**NTNU – Trondheim**
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# Pulsatile insulin infusion in closed-loop glucose control in diabetes mellitus type 1

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# Problem description

The Department of Engineering Cybernetics at NTNU has recently established the Artificial Pancreas Trondheim (APT) research group in cooperation with St Olavs Hospital and Faculty of Medicine at NTNU. In this assignment you are to design and assess a control system suitable for APTs approach for glucose control.

- Give a brief presentation of the glucose and insulin dynamics in humans with diabetes mellitus type 1 or 2, as well as in humans without diabetes. Describe extensions of a given mathematical model which can be used for in-silico studies of control algorithms.
- Select and implement suitable extensions into the existing MATLAB/Simulink-model.
- Discuss the theoretical aspects of implementing pulsatile intravenous infusion (Skjærvold, 2013) or pulsatile intraperitoneal infusion for the APT model. This may include possibilities for adaptive control.
- Implement the pulsatile insulin infusion for the APT model. Compare the controller performance to the control strategies already implemented (PID and MPC) for intravenous and intraperitoneal infusion sites.
- Discuss the results in terms of clinical relevance and consequences for the patient

# Preface

This thesis has been written as a part of my master degree in Engineering Cybernetics at the Norwegian University of Science and Technology. The project was given by the Artificial Pancreas Trondheim research group. I would like to thank my supervisor Øyvind Stavdahl, co-supervisors Anders Fougner and Konstanze Kölle, as well as Artificial Pancreas Trondheim research group for help during the thesis.

# Abstract

Diabetes is a chronic decease which affect the body's ability to regulate the blood glucose level(BGL). Not being able to maintain a steady BGL can lead to many severe complications. There is done much effort in order to develop a artificial pancreas. In healthy humans the BGL is regulated mainly trough insulin, which is secreted in pulses by the beta cells. This is believed to have greater hypoglycemic effect than normal continuous infusion. In this thesis a method for controlling the BGL by pulsatile infusion, both with intravenously and intraperitoneal approach was described. The pulsatile infusion showed good performance in closed loop simulations. However the effect of giving insulin in a pulsatile manner was little, giving no oscillation i BGL. In order to draw further conclusions about the controller, this effect must be included into the model.

An recursive least square scheme was implemented in order to test the possibility for adaptive control. Both the pulsatile and the normal controller gave about equal performance regarding online parameter estimation. When there was small fluctuations present, the online estimation worked in both case. Therefore it is likely that pulsatile control is more suitable for adaptive control because of the possibility for oscillations in BGL. In addition a model extension for physical activity is included into the glucose insulin model.

# Sammendrag

Diabetes er en kronisk sykdom som påvirker kroppens evne til å regulere blodsukkeret. Et dårlig regulert blodsukker kan føre til mange alvorlige komplikasjoner. Det gjøres store anstrengelser for å utvikle en kunstig pankreas. I friske mennesker reguleres blodsukkeret hovedsakelig av insulin, som skilles ut i pulser fra beta cellene i pankreas. Mye tyder på at pulsatil tilførsel av insulin gir større hypoglykemisk effekt enn hva kontinuerlig tilførsel gjør. I denne oppgaven er det beskrevet en metode for pulsatile innførsel både intravenøst og intraperitonalt. Metoden fungerte bra i lukket sløyfe simulering, men selve effekten av å gi insulin pulsatilt var liten, da det gav ingen svinger i blodsukkeret. For å kunne trekke videre konklusjoner må denne dynamikken implementeres i modellen.

En rekursive minste kvadraters metode ble implementert i modellen for å test muligheter for adaptiv kontroll. Både den pulsatile og den kontinuerlig innførselen av insulin gav omtrent samme ytelse med tanke på parameter estimering. Bare når det var små svinger tilstedte i blodsukkeret, konvergerte parameterne til riktig verdi. Derfor er det sannsynlig at pulsatil kontroll er mer egent for adaptive kontroll, da det er antatt at pulsatil insulin innførsel kan gi små svingninger i blodsukkeret. I tillegg er implementert en utvidelse for fysisk aktivitet i glukose insulin modellen.

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# 1 Introduction

## 1.1 Insulin glucose dynamics

All carbohydrates consumed by the body, gets broken down to glucose and is taken up in the bloodstream for transport, before it can be used for energy consumption inside the tissue cells. The insulin glucose dynamic is the process in the human body, which regulates the blood glucose level (BGL) to a steady level. The hormones which controls most of the process is secreted from the Islet of Lagerhans, located in the Pancreas.

There are in total around one million Islet of Langerhans, which constitutes for 1-2% of the total mass of the Pancreas.(*Diabetes research institute*, n.d.) The Islet of Langerhans consist of five major endocrine cell types called alpha, beta, delta, gamma(pp cells) and epsilon cells. The most important cell types for BGL regulation are alpha and beta cells which secretes glucagon and insulin. Around 50-80 % are beta cells and 15-20 % are alpha cell (Stefan et al., 1982). The other three cell types, delta, gamma and epsilon cells secrets the hormones somatosatin, pancreatic polypeptide and grehlin respectively.

The process start when the increased BGL is detected by the beta cells. This leads to secretion of insulin. Insulin is a hormone which primarily bounds with the receptor GLUT 4, which allows the transport of glucose through the cell membrane, so it can be used for energy consumption inside body cells, or stored inside liver cells as glycogen. To better regulate the BGL during a meal, the secretion of insulin happens in two faces. The first face is when the brain perceive a signal for food through either vision or taste. Then the signal is sent from the brain to the pancreas and insulin is secreted from the beta cells into the hepatic circulation. The presence of insulin stops the liver from breaking down glycogen to glucose(glycogenolysis). When insulin is absent the liver cells produces glucose from glycogen to ensure that the BGL do not get to low. When food

reaches the stomach, hormones from the gastrointestinal organs increases the sensitivity of glucose for the beta cells. The second phase begins when the nutrients get absorbed into the circulation and the secretion of insulin continues. When all carbohydrates are consumed, the body uses around two hours to get the BGL to normal.

The storage of glycogen is short term and if the BGl gets to low, alpha cells in the islet of Langerhans produces the hormone glucagon, which does the opposite of insulin. Glucagon makes the liver convert glucose from glycogen (glycogenolysis) and can also synthesize glucose from amino acids(gluconeogenesis) if necessary. When fasting for several hours the uptake of glucose in muscle cells is also minimized and free fatty acids is released from stored fat (lipolysis). When fasting longer than 12 hours the fatty acids becomes the main source for energy consumption for every cell in the body except for the brain which consumes glucose from gluconeogenesis on this point. The brain only uses glucose as energy source and needs a steady supply due to the lack of energy storage.

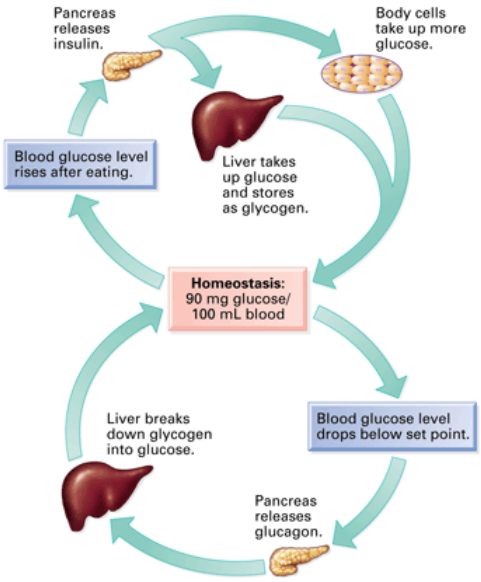


**Figure 1:** Glucose-Insulin dynamics.

A illustration of the process can be seen in figure 1. Besides insulin and glucagon which drives the main dynamic of the BGl regulation, other stress hormones contributes as adrenaline, cortisol and growth hormones.

## 1.2 Diabetes Melitus

Diabetes Mellitus is a chronic disease which affects the ability to control the BGL properly. There are different types of diabetes, where type 1, type 2 and gestational diabetes are the most common. The latter one only happens during pregnancy and is often resolved after the pregnancy but can lead to complication nevertheless. In 2013 there was estimated that 382 million people have diabetes melitus and the number is expected to rise to 592 million by year 2035 (Guariguata et al., 2014), where the prevalence for type 2 is expected to increase the most. An increase in prevalence for diabetes type 2 is often correlated with increased prevalence of obesity and it is expected that a healthy diet, physical activity and keeping a normal body weight can delay the onset of type 2 diabetes(WHO, 2011). Around 90 % of diabetics have diabetes type 2 (Alberti and Zimmet, 1998). In type 2 diabetes the the body cells do not respond appropriable to insulin. This is treatable with medicine in tablet form or in some cases, a healthy lifestyle is enough.

Whereas diabetes type 2 is the most common, type 1 is much more severe and stands for much of the complications connected with diabetes. In 2012 around 1.5 million deaths where directly caused by diabetes, over 80 % of these happened in low to middle income countries(WHO, 2014). In diabetes type 1 the beta cells produce to little or nothing insulin at all. Humans with diabetes type 1 needs therefore insulin injection in order to live a normal life.

Diabetes can also take place in intensive care patients. The hormone system is exposed for much stress when the patient undergoes for example a surgical

operation which may cause the glucose regulation to fail.

### 1.2.1 Hypoglycemia

In a healthy human the BGL lies around 4.5-5 mmol/L when fasting, considering a person with normal bodyweight. When consuming a meal the BGL will be elevated but will regulated down to normal after two hours. The BGL do normally not exceed 8 mmol/L. Not being able to proper regulate the BGL can give both short and long complication.

Hypoglycemia is a condition when the BGL drops under 4.0 mmol/l, but is often not noticed before it reaches 3.0 mmol/l. This will be life threatening if it is not treated. In diabetics this happens when a overdose of insulin is injected. In addition to having little or none insulin secretion diabetics often also have no secretions of glucagon and therefore no counter regulation. Since the insulin is injected subcutaneous, it takes some time before the insulin is absorbed into the bloodstream. Injected insulin cannot be cancelled. Hypoglycemia can be treated by just administrating glucose, in liquid or solid form. However when a hypoglycemic situation arises this needs to happen fast before the person goes into diabetic shock and can not take care of him/her.

### 1.2.2 Hyperglycemia

The opposite condition of is when the BGL get to high, which is called hyperglycaemia. This causes two problems where the most immediately problem is that most of the energy will come from metabolism of fatty acids instead of glucose which should be the primary energy source. Over some time the high level of ketone bodies may lead to diabetic ketoacidosis, which will affect the blood cells and be fatal if not treated.
The other problem is caused by having to high BGL over time. This can lead to micro and macro vascular diseases, which do damage to small or lager vessels. The most common complication is neuropathy, which is damage to nerves

and gives pain or loss of sensation for the specific area. This can lead to amputations if it progresses. Another complication is retinopathy, damage on the retina nerve. This can lead to blindness or visual impairment. Also the kidney, which have many small blood vessels is vulnerable for high BGl and may lead to dialysis or kidney transplant. These are all serious complications which are the result of bad BGl regulation.

## 1.3 Insulin infusion

### 1.3.1 Subcutaneous

Patients suffering from diabetes type 1 needs to inject insulin in order to regulate their BGL. There are three main sites to administrate insulin, subcutaneous, intravenous or intraperitoneal. The conventional therapy uses subcutaneous infusion, where the insulin is injected in the lower part of the skin. The most used method is 3-5 injections daily with an insulin pen, often in context with a meal. In order to monitor the BGL, 4-8 glucose measurement is recommended.

Another much used method is insulin pumps. This is a safer way to control the BGL in respect to hypoglycemic incidents. The pump administrates a continuous basal dose which is meant to keep the BGL stable during fasting. This dose needs to be calculated for every diabetic and can vary during the day. In addition the insulin pump gives insulin boluses to compensate for meal disturbances. This is controlled by the user. Compared with the insulin pen, the pump is much more expensive and also has the possibility to fail, because of problem with the pump itself or if the hose which delivers the insulin is blocked. Insulin injected subcutaneous gets absorbed through the subcutis before it enters the blood circulation where it affects the BGL. While the insulin gets absorbed, it forms a depot in the subcutis. This gives a long delay from injection to the effect kick in. Since the insulin also breaks down fat tissue, the time delay also varies a lot. This means that the injection site need to be changed often.

The absorption is also dependent on other parameters like blood circulation, temperature and pressure. All this give many uncertainties to the insulin injection when injected subcutaneous. Therefore good regulation through subcutaneous infusion is difficult. The main advantage with subcutaneous infusion is because the diabetic can without help, easily administrate the insulin dose.

### 1.3.2 Intravenous

A second way is intravenous injection, where the insulin is administered directly into the bloodstream through a vein. This yields for the fastest reaction in respect to insulin action for all the infusion methods. So regarding regulation intravenous infusion is the best alternative. However there are much harder to do intravenous injections compared to subcutaneous injections without any assistance. There is also a problem with having a intravenous catheter over time, because of the danger of forming blood clots, both in the catheter or in the vain. This is called thrombosis. Intravenous infusion is therefore not very well suited for daily administration of insulin. However intravenous infusion fits well for intensive care patients as they are already bedridden and there is health personnel present to handle the injections.

### 1.3.3 Intraperitoneal

A third option is intraperitoneal infusion, where the insulin is injected in the peritoneum. This gives faster and less variable absorption times than subcutaneous infusion. Peritoneum is also much closer to pancreas, where the insulin is normally secreted. The insulin is absorbed in the liver from the hepatic vain and then entering the peripheral circulation. Only half of the secreted insulin reaches the peripheral circulation. This makes the insulin concentration smaller in intraperitoneal injection compared to the other two infusion sites.

