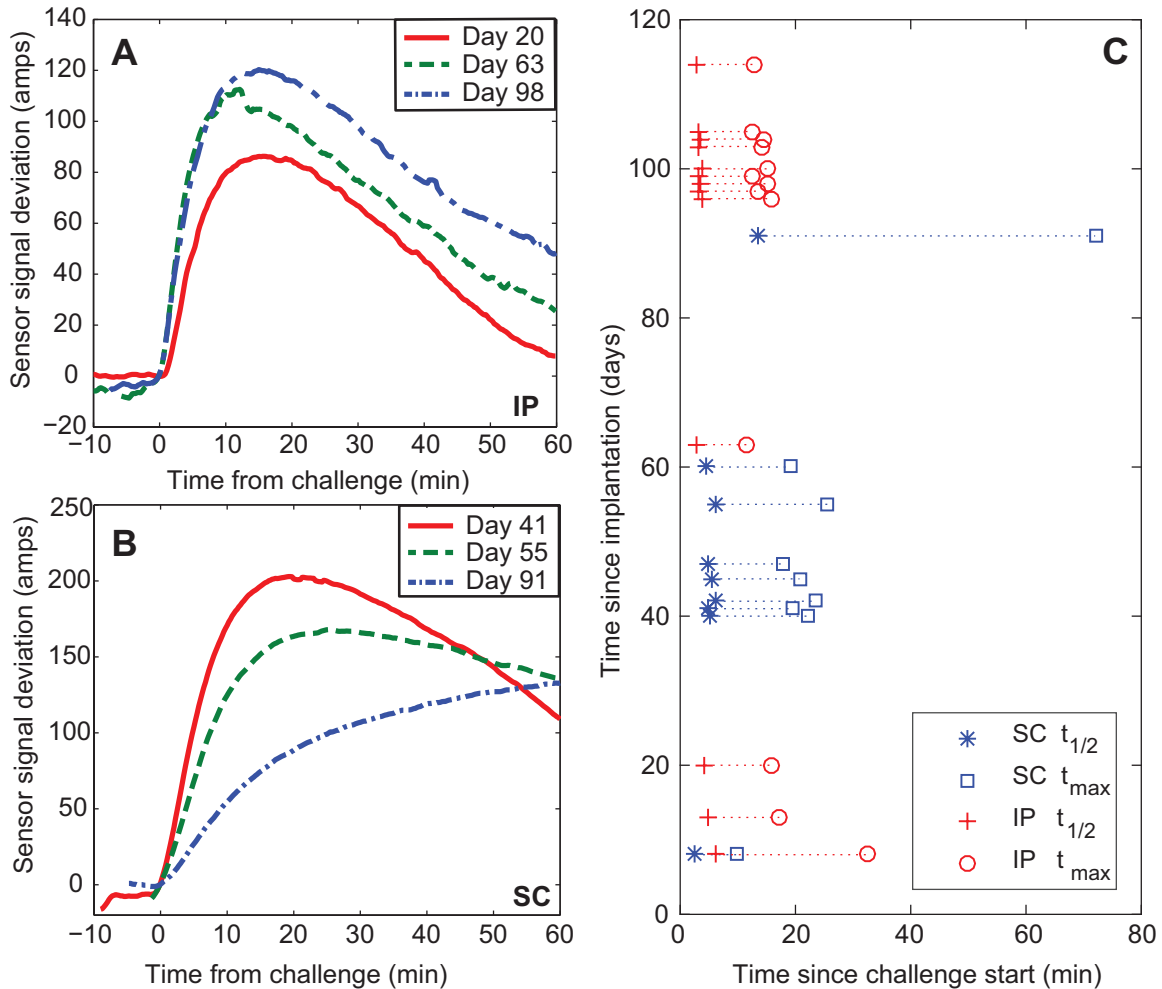


Figure 3.7: Demonstration of the sensor signal response to intravenous glucose challenge. (A) Representative signal response curves to IVGTT from sensor in the IP space which was flushed. The solid, dashed, and dash-dot lines represent days 20, 63, and 98, respectively. (B) Representative signal response curves to IVGTT from the sensor in the SC space without flushing. The solid, dashed, and dash-dot lines represent days 41, 55, and 91, respectively. (C) The number of days since insertion for each challenge is indicated on the y-axis, while the time-course of the challenge is shown on the x-axis. The time at which the signal reached half-maximum is indicated by a blue star for SC and a red plus sign for IP. The time at which the signal reached maximum is indicated by a blue square for SC and a red circle for IP. The length of the dotted line connecting each pair of points shows the amount of time that passed between reaching half-maximum and reaching maximum.

SC sensor signal did not peak within the 60 min testing period (see Figure 3.7B).

The development of long-term implantable CGMs is a key step toward making this technology more practical; however, CGM performance is hindered by diffusion lag and loss of sensitivity caused by encapsulation driven by the foreign body response [152, 191]. The IP space has already been shown to be valuable to AP applications, with experimental evidence showing both faster insulin action and faster glucose sensing in this space [19, 38]. The performance of the flushed IP sensor presented here far exceeded that of the conventional SC sensor, showing promise for further investigation of the flushing method. Further studies with a larger sample size will be needed to confirm this effect.

3.6 Conclusions and Future Work

The IP space shows promise for glucose sensing as part of a fully implantable AP. A direct comparison in an animal study showed that sensors placed in the IP space have about half of the dynamic lag of sensors placed in the SC space of the same animal. In order to make the IP sensor practical for long-term implantation, it needs to have protection from tissue encapsulation. A proof-of-concept study introduced the use of a flushing mechanism to allow CGM in the IP space with consistent responsiveness during 3 months *in vivo*. This flushing mechanism will be investigated in further studies with larger sample sizes and control sensors to verify its efficacy in preventing encapsulation. Future iterations of this system will utilize automated flushing of the sensing element with small volumes of fluid drawn from the patient's bodily fluids. Data generated from the studies presented in this chapter will guide the development of an IP CGM to enable an implantable AP and improve practicality of CGM use for day-to-day diabetes therapy. In the following chapter, the effect of

sensor lag on the closed-loop AP is considered.

3.7 Acknowledgments

I gratefully acknowledge the contributions of my collaborators from TheraNova, LLC to this chapter and corresponding publications [38, 148]. Dr. Daniel Burnett and Dr. Brett Mensh designed and conducted the experiments to provide the experimental data for the modeling analysis. They also contributed to discussions that informed the data analysis strategy and to the writing of the publication.

Chapter 4

Impact of Glucose Sensing Dynamics on the Artificial Pancreas¹

4.1 Introduction

As introduced in previous chapters, the artificial pancreas (AP) comprises a control algorithm, an insulin pump, and a glucose concentration sensor. The system is depicted by the block diagram in Figure 4.1. The control algorithm delivers insulin to maintain the blood glucose concentration (BG) within the clinically desired range. The performance of the AP is constrained by the physical limitations introduced by the choice of location for the insulin pump and glucose sensor. Most clinically tested AP devices have used subcutaneous (SC) insulin delivery and glucose sensing devices, which are minimally invasive and commercially available for use [1, 193]. However, as discussed in the previous chapter, the SC route introduces transport processes in both the absorption of insulin from the SC space to

¹Portions of this chapter are reproduced from L. M. Huyett, E. Dassau, H. C. Zisser, and F. J. Doyle III, "Impact of glucose sensing dynamics on the closed-loop artificial pancreas," *2015 American Control Conference (ACC)*, Chicago, IL, 2015, ©2015 IEEE, and portions were submitted for publication in *IEEE Control Systems* on 31 May 2016 [192].

the blood and the diffusion of glucose from the blood to the SC space, adding time lags to the control loop [1, 18, 186]. For this reason, most AP systems are not fully automated; instead, the system requires the user to manually enter the amount of carbohydrates in a meal before eating it to trigger a bolus of insulin. Such hybrid systems have been recently evaluated in clinical studies using model predictive control (MPC), proportional-integral-derivative control (PID), and fuzzy logic control schemes. These AP designs have been able to achieve an average of 68%-81% of time in the range 70-180 mg/dL, depending on the protocol, length of closed-loop, degree of supervision, and controller design [66, 67, 80, 106, 115, 119].

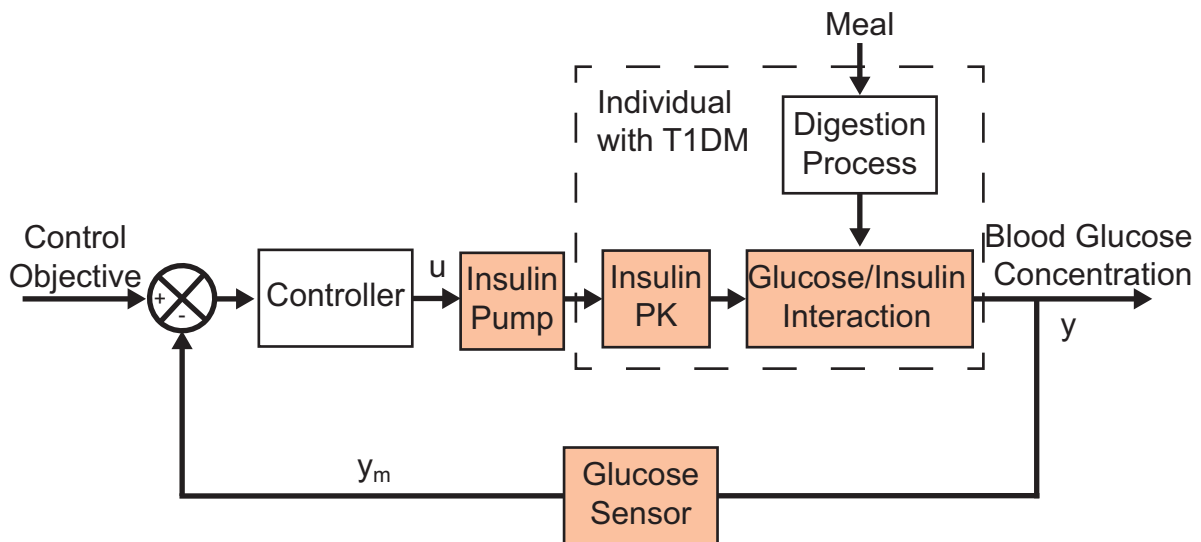


Figure 4.1: Block diagram representation of the artificial pancreas. The controller receives the measured glucose concentration, y_m , and compares it to the control objective. The controller then determines the desired insulin dose, u , and sends it to the insulin pump. Depending on the insulin delivery route, the insulin is absorbed into the bloodstream with a specific pharmacokinetic (PK) profile. The insulin then acts to change the glucose concentration, which is affected by other disturbances such as meals. The blood glucose concentration is measured by the sensor. Depending on the sensor type and placement, the transfer function may have a different characteristic time constant. The shaded blocks show the parts of the process that can be changed through pump and sensor site selection.

In order to improve the percentage of time spent in the desired range, it may be necessary to alter the system design. For example, there are means to reduce the lags observed with the SC route, such as implanting the pump and/or sensor in the intraperitoneal (IP) space. This location is closer to major vasculature, which increases the speed of glucose diffusion and insulin absorption as compared to that observed in the SC space. Insulin delivery through the IP route has been shown to reduce the frequency of hypoglycemic episodes and improve the glycemic control of people with type 1 diabetes mellitus (T1DM) [194–196]. Additionally, as presented in the previous chapter, placing the sensor in the IP space has been shown to reduce the lag associated with the glucose measurement. However, the benefit of this placement must outweigh the cost of increased invasiveness [19, 38]. Devices in the IP space require surgery to conduct the placement, while SC devices are primarily external and involve only a small transcutaneous insertion that can be done by the patient.

The improvement in AP performance gained by decreasing the insulin pharmacokinetic time constant was quantified in a previous study [188]. Additionally, improved controller performance has been observed in clinical studies using IP or inhaled insulin, which are both associated with faster pharmacokinetic and pharmacodynamic properties than the SC space [73, 90, 197]. In this chapter, a complementary study to [188] is performed to quantify the impact that glucose sensing lag has on an AP that uses either SC or IP insulin delivery.

4.2 Continuous Glucose Sensing

4.2.1 Modeling the Sensor Response

As discussed in the previous chapter, the diffusion process between the blood and the ISF means that the concentration measured by the glucose sensor may lag behind the BG, especially when the BG is increasing or decreasing at a high rate of change. A two-compartment model can be used to represent the glucose diffusion process and quantify this lag. The sensing dynamics can be expressed as a transfer function in the Laplace domain as initially introduced in Chapter 3:

$$G_S(s) = \frac{Y_m(s)}{Y_{IV}(s)} = \frac{K_S e^{-\theta_S s}}{\tau_S s + 1} \quad (3.6)$$

where $Y_m(s)$ and $Y_{IV}(s)$ are the Laplace transforms of the sensor measurement (mg/dL) and the BG (mg/dL), respectively. The identifiable parameters in this transfer function model are the sensor time constant τ_S (min), the time delay θ_S (min), and the model gain K_S . Note that from this point onward, θ_S will be set to zero, since it was found to be negligibly small through experimental evidence [38]. Also, the sensor measurement is expected to equal the BG measurement at steady-state when the sensor is calibrated properly, so the gain K_S is set to 1. The resulting simplified model of sensor dynamics is:

$$G_S(s) = \frac{1}{\tau_S s + 1}. \quad (4.1)$$

Since the most challenging aspects of AP design involve time periods where the BG is changing rapidly (after meals or during exercise), the filtering effect of the sensor dynamics is expected to have a detrimental impact on the control quality. This effect is demonstrated in the Bode plot in Figure 4.2. The smaller the sensor lag is, the

higher frequencies of input can be tolerated without losing response tracking.

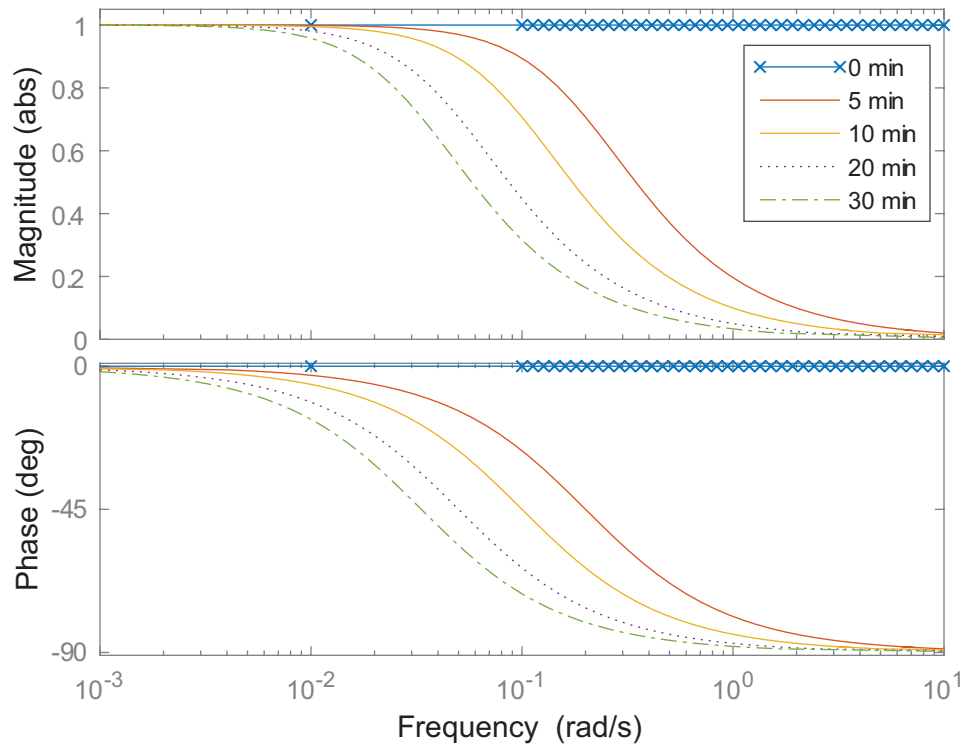


Figure 4.2: Bode plot showing the deterioration of sensor response for values of τ_s from 5 to 30 min. The smaller the sensor lag is, the higher frequencies of input can be tolerated without losing response tracking.

Placing the sensing mechanism in a more highly vascularized area, such as the IP space, has been shown to facilitate more rapid sensing of glucose changes. The experimental data presented in Chapter 3 was used to quantify the dynamic response of glucose sensors placed in either the SC or the IP space of non-diabetic swine. This animal model is often used for studies that require a model of the human endocrine system. The data showed that the sensors implanted in the IP space of swine had faster dynamics than the SC sensors placed in the same animal. The distribution of fitted time constants of the model in Equation (3.6) for sensors in each space was 5.6 ± 2.9 min for the IP sensors and 12.4 ± 3.6 min for the SC sensors [38]. In general,

the IP sensors had a lower mean time constant and a tighter distribution, while the SC sensors had a higher mean time constant and wider distribution. Data from a human clinical study found that SC sensors have time constants ranging from 2 to 20 min [55]. Lastly, the results of a tracer kinetics study showed that the time constant in the SC space for people with T1DM was 11.0 ± 3.3 min [53].

In the computational work presented in this chapter, τ_S is varied to investigate a wide range of sensor dynamics (0 to 30 min) using the model in Equation (4.1). The intent is not to replicate a specific sensor placement, but to interrogate the relationship between sensor lag and AP performance. In general, SC sensors that are already in use are expected to be on the higher end of the lag distribution, while IP sensors that are in development are expected to have a smaller lag [38]. An ideal BG sensor is represented by the case when $\tau_S=0$ min.

4.2.2 Dynamic Measurement Error

Dynamic lags in the measurement process lead to error between the true and measured BG values. One measure of this error can be computed by determining the measurement response to a ramp input [70]. The ramp should be selected to have the maximum rate of change that is expected for the process. For a ramp of slope a , the upper bound on the error is given by

$$\epsilon_{max} = |y_m(t) - y_{IV}(t)|_{max} \quad (4.2)$$

where $y_{IV}(t) = at$ (a ramp input in blood glucose concentration). The time-domain response to a ramp for a transfer function with first-order dynamics and unity gain, such as that in Equation (4.1), is determined by substituting the Laplace transform of the ramp ($Y_{IV}(s) = \frac{a}{s^2}$) into Equation (4.1) and taking the inverse Laplace transform

to get:

$$y_m(t) = a\tau_S(e^{-t/\tau_S} - 1) + at. \quad (4.3)$$

By substituting Equation (4.3) into Equation (4.2), the error reduces to

$$\epsilon_{max} = |a\tau_S(e^{-t/\tau_S} - 1)|_{max}. \quad (4.4)$$

The maximum error occurs when $t \gg \tau_S$, giving

$$\epsilon_{max} = |a\tau_S|. \quad (4.5)$$

The maximum rate of change expected in glucose concentration data can be estimated as between an absolute value of 4 and 5 mg/dL/min, as seen in clinical data [102, 198]. The upper bounds on the measurement error given a ramp of 4 and 5 mg/dL/min for sensor time constants ranging from 5 to 30 min are shown in Table 4.1. Reducing the glucose sensor lag will reduce the upper bound on the dynamic measurement error in a linear relationship.

The upper bound on the error provided by Equation (4.5) is a conservative estimate for BG monitoring applications, where the rate of change is unlikely to continue at the maximum value for times $t \gg \tau_S$. Therefore, it is useful to consider the transient error response to a ramp of maximum slope lasting 15 min. Figure 4.3 shows the transient response for simulated glucose sensors with τ_S equal to 5, 10, 20, and 30 min for a BG ramp of slope -4.5 mg/dL/min. The starting glucose concentration is set to 130 mg/dL. After 15 min, the BG has crossed the threshold into hypoglycemia; however, none of the simulated sensors would have detected this safety risk at the time it happened. Detection of rapid changes in BG is critical to the AP, especially if the change presents a safety risk such as hypoglycemia. Figure 4.3 demonstrates the

Table 4.1: Summary of dynamic error characteristics resulting from simulated glucose sensors with different values of τ_S . Sensor measurements are simulated based on experimental BG data (clinical data from [72], clinicaltrials.gov ID NCT01472406).

	τ_S (min)			
	5	10	20	30
ϵ_{max} (mg/dL)				
$a = 4$ mg/dL/min	20	40	80	120
$a = 5$ mg/dL/min	25	50	100	150
MARD (%)	1.9	3.6	6.4	8.6
Clarke Zone (%)				
A	98.9	98.4	95.5	90.1
B	1.1	1.6	4.5	9.7
C	0	0	0	0
D	0	0	0	0.16
E	0	0	0	0
A+B (%)	100	100	100	99.8

danger of a lagging sensor measurement, which produces an error that is correlated in time and becomes larger for higher rates of change.

The measurement error due to dynamic sensor lag that would occur for typical BG trajectories can be investigated using retrospective analysis of data from a previous clinical study. During a 24 h clinical evaluation of an AP device in 12 subjects, BG measurements were taken every 30 min, or every 15 min during exercise and hypo- or hyperglycemic episodes [72]. This study is registered on clinicaltrials.gov with clinical trial registration number NCT01472406. The BG measurements were taken from venous blood using a YSI 2300 STAT PlusTM glucose and lactate analyzer (Yellow Springs Instruments, Yellow Springs, OH), which is considered to be the gold standard in glucose measurement. Using this data and the sensor model in Equation (4.1), measurements from sensors with different time constants were simulated. An example of the experimental YSI measurements and simulated sensor measurements for one subject are shown in Figure 4.4.

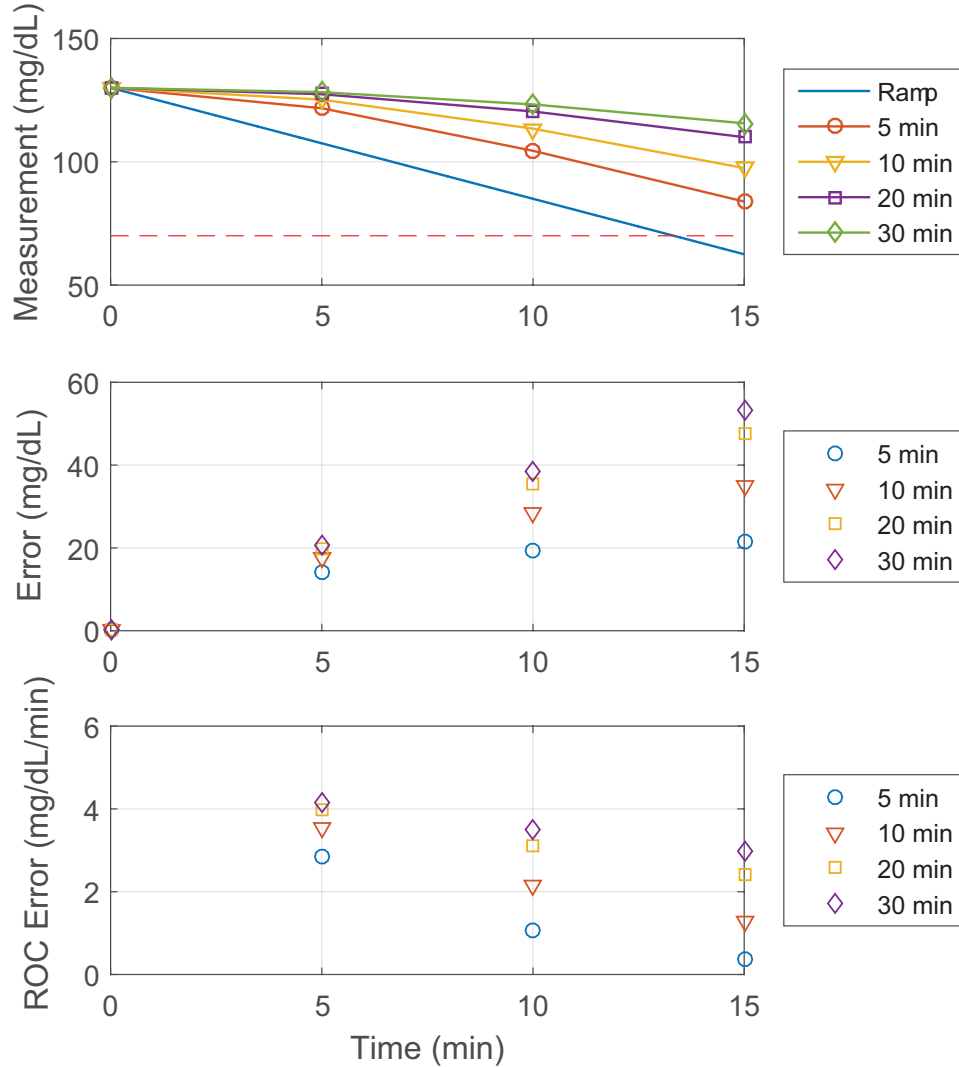


Figure 4.3: Error introduced by a sensor lag in the transient time response for a ramp BG change with slope -4.5 mg/dL/min. The red dashed line shows the hypoglycemia threshold of 70 mg/dL/min. The varying values of τ_S are represented by symbol type and color. The symbols indicate the sampling time of a glucose sensor, which is 5 min. (Top) The ramp BG and simulated sensor measurements over time. (Middle) The error between the ramp BG and the simulated sensor measurements. (Bottom) The error between the rate of change estimated from the sensor versus the rate of change of the ramp BG.