It is well established that there is a connection between diabetes and cancer, be-

cause there are to many cases where cancer and diabetes are diagnosed within the same individual.(Giovannucci et al., 2010). The exact reason for this is unclear but both diseases is associated with obesity, lack of activity and bad a diet. Since the insulin dosage given in conventional treatment is higher than needed if secreted from pancreas there is some suspicion that this is a factor for cancer as well, but there are currently no evidence that which linking insulin with cancer.(Home, 2013)

## 1.4 Artificial pancreas

Because of the extent and seriousness of the complications associated with diabetes there is much interest in creating a artificial pancreas(AP). A fully functional AP will be able to have much tighter regulation than the conventional method, insulin pens and insulin pumps have. In addition to reducing the chances for hypoglycaemic incidents, the long term complications due prolonged hyperglycemia will be reduced since the average BGL will be much lower. The goal of a AP is control the BGL with the same performance as in healthy persons.

Artificial Pancreas Trondheim is a research group, which is a cooperation between the department of engineering cybernetics at NTNU, St. Olavs Hospital and the Faculty of medicine at NTNU, have a goal to develop a artificial pancreas, which can be used in a daily life situation or in intensive care treatment. The AP should manage to keep the BGL around 4.5 mmol/L when fasting and between 4 mmol/L-8 mol/L when disturbance as activity or meal are introduced.

An AP will consist of a insulin pump together will an glucose sensor. The stability and robustness of the AP will be depended on the quality of the measurements from the sensor and the performance of the closed loop controller. A

closed loop control algorithm can be designed with or without a model. Modelless control algorithms designs a controller solely based on input and output data, which in this case is insulin and BGL. With modelless controllers there is not necessary to know the mathematics behind the process and they are often quicker to implement. On the other hand they have little predictive power and they offer little insight about the system dynamics.

Model based approaches are used since they give good understanding of the system and offers simulation possibilities without using patients. How useful a model is deepens on its accuracy. A mathematical model is often necessary, in order to do computer simulations to test closed loop algorithm. APT have therefore implemented a mathematical model of the glucose insulin dynamics in MATLAB/SIMULINK(Froyen, 2014).

# 2 Extension for the glucose insulin model

## 2.1 Insulin glucose model

When modelling the glucose insulin dynamics, compartment modelling is the most used method. In this type of modelling the system is split up in different compartments in order to describes the exchanges between them. The number of compartments and how accurate they are described determines the accuracy of the model. There are many proposed models in the literature with different complexity. Ackermans linear model (Ackerman et al., 1968) and Bergmans minimal model (Bergman et al., 1981) is two of the most cited models and describes the most basic dynamics of the insulin glucose system. Since then there have been proposed a number of more complex models like hovorka's model (Hovorka et al., 2002), Sorensen model(Sorensen et al., 1982) and the UVA/-Pandova model(Dalla Man, Rizza and Cobelli, 2007) (Dalla Man, Raimondo, Rizza and Cobelli, 2007). APT chose to implement the latter, since this has gotten approval from the Food and Drug administration to be used in preclinical trials instead of animal testing.

In short the model divides the system into different parts, the gastro-intestinal tract, liver, glucose system, muscle and adipose tissue, beta cells and the insulin system. These parts are again divided into one or more compartments for each depending of complicity. The UVA/pandova model use double subcutaneous approach, measuring glucose and administrating insulin both subcutaneous. Therefore the model was extended to also incorporate intraperitoneal insulin and intraperitoneal glucose measurement. The structure for the intraperitoneal insulin model was taken from (Matsuo et al., 2003) but because insulin in the portal vein and insulin in the rest of the blood circulation was not separated, the parameters to this model structure was found by using measured input output data from (Radziuk et al., 1994). In the intravenous approach insulin is modelled directly into the plasma which is a simplification but often used. In

addition dynamics from a glucose sensor from Glucoset was modelled, which is the sensor APT have been using in their research. The model can do simulations for diabetes type 1 and 2, and for normal persons with a functional pancreas. The model is described in detail in (Froyen, 2014).

## 2.2 Extension for the APT model

### 2.2.1 Glucagon kinetics

With a mathematical model like this it is always possible to make improvements by including new dynamics. One extension is to integrate the glucagon kinetics. This would give far more realistic simulation for normal people and for diabetes type 2. In diabetes type 1 the glucagon can be used as input in a closed loop controller to regulate the BGL better. The UVA/PANDOVA model have included glucagon kinetics into their model.(Dalla Man et al., 2014). The extension is modelled in one compartment. However the implementation was not done due to problems with finding right parameters values.

### 2.2.2 Physical activity

One other extension of the model is to incorporate physical activity. Exercise affects the body in different ways, for instance increasing heart rate, oxygen consumption and glucose uptake by the exercising muscles, which will effects the glucose insulin dynamics.

There is different approaches for modelling the behaviour of exercise in the literature. A comprehensive model given by (Kim et al., 2007) models the whole fuel homoeostasis during exercise. This is a compartmental model which divides the body into seven compartments, brain, liver, hearth, gastrointestinal tract, skeletal muscle, adipose tissue and other tissues. A simpler model presented by (Roy and Parker, 2007) incorporates the effects of exercise with respect to affecting the rate of glucose uptake, hepatic glucose production and

removal of insulin from the circulatory system, into Bergman's minimal model. Both models uses oxygen consumption as a measurement for exercise.

In (Marc D. Brenton, 2009) there is proposed a mathematical model which use heart rate to account for exercise. (Man et al., 2009) have used this model as foundations for three different models and selected one of these through in silco simulation. Compared to heart rate oxygen consumption gives a more precise measurement on exercise, but is harder to measure than heart rate. It was chosen to implement the model from (Man et al., 2009), partly because it is modelled as an extension to the UVA/Pandova which makes the implementation easier.

As mention (Man et al., 2009) suggested three different models, model A, B and C where all model the change in insulin dependent glucose uptake when exposed to physical exercise but with different accuracy and detail. The most important difference between the models are that model B dose not take into count the length or intensity of the exercise, and in model A the difference is small enough to be neglected. Model C take into count both length and efficiency of intensity and therefore was selected as the best model by the authors.

## 2.3 Mathematical formulation and implementation

The implementation is done is SIMULINK by changing the block for muscle and adipose tissue. The exercise affects the insulin dependent glucose utilization which is previously modelled as followed:

$$U_{id} = \frac{(V_{m0} + V_{mx} \cdot X(t)) \cdot G_t(t)}{K_m + G_t(t)} \tag{1}$$

with

$$\dot{X}(t) = -p_{2u} \cdot X(t) + p_{2u}[I(t) - I_b] \qquad X(0) = 0 \qquad (2)$$

Where 2 describes the insulin change outside of the cell. In order to model physical activity the insulin-dependent glucose utilization re-modelled as:

$$U_{id} = \frac{V_{m0}(1 + \beta \cdot Y(t)) + V_{mx}(1 + \alpha \cdot Z(t)W(t)(X(t) + I_b) - V_{mx}I_b}{K_m[1 - \gamma \cdot Z(t)W(t)((X(t) + I_b)] + G_t(t)} \qquad (3)$$

with

$$\dot{Y}(t) = -\frac{1}{T_{HR}} \cdot [Y(t) - (HR(t) - HR_b)] \qquad Y(0) = 0 \qquad (4)$$

$$\dot{Z}(t) = -\left[\frac{f(Y(t))}{T_{in}} + \frac{1}{T_{ex}}\right]\dot{Z}(t) + f(Y(t)) \qquad Z(0) = 0 \qquad (5)$$

$$W(t) = \int_0^t (HR(t) - HR_b)dt \quad for \;\; t < t_z, \quad else \;\; 0 \qquad (6)$$

and

$$f(Y) = \frac{(\frac{Y}{a \cdot HR_b})^n}{1 + (\frac{Y}{a \cdot HR_b})^n} \qquad (7)$$

Figure 2 shows how the different functions in the model react when exercise is simulated. When at rest(basal heart rate) the equation 3 is equal to equation 1. The basal heart rate is set to 60 beats per minute. Under exercise the heart rate is 120 beats per minute. The difference between heart rate and basal heart rate is shown in the first sub plot. The function Y(t) delays this curve in order to get a more natural increase in heart rate instead of a step. This function again activates f(Y) which drive Z(t) to one. This represent the activation of the glut-4 receptor. After exercise Y(t) drops fast to zero and forces the function Z(t) to slowly decay to zero, which is meant to model the increased insulin sensitivity which follows after exercise. The function W(t) takes into count the intensity and duration of the exercise.

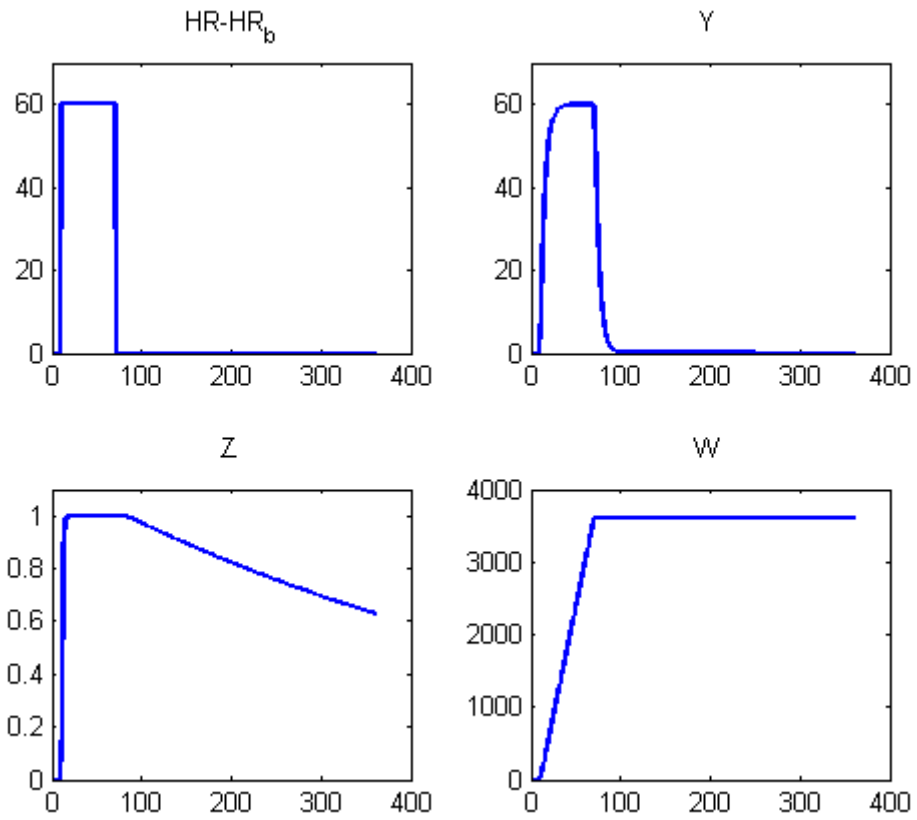


**Figure 2:** Time response for function Z, Y, W and difference in heart rate and basal heart rate

## 2.4 Simulation and Result

In order to verify the implementation of the physical activity model, it was chosen to run the same simulations as done in (Man et al., 2009) to compare the results. (Man et al., 2009) did Euglycemic-hyperinsulinemic Clamp plus exercise, exercise and meal plus exercise. In Euglycemic-hyperinsulinemic Clamp plus exercise BGL is regulated by glucose infusion. Since glucose infusion is not implemented in the APT model this simulation was not done.

In the two remaining simulations a basal dose of insulin is given to keep the BGL constant. The insulin was given intravenous in a open loop manner. The size of the basal dose was chosen to be 0.9 pmol/kg/min, found by trial and

error. The reference value for BGL was set to 140 mg/dl or 7,8 mmol/l. There is two levels of intensity, 90 beats per minute and 120 beats per minute refereed as mild and moderate exercise respectively. The basal heart rate is set to 60 beats per minute, meaning that mild intensity is 1.5 times of basal heart rate and moderate exercise is 2 times basal hearth rate. There are also two levels of duration, 15 min and 30 min, which makes in total 4 combinations. This is equal in both tests.