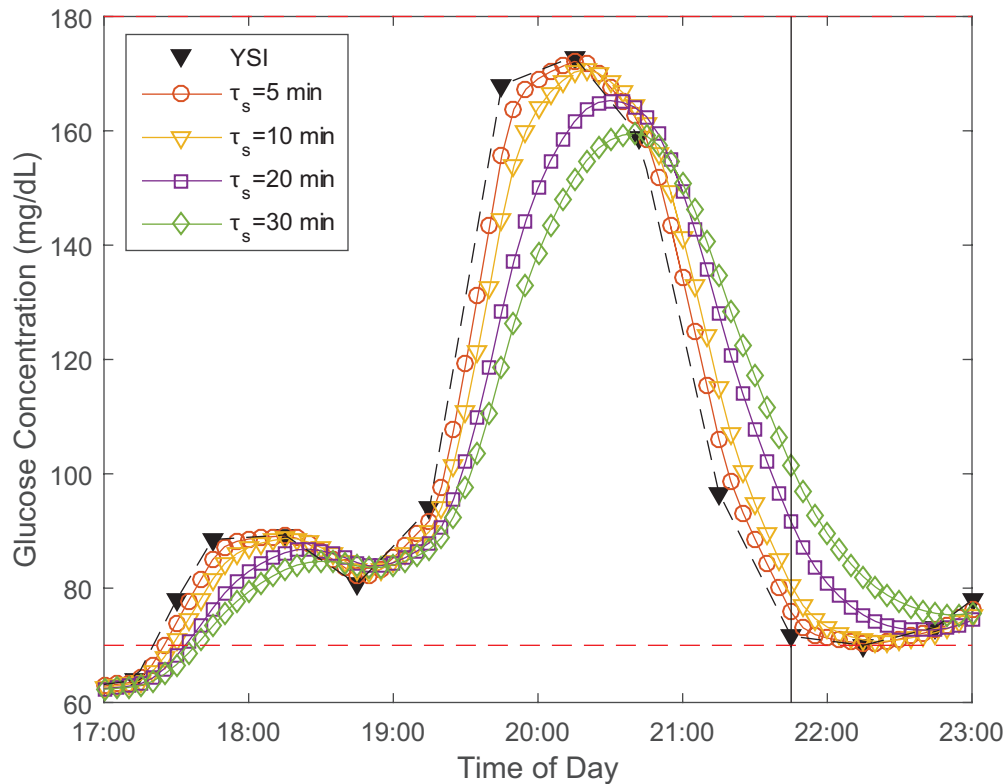


Figure 4.4: Blood glucose measurement data from a clinical trial of an AP. Simulated sensor measurements with different dynamic lags are shown with different types of icons. The vertical black line can be used to visualize the offset between the BG measurement and the sensor measurement at a given instant in time during a decrease toward hypoglycemia (clinical data from [72], clinicaltrials.gov ID NCT01472406).

A histogram of the error between BG measurement and simulated sensor measurement is shown in Figure 4.5. The mean absolute relative difference (MARD) is typically used to characterize glucose sensor error during a given time period. This measure is calculated as

$$MARD = \frac{1}{n} \sum_i^n \frac{|y_{m,i} - y_{IV,i}|}{y_{IV,i}} \times 100. \quad (4.6)$$

The MARD for each simulated sensor run on the clinical data is shown in Table 4.1. As seen in the table, the MARD ranges from 1.9% to 8.6% for a τ_S of 5 to 30 min. The MARD is considered an important value when reporting glucose sensor accuracy, and may determine whether the glucose sensor can be used as a replacement for capillary blood measurements to determine insulin dosing. For example, it is stated in [20] that glucose sensors must reach a MARD below 10% before they can be cleared for use in determining insulin dosage.

While the MARD gives a general idea of the glucose sensor performance, it does not demonstrate how that error might affect control action. For this reason, the sensor readings were examined using a Clarke Error Grid to determine the clinical implications of the error [52]. The simulated glucose sensor measurements were plotted against the corresponding reference measurements on a graph that was divided into five zones, as shown in Figure 4.6. The zones are: A, where the glucose sensor measurement was within 20% of the reference; B, where the error was greater than 20% of the reference, but the treatment determined from the glucose sensor and reference would have been the same; C, where unnecessary treatment would have been given that could have led to dangerous hyperglycemia or hypoglycemia; D, where dangerous hyperglycemia or hypoglycemia would have gone undetected; and E, where the treatment given would have been the opposite of the required treatment [52].

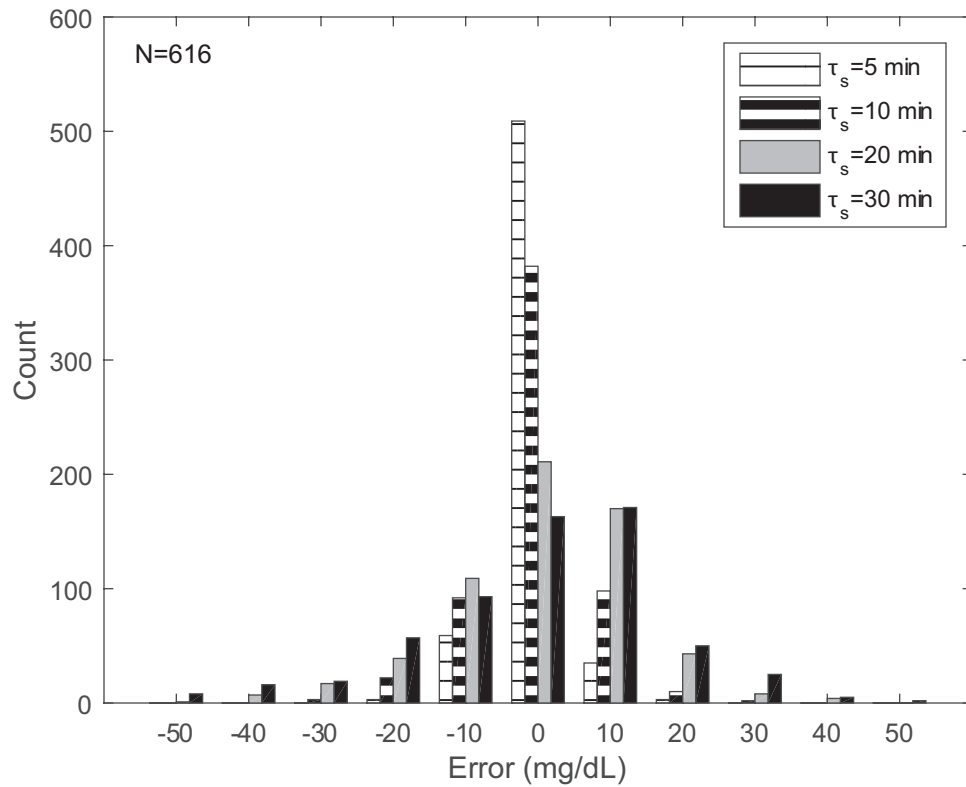


Figure 4.5: Histogram of the error induced by dynamic sensor lag for simulated sensors and experimental BG data. The error distribution becomes wider with higher sensor lag (clinical data from [72], clinicaltrials.gov ID NCT01472406).

According to one source, the percentage of points in the A and B zones should be higher than 98% to be acceptable [23].

As shown in Figure 4.6 and Table 4.1, 100% of points fell within the A or B zones for values of τ_S from 5 to 30 min. Therefore, as shown by the MARD and the Clarke Error Grid, the point-wise error caused by the dynamic sensor lag does not exceed limits for clinical usability. However, the dynamic nature of the error is expected to cause problems for the artificial pancreas, which relies on the glucose trajectory over time to make accurate and timely insulin dose recommendations. A lag in the measurement will lead to a lag in the controller action, especially when responding to large disturbances such as meals. In the following sections, control theory and simulation studies are used to quantify the effect of sensor lag on an artificial pancreas controller.

4.3 Controller Design and Tuning

Following an analogous approach to the one outlined in [188], a model-based PID controller design was chosen in this study to highlight the effects of sensor dynamics on control quality. The following third-order discrete-time model of insulin action on BG has been previously identified, with different parameters to represent either IP or SC insulin delivery [199, 200]:

$$M_D = \frac{K(TDI)^{-1}z^{-3}}{(1 - a_1z^{-1})(1 - a_2z^{-1})^2} \quad (4.7)$$

where TDI (U) is the total daily insulin dose of the patient and the sampling time is 5 min. The inclusion of the total daily dose allows the gain to be personalized based on each individual patient's response to insulin. The model parameters are given in

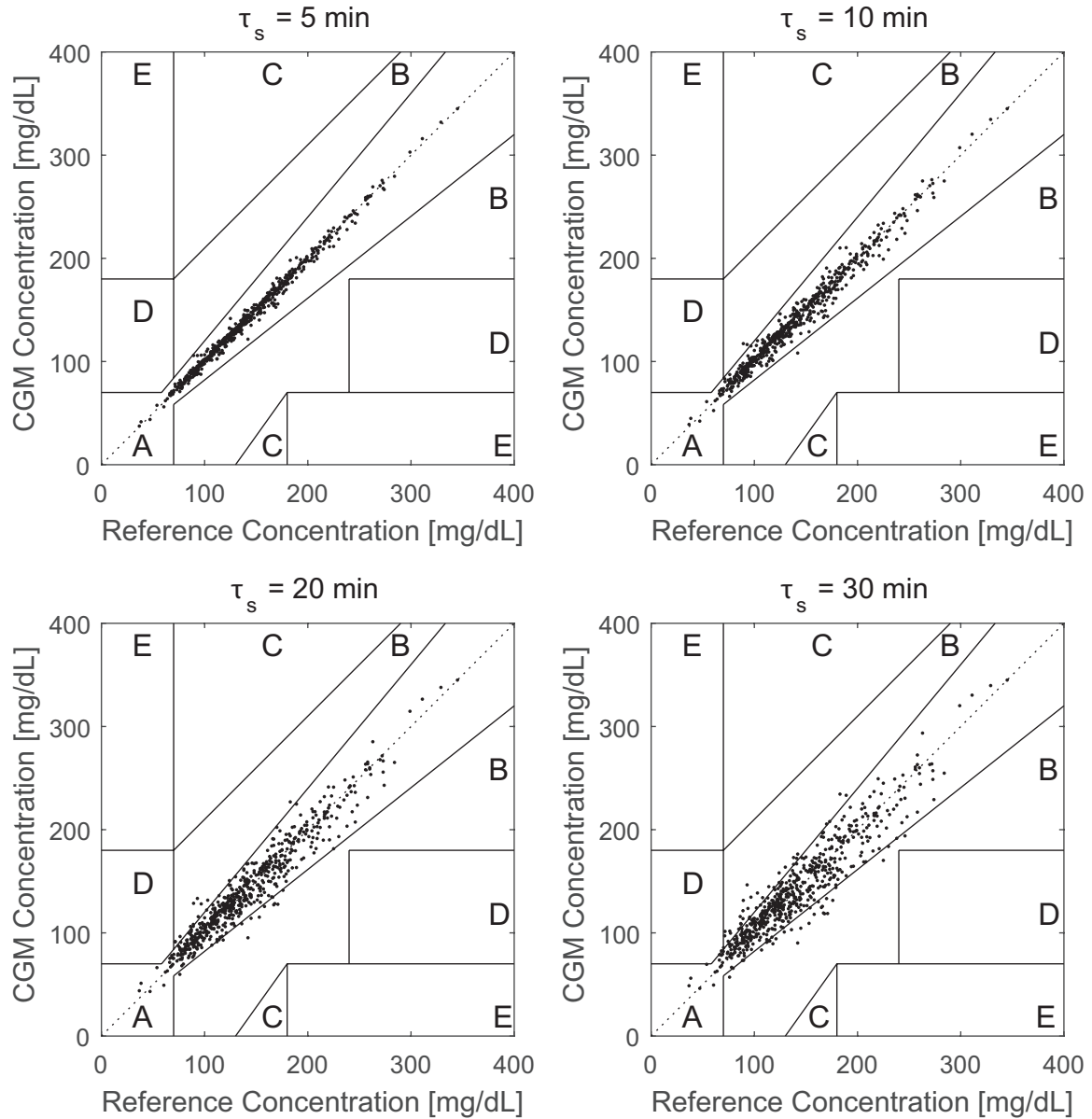


Figure 4.6: Clarke Error Grid for simulated sensors with different lags. The grid shows that for values of τ_s from 5 to 20 min, all of the points fall into the A+B (acceptable error) zones. For τ_s equal to 30 min, 99.8% of points fall into the acceptable error zones, with 0.16% in the D zone (clinical data from [72], clinicaltrials.gov ID NCT01472406).

Table 4.2, based on previous work [199–201].

Table 4.2: Parameters for the discrete, continuous, and reduced models of IP and SC insulin action. Reprinted from [202].

	Discrete			Continuous		
	K (h·mg/dL)	a_1	a_2	K' (h·mg/dL)	τ_1 (min)	τ_2 (min)
IP	-15	0.98	0.75	-12000	247	17
SC	-0.30	0.98	0.965	-12294	247	140

	Reduced		
	$\hat{\tau}_1$ (min)	$\hat{\tau}_2$ (min)	$\hat{\theta}$ (min)
IP	247	26	11
SC	247	210	73

The model was converted to continuous time using the zero-pole matching method [203] to obtain the following third-order continuous model:

$$M_C = \frac{K'(TDI)^{-1}}{(\tau_1 s + 1)(\tau_2 s + 1)^2}. \quad (4.8)$$

The parameters for the resulting continuous model are also shown in Table 4.2. The third-order model was then reduced to a second-order model using Skogestad's half rule [204] to obtain

$$G = \frac{K'(TDI)^{-1} e^{-\hat{\theta}s}}{(\hat{\tau}_1 s + 1)(\hat{\tau}_2 s + 1)}, \quad (4.9)$$

where the reduced-order model parameters are determined by the following relations:

$$\hat{\tau}_1 = \tau_1, \hat{\tau}_2 = \tau_2 + \frac{\tau_2}{2}, \text{ and } \hat{\theta} = \frac{\tau_2}{2} + \frac{\Delta t}{2}, \quad (4.10)$$

with the resulting reduced model parameters included in Table 4.2. Here, Δt is the

sampling time that will be used in the implementation of the controller. The controller parameters were determined from Equation (4.9) using internal model control tuning rules. Internal model control is a model-based controller design method developed to give an analytical expression for a controller based on a dynamic model of the process [70]. The design process leaves a single tuning knob, the characteristic time constant τ_C , which sets the robustness of the controller. Internal model control design for a second-order transfer function model yields an equivalent PID controller, so direct relations between the model parameters and the PID tuning parameters can be expressed [70]:

$$K_C = \frac{\hat{\tau}_1 + \hat{\tau}_2}{K'(TDI)^{-1}(\tau_C + \hat{\theta})} \quad (4.11)$$

$$\tau_I = \hat{\tau}_1 + \hat{\tau}_2 \quad (4.12)$$

$$\tau_D = \frac{\hat{\tau}_1 \hat{\tau}_2}{\hat{\tau}_1 + \hat{\tau}_2}. \quad (4.13)$$

The choices for τ_C in this study were determined from the dominant time constants (τ_{dom}) of the IP and SC models, which were found by inspection of the step response to be 285 and 564 min for the IP and SC systems, respectively. Values for τ_C were selected as $\tau_{dom}[0.1, 0.3, 0.5, 0.7]$ as indicated by the tuning guidelines in [70]. The PID controller was then implemented using the discrete position form with a sampling time of 5 min:

$$u(k) = \bar{u} + K_C[e(k) + \frac{\Delta t}{\tau_I} \sum_{j=1}^k e(j) + \frac{\tau_D}{\Delta t}[e(k) - e(k-1)]] \quad (4.14)$$

where $u(k)$ is the insulin delivery computed by the controller (U/h), \bar{u} is the steady state insulin delivery rate (U/h), K_C is the controller gain ([U/h]/[mg/dL]), τ_I is the integral time constant (min), τ_D is the derivative time constant (min), and $e(k)$ is the

difference between the glucose measurement and the setpoint of 110 mg/dL. While there is no obvious choice for setpoint based on physiology, 110 mg/dL was chosen because it is in the middle of the tight glycemic control range of 80-140 mg/dL. This setpoint has been used in previous AP designs, including in [188].

4.4 Frequency Response and Robustness Analysis

In order for the AP to be safe for clinical use, it must be robust to model uncertainty. The human body's reaction to insulin can vary depending on the time of day, hormonal changes, exercise, and other factors that are part of daily life. Changes in insulin sensitivity of up to 50% have been experimentally observed [205]. These changes can be considered as perturbations to the gain and delay of the nominal model. A controller is said to be robust if it is insensitive to differences between the actual system being controlled and the model of the system that was used determine the controller tuning parameters. Robustness is determined by checking that the system is stable and meets performance requirements even for the worst-case scenario of model uncertainty [206]. A robust design is crucial for AP applications, since the controller will be part of a medical device that needs to meet its design specifications even in the face of model uncertainty introduced between different patients or over time in the same patient.

4.4.1 Gain and Phase Margin

Gain and phase margins were used to perform a preliminary screening of the system robustness. These two measures are based on the frequency response analysis of the open-loop transfer function. The gain margin reflects how much the open-loop gain can increase before reaching instability, while the phase margin shows how

much the open-loop delay can increase before instability occurs.

4.4.2 Robust Stability and Performance

Robust stability and performance analysis is a more formal measure of system robustness to model uncertainty. The family of possible plants Π_I that exist given a nominal process model with specified uncertainty was represented using multiplicative uncertainty as follows:

$$\Pi_I : G_P(s) = G(s)(1 + w_I(s)\Delta_I(s)); \quad |\Delta_I(j\omega)| \leq 1, \quad \forall \omega \quad (4.15)$$

where G_P is a potential process model, and G is the nominal process model. The uncertainty weight fulfills the relation $|w_I(j\omega)| \leq l_I(\omega), \forall \omega$ where

$$l_I(\omega) = \max_{G_P \in \Pi_I} \left| \frac{G_P(j\omega) - G(j\omega)}{G(j\omega)} \right|. \quad (4.16)$$

The condition for robust stability (RS) is then given by:

$$RS \iff \|w_I T\|_\infty < 1 \quad \forall \omega \quad (4.17)$$

where T is the complementary sensitivity function and w_I is the multiplicative uncertainty weight as defined previously. The weight for parametric uncertainty in the gain and delay for the model in Equation (4.9) is given by

$$w_I = \frac{(1 + \frac{r_k}{2})\theta_{max}s + r_k}{\frac{\theta_{max}}{2}s + 1} \quad (4.18)$$

where $r_k = \frac{K_{max} - K_{min}}{K_{max} + K_{min}}$ and θ_{max} is the maximum uncertainty in the delay considered [206]. In this study, gains on the range $K_{nom}[1 - \delta, 1 + \delta]$ were considered, where

δ was allowed to vary from 0.1 to 0.9. The nominal gain K_{nom} was chosen as the non-personalized gain of -200 (mg/dL)/(U/h) [199–201]. The maximum delay uncertainty tested was 30 min.

The robust performance criterion is used to determine whether specified performance measures will be met in the presence of model uncertainty. The condition for robust performance (RP) is given by:

$$RP \iff \max_{\omega} (|w_P S| + |w_I T|) < 1 \quad (4.19)$$

where S is the sensitivity function. The performance weight w_P is given by

$$w_P(s) = \frac{\frac{s}{M} + \omega_B^*}{s + \omega_B^* A} \quad (4.20)$$

where M is the maximum peak of the sensitivity function, A is the steady state tracking error, and ω_B^* is the bandwidth frequency [206]. In this study, $A = 10^{-2}$, $\omega_B^* = 5 \times 10^{-5}$ rad/s, and $M = 2$. The value of A was chosen to be approximately zero because it is important for the controller to track the setpoint closely at steady state, even in the presence of model uncertainty. The value for M was chosen in accordance with the recommendation in [70]. The bandwidth frequency was selected based on the bandwidth of a closed-loop system using SC insulin delivery, which is the current state-of-the-art configuration used in clinical evaluations [1, 188].

4.4.3 Results and Discussion

The calculated gain and phase margins for varying values of τ_S and τ_C are shown in Tables 4.3 and 4.4. A Bode plot demonstrating the calculation of the gain and phase margin for IP insulin with $\tau_C = 0.1\tau_{dom}$ is shown in Figure 4.7. These values

show that increasing τ_S and/or decreasing τ_C reduces the margin for error before instability is reached. Overall, the IP system has higher margins than the SC system, which is due to the faster actuation available through the IP route.

Table 4.3: Gain margin for varying sensor time constants and tuning parameters. Reprinted from [202].

Intraperitoneal Delivery

$\tau_S \setminus \tau_C$	$0.1\tau_{dom}$	$0.3\tau_{dom}$	$0.5\tau_{dom}$	$0.7\tau_{dom}$
0 min	5.7	14	22	30
10 min	4.1	10	16	22
20 min	3.9	9.5	15	21
30 min	3.8	9.3	15	20

Subcutaneous Delivery

$\tau_S \setminus \tau_C$	$0.1\tau_{dom}$	$0.3\tau_{dom}$	$0.5\tau_{dom}$	$0.7\tau_{dom}$
0 min	2.8	5.2	7.6	10
10 min	2.5	4.7	6.8	9.0
20 min	2.3	4.4	6.4	8.4
30 min	2.2	4.2	6.1	8.0

A general recommendation for the gain and phase margin given in [70] states that a well-tuned controller will have a gain margin between 1.7 and 4.0 and a phase margin between 30° and 45° [70]. The gain and phase margins obtained for the controller design presented in this chapter are similar to those presented in [188], in which the impact of insulin pharmacokinetic and pharmacodynamic properties on the AP was evaluated. As in that study, the gain and phase margins in Tables 4.3 and 4.4 are within or higher than the range of published guidelines in [70] due to the conservative controller design required for safety in medical applications. Smaller values of gain and phase margin can lead to an oscillatory response, which must absolutely be

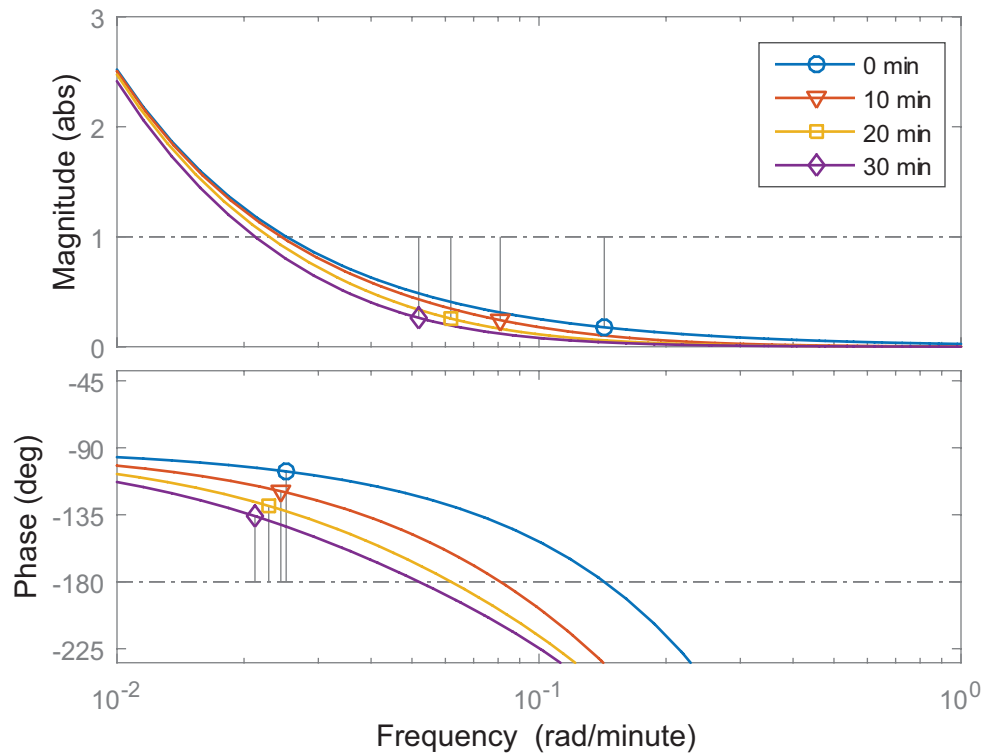


Figure 4.7: Bode plot demonstrating the calculation of the gain and phase margin for IP insulin. The plot is shown for $\tau_C=0.1\tau_{dom}$, and for various values of τ_S . The gain margin is calculated by $\frac{1}{AR_c}$, where AR_c is the magnitude at the critical frequency where the phase crosses -180° . The phase margin is calculated as $180+\phi_g$, where ϕ_g is the phase at the gain-crossover frequency where the magnitude equals 1 [70].

Table 4.4: Phase margin for varying sensor time constants and tuning parameters. Reprinted from [202].

Intraperitoneal Delivery

$\tau_S \setminus \tau_C$	$0.1\tau_{dom}$	$0.3\tau_{dom}$	$0.5\tau_{dom}$	$0.7\tau_{dom}$
0 min	74°	83°	86°	87°
10 min	61°	78°	82°	84°
20 min	51°	72°	79°	82°
30 min	44°	67°	75°	79°

Subcutaneous Delivery

$\tau_S \setminus \tau_C$	$0.1\tau_{dom}$	$0.3\tau_{dom}$	$0.5\tau_{dom}$	$0.7\tau_{dom}$
0 min	58°	73°	78°	81°
10 min	53°	70°	77°	80°
20 min	49°	68°	75°	79°
30 min	46°	66°	73°	77°

avoided in the AP system.

The robust stability analysis was conducted to determine how much model uncertainty in the gain and delay would be tolerated for a specified sensor time constant and controller tuning. The results are shown in Figure 4.8 (top panels). The results show that the system will remain stable for large model uncertainty for both IP and SC insulin, even with a sensor time constant of 30 min, for the most aggressive tuning tested ($\tau_C = 0.1\tau_{dom}$). For the larger three values of τ_C , robust stability is maintained for all gain and delay uncertainties tested.

Increasing the sensor time constant may cause a loss of robust performance even for small model uncertainty (Figure 4.8, middle and bottom panels). Thus, there is less tolerance for model uncertainty when the sensor time constant is increased, and it is possible that the robust performance specifications will not be met. In fact, the SC system does not meet robust performance specifications for gain uncertainties

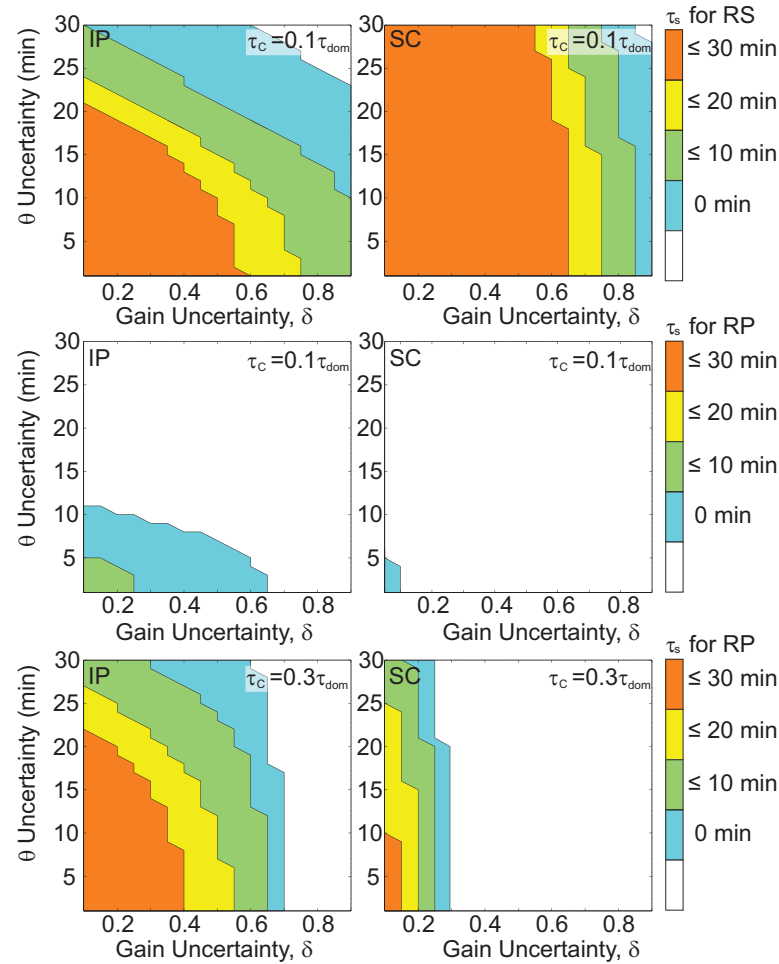


Figure 4.8: Gain and delay uncertainty allowed while still retaining robust stability and robust performance for various sensor time constants using IP and SC insulin. The top plot shows robust stability, while the middle and bottom plots show robust performance. The top and middle panels show the analysis for a fixed τ_C of $0.1\tau_{dom}$. Robust stability was met for large amounts of model uncertainty for both systems, but the IP system performance was more robust to model uncertainty than the SC system. The analysis was repeated for a more conservative τ_C of $0.3\tau_{dom}$, for which the robust performance results are shown (bottom panel). The robust stability results for $\tau_C = 0.3\tau_{dom}$ are not shown because the system was robustly stable for all conditions tested. Reprinted from [202].

greater than 0.1 when using the most aggressive tuning tested, even for the ideal sensor case. The same analysis for $\tau_C = 0.3\tau_{dom}$ shows that the SC system is able to retain robust performance for small amounts of model uncertainty. Overall, the IP system displays a higher robust performance than the SC system. This trend is expected as a result of the faster actuation afforded by IP insulin delivery.

Retaining stability in the AP system is of utmost importance, so it is encouraging to see that both the SC and the IP systems will be robustly stable even for large sensor time constants. Robust performance will be retained for low sensor time constants, but may be lost if there is too much lag in the glucose measurement. For this reason, more experimental data should be collected to determine the sensor lags present in systems being used in clinic, and new sensing methods that would provide a faster glucose measurement should be investigated. Two studies that have already been conducted to measure the lag between the intravascular and interstitial compartments of humans are presented in [58] and [57].

4.5 Simulation Studies

4.5.1 Methods

In silico tests were performed to evaluate the impact that sensor dynamics have on the time-domain performance of the AP. The simulations were conducted using the UVA/Padova metabolic simulator with ten unique simulated adult subjects with T1DM [207]. This simulator allows artificial pancreas controllers to be evaluated under many different scenarios to determine the best design before moving to clinical studies. The use of the simulator also allows controlled studies to be performed that would not be possible in real life, such as testing various specified sensor time

constants.

A block diagram depicting the simulation setup is shown in Figure 4.9. The intravenous port in the simulator was used to simulate IP insulin delivery. This approximation has been utilized previously, as the intravenous delivery in the simulator closely mimics IP delivery [200]. The sensor dynamics were implemented by passing the BG through the first-order model given by Equation 4.1 before sending the measurement to the controller. The sensor time constants tested, chosen to represent the range of experimental values observed in [38], were 0, 10, 20, and 30 min. The additive measurement noise was disabled in order to isolate the effects of the sensor dynamics on the controller performance. The protocol tested was a fasting period followed by an unannounced meal disturbance (output disturbance) consisting of 75 g of carbohydrates (CHO).

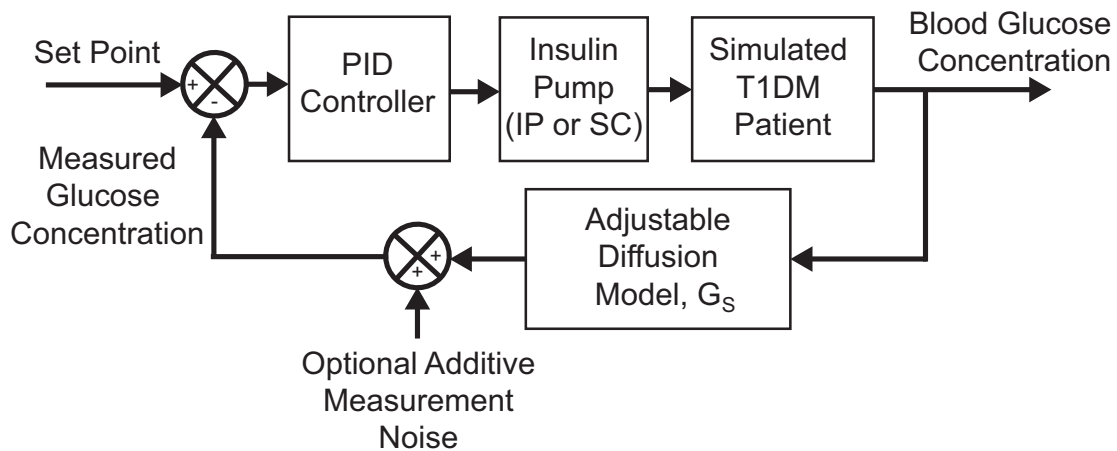


Figure 4.9: Block diagram showing the closed-loop simulation setup. The PID controller receives the error between the setpoint and the measured glucose concentration and sends an insulin dose to the simulated patient by using either the IP or SC delivery route. The resulting BG is passed through the glucose diffusion model with an adjustable time constant. Measurement noise can optionally be added before obtaining the measured glucose concentration. Reprinted from [202].

4.5.2 Results and Discussion

The data from one representative subject are shown in Figure 4.10. When the glucose measurement is delayed, it effectively filters the controller action. The peak insulin delivery is shifted later in time, and the overall response of the AP is more sluggish. The simulation results for all 10 subjects are summarized in Table 4.5. Presented in the table are the mean and standard deviation for the time spent in hyperglycemia ($BG > 180$ mg/dL, t_{hyper}), the area of the region below the glucose curve and above the 180 mg/dL hyperglycemia cutoff (AUC), the peak BG, and the minimum BG. For both IP and SC insulin delivery, increasing the sensor time constant significantly raised the maximum BG that was experienced, while it significantly lowered the minimum BG. This is the expected trend that would be caused by a lagging measurement.

More telling than the magnitude of the peak is the increased period of hyperglycemia caused by an increased sensor lag. The boxplot in Figure 4.11 shows the amount of time in hyperglycemia and AUC in hyperglycemia following the meal for the 10 simulated subjects using IP insulin. Both the time in hyperglycemia and the AUC in hyperglycemia increased greatly as the sensor time constant increased. For a sensor time constant as small as 10 min, the mean AUC was doubled when IP insulin delivery was used. The time spent in hyperglycemia increased by 21 ± 8 min for IP insulin and by 13 ± 3 min for SC insulin for a τ_s of 20 min as compared to the ideal sensor case. According to experimental data from [38] and [208], 20 min serves as a conservative estimate for the time constant of an SC sensor, so it would be possible to encounter this amount of lag in a clinical AP study. The cumulative time spent in hyperglycemia over a person's lifetime determines the severity of long-term health complications [7]. The increased hyperglycemia brought about by a lagging

Table 4.5: *In silico* performance measures for varying τ_S . The parameter $\tau_C = 0.1\tau_{dom}$. Reprinted from [202].

Intraperitoneal Delivery

τ_S (min)	t_{hyper} (min)	AUC (min·mg/dL)	Max BG (mg/dL)	Min BG (mg/dL)
0	38 ± 25	381 ± 343	192 ± 9	86 ± 5
10	50 ± 20*	761 ± 495*	202 ± 12*	83 ± 6*
20	59 ± 19*	1141 ± 670*	208 ± 14*	78 ± 7*
30	67 ± 19*	1508 ± 834*	213 ± 16*	72 ± 10*

Subcutaneous Delivery

τ_S (min)	t_{hyper} (min)	AUC (min·mg/dL)	Max BG (mg/dL)	Min BG (mg/dL)
0	107 ± 25	3643 ± 1829	231 ± 23	88 ± 5
10	113 ± 23*	4354 ± 2082*	237 ± 26*	80 ± 14
20	120 ± 22*	4957 ± 2329*	242 ± 28*	71 ± 17*
30	126 ± 22*	5510 ± 2577*	245 ± 30*	62 ± 17*

*Statistically different from $\tau_S = 0$ min by paired t-test.

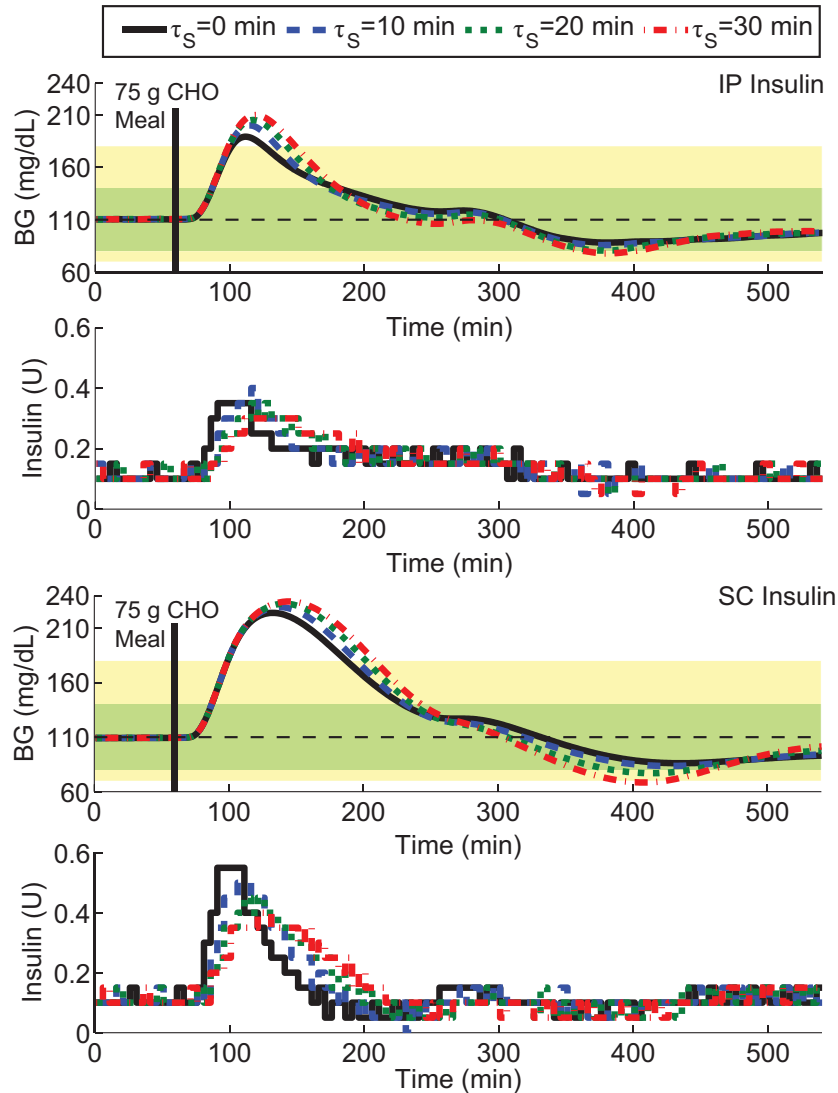


Figure 4.10: Representative result from one subject in the UVA/Padova metabolic simulator (adult subject 1) with four different values for the sensor time constant using (top) IP insulin and (bottom) SC insulin. In both cases, $\tau_C = 0.1\tau_{dom}$. The plot shows the glucose concentration and insulin delivery for one hour before and eight hours after an unannounced 75 g CHO meal disturbance. The green and yellow zones represent the tight clinical range (80-140 mg/dL) and safe clinical range (70-180 mg/dL) for the BG. The setpoint is shown by the horizontal dashed line at 110 mg/dL. Reprinted from [202].

measurement will add up each time there is a meal disturbance, and could result in a worse overall health outcome for the patient.

The effect of the characteristic time constant τ_C is demonstrated in Figure 4.12, which shows the results for the same representative subject as in Figure 4.10 for IP insulin using the four different values of τ_C . A larger value of τ_C leads to a slower and less aggressive response from the controller. A controller with a large value of τ_C is not able to respond in a timely manner to the rapid change in glucose caused by a meal. Using a smaller value of τ_C is desirable as long as the system will remain robust to model uncertainty and sensor lag.

Figure 4.13 shows a plot of the maximum versus minimum BG for all 10 subjects, with error bars showing the standard deviation. The plot includes three representative choices for τ_C based on the dominant time constant for each system. On this plot, improved controller performance is indicated by proximity to the lower left corner. In all cases, decreasing the sensor time constant improved the controller performance by moving the point on the plot down and to the left. The standard deviation spread also became narrower as the sensor time constant decreased, meaning that the system is more reliable for all subjects. An increased sensor lag is detrimental to SC control because it necessitates a more conservative tuning to be used to avoid dangerous hypoglycemia (BG < 70 mg/dL), at the expense of allowing more hyperglycemia.

A sensor with a small time constant would improve the ability of the AP to reject a meal disturbance. If a faster sensor is not available, other measures such as feed-forward action may be necessary to obtain the desired level of performance. For example, the user of the AP could announce that a meal is about to be consumed, which would cue the AP to deliver a preemptive dose of insulin. While this configuration is being used more often in clinical studies [1], it is not ideal because it involves a human in the loop, which could lead to safety risks. A faster sensor could

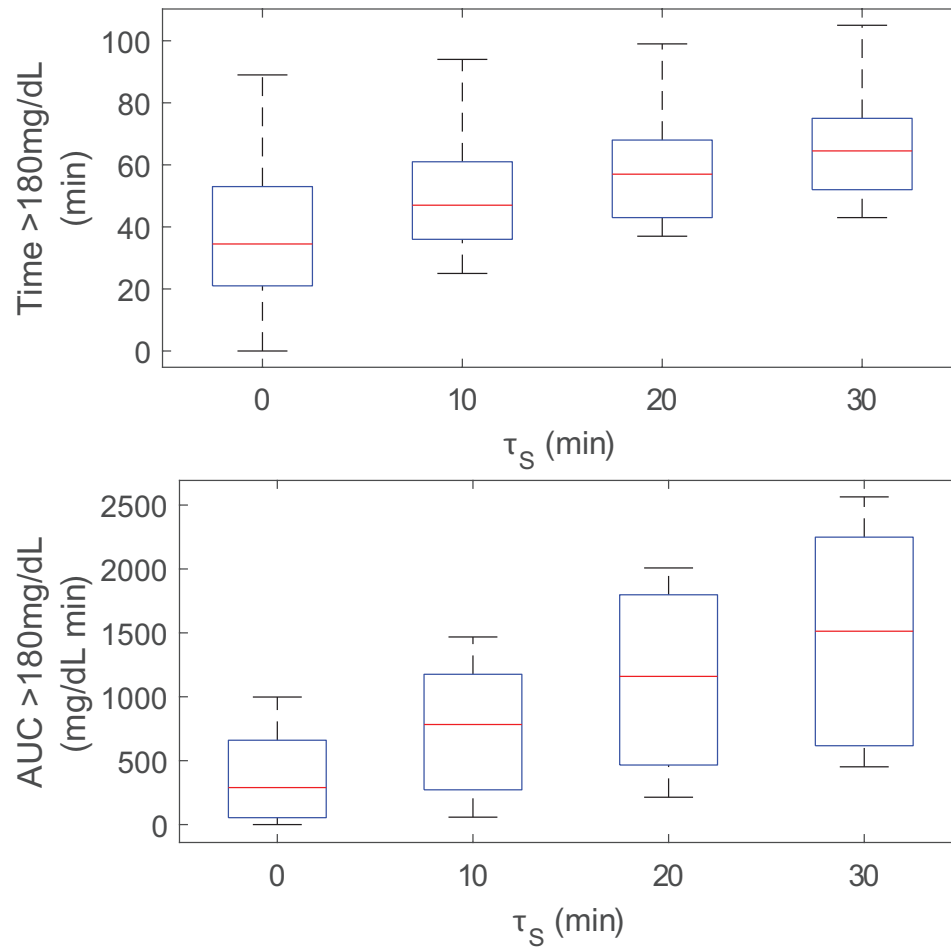


Figure 4.11: Boxplot showing the amount of time spent in hyperglycemia and the area under the curve in hyperglycemia for closed-loop control in 10 *in silico* subjects using IP insulin with $\tau_C = 0.1\tau_{dom}$. The results are compared for several different values of τ_S . The horizontal red line represents the median value, the blue box represents the interquartile range, and the vertical black bars represent the range.

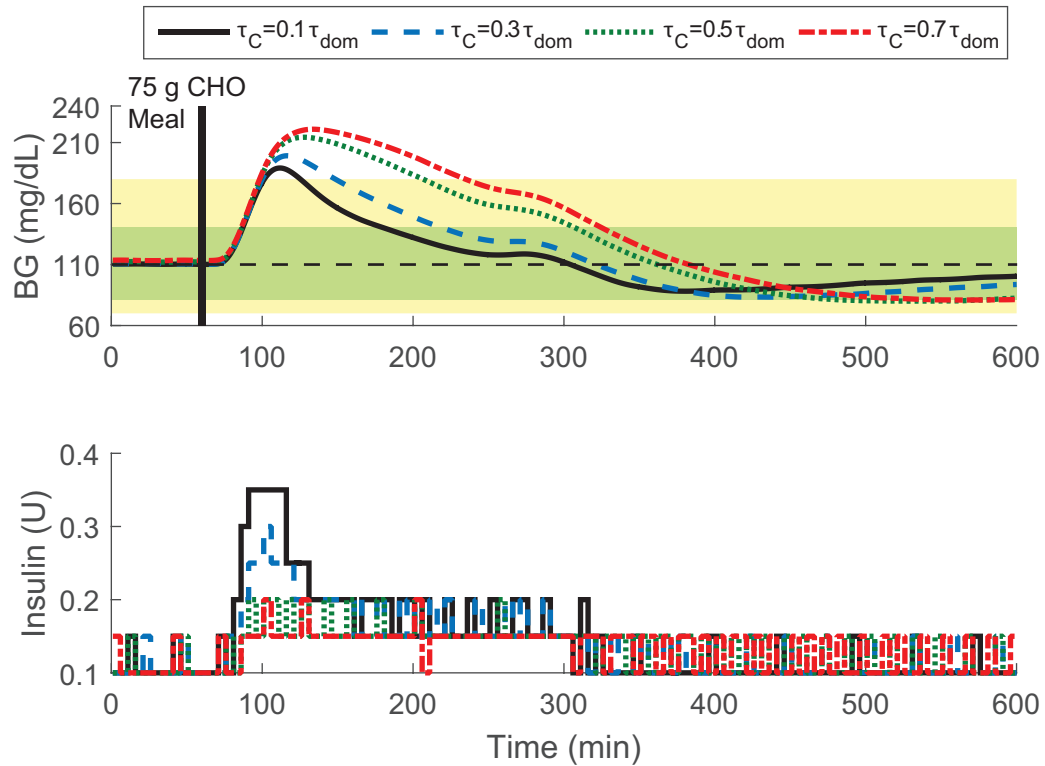


Figure 4.12: Representative result from one subject in the UVA/Padova metabolic simulator (adult subject 1) with four different values for the characteristic time constant using IP insulin. The sensor time constant for this case was 0 min. The plot shows the glucose concentration and insulin delivery for one hour before and eight hours after an unannounced 75 g CHO meal disturbance. The green and yellow zones represent the tight clinical range (80-140 mg/dL) and safe clinical range (70-180 mg/dL) for the BG. The setpoint is shown by the horizontal dashed line at 110 mg/dL.