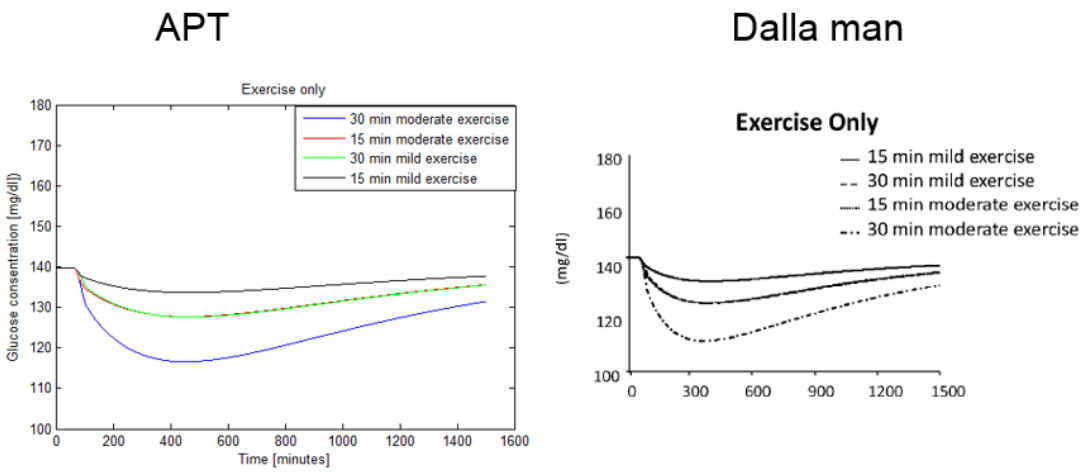


**Figure 3:** Only Exercise.

Figure 3 shows a simulation with exercise starting at t=60. The simulation is continued 24 hours(1440) min. The sub plot to the left shows the implementation done in the APT model whereas the right sub-plot is taken from (Man et al., 2009). As expected the response is pretty much equal since the models are very similar maybe. There may be differences in parameter values. The result shows that increased intensity or durations leads to higher insulin dependent glucose uptake which gives lower BGL. The BGL is affected long after the exercise is finished This is because the glucose utilization remains elevated also after exercise due to higher insulin sensitivity modelled with the slowly decreasing Z(t) function. According to the authors of (Man et al., 2009) the insulin sensitivity

is increased in 22 hours after the exercise.

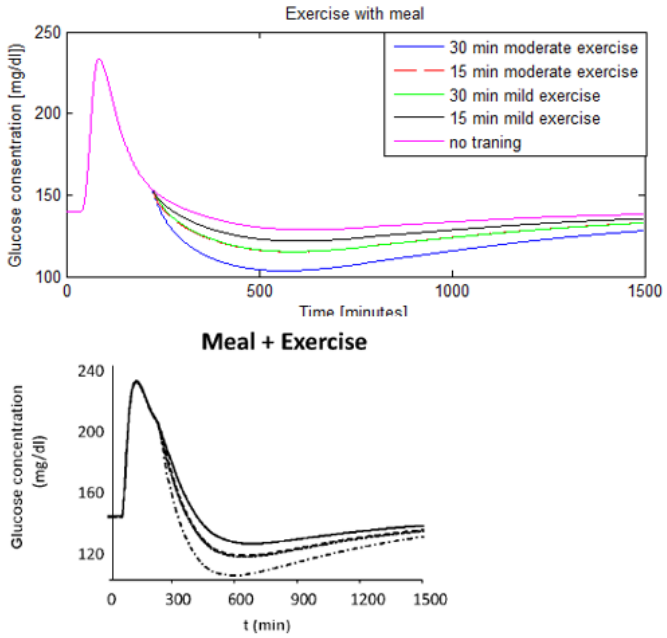


**Figure 4:** Meal plus exercise.

In figure 4 the exercise is combined with a meal. The meal contains 85 carbohydrates and is consumed from t=30 to t=50. A insulin bolus is given intravenously at the same time. Exercise is simulated three hours(180 minutes) after the meal was eaten. There are included a curve without training to see how the insulin bolus affects the meal disturbance. The response of the two models are a little different. This may come from different parameter values. The UVA/Pandova model have many different parameters sets. The parameters used in the APT model is the meal value for these set.

The physical activity model gives the possibility to simulate exercise into the glucose insulin dynamics for diabetes type 1. The model increases the insulin dependent glucose utilization during exercise. After the exercise the glucose utilization is still elevated due to the increased insulin sensitivity. The model

can simulated exercise with different intensity and duration.

## 2.5 Discussion and Remarks

There are some limitations with the model extension and the simulation. First of all the exercise is very simplified, only given as one pulse with a constant hearth rate. It is not pointed out which population with respect to gender or age the model extension is meant for. Since there is a enormous difference between having 120 beats per minute for a 20 year old male, compared to 70 year old female. Also a well trained person will manage to transport more oxygen at a lower hearth rate due to higher maximal oxygen uptake, and therefore increase the glucose utilization at a lower heart rate compared to a normal person.

Another shortcoming is how intensity and duration is weighted. This is weighted through the function W(t) and they are about equal as seen in figure 3 and figure 4, where 90 bpm(1.5 basal hearth rate) in 30 min gives approximate the same response as 120 bpm(2 basal heart rate) in 15 min. This linear relationship between glucose utilization and heart rate a simplification.

The human body have two main ways to produce energy, either through burning carbohydrate/glucose or through fat burning. How large share of carbohydrates or fat are dependent on the situation. (Roberts et al., 1996) quantified the use of fat versus carbohydrates in exercising dogs and goats at certain intensity. The intensities used where 40%, 60% and 85% of the maximal rate of oxygen consumption. When exercising at 85% it took 5-10 min to reach a steady state with respect to distribution of fat and carbohydrate consumption. In this situation the dogs and the goats were burning roughly around 20% fat and 80 % carbohydrates. When exercising in lower intensity, 40 % and 60 % it took around 20-30 minutes to reach a steady state. When exercising 40 %

intensity, fat stands for over 75% of the total energy consumption. At 60 % intensity, 40 % of the total energy consumption came from fat.

An explanation is that fat needs more oxygen in order to be used for energy consumption compared to carbohydrates. So when the intensity is increasing, the need for more energy happens immediately and the body chooses to use more glucose since this is faster. When holding the intensity over time(20-30 min) the body adapt and goes back to burning more fat. If the intensity rises to high fat burning it not efficient and the body runs predominant on glucose. Steady state is therefore achieved faster when the intensity is higher. The time the body uses to reach steady state can also change depending on how fit the person is.

If possible the body tries to burn fat since the fat reservoirs last must longer than the storage of glycogen. In the simulation the time of exercise was pretty short, which gives the body a little time to adjust to the change, therefore burning more glucose than fat. The model will be off when exercising one or two hours at mild intensity since then glucose will only contribute with 25 % of the total energy consumption.

# 3 Pulsatile control

## 3.1 Pulsatile behaviour

Pulsatile control means that the input, which in this case is insulin, should be administered as boluses/pulses instead in a continuous manner. The pulses can vary in both length, amplitude and frequency. There are many processes in the human body which is believed or known to have a pulsatile or oscillatory behaviour, as the neural system, cardiac system, circadian system and hormone system. A known example with the hormone system is the secretion of the hormone GnHR, which was found to be secreted in monkeys with six minutes pulses every hour (WILDT et al., 1981). It was tested to give the GnRH hormone with different pulse length and frequency, but only the infusion with six minutes pulse every hour gave a wanted response.

This pulsatile behaviour also applies for the secretion of insulin. The first findings of this dates long back to 1923 when (Hansen, 1923) found oscillations in blood glucose concentration, which later gave indications that this could be related to pulsatile insulin secretion by beta cells.(Matthews et al., 1983) found by taking intravenous samples from humans every min in a period of 2.5 hour, insulin oscillation with periods of 14 min and a 40% increase every 7 min. There are however many studies which have measured the frequency of insulin burst but the periodicity it not completely decided, due to different results.

In a comprehensive review on pulsatile insulin secretion by (Pørksen, 2002) the frequency from studies was varying between 4-15 min in test done in vivo. Tests done in vitro with isolated perfused pancreas reported oscillations of 6-10 min. There is also measured time between pulses in isolated perfused islet of lagerhans where the pulses is found to be 3-5 min. The review further points out that observations shows that most of the beta cells secrete their pulses at the same time.

Is also important to emphasise that even if the beta cells have a pulsatile nature, not all of the insulin is secreted in pulses. Around 30 % is given as a basal dose (Pørksen, 2002). In (PAOLISSO et al., 1991) nine males was given insulin continuous, in pulses with 13 min frequency and pulses with 26 min frequency. The insulin was administrated over 2 minutes. The 13 min frequency increased inhibition of endogenous glucose production which did not occur in the continuous or 26 min frequency case. There was concluded that a certain frequency is needed to increase inhibition of endogenous glucose production. Insulin given in pulses with the right frequency will therefore have more effect with lowering the BGL. When exposed for a high steady concentration of insulin the receptors become less sensitive (PAOLISSO et al., 1991).

## 3.2 Properties of a pulsatile controller

Since insulin oscillation measured in vivo lies between 4-15 min it is desirable to design a controller which is able to release insulin in a pulsatile manner in this time frame. The pulsatile controller will be compared to the a normal/-continuous controller already implemented. Since pulsatile insulin delivery do not have better effect in lowering the BGL in the model since this effect is not implemented, the goal is to get the performance of the controller close to the continuous controller

As mention briefly in chapter 2 the model has support for both insulin infusion and glucose measurement for intravenous, intraperitoneal and subcutaneous approach. The goal is to design a controller for intravenous and intraperitoneal approach only. This is because Chan et al. (2008) small insulin boluses given in intervals around 15 min is indistinguishable from giving a continuous basal rate. It is therefore no use to implement a pulsatile controller for a subcutaneous approach.

## 3.3 Pulsitile infusion for clinical treatment

Since commercial treatment uses double subcutaneous approach diabetics is not treated with pulsatile infusion. Only in intensive care patients pulsatile infusion is used. How frequent the blouses is given depend on how frequent glucose measurements are taken and with respect to workload for the health personnel. A example is the glucomancer algorithm, where one bolus is set every hour based on one glucose measurement. The frequency is therefore to seldom in order to get the advantages from pulsatile infusion.

In Skjærvold et al. (2013) there is presented an algorithm designed for pulsatile intravenous infusion. The algorithm is based on a series of if and then sentences to decide the time and amount of the insulin bolus. The algorithm is divided into two parts. The first part is to lower a high initial value in BGL, which often is the case in a intensive care setting in the patients. While the second part maintains the BGL at a steady oscillating state. The trial was preformed on four pigs, which had developed a mild diabetics state due to streptozotocin pretreatment. The algorithm was set to maintain glucose level at the range of 4.5-6.0 mmol/l. The BGL was continuously measured by a glucose sensor from Glucoset and the insulin was given in boluses, both intravenous. The amount of insulin given was estimated from the change in BGL given by the previous bolus. The dose was either kept, doubled or halved. The frequency was not strict, but given according to the float diagram presented in the paper. On average there were administrated around 4-5 boluses every hour. The algorithm is not directed against against meal disturbances.
There was tried to implement this algorithm in MATLAB but the performance was not satisfying. This is shown in figure 5. The initial value was set to 12.5 mmol/L. The algorithm handles the high initial value and brings the BGL to a oscillatory state. The fluctuations have an amplitude around 1 mmol/L which is

a little much. The main problem however is the frequency of the boluses compared with the original article Skjærvold et al. (2013), which is to seldom. The algorithm where also changed a little in order to make the simulation work. The issue came from to slow decease in BGL when administering a bolus in the model. In Skjærvold et al. (2013) it was stated that every bolus should yield an decrease in BGL with 1 mmol/L, which took considerable longer time in the model. The total decrease of one bolus was around the same, so increasing the dosage made the simulation unstable. There was tried to alter the scheme in

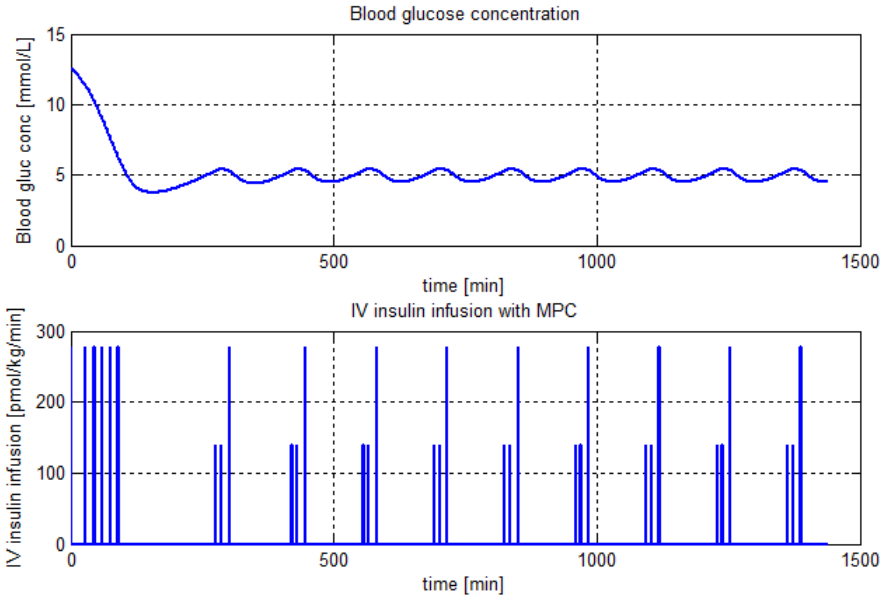


**Figure 5:** Skjævold algorithm for controlling BGL without any disturbances

order to get faster frequency for the injections but this was not successfully. In retrospect it could be possible that the pulsatile infusion induced in the pigs gave a much faster decrease in BGL than normal continuous infusion, because of the mentioned effect with the receptors being more sensitive. Since this dynamics is not implemented in the glucose insulin model, this was not captured by the model simulation.

## 3.4 Control methods already implemented in the model

There are implemented two different control methods for controlling the BGL in the model in SIMULINK(Froyen, 2014). The methods are proportional integral derivative(PID) controller, model predictive control(MPC) and lastly there is the possibility to give the insulin in a open loop manner.