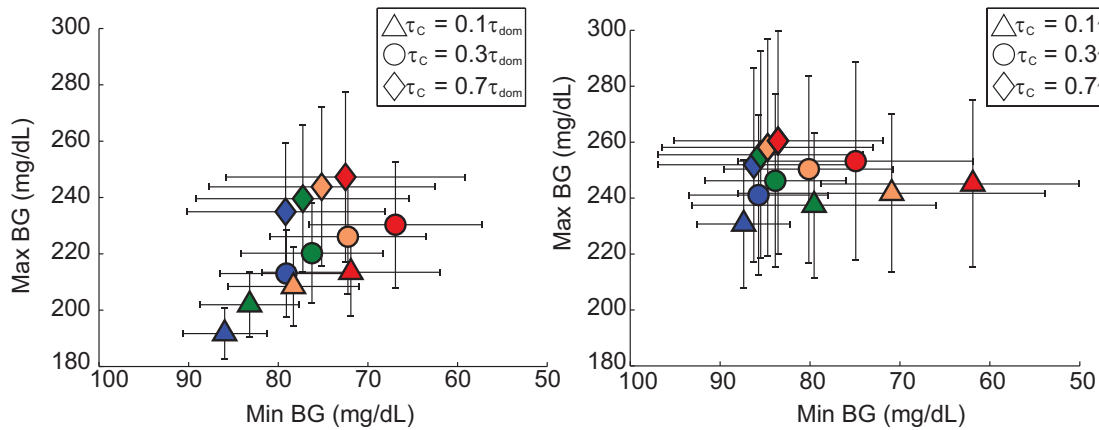


Figure 4.13: Mean maximum versus mean minimum BG for different sensor time constants (0 (blue), 10 (green), 20 (orange), and 30 (red) min) and tuning parameters for (A) IP insulin delivery and (B) SC insulin delivery after a 75 g CHO meal disturbance. Error bars show plus or minus one standard deviation. Decreasing the sensor time constant causes the data points to move down and to the left, indicating an improvement of controller response to the meal disturbance. Reprinted from [202].

potentially avoid the need for this feed-forward action, leaving less burden on the AP user. Still, there may be a limit to the sensing speed that can be achieved. The cost of developing and manufacturing a faster sensor must be weighed against the benefit gained from the reduced lag.

4.6 Conclusions and Future Work

When evaluating a new sensor technology, the point-wise error is frequently reported as a measure of the acceptability of that sensor's accuracy. A point-wise error that passes thresholds for safety could still include error from a dynamic lag that could cause problems for an artificial pancreas controller. Decreasing the glucose sensor lag leads to a decreased period of hyperglycemia following a meal disturbance, which could in turn lead to a better health outcome for the patient. The relative improvement is higher for the IP system than the SC system. This difference

is attributable to the fact that delays present in SC insulin actuation cause the sensor lag to have less of an impact. In addition, systems with an increased sensor lag have a lower tolerance for model uncertainty resulting from inter- and intra-patient variabilities.

The use of an insulin delivery route with faster pharmacokinetic and pharmacodynamic characteristics (IP rather than SC) improves control performance greatly, but that improvement is only partially realized if a sensor with a dynamic lag is used. Further experimental investigation of glucose sensor placement will reveal the extent to which the diffusion lag can be eliminated. The benefit gained from this lag reduction must be weighed against the cost and invasiveness of such a sensor to determine the best solution for the patient. In the next chapter, the design and evaluation of a PID control algorithm for a fully implantable AP using both IP insulin and IP glucose sensing is presented.

Chapter 5

Robust PID Control for an Implantable Artificial Pancreas¹

5.1 Introduction

As discussed in Chapters 1 and 2 of this dissertation, many variations of the artificial pancreas (AP) have been tested in clinical studies. Current iterations of the AP have moved past the inpatient clinical testing phase and into the outpatient environment. The AP designs used in these studies show promising results, but their performance is limited by the use of commercially available external insulin pumps and glucose sensors that operate in the subcutaneous space, introducing severe delays into the control loop. In this chapter, we present a design process for a controller that will work with implantable insulin pumps and glucose sensors, greatly reducing the delays and resulting in overall better glycemic control.

¹Reproduced with permission from L. M. Huyett, E. Dassau, H. C. Zisser, and F. J. Doyle III, "Design and evaluation of a robust PID controller for a fully implantable artificial pancreas," *Industrial & Engineering Chemistry Research*, vol. 54, pp. 10311-21, 2015. Copyright 2015 American Chemical Society (available at <http://pubs.acs.org/articlesonrequest/AOR-HTwYV5f3SkycCeZNfSD>) [209].

5.1.1 Control Objective, Challenges, and Constraints

A primary objective of the AP is to provide safe and effective glycemic control for people with T1DM by delivering doses of insulin. This objective is typically quantified as maximizing the percentage of time spent within a desired range of glucose concentrations. The most frequently used ranges are 70-180 mg/dL or 80-140 mg/dL [1]. In addition, the controller must prevent hypoglycemic episodes. Since safety must remain the top priority in any medical device system, some AP designs introduce glucagon as a second manipulated variable [94]. This hormone stimulates the natural conversion of glycogen stored in the liver to glucose, and may be used as a rescue treatment when a person's BG approaches hypoglycemia. However, there are practical difficulties with using glucagon in a closed-loop system, and the effects of long-term glucagon use are unknown [133]. In addition, a clinical study designed to compare an AP with and without glucagon did not find any significant improvement made by including glucagon in the system [94]. For these reasons, we focus on the design of an insulin-only system. An important constraint in this system is that insulin cannot be removed once it has been delivered, so the AP must be tuned accordingly to avoid a potentially dangerous situation.

There are several disturbance challenges that the AP must face to successfully control BG. The most difficult disturbances to control occur following the ingestion of a meal, when the BG concentration increases rapidly. Other challenges include periods of exercise, which can result in unpredictable BG changes, and overnight periods, during which the AP user is asleep and therefore dependent on the AP to maintain the BG within a safe range [1]. Periods of illness and stress, along with hormonal changes, affect the way the body responds to insulin [210]. The AP must be able to adapt to changing insulin sensitivity to maintain glycemic control.

5.1.2 An Implantable System

To effectively reject glycemic disturbances, the AP controller must have access to sensing and actuation with characteristics that allow the controller to detect and react to glucose concentration changes. The majority of AP designs tested thus far rely on commercially available insulin pumps and glucose sensors that operate in the subcutaneous space [1]. These devices have several advantages: they are minimally invasive, already approved by the United States Food and Drug Administration, and easy to use. Unfortunately, diffusion lags between the interstitial fluid and the blood introduce severe delays in both glucose sensing and insulin action, reducing the ability of the controller to respond to and correct changing glucose concentrations in a timely manner [57, 58, 79]. To overcome these delays and improve the glucose control achieved, most iterations of the AP have incorporated meal announcement, a type of feedforward action initiated by the user to trigger a bolus of insulin before the meal is consumed. While the addition of the meal announcement improves the resulting BG profile following a meal, it also poses a safety risk by requiring the user to accurately and reliably perform an action [211]. The best solution would be to reduce delays in the system so that fully-automated control is possible. The reduction of delays may be accomplished with the use of alternate insulin delivery, more rapid-acting insulin formulations, and glucose sensing methods.

The intraperitoneal (IP) space was first introduced as an alternative insulin delivery route in the 1970s [174]. Insulin delivered through the intraperitoneal route has faster pharmacokinetic and pharmacodynamic characteristics than insulin delivered through the subcutaneous route: when insulin is delivered through the SC route, the absorption peak occurs 50-60 minutes later [175], as opposed to 20-25 minutes when using the IP route [176]. The insulin is also cleared more quickly: insulin delivered

through the SC route has a residence time of 6-8 hours [175], while IP insulin has a much shorter residence time of 1-2 hours [176]. A further advantage of IP insulin delivery is that it mimics healthy pancreatic activity by allowing a high uptake of insulin by the liver and producing a positive portal-systemic insulin gradient [212]. The use of implanted insulin pumps can also lead to improved quality of life: a randomized crossover study showed that continuous intraperitoneal insulin infusion resulted in improved health-related quality of life and treatment satisfaction over continuous subcutaneous insulin infusion [213]. The main obstacle barring adoption of IP insulin delivery is that it requires either a pump to be surgically implanted, as in Logtenberg, et al. [214] or a percutaneous port to be created, as in Liebl, et al. [194]. The disadvantages of this system are that it is invasive, and may be associated with higher cost and higher risk of infection [18]. There is no IP insulin delivery system currently approved for use in the United States, so this hurdle would need to be passed before the implantable AP could be tested in human clinical trials.

The improvements gained by faster actuation through IP insulin delivery will be limited without the implementation of fast glucose sensing. In initial clinical studies, an AP using intraperitoneal insulin delivery did not perform as well as expected because the sensor introduced a lag to the glucose measurement [215]. As discussed in Chapters 2 and 3 of this dissertation, several studies have shown that there is a diffusion lag between the blood and the interstitial fluid, resulting in measurements that lag behind the blood glucose concentration [57, 58, 184]. The preliminary animal studies discussed in Chapter 3 have demonstrated that sensors placed in the IP space provide a more rapid measurement of blood glucose than sensors placed in the SC space due to the proximity to a highly vascularized area, with the diffusion process modeled as a first-order transfer function with time constant τ_S (min) [38, 216]. The time constants identified from experimental data in a swine model for sensors placed

in the intraperitoneal and subcutaneous space are shown in Figure 5.1. The IP sensor time constants were lower and had a tighter distribution than the SC time constants. This evidence suggests that a glucose sensor implanted within the IP space will provide a more useful estimation of the blood glucose concentration by reducing the diffusion lag. As was shown in Chapter 4, reducing the sensor lag leads to a more robust controller, with better performance in simulation studies.

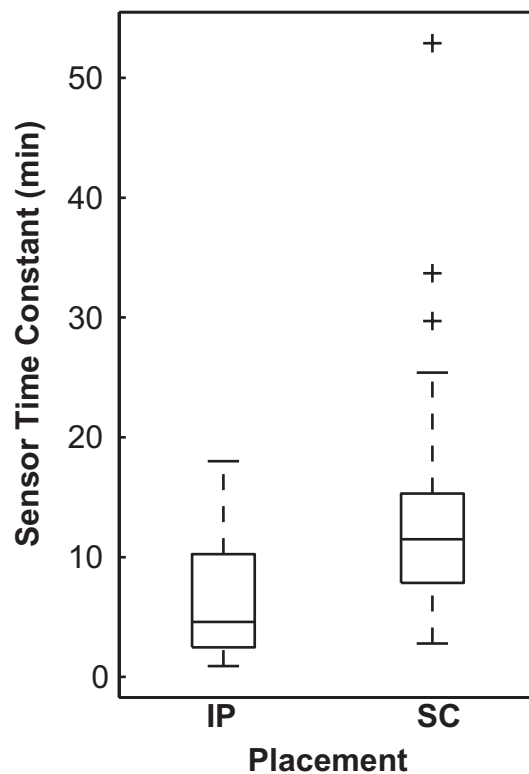


Figure 5.1: Sensor dynamics in experimental data. Boxplot showing the statistical properties of the fitted time constants for sensors placed in the IP space or the SC space of swine, demonstrating that the IP sensors had a lower mean time constant and a tighter distribution than the SC sensors.

The primary differences between IP and SC devices are summarized in Table 5.1. A fully implanted AP will make use of both intraperitoneal insulin delivery and glucose sensing. The pump, sensor, and controller will all be implanted, and the system will be operated using a handheld remote. This approach will eliminate the need to

remove and apply new sensors and insulin infusion sets, as must be done with subcutaneous devices. Externally worn devices can be cumbersome, so this approach may also increase patient compliance. We hypothesize that the glycemic control provided by a fully implantable system will be superior to that which is possible with a subcutaneous system. Since the sensing time constant is up to two times faster, the controller can react promptly to impending hypo- and hyperglycemia [38]. Additionally, pump suspension will have an almost immediate effect on the BG, while with the SC system the insulin depot in the SC space may delay the effect by up to 60 minutes [217]. An IP insulin bolus results in a peak in plasma insulin within 40 minutes, and returns to baseline after 113 ± 63 to 154 ± 55 minutes [176]. The faster insulin action and clearance will lead to more predictable dynamics, making closed-loop control more successful.

5.2 Methods

5.2.1 Controller Design and Tuning

As discussed in Chapter 1, several control strategies have been evaluated for AP applications, including proportional-integral-derivative control (PID), model predictive control (MPC), and fuzzy logic [1]. Records of information related to clinical trials using each type of controller are available in the searchable database located at www.thedoylegroup.org/apdatabase. MPC has been proposed as a suitable strategy for AP designs using subcutaneous insulin delivery and sensing because of the large delays in these systems. Additionally, this advanced control strategy can directly incorporate system constraints and other features within the optimization problem that is solved to calculate the insulin delivery [71, 72]. PID control has also been

Table 5.1: Summary of differences between subcutaneous and intraperitoneal insulin pumps and glucose sensors.

Characteristic	Subcutaneous Space	Intraperitoneal Space
Insulin absorption peak	50-60 min [175]	20-25 min [176]
Insulin residence time	6-8 h [175]	1-2 h [176]
Sensor measurement time constant	12.4 min [38]	5.6 min [38]
Device placement	External, placed on skin with adhesive patches and tubing [13, 23]	Implanted, no components attached to skin [38, 214]
Device lifetime	Replace sensor every 7 days and pump infusion set every 2-3 days [13, 23]	Implanted pumps last years, with transcutaneous insulin refills every few months [218]
Device invasiveness	Minimally invasive [13, 23]	Requires surgery [38, 218]
Device availability	Commercially available [13, 23]	In development [38, 215]

promoted and implemented widely for AP applications. Promising clinical results have been demonstrated by AP systems using MPC controllers and by ones using PID controllers [1, 219].

When using intraperitoneal insulin delivery and glucose sensing, the system lags are highly reduced and we are left with a standard single-input, single-output control problem. In this case, we anticipate that the advanced control capability of MPC may no longer be needed, and that a PID controller will provide satisfactory performance. Because the insulin will act quickly and glucose changes will be sensed rapidly, the system can operate well without the predictive power offered by MPC. Additionally, PID control is less computationally complex, which may be an advantage when the system must be embedded on a chip where space and battery power will be at a premium.

The use of model based tuning is recommended for the AP because online tuning through trial and error is not acceptable for a medical application; however, we need to find a balance between a general and personalized model. Completing time-consuming model identification procedures for individual subjects is not feasible, especially if the AP is to be adopted on a large scale. Still, individual subjects have widely varying insulin sensitivities [205]. In a previous study, a third-order discrete-time model structure was identified that adequately captures the behavior of insulin action on the blood glucose concentration [199, 200]. The poles of the model were found to be consistent between subjects, while a personalization factor was added in the model gain. The model that was identified for intraperitoneal insulin action on blood glucose concentration is:

$$M_D = \frac{G(z^{-1})}{U_D(z^{-1})} = \frac{-15(TDI)^{-1}z^{-3}}{(1 - 0.98z^{-1})(1 - 0.75z^{-1})^2} \quad (5.1)$$

where TDI is the total daily insulin dose of the patient (U), G is the blood glucose concentration (mg/dL), U_D is the insulin delivered through the IP route (U/h), and the sampling time is five minutes. The inclusion of the TDI allows the model gain to be tailored to an individual subject's insulin sensitivity.

Internal model control (IMC) is a comprehensive tuning method that allows PID parameters to be calculated directly from the process model. This method leaves a single tuning parameter, τ_C , which is used to set the closed-loop time constant [70]. Internal model control tuning has been used successfully in AP designs for SC insulin delivery [84, 188]. To make the model easier to work with for controller tuning and robustness analysis, the model M_D is converted to continuous time. This conversion can be done using several methods, but the zero-pole matching method was determined to best preserve the model characteristics [203]. It should be noted, however, that the final tuning parameters obtained using other methods of conversion are the same within choice of τ_C . Therefore, the final tuning parameters are robust to the conversion method.

The model resulting from the conversion from discrete to continuous time is:

$$M_C = \frac{-12000(TDI)^{-1}}{(247s + 1)(17s + 1)^2} \quad (5.2)$$

where the time constant units are minutes. Internal model control tuning rules require a second-order model to obtain a PID controller. Skogestad's half rule can be used to reduce higher-order models to the first- or second-order model required to use IMC PID tuning rules [204]. Using this method, the reduced-order model

parameters are determined by the following relations:

$$\hat{\tau}_1 = 247 \quad (5.3)$$

$$\hat{\tau}_2 = 17 + 17/2 \quad (5.4)$$

$$\hat{\theta} = 17/2 + 5/2. \quad (5.5)$$

The final model obtained is:

$$G_P = \frac{-12000(TDI)^{-1}e^{-11s}}{(247s + 1)(26s + 1)}. \quad (5.6)$$

Using this model, the tuning parameters are determined using IMC tuning relations [70]:

$$K_c = \frac{\hat{\tau}_1 + \hat{\tau}_2}{\hat{K}'(TDI)^{-1}(\tau_C + \hat{\theta})} \quad (5.7)$$

$$\tau_I = \hat{\tau}_1 + \hat{\tau}_2 \quad (5.8)$$

$$\tau_D = \frac{\hat{\tau}_1 \hat{\tau}_2}{\hat{\tau}_1 + \hat{\tau}_2}. \quad (5.9)$$

The digital PID controller is implemented using the velocity form [70], with:

$$u(k) = u(k - 1) + \Delta P(k) + \Delta I(k) + \Delta D(k) \quad (5.10)$$

where

$$\Delta P(k) = K_C[e(k) - e(k - 1)] \quad (5.11)$$

$$\Delta I(k) = K_C \frac{\Delta t}{\tau_I} e(k) = K_I e(k) \quad (5.12)$$

$$\Delta D(k) = K_C \frac{\tau_D}{\Delta t} [e(k) - 2e(k - 1) + e(k - 2)] \quad (5.13)$$

$$e(k) = G_{sp}(k) - G_m(k). \quad (5.14)$$

In this set of equations, u (U/h) is the insulin delivery calculated by the controller, P , I , and D (U/h) represent the proportional, integral, and derivative action terms respectively (U/h), Δt is the time step (5 min), and the integer k denotes the sample number. An important feature of the velocity PID form is that it must include the use of integral action. If it is desired to exclude integral action, the position form should be used instead [70].

A derivative filter can be implemented with this controller. The derivative filter prevents excessive controller action in the presence of measurement noise. In this case, the derivative term becomes:

$$\Delta D(k) = \frac{\beta \tau_D}{\Delta t + \beta \tau_D} \Delta D(k - 1) + K_C \frac{\tau_D}{\Delta t + \beta \tau_D} [e(k) - 2e(k - 1) + e(k - 2)]. \quad (5.15)$$

The parameter β determines the level of filtering of the derivative term, with a larger value indicating a higher filtering effect. After preliminary testing we selected β as 0.1, which is a commonly used value [70]. The derivative filter was used when sensor noise was added during simulation studies.

The tuning parameters obtained using the procedure outlined above are shown in Table 5.2, along with parameters determined for a PID controller using SC insulin in Laxminarayan, et al. [82]. The remaining parameter τ_C will be selected using robust

stability and performance considerations.

Table 5.2: Parameters for PID control using IMC tuning for intraperitoneal insulin compared to parameters previously identified for PID control using subcutaneous insulin.

Parameter	IMC for Intraperitoneal Insulin	Previously Suggested for Subcutaneous Insulin [82]
$K_C (\frac{U/h}{mg/dL})^*$	$0.023(TDI)(\tau_C + 11)^{-1}$	$0.0026 \frac{TDI}{bodyweight}$
τ_I (min)	273	450 (day), 150 (night)
τ_D (min)	23.5	98

*The units on the variables in this row are: bodyweight (kg), TDI (U), and τ_C (min).

5.2.2 *In Silico* Artificial Pancreas Evaluation

As described in previous chapters, the metabolic simulator developed by at the Universities of Virginia and Padova can be used to evaluate AP controllers *in silico* before considering them for use in *in vivo* application [207, 220]. This platform allows the algorithm to be evaluated on 10 *in silico* T1DM subjects. In this study, the metabolic simulator was used to determine the optimal tuning parameters and evaluate the controller performance. The setup that was used in this work is shown in Figure 5.2.

To evaluate the intraperitoneal insulin and intraperitoneal sensing (IP-IP) design we used the intravenous (IV) insulin port and a simulated IP sensor. The IV port was used to approximate the delivery of IP insulin, as was done in Lee, et al. [200]. The IP sensor was implemented by a first-order diffusion model from the IV glucose input with a time constant of five minutes. This value was chosen based on the data presented in Burnett, et al. [38].

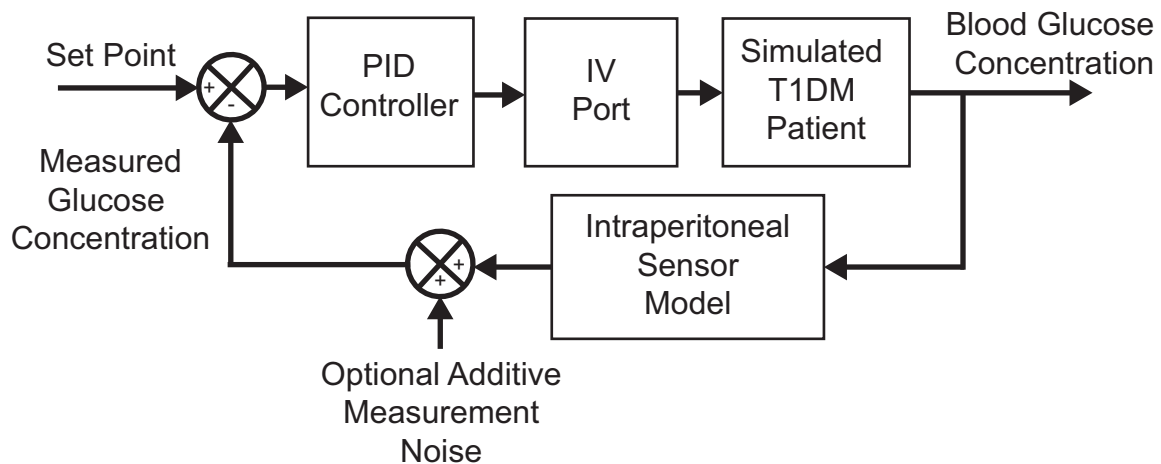


Figure 5.2: Schematic representation of the UVA/Padova metabolic simulator. Block diagram representation of the configuration of the UVA/Padova metabolic simulator used in this work to test a fully implantable AP.