Proportional, integral and derivative(PID) controller is by far the most used controller in the industry. About 95 % of all industries application is controlled by a PID controller(Aastrom, 1995). PID is model less controller, which uses three parameters to control the process. The three parameters are weigths to error, the rate of change in the error and the stationary error. The parameters is calculated by either tuning the system until the wanted response is achieved with methods such as Ziegler-Nichols or Skogestad, or calculate them directly by estimating a polynomial to the input output data, or some other calculation method. Advantage with PID control is its fast implementation and is rather cheap computational. PID does however have little prediction power. The PID implemented in the model have a sampling time equal to 0.05, which is 3 seconds since the model is simulated in minutes.

Model predictive control(MPC) is the most used model based controller in the industry. The method uses a model of the process and calculates an optimal solution sequence based on an objective function. The first number in this sequence is used as input to the plant. This repeats every time step. MPC have a much high computational cost. The great advantages with MPC is the possibilities for including constrains into the problem. This makes it ideally for glucose insulin regulation. A MPC have much lower samplings rate due to computational cost than for example a PID controller. In (Froyen, 2014) the sampling time is set to 5 min with 100 minutes prediction horizon.

As mentioned the controller should deliver boluses in the frequency of 4-15 minutes. Since the sampling time for the MPC is 5 minutes this algorithm seem well suited for pulsatile infusion. The PID controller on the other hand need sufficient sampling time in order to be accurate and is therefore not very fitted for this task. Therefore it was chosen to use the MPC algorithm as basis for the pulsatile controller.

## 3.5 MPC formulation

This section will describe the MPC controller implemented in (Froyen, 2014) The implemented MPC controller is set to regulate the BGL to the reference value of 4.5 mmol/L. In addition the BGL have a lower and upper bound on 4 mmol/L and 8 mmol/L respectively. The input have a lower and upper bound equal to zero and 900 pmol/kg/min. The upper bound is never reached in practice but are implemented to make the simulation as realistic as possible. There are also included slack variables to not make the problem infeasible when BGL is outside the bounds due to meal disturbances.

The formulation have three weights, q punishes the deviation in BGL from the reference, r is the cost of the input and s punishes the deviation from the feasible area. The last parameter is set high to avoid hyperglycemia or hypoglycaemia. The most optimal is to have a asymmetric function such that low values of BGL is punished harder, due to the fact that hypoglycemia is a much more sever state than hyperglycemia is, but this not implemented. With sampling time equal 5 minutes and prediction horizon equal 100 minutes the optimization problem have 60 variables to calculate, 20 states, 20 inputs and 20 slack variables. The

MPC problem is formulated in following manner

$$min \;\; J = \frac{1}{2} \sum_{t=0}^{N-1} x_{t+1}^T \; q \; x_{t+1} + u_t^T \; r \; u_t + \epsilon_t^T \; s \; \epsilon_t \tag{8}$$

which is subject to

$$x_{t+1} = -a_1 \; x_t - a_2 \; x_{t-1} .. - a_n \; x_{t-n-1} + b_1 \; u_t + b_2 \; u_t .. + b_m \; u_{t-m} \tag{9}$$

$$x^{min} - \epsilon_t \;\; \leq \;\; x_t \leq x^{max} + \epsilon_t \tag{10}$$

$$u^{min} \leq \;\; u_t \leq u^{max} \tag{11}$$

$$\epsilon_t \;\; \geq \;\; 0 \tag{12}$$

$$q \;\; \geq \;\; 0 \tag{13}$$

$$r \;\; \geq \;\; 0 \tag{14}$$

$$s \;\; \geq \;\; 0 \tag{15}$$

A linear auto-regressive model with exogenous input(ARX) was chosen over a state space formulation as a control model due to advantages with adaptation of model parameters. To determine the number of parameters, the model was simulated several times with different inputs in order to get data to perform off-line estimation. The simulations were done without meal disturbances. Since the main model can simulate insulin infusion and glucose measurement subcutaneous, intraperitoneal and intravenous, it is important that this also is reflected in the control model. The model shown in equation 16 was chosen as the best fit for all the situation.

$$y(t) = -a_1 \; y(t-1) - a_2 \; y(t-2) - a_3 y(t-3) + b_1 \; u(t-1) \tag{16}$$

The off-line estimation where preformed in MATLAB with the command tfest, which estimates a transfer function based on the input output data given. The function is discrete with 5 min sample time. There are estimated different parameters for all the nine combination.

In MATLAB the problem is formulated in one state vector Z, that contains all states, x, u and $\epsilon$ and supplied to the solver fmincon. Fmincon can tackle non linearities both for objective function and for constrains. Since this solver is costly computational wise, it is only efficient to use it in optimization problems with non linearities.

Since the control model is a linear ARX model and the objective function is quadratic, it was chosen to use quadprog instead of fmincon. Quadprog is able to solve this problem with much smaller computational cost.

## 3.6 Pulsatile control with MPC

### 3.6.1 Pulsatile infusion

There is probably several ways to use the MPC controller for pulsatile infusion. For simplicity the frequency between boluses is considered constant. A straight forward way to generate boluses with the MPC algorithm is to multiply the insulin output with the sample time for the MPC, divided with the length of the bolus, and administrate the dosage over this time.

$$I_{pulsatile} = I_{continous} \frac{Ts_{\,mpc}}{Bolus_{\,length}}$$

The frequency of the pulsatile infusion will then be equal to the sampling time of the MPC controller. There was not found a specific pulse length in the, so the length of the pulse was chosen to be 30 seconds. If wanted this can be easily changed and is not important to the method itself.

In order to simulate the model with another sampling time, it is necessary to change the model parameters so they fit the sample time. The parameters was found by just re-sampling the 5 min model with the MATLAB command d2d, which resamples a discrete system for any given sampling time. Is not possible to specify the number of coefficients in the nominator to the d2d command. The number of coefficients in the denominator are the same. This is perhaps done by MATLAB to generate the best performance for the resampling. To test the controller it was chosen to give pulsatile infusion with frequencies at 5 minutes, 10 minutes and 15 minutes to cover the wanted rage of 4-15 minutes. It is natural to presume that faster sampling time give better performance so 4 minute frequencies was not simulated. The 5 minutes model were therefore resampled into 10 minutes and 15 minutes model. Figure 6 shows the step response of these three model.

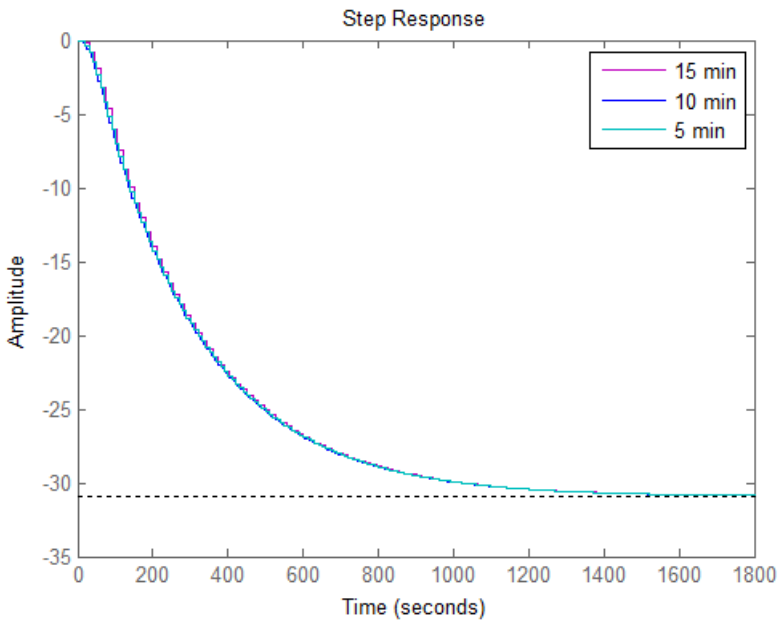


**Figure 6:** Step response of control model with different sample time.

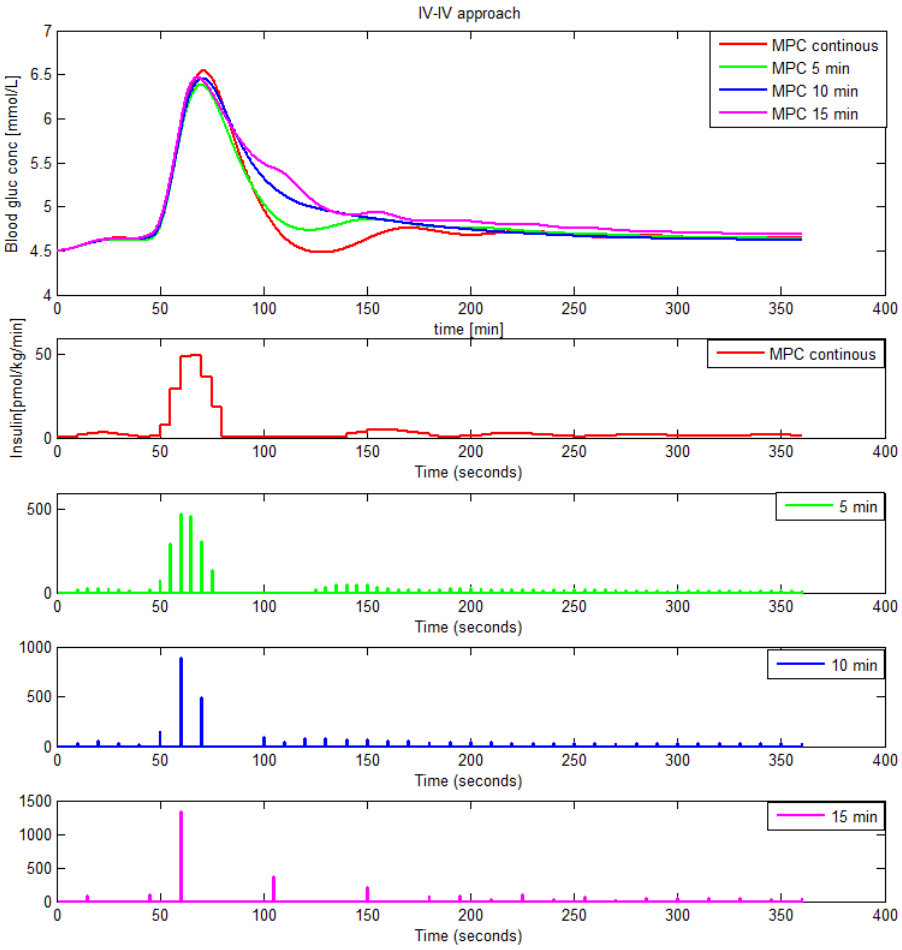


**Figure 7:** Continuous and pulsatile infusion.

Figure 7 shows a six hour simulation with one meal ingested from t=30 to t=50, with the total of 60 gram of carbohydrate. Both the infusion of insulin and glucose measurement is done intravenous. The red curve shows the original MPC algorithm with 5 min sample time. In the green curve the same amount of insulin is delivered over 30 seconds instead over 5 minutes. The amplitude is therefore ten times higher in the pulsatile case, as seen in sub plot 2 and sub plot 3 in figure 7. It was chosen to give in insulin in the beginning of each interval since then the insulin is administrated 2.15 minutes earlier in average with respect to the continuous case(Normal MPC). This gives the pulsatile curve a

slightly lower peak and drops less after the meal disturbance than compared to the continuous curve.

The blue and magenta curve shows the pulsatile delivery with frequency of 10 minutes and 15 minutes. The prediction horizon was kept to 100 minutes for the former case and 105 minutes for the latter, since 100 is not dividable by 15. It was also tried to expand the prediction horizon, but this did not effect the performance. The performance is acceptable in all cases since the BGL is in between 4mmol/L-8 mmol/L at all time, which is the overall goal for the regulation. However the performance for 10 minutes and especially 15 minutes is a little slower.

### 3.6.2 Impulse invariant model

The standard method for discretiaction of a system in MATLAB is zero order hold, which assumes that the input is continuous over the sample time. This method maps the step response of the system and fits well for the normal MPC, since the input is a series of steps. Another possibility is to use the impulse invariant method. This method produces a discrete model with the same impulse response as the continuous model. This may fit the pulsatile controller better since the input consist of short pulses.

A continuous model were estimated with the same script as done in(Froyen, 2014), and then discretized with the impulse invariant method afterwords. The discretization is done with the c2d(continous to discrete) command in MATLAB, where the impulse invariant method can be chosen as an option. The discretization goes as follows, starting with a continuous transfer function.

$$H(s) = \frac{b_{n-1}\ s^{n-1}\ ... + b_1\ s + b_0}{s^N + a_{n-1}\ s^{n-1}\ ... + a_1\ s + a_0} \tag{17}$$

Then write the system as a sum of first order terms.

$$G(s) = \sum_{i=1}^{N} \frac{K_i}{s - s_i} \tag{18}$$

Note that the transfer function needs to be at least marginal stable. Now taking the inverse Laplace transform gives

$$G(t) = \sum_{i=1}^{N} K_i \; e^{s_i \, t} \tag{19}$$

Sampling the expression.

$$G(n) = \sum_{i=1}^{N} K_i \; e^{s_i \, n \, T} \qquad n = 0, 1, 2.. \tag{20}$$

Taking the z transform gives

$$G(z) = \sum_{i=1}^{N} \frac{K_i}{1 - e^{s_i \, T} \, z^{-1}} \tag{21}$$

The simulation is done in the same manner with meal disturbance, starting at t=30 min and ending at t=50 min. The result in shown in figure 8. The continuous infusion and the 5 minutes pulsatile infusion is now pretty similar, while the two other have gotten worse. The input given by the pulsatile controller resembles an impulse more than a step, and in that way the discretization should be more correct. However as mention with the discretization command in MATLAB, the number of coefficients in the nominator can change during the discretization. The output value only depends on the last value with respect to input, since the model normally have one b coefficient. If two or three b coefficient are used because of the discretization the performance can be much different.

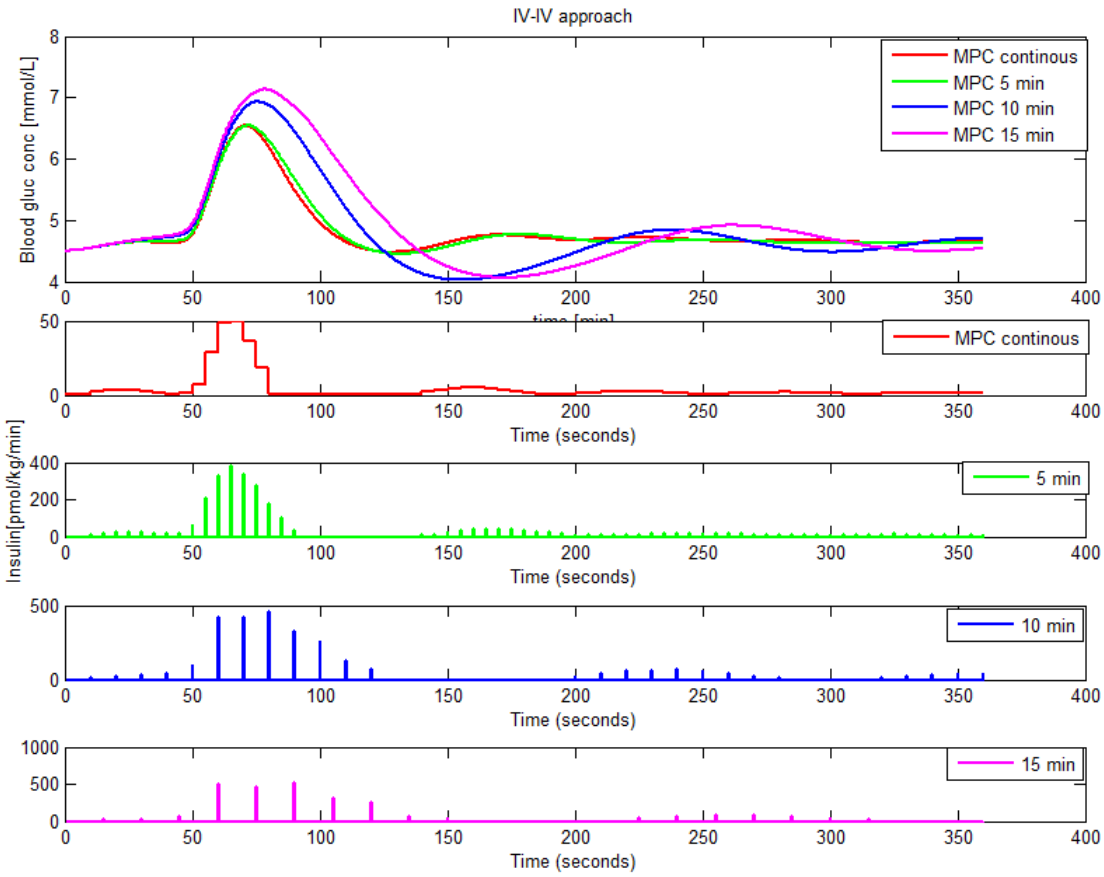


**Figure 8:** Continuous and pulsatile with impulse invariant discretization

### 3.6.3 Adding constraint

Instead for using different model parameters for the different frequencies, it is possible to implement a constraint to the MPC problem instead to avoid resampling of the model. The pulsatile controller would then use model parameters for the 5 min model but be able to give insulin with all the three used frequencies.

For pulsatile delivery with 10 minute frequency the constraint 22 is implemented.

$$u[1\ ,3\ ,5\ ,7\ ...99] = 0 \tag{22}$$

which gives the following output from the optimization algorithm.

$$u = [u_0\ 0\ u_2\ 0\ u_4\ 0\ u_6\ 0\ u_8\ ...u_{98}\ 0] \tag{23}$$

The optimization problem is executed every 10 min, but it calculates states variables for every 5 minutes and with a prediction horizon of 100 minutes. The problem now contains 20 states, 20 input where 10 of them is zero, and 20 slack variables. The constraint was implemented by setting higher input weights on the inputs that should be zero. Since the algorithm will try to minimize the cost function, the other inputs will be used instead.

A better solution is to implement this as a hard constraint. Then the solution space would be smaller since the algorithm only would know about 10 inputs. When adjusting the input weights the problem have 20 input to calculate, where ten of them becomes approximately zero, giving more computational cost. It was not found a good way to implement this. However the adjustment of the inputs weight should yield the same answer.

The exact same is done for pulsatile delivery with 15 minute frequency.

$$u[(1:2)\ ,(4:5)\ ,(7:8)\ ...(103:104)] = 0 \tag{24}$$

which gives the following output from the optimization algorithm.

$$u = [u_0\ 0\ 0\ u_3\ 0\ 0\ u_6\ 0\ 0\ u_9\ ...u_{105}] \tag{25}$$

In this cases every third input is non zero, giving a 15 min frequency for the bolus.

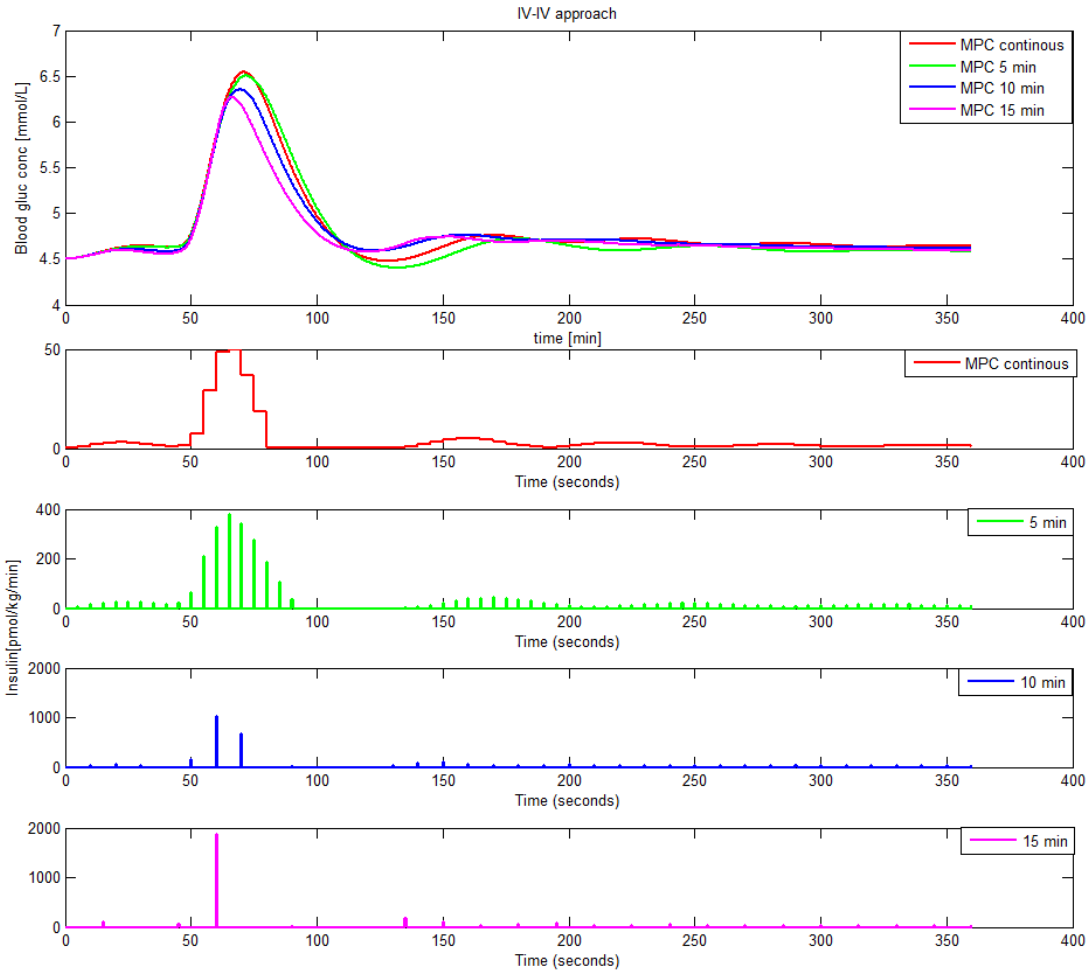


**Figure 9:** Continuous and pulsatile infusion with input constraint.

Figure 9 show a simulation with this implemented. Now the performance is good, for all three frequencies of pulsatile infusion. The model parameters in taken from the normal model since this gave better simulation result than the impulse invariant model.

In figure 10 and figure 12 the model is simulated for 24 hours, starting at midnight and contains three meals, breakfast, lunch and dinner and contains 40, 60 and 70 gram carbohydrate respectively. The timing of the meals are seen in figure 11. Figure 10 is done with double intravenous method while figure 12