The four clinical scenarios shown below were used to evaluate the controllers.

- Scenario 1: A large meal of 100 g of carbohydrates (CHO) was administered to evaluate the meal response and the setpoint undershoot.
- Scenario 2: A 30% decrease in insulin sensitivity was tested. The change was simulated by multiplying the insulin delivered by 0.7.
- Scenario 3: A 30% increase in insulin sensitivity was tested by multiplying the insulin delivered by 1.3.
- Scenario 4: A 27 hour clinical protocol was simulated to evaluate the controller performance for a typical real-life scenario. Closed-loop control was initiated at 14:00, followed by a 70 g CHO meal at 19:00. This meal was followed by an overnight period from 24:00 to 08:00. A breakfast of 40 g CHO occurred at 08:00, and then a lunch of 70 g CHO followed at 13:00. Closed-loop control was ended at 17:00.

Scenarios 1-3 were previously tested in Laxminarayan, et al. [82] for an AP using subcutaneous insulin. The scenarios were repeated here to allow for direct comparison to show the improvement gained by using IP insulin and the design procedure implemented in this chapter. The best controller design was selected using Scenarios 1-3. The final controller was tested in Scenario 4, including simulated sensor noise to demonstrate a true-to-life protocol with potential measurement errors. Scenario 4 was used in Lee, et al. [200] to test a zone-MPC controller using IP insulin delivery and SC glucose sensing. We repeated this protocol to show that we achieved comparable results with our IP-IP PID approach.

5.2.3 Introduction of Anti-Reset Windup

The PID controller may cause the BG to undershoot the setpoint after a large meal, as shown in Figure 5.3. In this figure, PID control was used on subject 1 in the UVA/Padova metabolic simulator to control a 100 g CHO meal disturbance. The bottom panel shows the buildup of the integral term that occurs during the large meal disturbance, leading to the setpoint undershoot.

This undershoot is highly undesirable because it indicates insulin over-delivery and increases the risk of hypoglycemia. Several approaches have been used to circumvent this effect. One option, applied in several clinical studies [88, 210, 221–224] and the *in silico* study presented by Laxminarayan, et al. [82] is to remove the integral component and use a proportional-derivative controller. However, the use of PD control is not ideal because setpoint tracking is sacrificed. Without setpoint tracking, the controller will not be able to react to changes in insulin sensitivity. Other clinical studies have detuned the integral component to prevent insulin over-delivery. For example, in Steil, et al. [77] and Laxminarayan, et al. [82] the integral time constant was set to 150 min at night and increased to 450 min during the day when meals

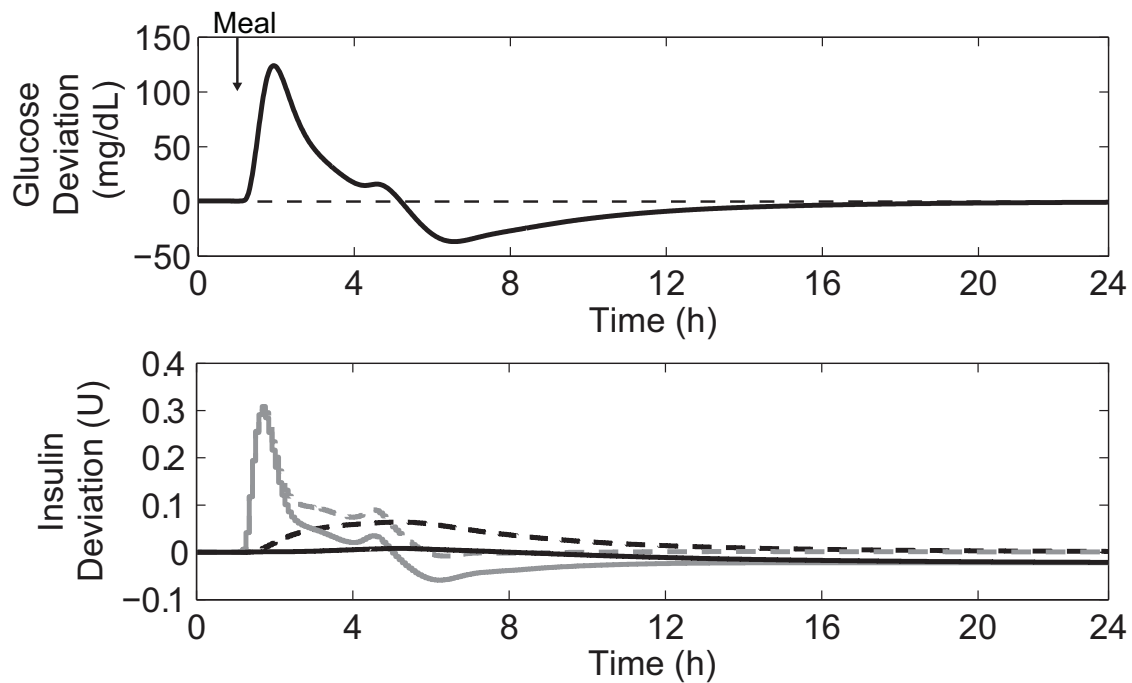


Figure 5.3: Demonstration of setpoint undershoot encountered when using integral action after a 100 g CHO meal occurring at 1 h. The top panel shows the glucose deviation from the setpoint after the meal for subject 1 under PID control. The bottom panel shows the insulin trace for PID control (dashed gray line) with the integral component plotted separately (dashed black line). Also on the bottom panel are the advisory mode calculations for PID with anti-reset windup protection (solid lines) with the gray line showing the total insulin and the black line showing the integral component.

are expected to occur. Nearly all clinical studies using PID control for the AP have placed an upper limit on the integral term as an additional safety feature. For example, in Steil, et al. the integral term was constrained to be less than three times the 06:00 basal rate when $BG > 60$ mg/dL, and was restricted to $K_C (G_{SP} - 60)$ U/h when $BG < 60$ mg/dL [77]. In Laxminarayan, et al. the integral limits were set to 1.4 times the basal rate when $BG > 80$ mg/dL, 0.7 times the basal rate when $BG < 60$ mg/dL, and a linear interpolation between those two limits for $60 < BG < 80$ mg/dL [82].

During initial testing, we found that placing an upper limit on the integral term to reduce the undershoot negatively affected the setpoint tracking ability of the controller. We found that the best option is to instead implement an anti-reset windup strategy. The relevant approach here is to use conditional integration, which involves increasing or decreasing the amount of integration depending on specified conditions. A key feature of the AP is that the controller will frequently encounter large output disturbances. Even with IP insulin delivery it is anticipated that BG will be elevated for approximately 3 hours following a meal. The ideal AP would exhibit the characteristics of a PD controller during large but temporary disturbances, while retaining the characteristics of integral action during smaller but persistent disturbances.

The method of anti-reset windup described in Hanssen, et al. can be used to meet these requirements [225]. The idea behind the method is to attenuate the rate of change of the integral term, $I(k)$, based on the size of the error term, $e(k)$. When the error is large, the rate of change of the integral term should approach zero. When the error is small, the rate of change should be unmodified. To accomplish this goal, the authors introduced a fuzzy logic scheme with two rules: when error is small, K_I remains at its nominal value ($K_I = K_C \frac{\Delta t}{\tau_I}$), and when error is large, K_I is equal to zero.

By using the membership functions defined in Hanssen, et al. and applying the

min-max inference rule, the equation for the integral term in (8) is adjusted to:

$$I(k) - I(k - 1) = K_I K_W e(k) \quad (5.16)$$

$$K_W = e^{-\alpha|e(k)|}. \quad (5.17)$$

This method introduces a single tuning parameter, α , which sets the degree of attenuation for the integral term. Figure 5.4 shows a plot of K_W versus $|e(k)|$ for increasing values of α .

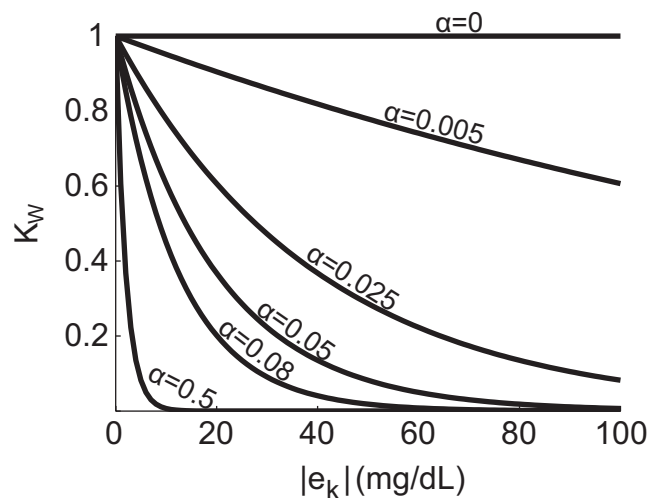


Figure 5.4: Degree of integral attenuation as a function of error. Plot of K_W versus $|e(k)|$ (mg/dL) for increasing values of α . Error sizes are typical to those encountered after a large meal.

This strategy is ideal for the AP because it is a flexible and dynamic method characterized by a simple algebraic expression. Instead of placing fixed limitations on the integral term that apply for all BG levels, it instead applies a weighting factor appropriate for the current situation. This method is equivalent to using an increasing value for τ_I as the error becomes larger. The flexibility provided by this method allows for the minimization of undershoot after large meals, while still offering set-point tracking to react to changes in insulin sensitivity. In addition, no information

about meal timing needs to be supplied for the algorithm to function well. The bottom panel of Figure 5.3 shows an advisory mode calculation of insulin action that includes anti-reset windup protection. The buildup of the integral term that was observed when using PID control was prevented, leading to a lower recommended insulin dose during the meal.

5.2.4 Insulin Feedback

When designing the AP, it is prudent to draw inspiration from nature by examining how the pancreas is able to achieve glycemic control in people without T1DM. A key feature of physiological glycemic control that is missing from a single-input single-output PID design is that insulin in the blood suppresses further insulin production [226]. This feature is necessary to prevent insulin stacking. Most studies using PID control with subcutaneous insulin have incorporated this feature by using an insulin feedback (IFB) algorithm [77, 101]. Since it is currently not possible to measure plasma insulin concentration in real time, this method relies on a model of insulin pharmacokinetics to estimate the plasma insulin concentration based on past insulin delivery. In the original description of IFB, insulin pharmacokinetics were represented by a second-order continuous-time transfer function between insulin delivered and plasma insulin concentration, with time constants determined from experimental data [101]. This continuous-time model can be discretized to match the sampling period of the controller, resulting in the following equation:

$$\hat{C}_P(k) = a_1\hat{C}_P(k-1) + a_2\hat{C}_P(k-2) + b_1U_D(k-1) + b_2U_D(k-2). \quad (5.18)$$

Here, U_D (U/h) is the closed-loop insulin delivery profile and $\hat{C}_P(k)$ is the estimated plasma insulin concentration. The final insulin dose is then calculated as:

$$U_D(k) = \left(1 + \frac{\gamma}{K_{PI}}\right)u(k) - \gamma\hat{C}_P(k-1) \quad (5.19)$$

where $u(k)$ is the insulin dose that was calculated in Equation (5.10). Typically, the insulin plasma concentration units are normalized so that the gain K_{PI} is equal to one [77, 101]. The parameter γ determines the degree to which the presence of plasma insulin suppresses insulin delivery. The factor $(1 + \frac{\gamma}{K_{PI}})$ is needed so that the insulin delivery $U_D(k)$ is equal to the basal rate when the system is at steady-state. In subcutaneous insulin applications, the parameter γ is selected to be 0.5 to achieve good performance [77, 101].

More complex models have also been developed for subcutaneous pharmacokinetic behavior. In Ruiz, et al. [227], the insulin concentration is divided into three compartments: subcutaneous insulin (I_{SC}), plasma insulin (I_P), and interstitial/effective insulin (I_{EFF}). These three concentrations are estimated by:

$$I_{SC}(k) = \alpha_{11}I_{SC}(k-1) + \beta_1U_D(k-1) \quad (5.20)$$

$$I_P(k) = \alpha_{21}I_{SC}(k-1) + \alpha_{22}I_P(k-1) + \beta_2U_D(k-1) \quad (5.21)$$

$$I_{EFF}(k) = \alpha_{31}I_{SC}(k-1) + \alpha_{32}I_P(k-1) + \alpha_{33}I_{EFF}(k-1) + \beta_3U_D(k-1) \quad (5.22)$$

$$I_{IFB}(k) = \gamma_1I_{SC}(k) + \gamma_2I_P(k) + \gamma_3I_{EFF}(k) \quad (5.23)$$

where the parameters α_{ij} and β_i are constants and I_{IFB} is the combination of the three compartments, with weighting factors γ_i . The numerical values of the parameters α_{ij} ,

β_i , and γ_i are given in [227]. The final insulin dose is then calculated as:

$$U_D(k) = (1 + \gamma_1 + \gamma_2 + \gamma_3)u(k) - I_{IFB}(k). \quad (5.24)$$

This method is further described in a patent held by Medtronic Minimed, Inc. [228].

There is limited information available in the literature to supply a pharmacokinetic model of IP insulin. For SC insulin, the second-order continuous-time model was identified to have time constants of 70 min and 55 min [101]. One study that was completed to identify corresponding parameters for IP insulin delivery found time constants of 60 ± 8.7 min and 27.2 ± 9.3 min [229], while an earlier study by the same authors found parameters to be 34.6 ± 5.9 min and 17.4 ± 4.7 min [230]. In the absence of further modeling data, we chose the more recently identified model parameters to use in the implementation of IFB for our system. Once further experimental data is obtained for the pharmacokinetics of the specific insulin to be used, the model can be updated to provide a more accurate estimation.

5.3 Controller Optimization and Evaluation

The controller design procedure outlined above leaves several design parameters to be determined: τ_C , α , and γ . First, candidate values for τ_C were selected using robust stability and performance analysis. The other two parameters were selected using simulation studies with Scenarios 1-3. The best value for α was determined without IFB by examining the trade-off between the amount of postprandial undershoot and offset after a change in insulin sensitivity. Next, the best value for γ was chosen without anti-reset windup protection (AWP) by examining the minimum and maximum postprandial BG values. Lastly, the controller was tested with both IFB

and AWP implemented.

5.3.1 Robust Stability and Performance

As discussed in Chapter 4, the AP must be robust to model uncertainty in order to be safe for clinical use. The manner in which the body responds to insulin can change as a function of the time of day, hormonal changes, exercise, and other factors that are part of daily life. Experimental evidence shows that the insulin sensitivity may vary by up to 50% [205]. The changes in the body's insulin response can be represented as perturbations to the gain and delay of the nominal model. In order to determine whether the system will be stable for a specified model uncertainty, the robust stability condition can be evaluated. A robust controller will be able to perform according to its design specifications, even in the worst-case scenario of model uncertainty [206].

In order to use this method, we must first represent a suitable family of possible plants Π_I , in this case using multiplicative uncertainty. Revisiting the equations from Chapter 4, we define Π_I as:

$$\Pi_I : G_P(s) = G(s)(1 + w_I(s)\Delta_I(s)); \quad |\Delta_I(j\omega)| \leq 1, \quad \forall \omega \quad (4.15)$$

where G_P is a possible process model, G is the nominal process model, and the uncertainty weight satisfies the inequality $|w_I(j\omega)| \leq l_I(\omega), \forall \omega$ where

$$l_I(\omega) = \max_{G_P \in \Pi_I} \left| \frac{G_P(j\omega) - G(j\omega)}{G(j\omega)} \right|. \quad (4.16)$$

The stability criterion is then given as:

$$RS \iff \|w_I T\|_\infty < 1 \quad \forall \omega \quad (4.17)$$

where T is the complementary sensitivity function and w_I is the multiplicative uncertainty weight. To represent the parametric uncertainty in the gain and delay of the nominal model, we use

$$w_I = \frac{(1 + \frac{r_k}{2})\theta_{max}s + r_k}{\frac{\theta_{max}}{2}s + 1} \quad (4.18)$$

where $r_k = \frac{K_{max} - K_{min}}{K_{max} + K_{min}}$ and θ_{max} is the maximum delay considered [206]. Robust performance analysis allows us to determine whether certain specified performance measures will be met even in the presence of model uncertainty. The necessary relation to show robust performance is given by:

$$RP \iff \max_{\omega} (|w_P S| + |w_I T|) < 1 \quad (4.19)$$

where S is the sensitivity function and w_P is the performance weight

$$w_P(s) = \frac{\frac{s}{M} + \omega_B^*}{s + \omega_B^* A} \quad (4.20)$$

where M is the maximum peak of the sensitivity function, A is the steady state tracking error, and ω_B^* is the bandwidth frequency where the sensitivity function crosses the magnitude of 0.707 [206]. In this study, $A \approx 0$, $\omega_B^* = 5 \times 10^{-5}$ hz, and $M = 2$, as recommended in Skogestad, et al. [206].

We can use the robust stability and performance analyses to inform our choice of τ_C . Figure 5.5 shows whether the RP and RS conditions were met under a specified

model uncertainty for varying values of τ_C . In order to be able to retain RP and RS for a delay uncertainty of 10 minutes and a gain uncertainty of 0.5, we should choose a τ_C between 40 and 150 minutes. The lower value will result in faster, more aggressive control, while the higher value will result in slower, more conservative control. Setting τ_C to 40 min to obtain the fastest response, the controller designs in

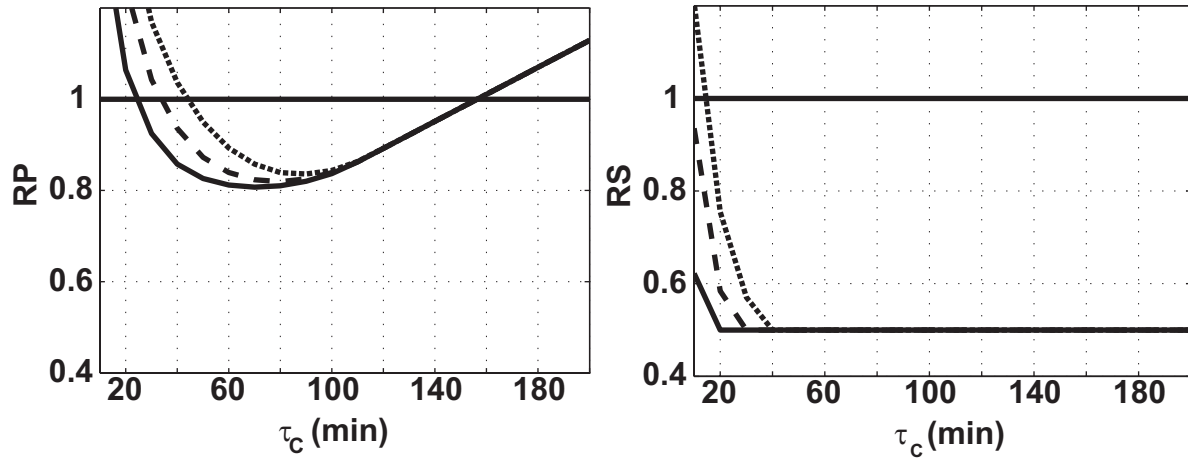


Figure 5.5: Robust stability and performance as a function of controller tuning. Robust stability (left) and robust performance (right) for varying values of τ_C . The analysis was done for three values of delay uncertainty: 5 minutes (solid line), 10 minutes (dashed line), and 15 minutes (dotted line). The gain uncertainty was kept constant at 0.5.

Table 5.3 were evaluated.

To evaluate the controller with no integral action, the position form was used:

$$u(k) = \bar{u} + P(k) + D(k) \quad (5.25)$$

where

$$P(k) = K_C e(k) \quad (5.26)$$

$$D(k) = \frac{K_C \tau_D}{\Delta t} [e(k) - e(k-1)] \quad (5.27)$$

and \bar{u} is the basal rate needed to maintain a fasting glucose concentration of 110 mg/dL.

5.3.2 Evaluation of the Anti-Reset Windup Protection

To determine the best parameter α to use for the anti-reset windup algorithm, we examined the trade-off between undershoot mitigation and setpoint tracking using Scenarios 1 and 2. The undershoot was characterized by the minimum blood glucose concentration during the postprandial period after a large meal. The setpoint tracking was evaluated by examining the offset remaining at two time points following a change in insulin sensitivity for the different AWP tunings as compared to the PID controller with no AWP. The PID controller with no AWP represents the ideal tracking case at each time point since it has full integral action. The first time point, 11 h, was chosen because after this amount of time the PID controller had made partial progress toward the setpoint. The 20 h time point was chosen because after this amount of time, the PID controller had nearly returned the BG to the setpoint. By examining the offset at these two time points, we compared the asymptotic setpoint tracking of the PID+AWP controllers to the ideal PID tracking on both a short- and long-term time scale. We then plotted the offset versus the minimum BG for various values of α , as shown in the left panel of Figure 5.6.

From this analysis, we determined that a good choice for α is 0.04. This option keeps the undershoot above 100 mg/dL but also reduces the offset after a change in insulin sensitivity. Note that the offset will be eliminated over time for all values of α . The larger α is, the longer it takes to reach the setpoint again after a change in insulin sensitivity. Figure 5.7 shows the simulation results for Scenarios 1-3 for the optimal value of α , PID control with no anti-reset windup, and PD control.

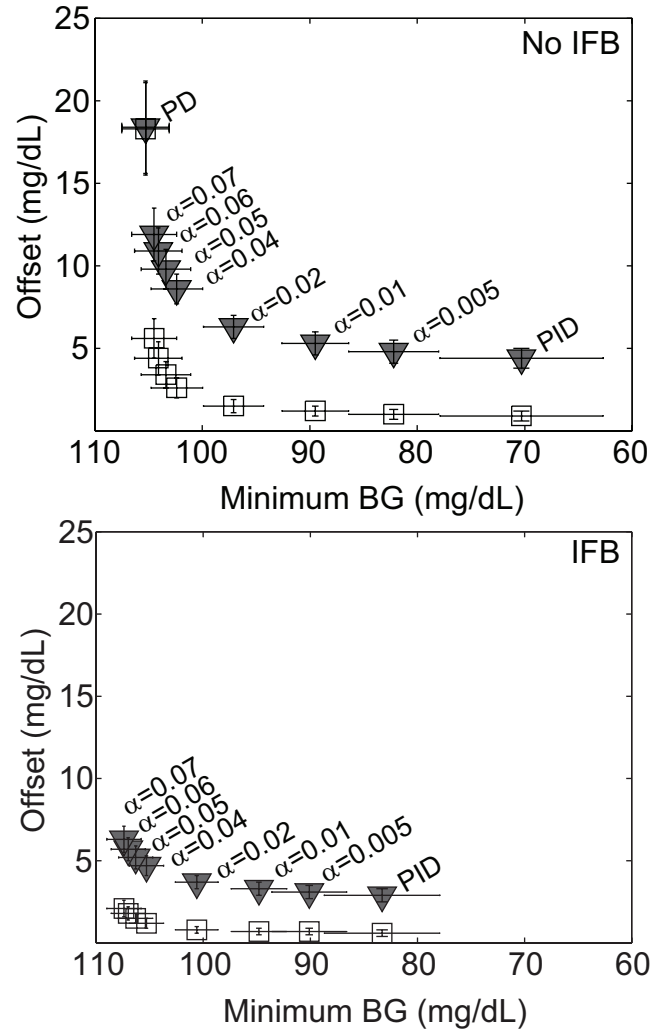


Figure 5.6: Evaluation of the trade-off between setpoint undershoot and offset. Offset 11 h (black triangles) and 20 h (white squares) after a decrease in insulin sensitivity plotted versus minimum BG after a 100 g CHO meal for varying values of anti-reset windup parameter α . The top panel shows the offset versus minimum BG for PID+AWP, while the bottom shows the results for PID+AWP+IFB ($\gamma=0.5$). The data points represent the 10-subject mean and the error bars show standard deviation.