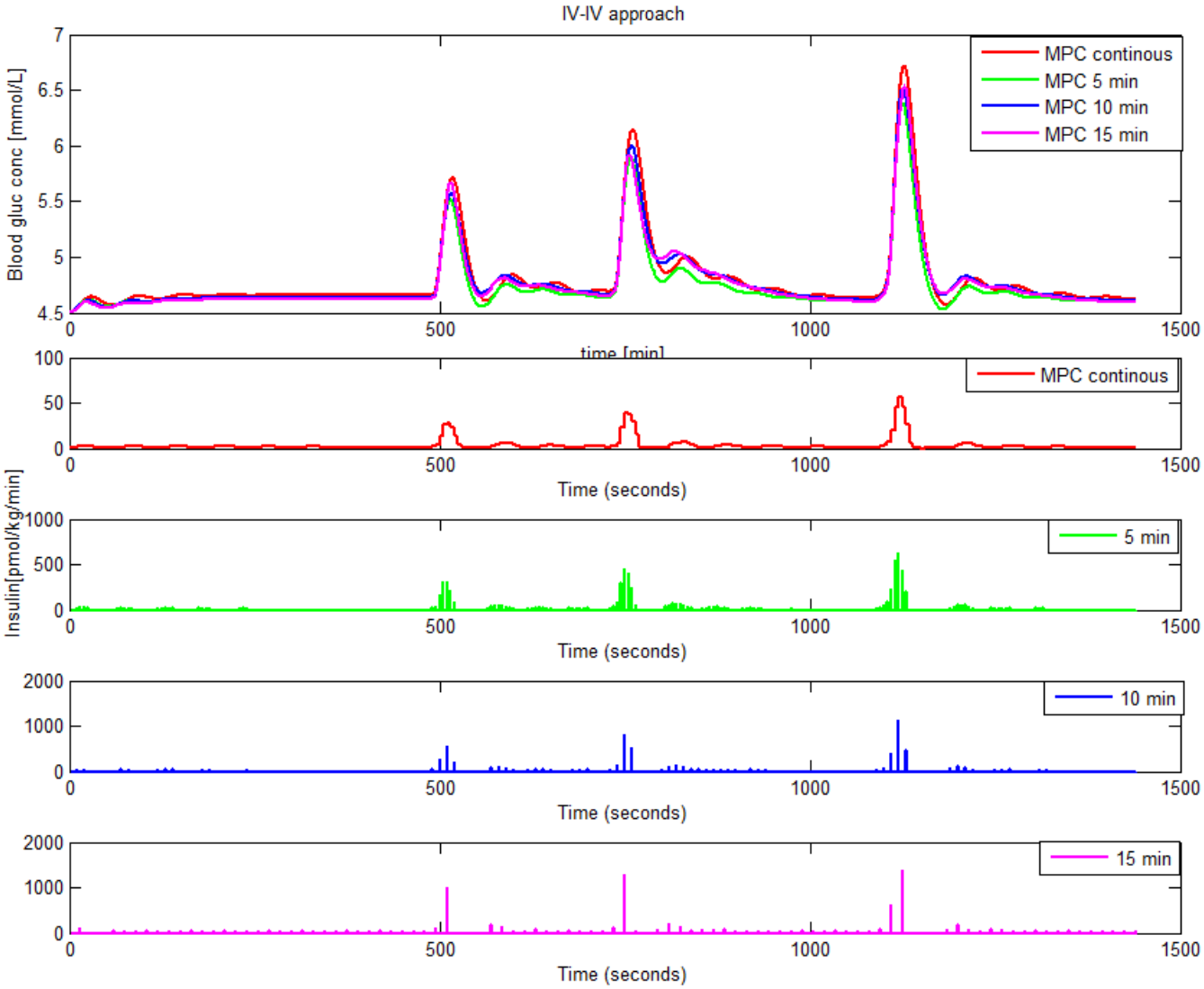


**Figure 10:** 24 hour simulation with IV approach

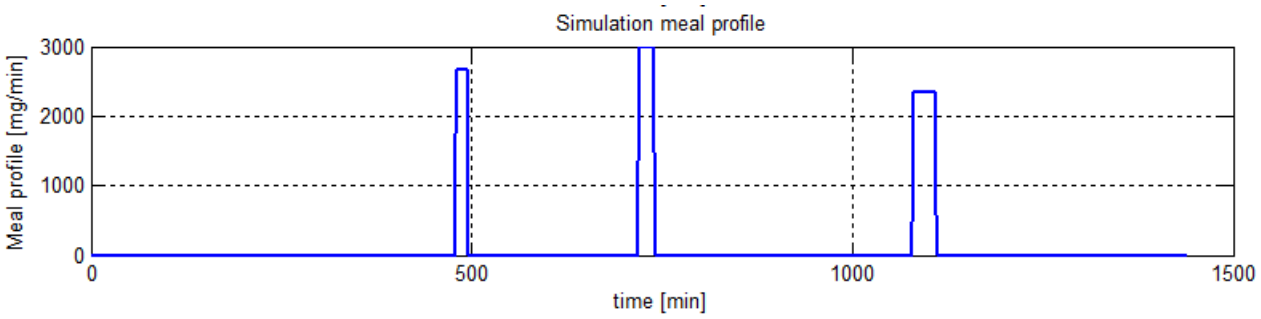


**Figure 11:** Meal profile

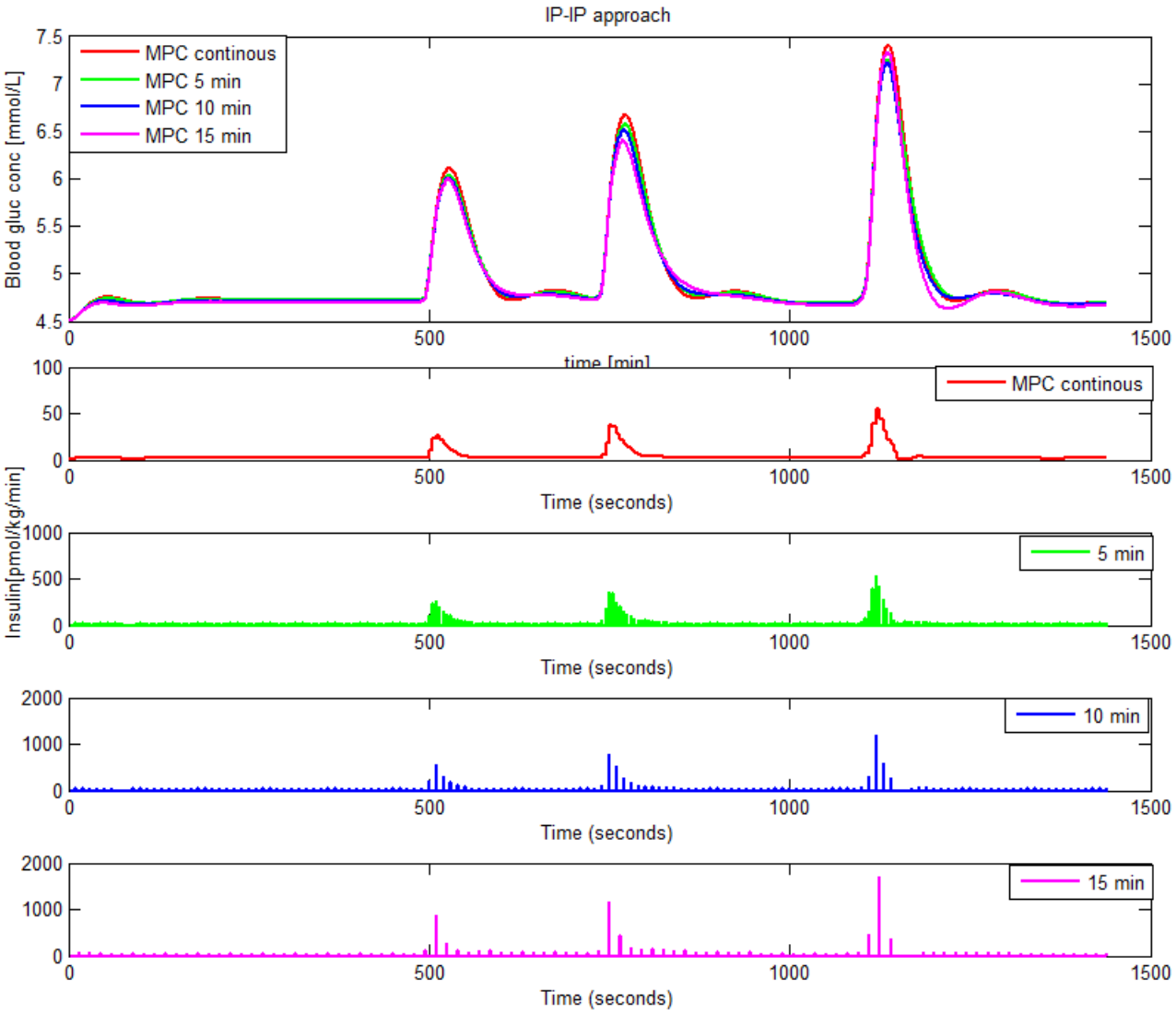


**Figure 12:** 24 hour simulation with IP approach.

is double intraperitoneal method. As mention in chapter 1, intravenous infusion is modelled directly into plasma and have no time delay. The glucose is value is measured directly from plasma as well.

Since there is a time delay from injecting insulin intraperitoneal, the BGL rises higher when exposed to meal disturbances compared with intravenous infusion. The amount of insulin used do not differ with regards to continuous or pulsatile

infusion. In the intravenous case the amount of insulin given is around 51 units insulin, given a body weight on 78 kilos. In the intraperitoneal case however the insulin amount is around 64 units insulin.

This method allows for a pulsatile control with a frequency of 5 minute, 10 minute, 15 minute, where the performance are about equal. Giving boluses every 5 min is most secure because the controller faster can answer if disturbances are introduced.

## 3.7 Effect off Pulsatile control

As seen in the previous section it is possible to give the insulin injection in boluses instead of continuously infusion, and this can be done both intravenous and intraperitoneal. This is no point however if there are no insulin oscillations in the blood. In figure 13 shows the insulin concentration. All the three pulsatile cases have clear oscillations equal to their own sampling time. The peek to peek value for the 5, 10, and 15 minutes pulsatile infusion is around 118 pmol/L, 235 pmol/L and 345 pmol/L respectively. The peak to peak value increases in a linear manner in respect to increased sampling time. This is realistic since the insulin is modelled directly into plasma without any delay and the insulin amount used, are around equal in all cases.
Figure 21 shows the same type of simulations only with intraperitoneal approach instead. The peek to peek values are around 2 pmol/L, 7.5 pmol/L and 16.8 pmol/L for the three cases, which are much more damped compared to the intravenous case. There is no linear relationship between increased peak to peak value and increased sampling time. By doubling the sample time from 5 minutes to 10 minutes the peak values increases 3.5 times, while tripling the sample time from 5 minutes to 10 minutes increases the peak to peak value to 8.4 times.

Figure 6 shows a closed up from subcutaneous infusion while fasting in order to compare the to intraperitoneal approach. As mention before there is no point using pulsatile subcutaneous infusion because the result would be the almost the same as continuous infusion because of the slow uptake from the subcutis. Injecting boluses every 15 minutes manages to create oscillations with peak to peak value equal to 1 pmol/L.