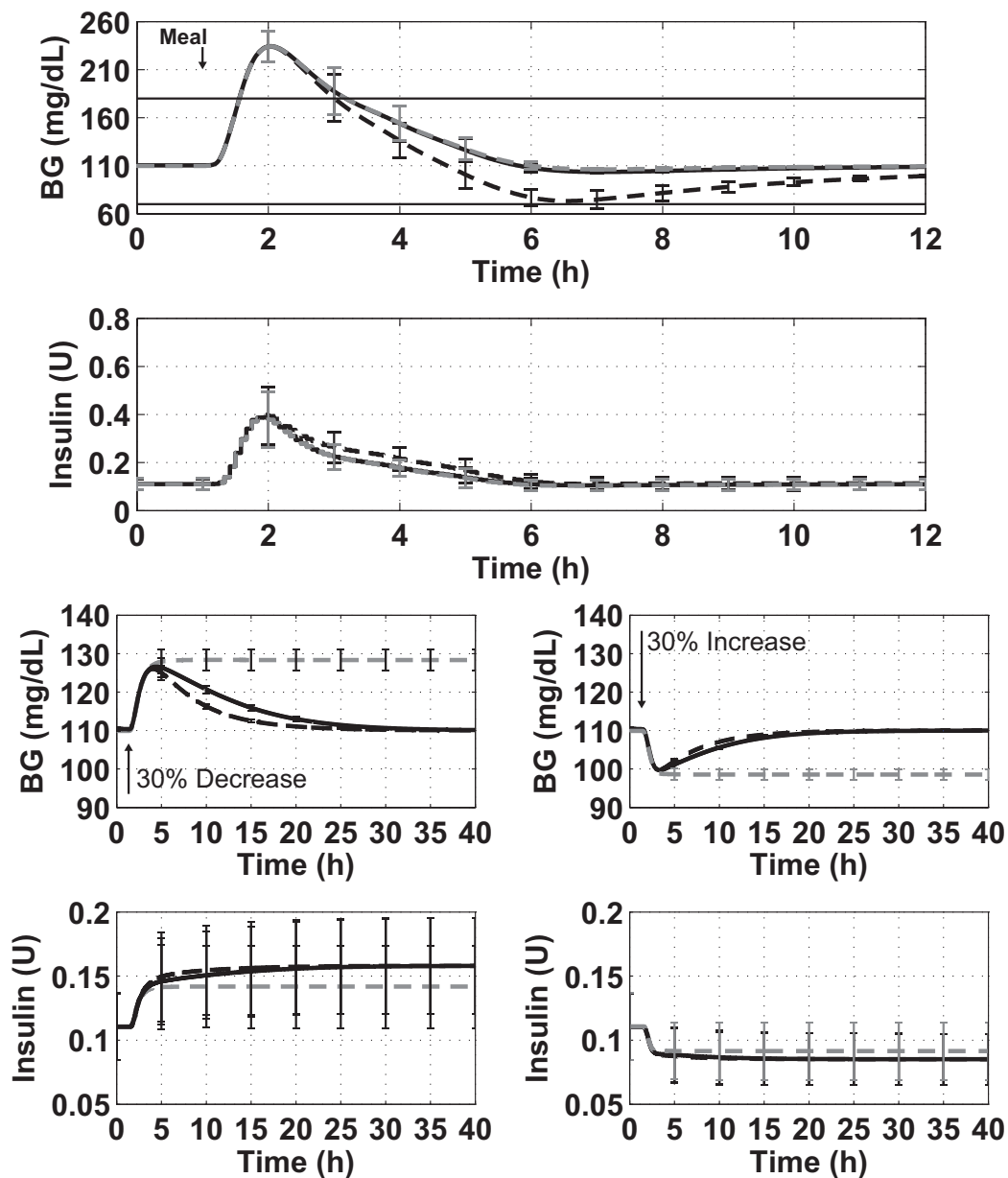


Figure 5.7: Evaluation of the anti-reset windup in simulation. Demonstration of the best anti-reset windup tuning (solid black line) compared to PID (dashed black line) and PD (dashed gray line) control. The top panel of each plot shows the blood glucose concentration over time, while the bottom panels show insulin delivered over time. The figures show the results from Scenario 1 (100 g CHO meal, top), Scenario 2 (30% decrease in insulin sensitivity, bottom left) and Scenario 3 (30% increase in insulin sensitivity, bottom right). The lines show the mean of the 10 subjects, and the error bars show standard deviation.

Table 5.3: Variations on the PID controller design tested in this work.

Controller	Integral Action	Anti-Reset Windup (AWP)	Insulin Feedback (IFB)
PD	✗	✗	✗
PID	✓	✗	✗
PID+AWP	✓	✓	✗
PID+IFB	✓	✗	✓
PID+AWP+IFB	✓	✓	✓

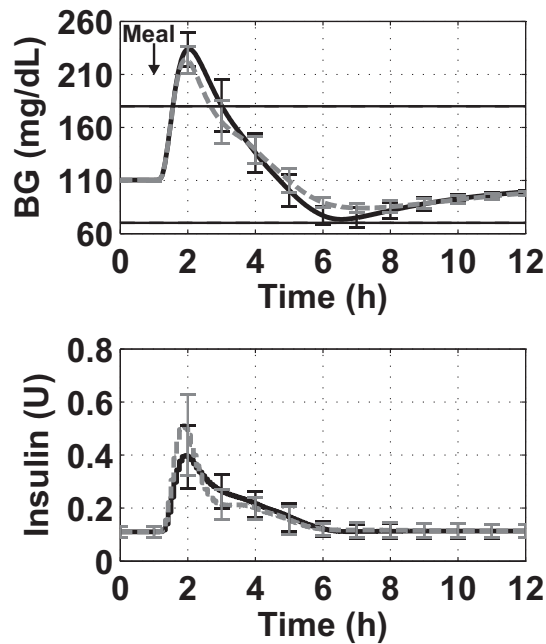


Figure 5.8: Evaluation of IFB in simulation. Demonstration of best IFB tuning (dashed gray line) compared to unmodified PID control (solid black line) for a 100 g CHO meal. The top panel shows the blood glucose concentration over time and the bottom panel shows the insulin delivered. The lines show the mean of the 10 subjects, and the error bars show standard deviation.

5.3.3 Tuning the Insulin Feedback Algorithm

The IFB strategy was tested using Scenario 1 for several values of γ with no anti-reset windup protection. Values of γ were tested from 0 to 0.5. The value of 0.5, which has been used previously for SC insulin, gave the best performance. When IFB was added to PID control, the minimum BG was raised by an average of 13.3 ± 2.4 mg/dL and the maximum BG was lowered by an average of 9.8 ± 3.8 mg/dL. When using a paired-sample t-test to compare the minimum BG for each subject with and without IFB, the difference is significant with a p-value of 3×10^{-8} . The same statistical test for the maximum BG for each subject with and without IFB showed significant difference with a p-value of 1.8×10^{-5} . The results of the simulation are shown in Figure 5.8.

To determine whether adding IFB to the controller affects the choice of anti-reset windup parameter α , we repeated the anti-reset windup evaluation with IFB added ($\gamma = 0.5$). The results are presented in the right panel of Figure 5.6. As seen in the figure, the shape of the data curve and optimal value of $\alpha = 0.04$ remain the same when IFB is added. For all values of α , the performance is better with IFB than without it.

5.3.4 Evaluation of Finalized Design

Figure 5.9 shows a plot of the maximum versus minimum BG achieved by the 5 controller designs tested in this work following a 100 g CHO meal. The IFB algorithm is able to raise the minimum BG, but not to the same degree that anti-reset windup does. IFB has the added benefit of lowering the maximum BG peak. Overall, PID plus IFB and anti-reset windup provides better control than either strategy alone, and both provide great improvements over PID alone. The PD, PID+AWP, and PID+AWP+IFB

controllers have some overlap on the plot in Figure 5.9; however, the PID iterations have a clear advantage over the PD approach since they include setpoint tracking while PD does not. The most important comparison to make is to determine whether adding IFB to the PID+AWP controller results in significant improvement. These two cases were compared using a paired-sample t-test to compare the maximum BG and the minimum BG following the 100 g CHO meal. The maximum BG was decreased by an average of 10 ± 3.8 mg/dL when IFB was added to the PID+AWP controller. This difference is significant with a p-value of 1.5×10^{-5} . The minimum BG was raised by an average of 2.9 ± 1.5 mg/dL when IFB was added. While the difference in the minimum BG is relatively small and not likely of clinical significance, it is still statistically significant with a p-value of 2×10^{-4} . The benefit of adding IFB in addition to AWP is the more aggressive initial action that is taken when there is little insulin already in the body. Additionally, including the IFB mechanism is superior clinically because it adds a safety layer to prevent insulin over-delivery. This type of mechanism is a must for clinical application since preventing hypoglycemia is the first priority.

The results achieved with IP insulin using IFB+AWP in this work are compared to those achieved for Scenarios 1-3 with SC insulin in Laxminarayan, et al. [82] in Table 5.4. The IP approach resulted in a much lower peak BG than the SC approach. In addition, the IP system did not drive the BG as low as the SC system following the meal, resulting in an overall safer scenario. The time to return to setpoint after a change in insulin sensitivity was also much faster using IP insulin with the anti-reset windup strategy presented in this work.

The final controller design was evaluated for Scenario 4 with sensor measurement noise to create a realistic test. The measurement noise included in the metabolic simulator was designed to emulate an SC sensor. There is currently no IP sensor

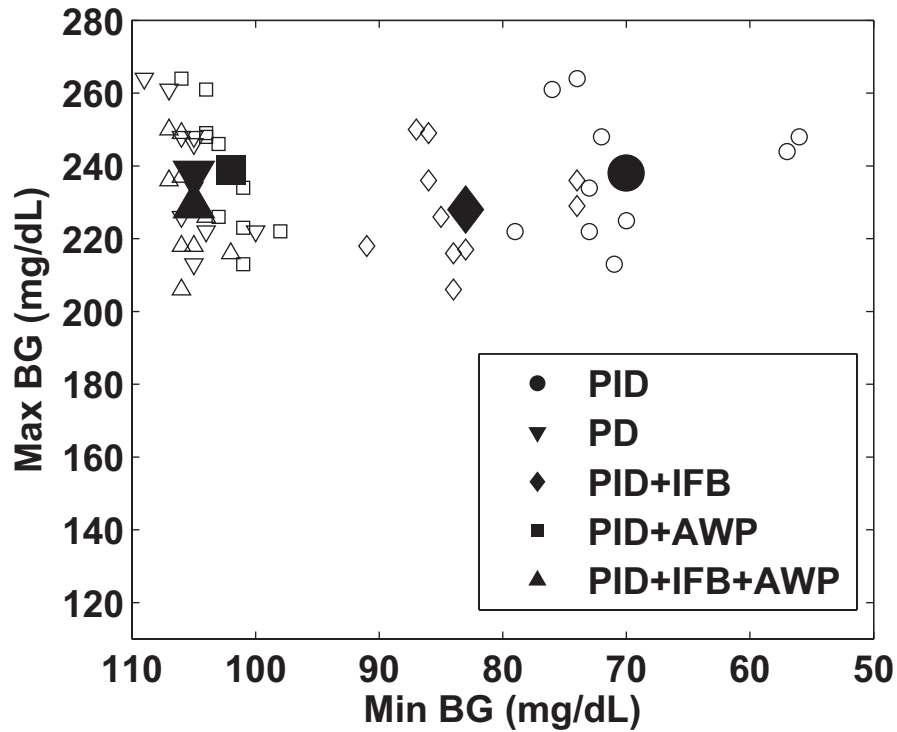


Figure 5.9: Plot of the maximum BG versus the minimum BG following a 100 g CHO meal. The large icon shows the mean, and the small icons show the individual 10 subjects for each case. The PID with IFB and anti-windup strategy was able to raise the minimum BG while also lowering the maximum BG, leading to better and safer control than using either strategy alone.

Table 5.4: Comparison of results with the intraperitoneal system to those achieved with the subcutaneous system in a previous study (shown as mean (standard deviation)).

	IP System	SC System [82]
Scenario 1 Max BG (mg/dL)	229 (15)	279 (14)
Scenario 1 Min BG (mg/dL)	105 (1.6)	92 (3)
Scenario 2 Return to setpoint (h)	20-30	≈80
Scenario 3 Return to setpoint (h)	20-30	≈80

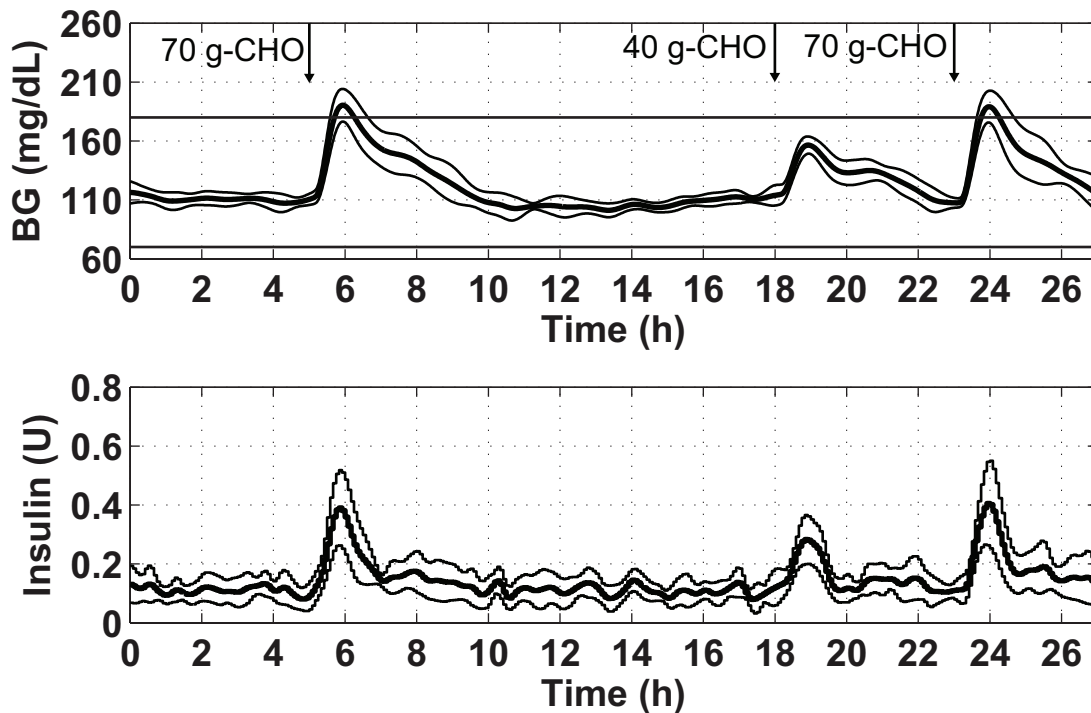


Figure 5.10: Simulation evaluation of the final controller design. Blood glucose and insulin trace for the final controller design evaluated on 10 *in silico* subjects using the 27 hour protocol from Scenario 4. The acceptable glycemic zone of 70-180 mg/dL is shown by the black horizontal lines on the top panel. The thick line shows the mean of the 10 subjects, and the thin lines show plus and minus one standard deviation.

model available due to the paucity of data. The SC sensor noise model included in the simulator is described in Breton, et al. [183]. The results are shown in Figure 5.10.

The controller was able to maintain the BG within the tight glycemic range of 80-140 mg/dL for 79% of the time, even in the presence of measurement noise. The added noise did cause a lower minimum BG to occur during the simulation, but hypoglycemia was still avoided. These results are comparable to those achieved in Lee, et al. using a zone MPC control strategy with IP insulin and SC sensing [200].

Table 5.5: Summary of the numerical results from the final controller evaluation.

Max BG (mg/dL)	Min BG (mg/dL)	% Time BG 80-140 mg/dL	% Time BG<70 mg/dL	% Time BG>180 mg/dL
196 ± 14	93 ± 7.3	78 ± 6	0 ± 0	5 ± 4

5.4 Discussion

An AP that uses IP insulin combined with IP sensing has the potential to greatly improve closed-loop glycemic control. Since IP insulin has faster pharmacokinetic and pharmacodynamic characteristics than SC insulin, the AP will be able to bring the BG back to the desired setpoint faster after glycemic disturbances occur. Also, since the insulin is cleared more quickly, there is less risk of hypoglycemia due to delayed insulin action [195, 231].

In this study, the tuning of the PID controller was informed using robust stability and performance analysis. The robustness of the controller is of great importance, due to inter- and intra-patient variability in the response to insulin. The controller was designed to maintain robust performance and stability even in the presence of 50% gain uncertainty and 10 minute delay uncertainty. These estimations of uncertainty were based on Lee, et al. [188], and are intended to capture changes in insulin sensitivity that can occur throughout the day, as well as unexpected delays due to measurement dropouts, temporary pump failures, or other problems.

The addition of the anti-reset windup strategy used in this work decreases the risk of hypoglycemia after meals, without increasing time spent in hyperglycemia. In addition, setpoint tracking is maintained following changes in insulin sensitivity. The anti-reset windup strategy used in this chapter can also be applied when SC

insulin is used, although the tuning factor may need to be adjusted. This method is recommended because it dynamically adjusts the amount of integration based on the situation, leading to better control for both large, temporary disturbances and smaller but persistent disturbances.

IFB is an important addition to an AP controller because it imitates the physiology of the human body. Increased plasma insulin concentration inhibits the delivery of more insulin, meaning there is less chance for insulin stacking and hypoglycemia. IFB was initially introduced after the first clinical study of PID control with SC insulin resulted in postprandial undershoot leading to hypoglycemia [79]. A following clinical study applying IFB showed that the postprandial hypoglycemia was reduced, but there were still episodes requiring rescue CHO to be delivered [77, 232]. Our study shows that IFB alone is not enough to attenuate postprandial undershoot, and that an anti-reset windup strategy in combination with IFB provides the best results. A more accurate model of insulin pharmacokinetics may lead to improved performance of the IFB algorithm. We recommend that such a model be identified before *in vivo* studies using IFB with IP insulin are conducted.

There are other benefits to using intraperitoneal insulin delivery beyond faster insulin action. This route better mimics the natural insulin production process by the pancreas. When the insulin is delivered into the intraperitoneal space, it introduces a positive portal-systemic insulin gradient throughout the body. This gradient is expected to lead to better overall health. Other hormones involved in the metabolism are also affected by the use of IP insulin, and there is some evidence to suggest that the benefits of IP insulin use extend beyond improved glycemia. A thorough explanation of these benefits is presented in Van Dijk, et al. [19].

5.5 Conclusions and Future Work

A fully implanted AP operating in the IP space allows many of the challenges associated with subcutaneous insulin delivery to be overcome. Faster insulin transport and action, along with more rapid glucose sensing, allow the controller to maintain excellent glycemic control. In addition, IP insulin delivery may also have beneficial endocrine effects, as discussed in van Dijk, et al. [19]. In this chapter, a model-based tuning strategy was introduced to develop a PID controller for a fully implantable AP. Furthermore, a dynamic anti-reset windup strategy was applied to minimize undershoot of the setpoint after meals while still maintaining setpoint tracking. IFB was also added to improve the controller response. This design may be further refined with the development of more accurate models based on experimental data. Once this data has been collected and analyzed, the updated controller will be evaluated in an animal model to quantify the improved performance offered by this controller *in vivo*.

Chapter 6

Conclusions and Future Work

This dissertation explored the impact of sensing and actuation characteristics on the closed-loop artificial pancreas (AP) for people with type 1 diabetes mellitus (T1DM). Conclusions from this work are presented below. Additionally, recommendations for future work building from this dissertation are discussed.

6.1 Conclusions

Under current standards of treatment, people with T1DM must manually monitor their BG and deliver insulin as needed. This process is difficult to accomplish, and often results in hyperglycemia or hypoglycemia, both of which lead to long- and short-term health complications. New developments in medical device technology, such as the invention of insulin pumps and continuous glucose monitors (CGMs), have provided additional tools to aid people in managing this disease, but even these advanced tools still require manual monitoring, decision-making, and ongoing education on the part of the user.

In this dissertation, the application of process control to T1DM treatment was

explored. The development of an AP system to automatically deliver insulin using feedback control based on CGM measurements will lead to better health outcomes for people with diabetes, while also reducing the amount of effort required for successful treatment. The necessary components of an AP are a CGM, a control algorithm, and an insulin pump, plus a means of communication between the three. State-of-the-art implementations of the AP being evaluated in clinical trials use both subcutaneous (SC) glucose sensors and SC insulin pumps. These trials have shown promising results, but there is still room for improvement, especially during the postprandial period and other times when the BG is changing rapidly. Most SC-SC designs are hybrid systems that require the user to announce a meal to the controller to trigger a preemptive preprandial insulin bolus in order to achieve satisfactory results. The use of the intraperitoneal (IP) space as an alternative site for insulin delivery and glucose sensing is expected to reduce the lags in the control loop and improve AP performance, allowing for a fully implantable, fully automated glucose regulation system.

6.1.1 Clinical Evaluation of the AP in Adolescents

As discussed in Chapter 2, an AP system using zone model predictive control (ZMPC) and the Health Monitoring System (HMS) hosted on the Diabetes Assistant (DiAs) mobile platform was evaluated for feasibility in the adolescent population. Adolescents frequently struggle to meet the recommended glycemic control criteria, making them excellent candidates for AP use. The study took place in the outpatient hotel environment with highly ambulatory conditions, thus serving as a transition between the inpatient setting and the fully unsupervised outpatient setting. The protocol included mild to moderate intensity exercise sessions at least twice per day that were not announced to the controller. There were also free-choice announced

meals to emulate free-living conditions.

Ten adolescents with T1DM completed 72 h of closed-loop control (CLC) during this trial. The study showed that the ZMPC+HMS/DiAs system was feasible for use in the adolescent population in a highly ambulatory hotel environment with frequent unannounced exercise and announced meals. During CLC, the subjects spent 71% of time in the desired range of 70-180 mg/dL. Additionally, the controller was able to react to changes in the CGM during exercise sessions to suspend insulin delivery as needed. The ZMPC+HMS algorithms were determined to be feasible for use in adolescents. The results from this preliminary study indicate that an AP using the ZMPC+HMS algorithms is likely to improve glycemic control in this population as compared to the standard therapy.

6.1.2 Modeling of Glucose Sensor Dynamics

CGMs placed in the SC space are known to experience a measurement lag caused by the diffusion of glucose from the blood vessels to the interstitial fluid. It was hypothesized that a CGM placed in the IP space would have a smaller lag than one placed in the SC space due to the increased proximity to major vasculature. The study presented in Chapter 3 was conducted to compare the response of enzymatic CGMs placed in the SC and IP space of non-diabetic swine, which provides a model for the human endocrine system. Multiple sensors were placed in the IP, SC, intravenous (IV) and intra-arterial (IA) spaces of eight animals. BG measurements were also taken using a glucometer. The IP and SC sensor signals were modeled as a function of the BG to determine the time constant of the sensor response. The results showed that the sensors placed in the IP space were characterized by a time constant that was approximately half that of sensors placed in the SC space of the same animal. This study demonstrated that IP sensor placement is a promising alternative to SC

placement, especially for use in AP applications.

A follow-up study was done to investigate the effects of long-term implantation of fluorescent CGMs in the IP versus SC space of a non-diabetic sheep. Fluorescent sensors may be better suited for long-term implantation than enzymatic sensors due to their demonstrated longevity. The purpose of this study was to provide the proof-of-concept of a novel flushing mechanism developed by TheraNova, LLC to prevent sensor encapsulation, which is known to deteriorate the sensor response. The mechanism was used to flush the IP sensor with saline, thus cleaning the surface and allowing the sensor to maintain the same level of responsiveness over three months. Further investigation with an increased sample size will determine whether the flushing mechanism creates a significant improvement in sensor response as compared to non-flushed sensors in the IP space.

6.1.3 Impact of Sensor Dynamics on AP Performance

Several studies have demonstrated that the use of an insulin delivery route with faster pharmacokinetic and pharmacodynamic properties can lead to improved AP performance. In Chapter 4, a parallel study was conducted to determine the impact of glucose sensor dynamics on the control achieved by an AP. An initial analysis was done to evaluate the error caused by a dynamic lag in the glucose measurement. The study showed that a dynamic lag as large as 30 min resulted in a point-wise sensor accuracy that would be considered clinically acceptable; however, the dynamic nature of the error could be detrimental to AP performance.

A proportional-integral-derivative (PID) controller was designed using a model-based method to evaluate the impact of sensor dynamics on an AP using IP or SC insulin. Due to intra- and interpatient variabilities in the response to insulin, model uncertainty is an important consideration in the development of an AP system. An

analysis using robust performance and robust stability criteria determined that decreasing the sensor lag resulted in a system that was more robust to model uncertainty.

In order to analyze the effect of sensor lag on the glycemic control achieved by an AP, the glucose sensor model developed in Chapter 3 was integrated into the University of Virginia (UVA) and University of Padova metabolic simulator. This metabolic simulator allows AP controllers to be evaluated on 10 *in silico* patients with T1DM using either IP or SC insulin. The addition of the glucose sensor model allowed the sensor lag to be specified for the simulation. A series of simulations were conducted to evaluate the performance of the PID controller using either IP or SC insulin with a sensor time constant varying from 0 to 30 min. Decreasing the sensor lag was found to significantly decrease the time spent in hyperglycemia following a meal challenge. While designing the AP to use IP insulin rather than SC insulin results in a large improvement in the quality of glycemic control achieved, the results can be improved even further by decreasing the lag in the glucose sensor.

6.1.4 Implantable Artificial Pancreas Design

As discussed in Chapters 3-5 of this dissertation, the performance of the AP can be improved by altering its design in order to reduce lags in the control loop. A fully implantable AP using devices placed in the IP space is a promising solution. The IP placement will reduce the delays in both insulin action and glucose sensing that are currently experienced with SC devices. Additionally, the use of IP insulin better mimics physiological insulin delivery by the pancreas, and therefore may lead to better metabolic health. A fully implanted system will also eliminate the inconvenience of having external devices attached to the skin, along with the need to perform frequent infusion set and CGM changes.

In Chapter 5, a procedure for robust PID controller design for a fully implantable AP was presented. The tuning parameters were selected using internal model control, leaving a single tuning parameter to determine the robustness of the controller. This parameter was selected to be as small as possible while still maintaining robust performance and stability for the anticipated model uncertainty.

The controller was evaluated in a series of simulation studies in the UVA/Padova metabolic simulator. The initial design was found to result in an undesirable undershoot of the setpoint following a meal. An anti-reset windup strategy was implemented to eliminate this undershoot by attenuating the buildup of the integral term when the measured variable is far from the setpoint. Incorporating this strategy into the controller eliminated the undershoot, while still maintaining setpoint tracking in the case of a change in insulin sensitivity.

Insulin feedback (IFB) was also incorporated into the controller design. The IFB algorithm uses a model to estimate the concentration of insulin in the blood and modulate the insulin delivery computed by the controller accordingly. This physiologically inspired method prevents insulin over-delivery when there is already active insulin in the body. Incorporation of the IFB algorithm using a model for IP insulin pharmacokinetics from the literature resulted in safer control by delivering less insulin once there was already a high concentration of insulin in the blood following a large meal. The final controller design incorporated the IFB algorithm in combination with the anti-reset windup strategy, as this configuration lead to the best results in the simulation studies.

6.2 Recommendations for Future Work

The work presented in this dissertation can be expanded upon to generate further progress in the development of the AP. Potential future directions for work are described below. Two main topics are discussed: future work in the outpatient clinical evaluation of the ZMPC+HMS/DiAs system (a continuation of the work presented in Chapter 2) and future work towards the development of a fully implantable AP (a continuation of the work presented in Chapters 3-5).

6.2.1 Outpatient Use of the ZMPC+HMS/DiAs System

In Chapter 2, the evaluation of the ZMPC+HMS/DiAs system in adolescents in the transitional hotel environment was presented. This study protocol emphasized frequent physical activity and free-choice meals to emulate the conditions typically experienced by active adolescents with T1DM. The results from this trial established feasibility of the system in this population and setting, but there is still more work to do to establish efficacy as compared to subjects' usual therapy, especially over longer periods of time and in the unsupervised fully outpatient environment.

A follow-up study to the one presented in Chapter 2 is currently underway at Stanford University and the Barbara Davis Center for Diabetes. This study is following a supplemental protocol that was submitted to the Food and Drug Administration (FDA) to expand upon the work from the initial study. A total of 20 adults will use the ZMPC+HMS/DiAs system for two weeks of CLC in the unsupervised fully outpatient setting. The Automated Notification System (ANS), part of the DiAs Web Monitoring system, is in place to alert clinical staff on-call to any potential safety risks during CLC. Additionally, fault detection algorithms developed at the University of

California San Diego and Rensselaer Polytechnic Institute will be run in real-time to evaluate their ability to detect failures in the insulin infusion set or CGM. These types of fault detection algorithms are important to include in an AP to improve the safety of the design, as an undetected failure of the insulin infusion set or glucose sensor could lead to a health risk such as diabetic ketoacidosis.

One advantage of this study is its randomized crossover design. Half of the subjects will use their usual sensor augmented pump therapy (SAP) during the first two weeks, while the other half will use CLC. Then each subject will switch to the other therapy for the second two weeks. This crossover design, combined with the extended CLC period of 2 weeks rather than 3 days, will allow the efficacy of the system to be evaluated. However, unlike the first study, the subjects in this trial are all adults. This transition was made because the AP system requires too much interaction to be practical for use by adolescents attending school. Additionally, it may be necessary to first demonstrate the safety and efficacy of fully unsupervised outpatient use of the ZMPC+HMS/DiAs system in the adult population before performing studies in the higher-risk adolescent population. It is anticipated that this criteria will be met soon, as the ZMPC+HMS/DiAs system is already being evaluated in a separate 12 week fully unsupervised outpatient study in adults.

One weakness in the ZMPC+HMS/DiAs system revealed by the clinical study is the frequent disruption of communication that can occur between the CGM or insulin pump and the DiAs system. While clinical staff were on-site to assist the subjects with reestablishing communication between the devices, this type of disruption may cause more time to be spent out of closed-loop in the unsupervised outpatient environment if users become frustrated with the device or cannot respond to disconnections in a timely manner. Device usability is an increasingly important factor to include in the design as the system moves further from being an experimental device and closer to a

commercial product. An AP system that requires frequent adjustment or interaction to remain in CLC may not be acceptable to patients. It will be important to include user satisfaction surveys as part of the longer outpatient clinical trials in order to receive feedback on user needs for the device. The user feedback can be used to prioritize which features should be enhanced or changed by research engineers.

An important area for further engineering research is the optimization of the method used to incorporate the announced meal bolus within the ZMPC+HMS system. The results from the study in Chapter 2 revealed a pattern of hypoglycemia in the period 2-4 hours following a meal. It is possible that this hypoglycemia occurred due to the over-estimation of the meal size used to calculate the bolus, or due to a sub-optimal insulin to carbohydrate ratio. The current iteration of the ZMPC+HMS/DiAs system delivers only 80% of the calculated meal bolus if the BG value entered with the meal announcement is less than 120 mg/dL. This reduction is intended to reduce potential hypoglycemia following the meal. The full bolus is given for meals announced with a BG greater than 120 mg/dL, with an additional correction dose to 150 mg/dL if the BG is higher than that value.

While the meal bolus scheme has provided acceptable results in clinical studies, its performance could potentially be improved by altering its parameters. As more clinical data is gathered from the outpatient studies described above, each meal announcement (size, SMBG, and resulting bolus amount) should be examined to determine whether any of the meal announcement factors were correlated with hypoglycemia in the postprandial period. Additional factors could be examined for inclusion in the meal bolus calculation, such as the current rate of change of the CGM. Inclusion of an additional correction bolus when the controller has already acted and the CGM is high but decreasing could lead to an over-delivery of insulin. Using the CGM rate of change in the bolus calculation could potentially prevent this

over-delivery.

The clinical study showed that the controller responded as desired to exercise, but there were still some hypoglycemic episodes with $\text{CGM} < 70 \text{ mg/dL}$ that occurred during or after the exercise periods. Since the exercise was not announced to the controller, it was not able to take action in the form of a pump suspension until the feedback from the CGM indicated a rapid decrease or movement toward hypoglycemia. A promising area of research is the inclusion of an algorithm to detect exercise based on heart rate and accelerometer data. In a clinical study, a detection algorithm using principal component analysis based on these two signals was able to detect the start and end of exercise in approximately 5 min, before the CGM had changed noticeably [233]. This algorithm could be added to the AP system to detect the exercise and adjust the insulin delivery accordingly. The action taken when exercise is detected could be to raise the target zone, to reduce the controller gain, or to use a lower basal rate of insulin. Each of these options should be investigated to determine which would best decrease the risk of hypoglycemia during exercise.

6.2.2 Towards a Fully Implantable Artificial Pancreas

In Chapter 5, a procedure for designing and evaluating a robust PID controller for a fully implantable AP was presented. The control algorithm was designed and tuned using models that were available in the literature [229] and identified from the UVA/Padova metabolic simulator [200], and its performance was validated *in silico*. The next step in this project will be to evaluate the implantable AP *in vivo* in an animal model, as the system must first be shown to be safe in the animal model before it can be tested in human studies. Before testing the controller in the animal model, a crucial step will be to perform a system identification in the particular animal species with the specific devices and insulin formation that will be used in the closed-loop

testing. The models can then be updated to be accurate for this system, which will lead to optimal results.

Collaborators have been identified who will conduct the system identification and closed-loop experiments in canines, which are frequently used as a model in T1DM research. A diabetic state can be induced in the animals either through surgery or medication. The animal will be equipped with the implanted insulin pump and glucose sensor, as well as a line for sampling intravenous blood. The system identification experiments will begin with the animal in hyperglycemia. An IP insulin bolus will then be administered to reduce the BG to the upper end of the euglycemic range. After the BG has stabilized, another bolus will be delivered to bring the BG to the lower end of the euglycemic range. Once again, after the BG has stabilized, a third bolus will be delivered to bring the BG to a mild hypoglycemic state. At this point a glucose bolus will be delivered to quickly raise the BG to the euglycemic range. The following data will be recorded throughout the testing period: plasma insulin concentration over time, plasma glucose concentration over time, signal from implanted glucose sensor over time, quantity of glucose delivered, and quantity of insulin delivered. The experiment should be repeated in at least two additional animals, and may also be repeated in the same animal.

The wealth of data gathered from the animal studies will be used to improve the models of both IP insulin pharmacokinetics and pharmacodynamic properties that are used to tune the controller and implement the IFB algorithm. The methods described in [234] and [70] can be used to assist in the modeling process. An important consideration will be to divide the data so that the model and parameters identified from one dataset can be validated on the second dataset.

The plasma insulin concentration time series will be used to identify a model describing the plasma insulin concentration as a function of insulin delivered. The

initial model structure can be the second-order transfer function described in Chapter 5, but additional model structures may be explored as appropriate based on the data. The model and parameters identified will be used in the IFB algorithm. The plasma glucose time series will be used to identify a model describing the plasma glucose concentration as a function of insulin delivered. This process model will be used to update the PID controller tuning using internal model control tuning rules. This model may also be used in the future to develop an MPC controller for this system. Lastly, the implanted glucose sensor time series will be used to identify the lag between the plasma glucose concentration and the sensor measurement. The same procedure described in Chapter 3 can be used to perform the modeling.

In addition to the *in vivo* studies, another important avenue of research will be to continue work to improve the controller design. While the PID controller was able to provide excellent results in simulation studies, an MPC design should also be evaluated as a comparison. The candidate controllers should be evaluated based on the quality of control achieved in simulation, as well as the computational complexity that will affect their ability to be embedded in a fully implanted system, where space and battery power will be at a premium.

Once the system identification has been performed and the controller design has been finalized, the fully implantable AP will be evaluated in the animal model. Animal studies are required because the implantable insulin pump and glucose sensor being used for this system are also under development and not yet approved for use in humans. These studies should include challenges to the AP system such as large meals and exercise in order to fully characterize the design performance. The studies may also be used to evaluate and select between a subset of controller designs. The results of these studies will provide the support to pursue human clinical testing.

The long term goal of this project is to evaluate the developed technology in

human clinical trials so it can move toward being approved for outpatient use by T1DM patients. Clinical evaluation of the fully implantable system will be much more complex than the current clinical studies using SC devices because surgery will be required to implant the IP insulin pump and glucose sensor. Additionally, before the system can be used in humans, an additional system identification step will need to be carried out to convert the model parameters from the animal system to the human system.

A protocol will be developed for a proof-of-concept study to show that a fully implantable IP-IP system can provide control successfully in human subjects. After analyzing the outcomes of this pilot study, a more extensive clinical trial design will be developed to compare the fully implantable system to a system using SC devices. The hypothesis will be that the fully implantable controller will be able to maintain more steady control of the BG, with better meal compensation than the SC-SC system.

6.3 Summary

The dream of an AP that uses feedback control to provide automated treatment for people with T1DM is rapidly becoming a reality. Different versions of this device are currently being evaluated in the unsupervised, fully outpatient setting under daily-life conditions. It is only a matter of time before this technology becomes available as a standard treatment option for people with T1DM. The AP is designed to relieve T1DM patients from the burden of constant self-monitoring. In addition, it will improve glycemic control relative to what is possible with manual treatment. Improved glycemic control will lead to fewer long-term health complications, while also avoiding dangerous hypoglycemia.

A crucial part of the AP control scheme, no matter which algorithm is used, is

the choice of sensor and actuator. For this reason, it is important to understand the performance and capabilities of these devices. By characterizing different routes of glucose sensing and insulin delivery and their impact on the AP performance, safer and more effective controllers can be created to meet the treatment needs of people with T1DM.

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Appendix A

Artificial Pancreas Clinical Bibliography

There have been many clinical evaluations of the artificial pancreas (AP) published since 2004. These studies have been compiled into a database to be used by the research community to analyze trends and inform future decisions about protocol design. At the time this dissertation is published, the searchable database of clinical studies is publicly available at www.thedoylegroup.org/apdatabase. The following pages contain a bibliography of all of these studies as of May 2016. The studies are sorted in descending order by date.

List of Published AP Clinical Studies

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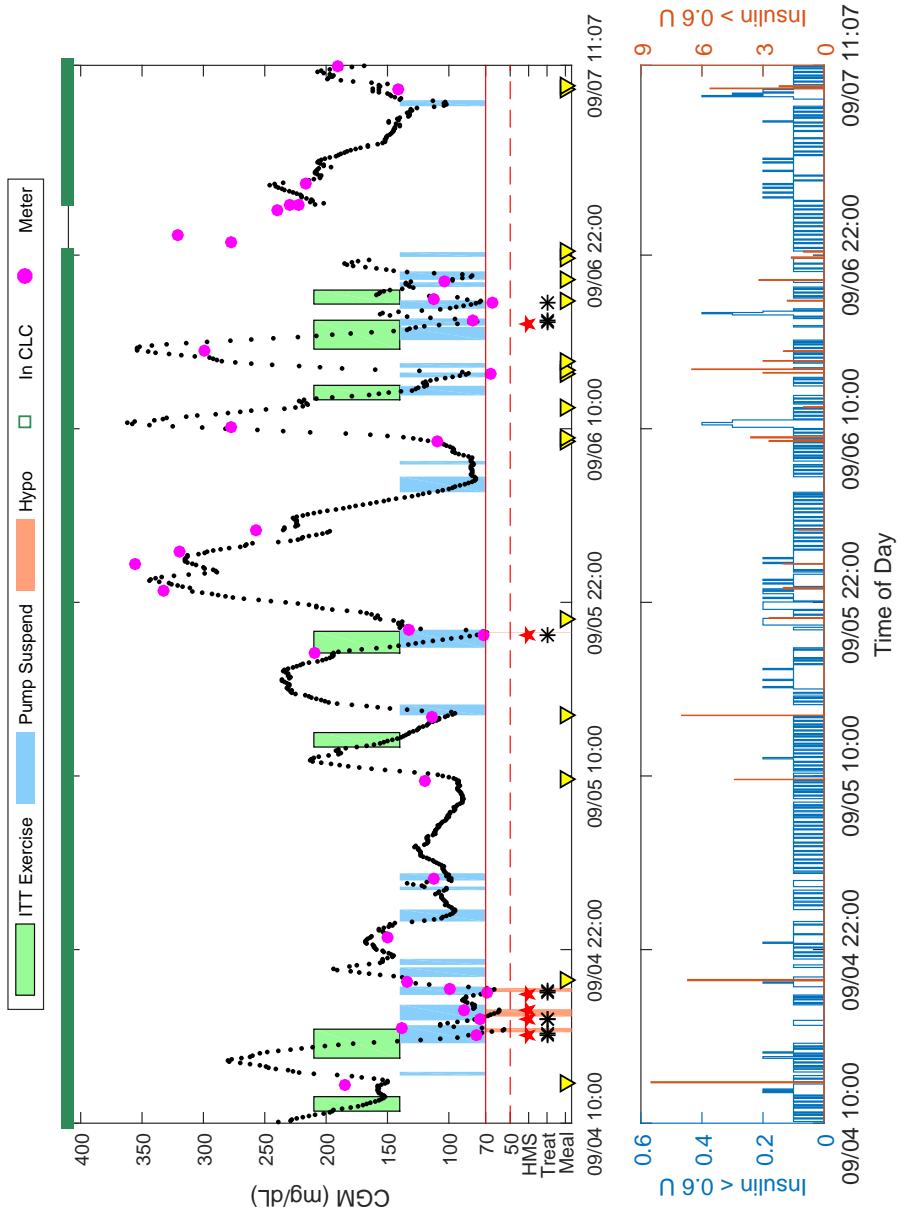
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Appendix B

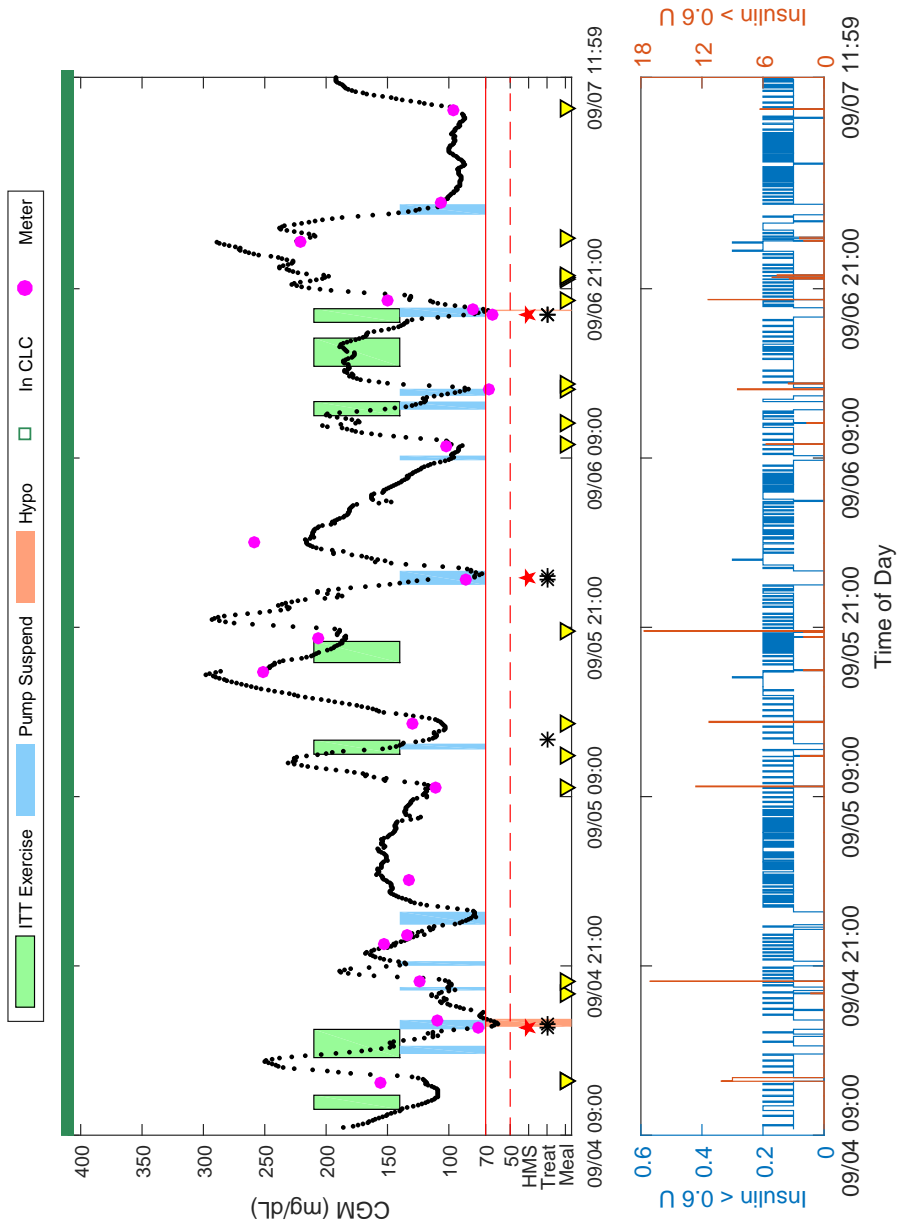
Individual Glucose Traces

The following pages contain the individual glucose and insulin traces for each of the 10 subjects from the clinical study presented in Chapter 2. This study is registered on clinicaltrials.gov with clinical trial registration number NCT02506764. The legend for each graph is as follows: (Top) The CGM is plotted over time as black circles. The red solid and dashed lines show hypoglycemia thresholds of 70mg/dL and 50mg/dL. The green shaded areas show times of exercise, the blue shaded areas show times of pump suspension and the red shaded areas show times where the CGM was less than 70mg/dL. The magenta circles show the meter glucose values. The red stars indicate the time of HMS alerts, the black asterisks indicate the time of carbohydrate treatments, and the yellow triangles indicate the time of meals. (Bottom) The insulin is plotted over time. The left axis shows insulin doses that were less than 0.6U and the right axis shows insulin doses that were greater than 0.6U.