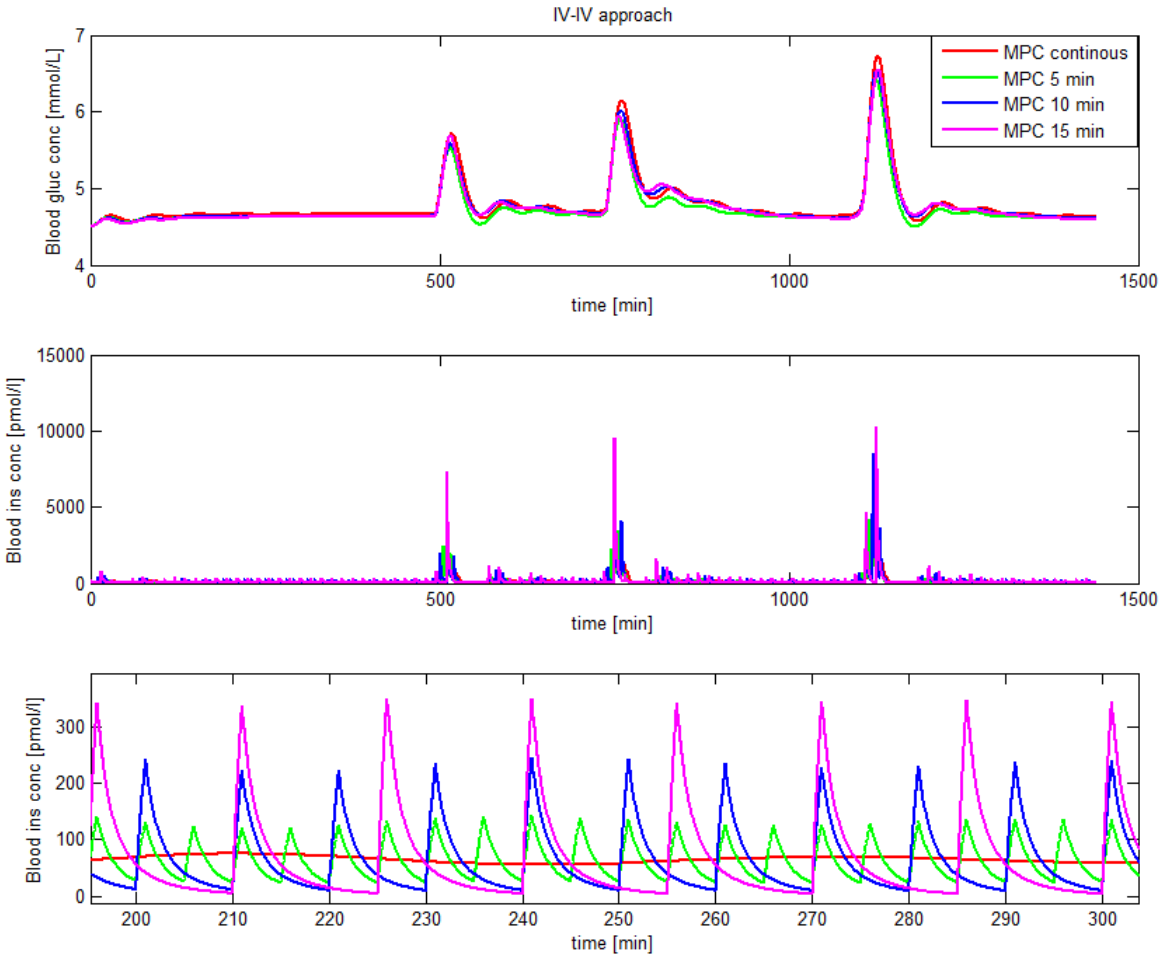


**Figure 13:** Simulation of BGL and insulin concentration with IV.

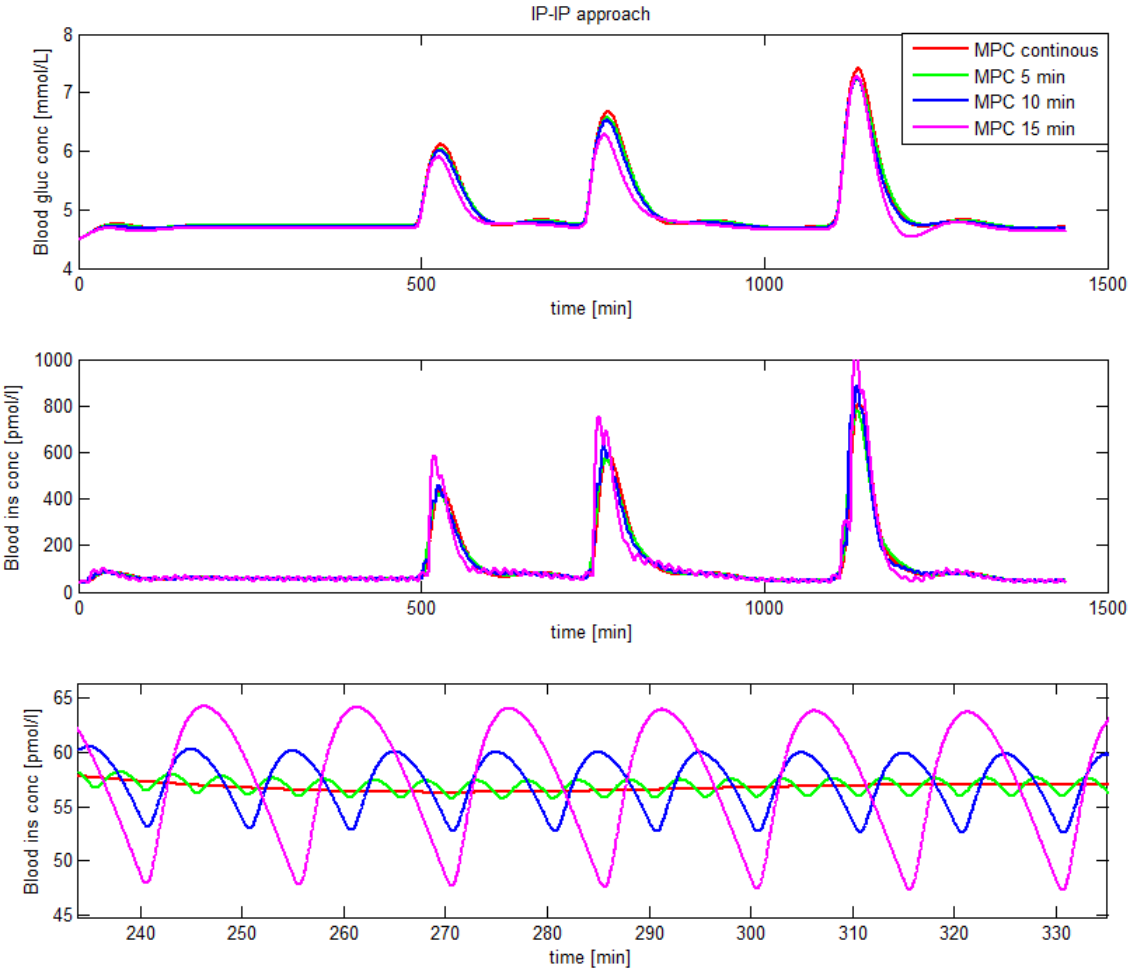


**Figure 14:** Simulation of BGL and insulin concentration with IP.

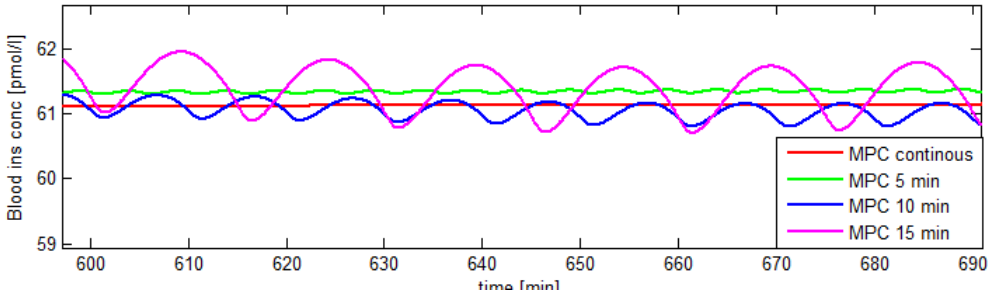


**Figure 15:** Insulin oscillation while fasting with subcutaneous approach.

# 4 Adaptive control

Adaptive control is useful when there are uncertainties or changes over time in the model parameters. The parameters for the glucose insulin system will vary from person to person, but do also vary during the day, or day to day. The purpose of a adaptive controller is to try to estimate some parameters in order to regulate the system more accurate than a normal controller with rigid control parameters. Adaptive control can be divided into two groups, direct or indirect. In the former case the adaptation happens directly on the control parameters, while in the latter case the adaptation happens on the model parameters and then calculating the new control parameters. Since this regulation uses a MPC controller with a ARX model structure the adaptation will be indirect by adapting the parameters for the ARX model then supplying it to the MPC algorithm. This means the algorithm only needs to estimate four parameters.

As with offline estimation, parameter convergence happens only if the input is "varied" enough, also called persistent excitation. As a rule of thumb one sinusoidal is enough to estimate two parameters. This stands in conflict with the main goal which is to keep the BGL steady at the reference level. Perfect regulation gives therefore no chance for adaptation. The controller needs however to give insulin regularly(basal dose) to keep the insulin at reference level, since total absent of insulin would make the BGL increase. Small fluctuations in the BGL can therefore give room for adaptation.

The input from the MPC controller is given in steps. In an ideal step the number of frequencies is infinite since the derivative is infinite. However in a practical simulation where the derivative is finite, the step response is not so good regarding adaptation purposes. Also with good regulation, the insulin infusion from the MPC can be kept constant under fasting making adaptation harder. In

the pulsatile case the input is also given in steps but have much shorter length resembling more an impulse. This gives more variation in the input as well as possible fluctuations in output and is perhaps more suitable for online estimation than the normal MPC controller.

In order to assess if a pulsatile controller is beneficial in respect to online estimation, compared to a continuous controller, a recursive least square algorithm(RLS) was implemented in SIMULINK to test the response of both methods. The RLS method was chosen because of its wide use in many application, also within glucose regulation(Eren et al., 2007).

## 4.1 Least square method

The least square algorithm is much used, both for offline and online estimation. The following section will derive the expression for the offline and online least square estimate. The ARX model is written in the following general form

$$y(t) = -a_1\ y(t-1) - a_2\ y(t-2) - ...a_n\ y(t-n) + b_1\ u(t-1) + b_2\ u(t-2) + ...b_m\ y(t-m) \tag{26}$$

This can be rewritten as matrices in the standard form 27,

$$y(t) = \phi^T\ \theta \tag{27}$$

$$\phi^T = [-y(t-1)\ \ -y(t-2)...\ \ -y(t-n)\ u(t-1)\ u(t-2)...\ u(t-m)]$$

$$\theta^T = [a_1\ a_2\ ...a_n\ \ b_1\ b_2\ ..b_m]$$

The least square estimate is

$$\theta^{LS} = min = \frac{1}{2N}\ \sum_{t=0}^{N} \epsilon^2$$

with

$$\epsilon^2 = y(t) - \hat{y(t)} = y(t) - \phi^T(t)\ \theta$$

The optimum is found by differentiating with respect to the parameter vector and setting the result equal to zero.

$$\frac{\delta}{\delta\epsilon}\ \theta^{ls} = \frac{\delta}{\delta\epsilon}\frac{1}{2n}\ \sum_{t=0}^{n}(y(t) - \phi^T\ \theta)^2$$

$$-\frac{1}{n}\sum_{t=1}^{N}\ \phi(t)(y(t) - \phi^T\ \theta) = 0$$

$$\hat{\theta}(n) = \left(\sum_{t=0}^{n}\phi(t)\phi^T(t)\right)^{-1}\sum_{t=0}^{n}\phi(t)y(t)$$

$$\hat{\theta}(n) = P(n)\ \sum_{t=0}^{n}\phi(t)y(t) \tag{28}$$

Equation 28 is the offline version of the least square algorithm with P equal the covariance matrix. To be able to use this online, a recursive expression for the covariance matrix and the parameter vector is needed.

$$P(n)^{-1} = \sum_{t=0}^{N}\phi(t)\phi^T(t) \tag{29}$$

In order to weight the parameters it is common to include the forgetting factor in the equation where $\lambda$ have a value between one and zero. Lower value means that the estimation care less about the older the estimates.

$$P(n)^{-1} = \sum_{t=0}^{n}\lambda^{n-t}\ \phi(t)\phi^T(t) \tag{30}$$

$$P(n)^{-1} = \sum_{t=1}^{n-1}\lambda^{n-1)-t}\ \phi(t)\phi^T(t) + \phi(n)\phi^T(n) \tag{31}$$

$$P(n)^{-1} = \lambda\ P(n-1)^{-1} + \phi(n)\phi^T(n) \tag{32}$$

$$P(n) = (\lambda\ P(n-1)^{-1} + \phi(N)\phi^T(n))^{-1} \tag{33}$$

Using the Woodbury identity

$$(A + UCV)^{-1} = A^{-1} - A^{-1}\ U(C^{-1} + VA^{-1}U)^{-1}V\ A^{-1}$$

where

$$A = \lambda\ P(n-1)^{-1} \quad U = \phi(n) \quad V = \phi^T(n) \quad C = 1$$

This gives

$$P(n) = \lambda^{-1}\ P(n{-}1) - \lambda^{-1}P(n{-}1)\phi(n)(1{+}\phi^T(n)\lambda^{-1}P(n{-}1)\phi(n))^{-1}\ \phi^T(n)\lambda^{-1}P(n{-}1)$$

$$P(n) = \lambda^{-1}\ P(n-1)\ - k(n)\phi^T(n)\lambda^{-1}P(n-1) \tag{34}$$

$$k(n) = \lambda^{-1}P(n-1)\phi(n)(1 + \phi^T(n)\lambda^{-1}P(n-1)\phi(n))^{-1}$$

$$k(n) = P(n-1)\phi(n)\ (\lambda + \phi^T(n)P(n-1)\phi(n))^{-1} \tag{35}$$

$$k(n)(1 + \phi^T(n)\lambda^{-1}P(n-1)\phi(n)) = \lambda^{-1}P(n-1)\phi(n)$$

$$k(n) = \lambda^{-1}P(n-1)\phi(n) - k(n)\phi^T(n)\lambda^{-1}P(n-1)\phi(n)$$

$$k(n) = (\lambda^{-1}P(n-1) - k(n)\phi^T(n)\lambda^{-1}P(n-1))\phi(n)$$

$$k(n) = P(n)\ \phi(n) \tag{36}$$

Lastly a recursive expression for the parameter vector is needed. Rewriting equation 32

$$\lambda\ P(n-1)^{-1} = P(n)^{-1} - \phi(n)\phi^T(n) \tag{37}$$

Substitute N-1 for N in equation 28

$$\hat{\theta}(n-1) = P(n-1)\ \sum_{t=1}^{n-1}\phi(t)y(t) \tag{38}$$

Rearranging equation 37 and insert 38 yields

$$\sum_{t=1}^{n-1} \phi(t)y(t) = P(n-1)^{-1}\ \hat{\theta}(n-1) = (P(n)^{-1} - \phi(n)\phi^T(n))\ \hat{\theta}(n-1) \quad (39)$$

Using equation 28 again and rewrite this to

$$\hat{\theta}(n) = P(n)\ \sum_{t=1}^{n} \phi(t)y(t)\ = P(n)\ \left(\sum_{t=1}^{n-1} \phi(t)y(t) + \phi(n)y(n)\right) \quad (40)$$

Substitute equation 39 into equation 40

$$\hat{\theta}(n) = P(n)\ (P(n)^{-1} - \phi(n)\phi^T(n))\ \hat{\theta}(n-1) + \phi(n)y(n)) \quad (41)$$

$$\hat{\theta}(n) = \hat{\theta}(n-1) - P(n)\ \phi(n)(y(n) - \phi^T(n)\ \hat{\theta}(n-1)) \quad (42)$$

$$\hat{\theta}(n) = \hat{\theta}(n-1) - k(n)\ (y(n) - \phi^T(n)\ \hat{\theta}(n-1)) \quad (43)$$

The implementation is done in a SIMULINK using the three equation 34, 35 and 43. The RLS method calculates a new estimate every time step, which is set to 5 min, same as the sample time for the MPC controller. The initial values for diagonal in the P matrix is 10000. When the diagonal values become low the parameter estimates gets less affected and converges to a value.

## 4.2 Results

### 4.2.1 Normal adaptive control

Figure 16 shows a 24 hour simulation with the normal model parameters and with adaptive model parameters both in a continuous manner. The adaptive controller starts of with the same model parameters as in the normal case and do not use the online estimation values until the diagonal values in the covariance matrix passes a lower threshold. As seen in the simulation there is small fluctuations in the beginning and the lower threshold is passed at t = 145.

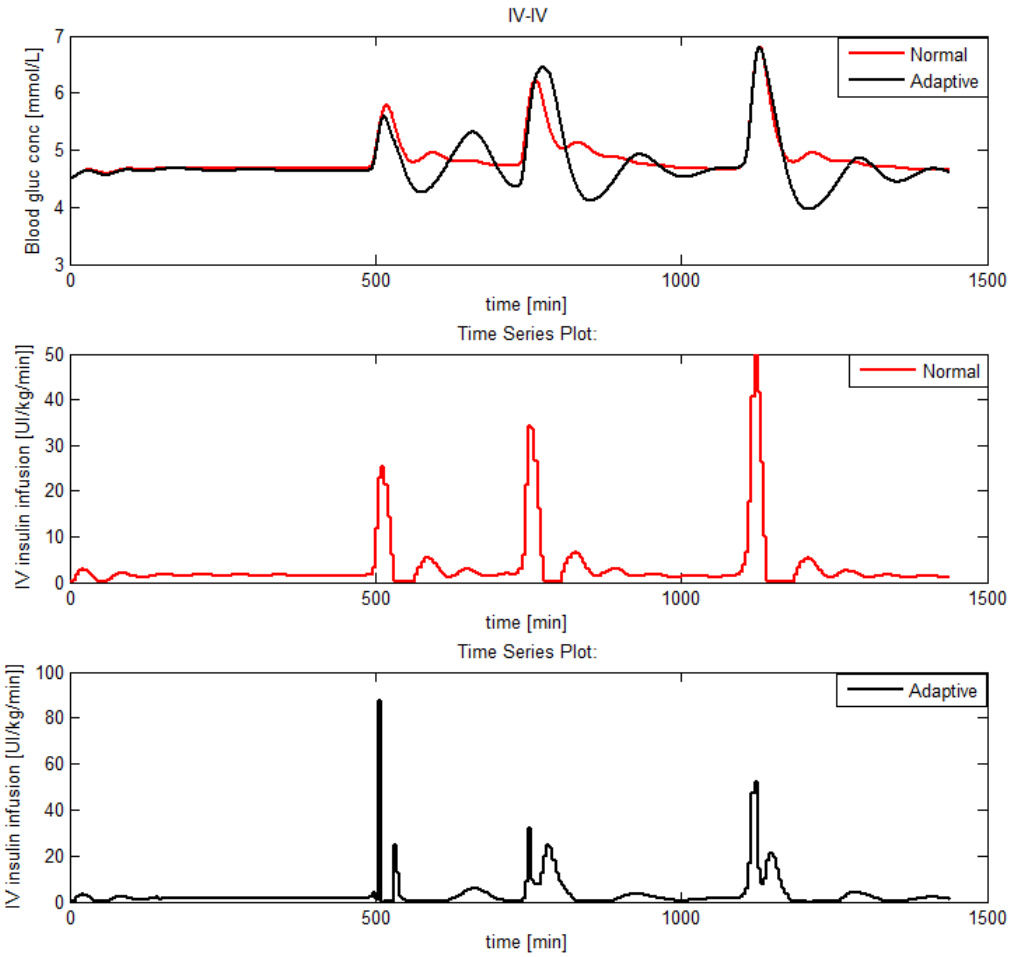


**Figure 16:** Simulation with normal and adaptive controller.

The recursive least square estimator have no knowledge about initial conditions. However the controller needs a set of parameters in the beginning so there would always exist a guess for some initial condition but this is not included since it did not effect the estimation significantly. Regardless of initial condition the transient phase of the estimation will often be some what unpredictable anyway and therefore the initial conditions is set to zero for all parameters. More important the RLS algorithm have global converges since the problem is convex so initial conditions does not matter if the input is PE. The forgetting factor is set to one meaning none of the information will be disre-

garded over time. When using forgetting factor equal to one the estimates will converges to value eventually. How to chose the forgetting factor depends on how fast the parameters are expected to change. If the system is expected to change rapidly a low forgetting factor is needed and the input must be PE in other to adapt to the changes. If the changes in parameters are expected to be slower the forgetting factor is not as important. In the simulation the forgetting factor was set to one in order to get convergence. Leaving out the forgetting factor when there is rapid changes will mean that the parameters will coverage to an average value.