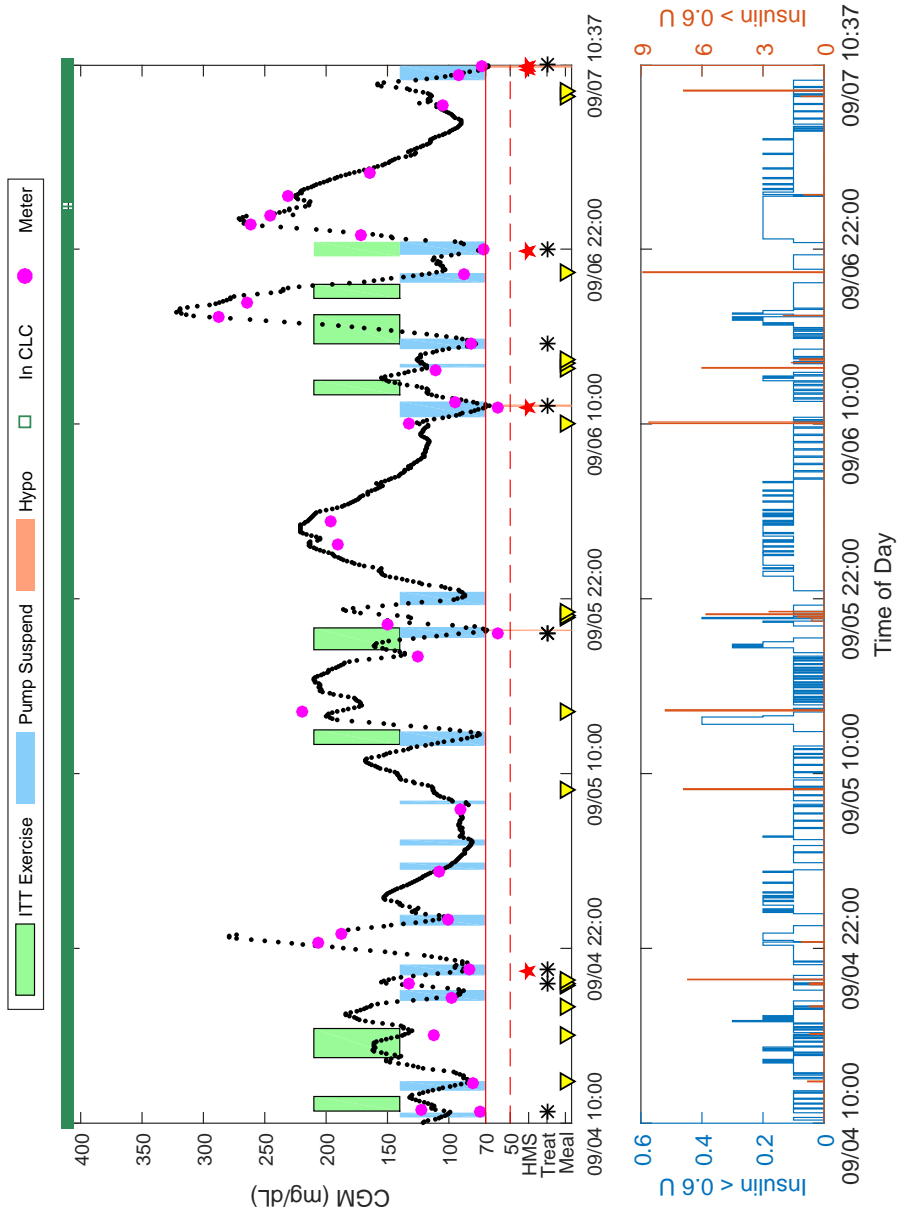
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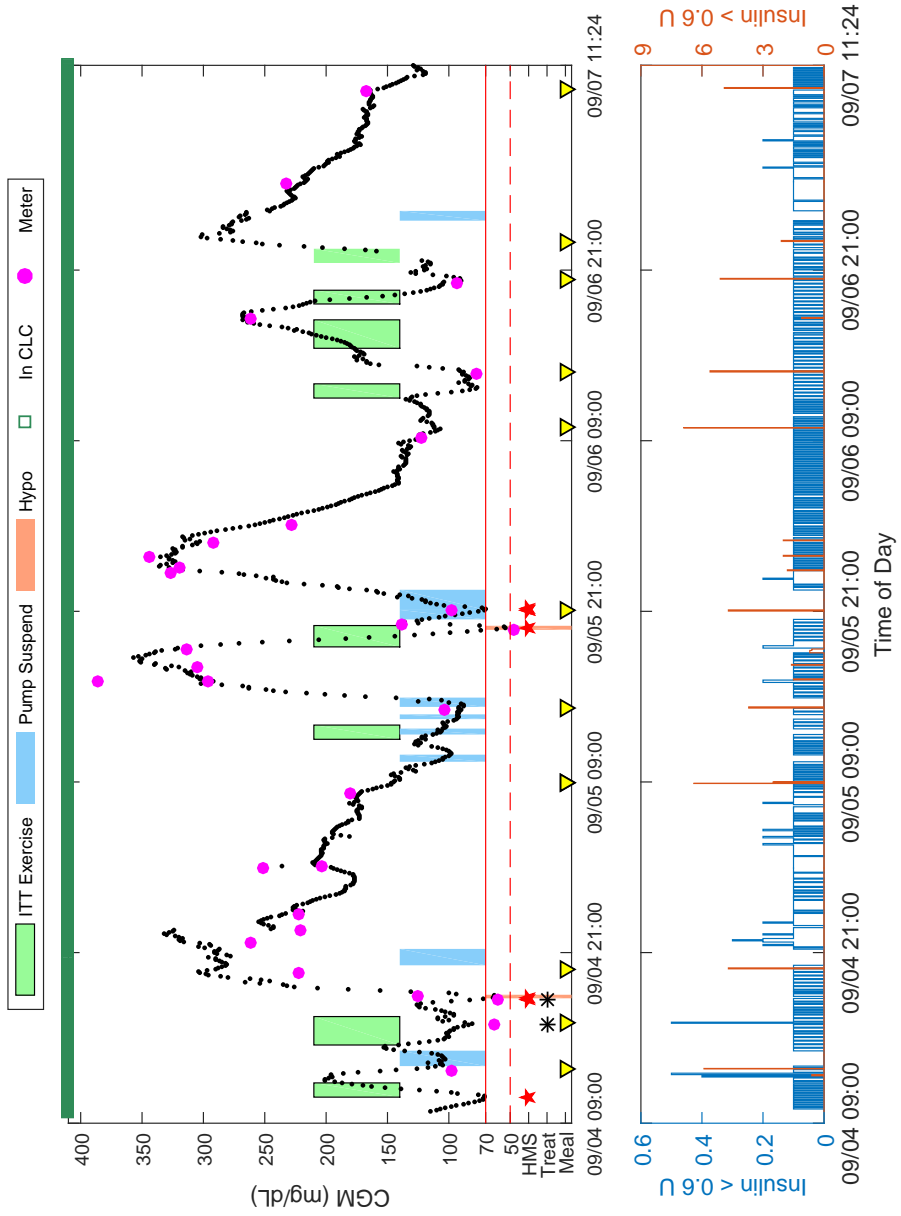
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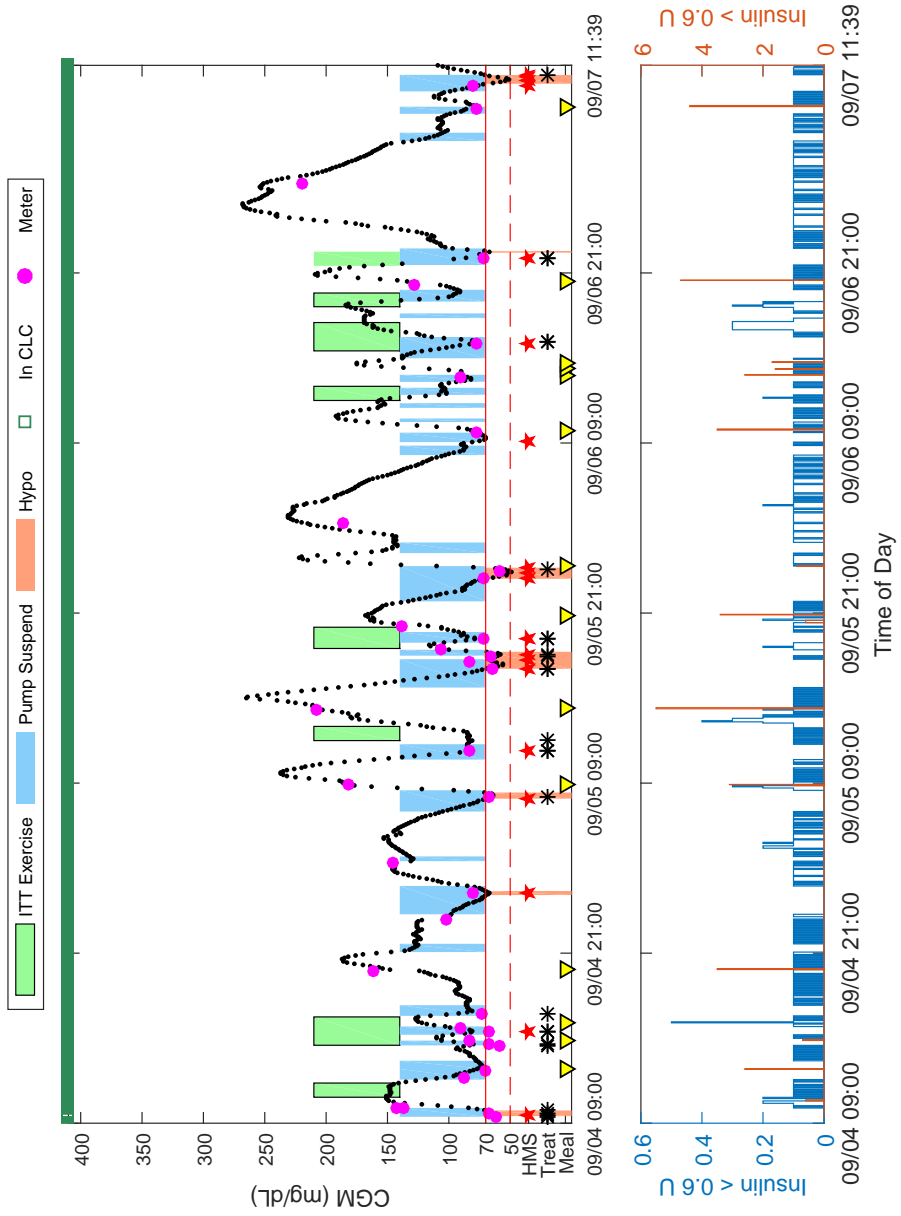
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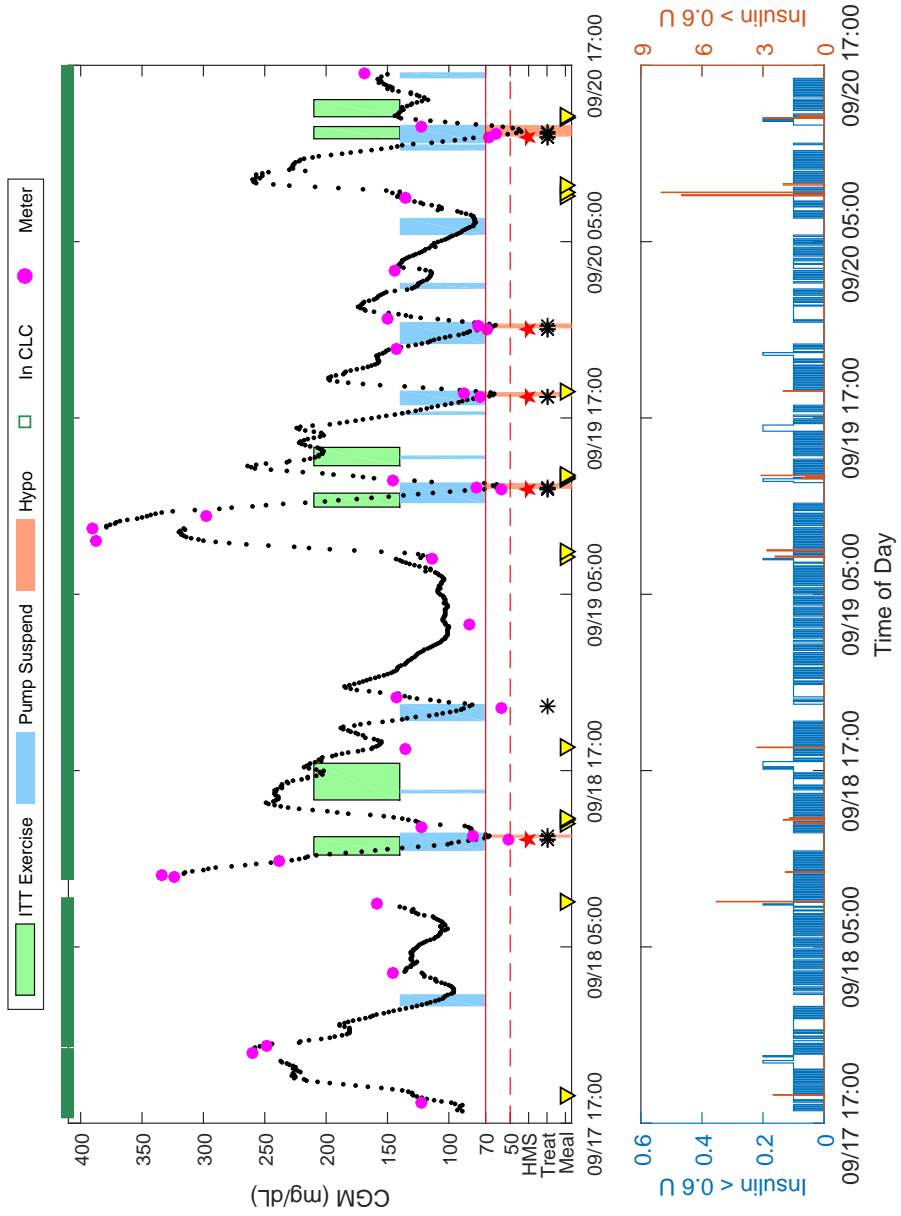
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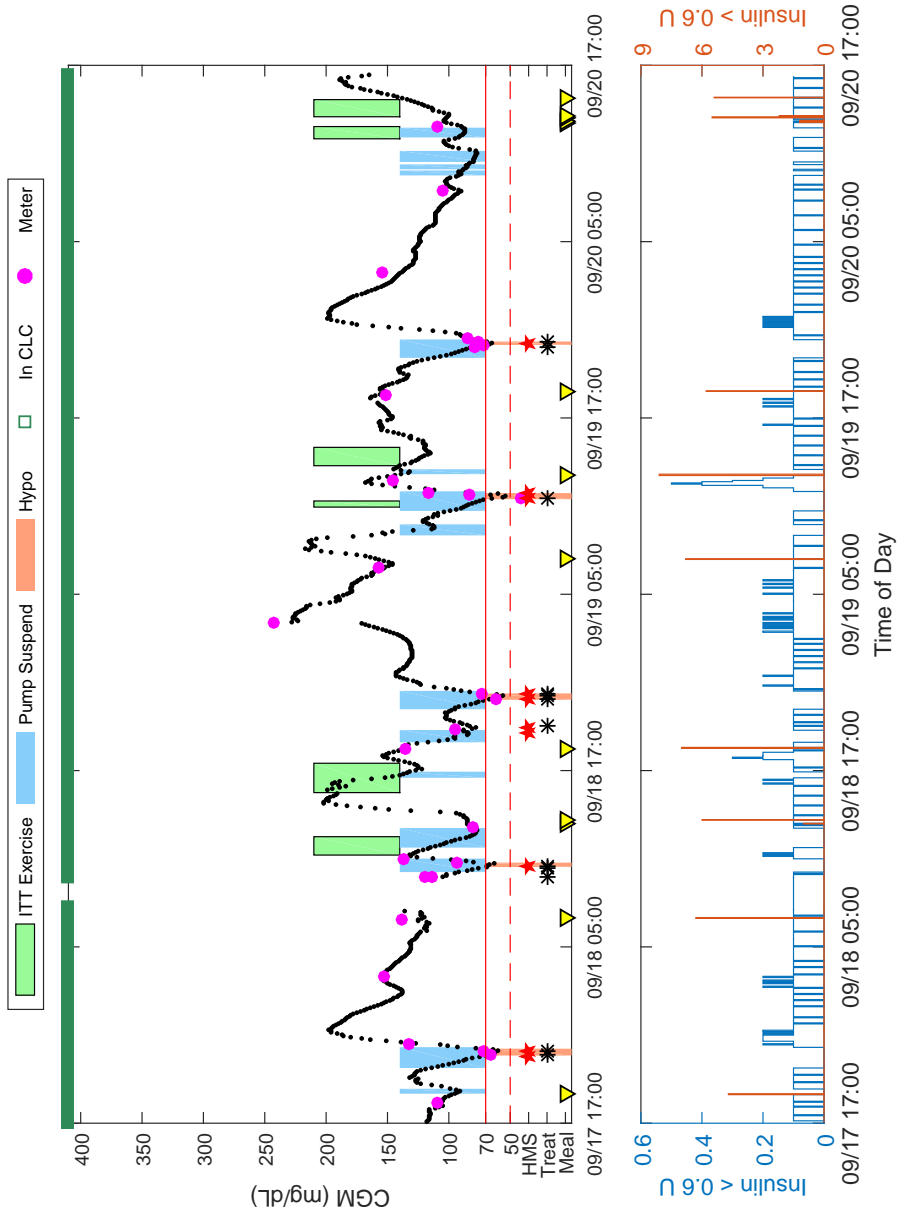
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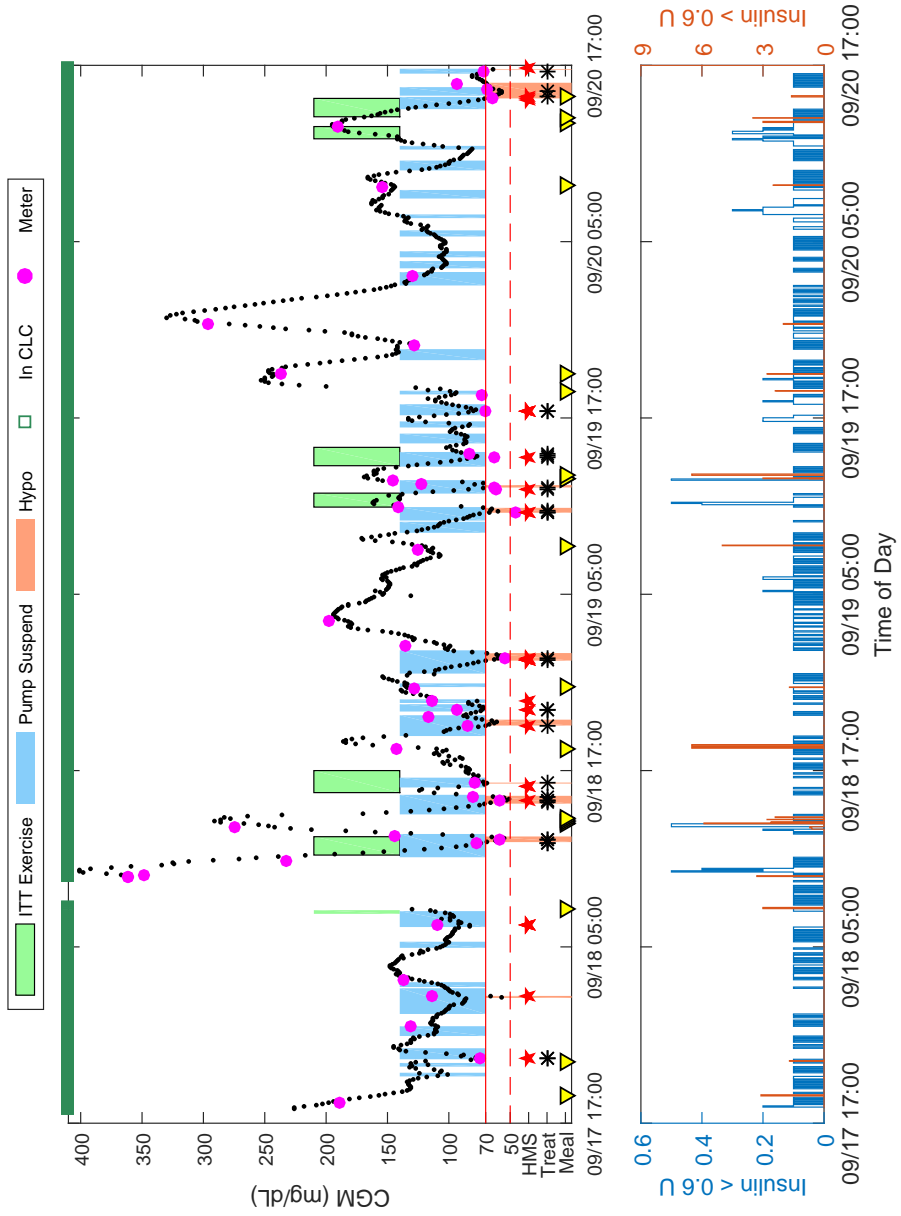
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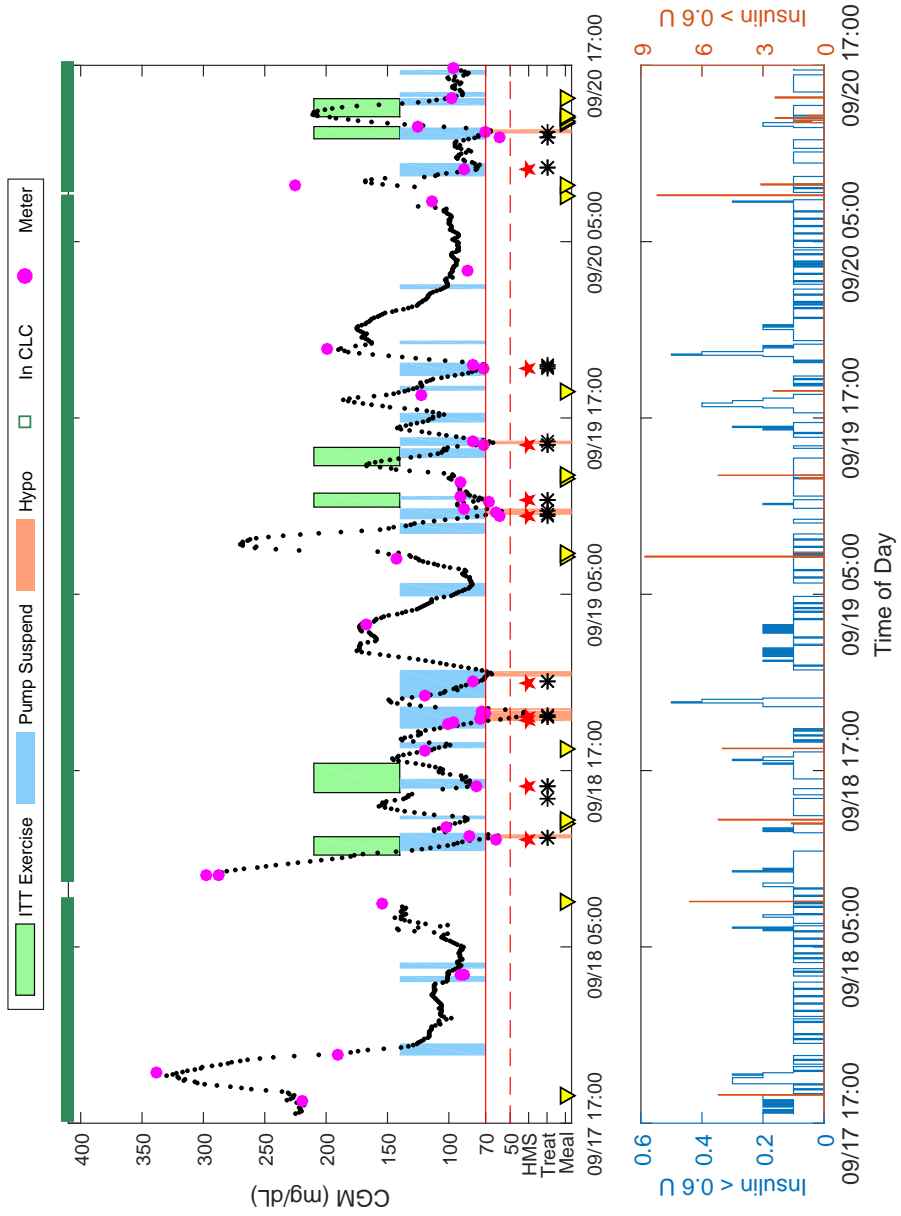
Subject 7



Subject 8



Subject 9



Subject 10