In figure 17 shows the parameter estimate over time. Note that the reference values not is taken from the normal model since they are estimated with the tfest command. Instead the reference parameters is estimated with a offline least square(LS) method instead. Even if the performance of the estimates from tfest and LS are pretty similar the exact values of parameters is not the same. The LS algorithm was applied on the same dataset as Froyen (2014). The offline LS estimation should on the other hand look similar to the online RLS estimation and be more suitable.

The estimation converges to a value after approximately 120 min for all parameters and is applied after t = 145. The parameters do not converge to the exact value which is to be expected since the linear ARX model is very simplified compared to the non linear model and is therefore most accurate around the working point. The estimate will therefore be dependent on how the BGL is affected. It is also possible that input is not "varied" enough since the changes in both input and output is relative small. It was tried to inject more insulin the first 100 minutes in order to affect the BGl more, but the parameter did not converge further. At t=500 the first meal begins to raise the BGl. This changes the dynamics of the system completely since the RLS algorithm do not know

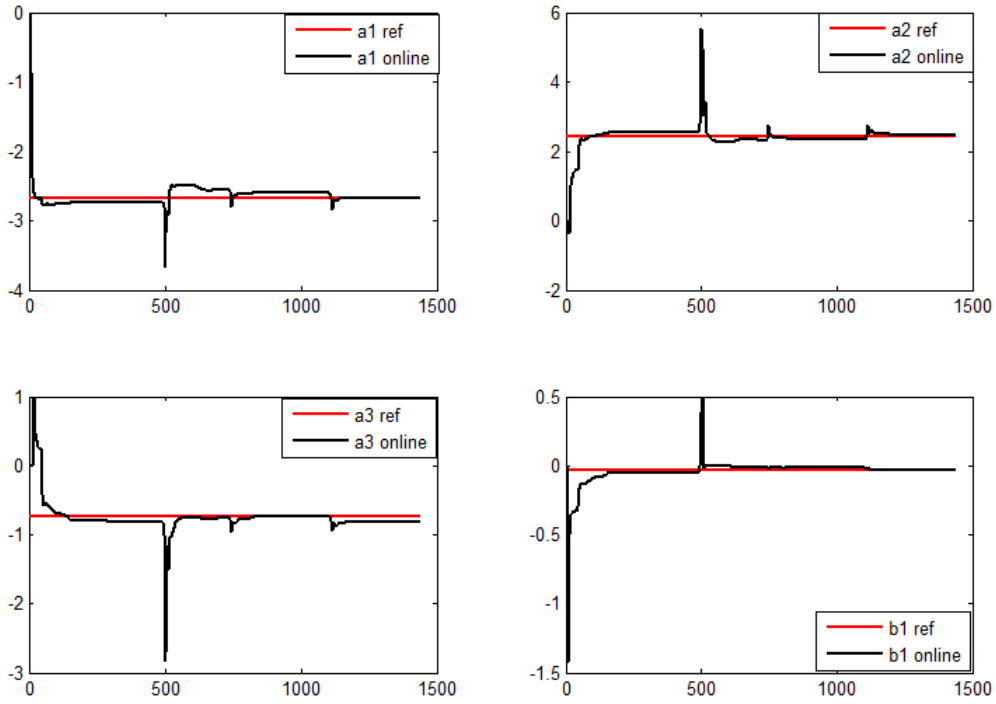


**Figure 17:** Parameters in ARX model.

about any disturbances. This affects all four parameters. The main problem is because the BGL rises due to meal disturbance and insulin is given in order to lower the BGL to the reference level. However the estimator misinterpret this as if the insulin is the reason for the increase in BGL since it have no information about the meal. Therefore the parameter b1 which weight the former input becomes positive. This is illustrated in the sub plot down to the right in figure 17. This would make the model highly unstable since giving insulin at the time t would lead to increased dose at time t+1 etc and lead to hypoglycemia. To avoid this the b1 coefficient from the online estimation is only used if the value is negative. After the first meal disturbance the estimate drop under zero again. The online parameter is updated when the estimation get negative again. Even if the b1 coefficient in keep in check the other parameters changes values which make the performance bad with much oscillations as seen in figure 17

It is also worth noticing that the estimation do not get affected as much during the two other meals, lunch and dinner. This is because the P matrix is close to zero, which means the new estimate do not affect the overall estimate much. The simulation will therefore yield a much worse result if the meal disturbance should have entered earlier or the initial condition for the P matrix have been higher. In addition to meal disturbances, exercise will also affect the estimate. Exercise on the other hand will give the opposite effect for the controller. When doing exercise the blood sugar will fall due to the extra energy consumption needed in the cell. This will lower the b coefficient and the controller will give less insulin in the next time step. This will not make the model directly unstable as with meal disturbance but will affect the controller.

It is apparent that the adaptation cannot take place during meal disturbances in its current form. One possibility is to do the online estimation only at night since the parameter did converged to reasonable value after 150 min. Figure 18 show the simulation with online estimation from midnight to half eight in the morning shown in the blue curve and there is also included a black curve where the online estimation happens all day except meals. The performance is very good in both estimation cases. There are little difference between them, the black curve perhaps slightly better but there is difficult to determine the meal schedule. It was decided that the controller should have no knowledge about time or amount regarding meals to best reflect a real situation. The meal times must therefore be estimate if this is to be used, but this demands that the diet is pretty similar day to day. Also a small snack is enough to affect the estimation significantly. Therefore it was decided to use the online estimation only during night.

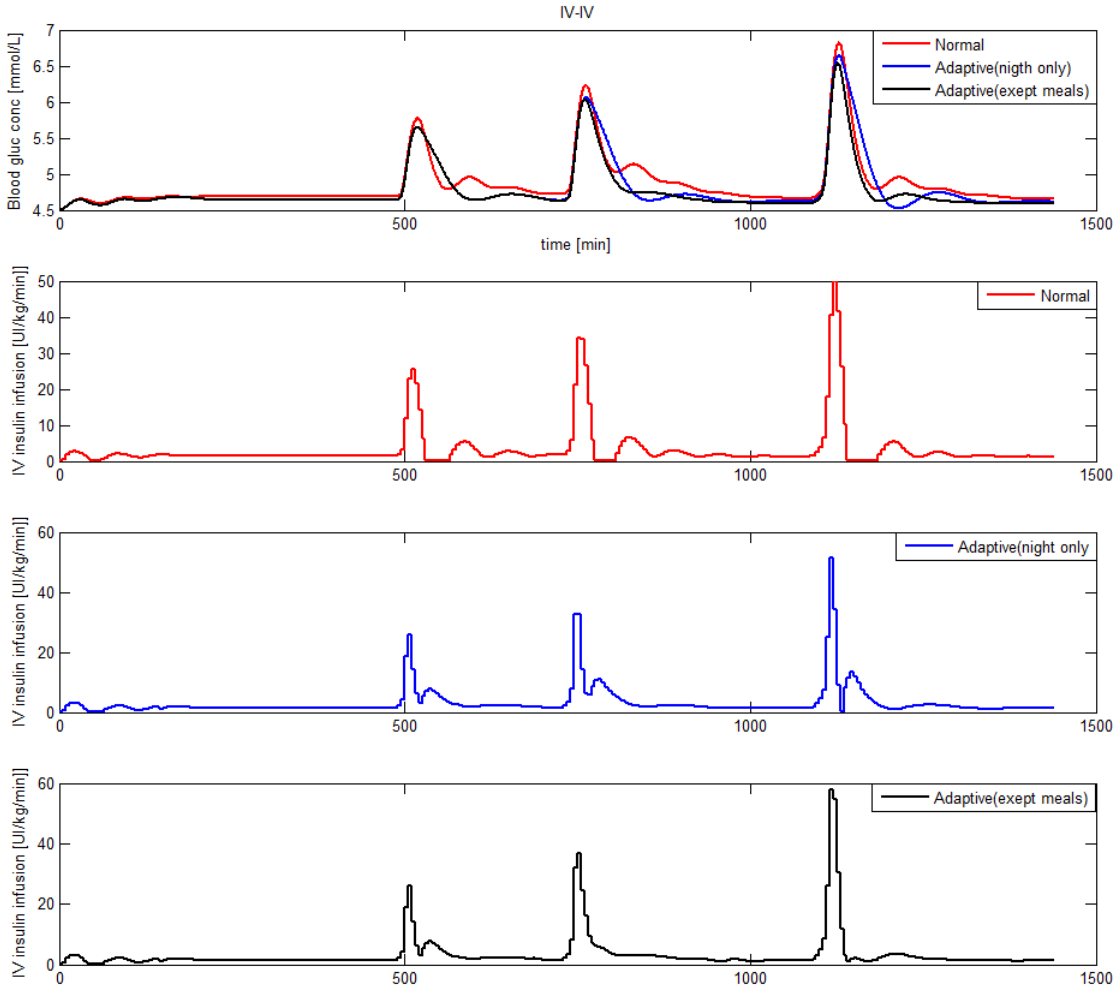


**Figure 18:** Adaptive control with online estimation during night and between meals.

Figure 19 shows the simulation with two different models. The black curve show the simulation with online estimation at night with good parameter convergens. In the simulation showed with the blue curve the are no fluctuations in the beginning which makes adaptation not possible and the adaptive parameters are never used, since this would crash the simulation. So in order to get parameter convergences some fluctuations are needed.

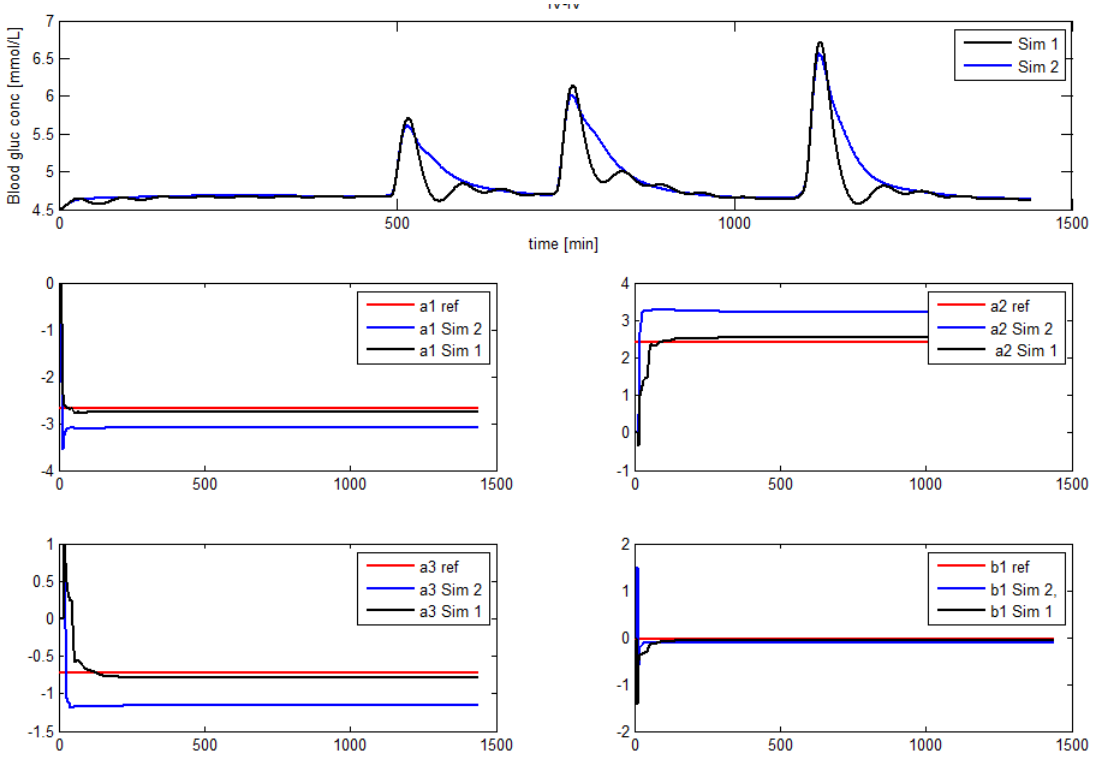


**Figure 19:** Simulation with and without parameter convergence.

### 4.2.2 Pulsatile adaptive control

In the pulsatile case there is the option to do online estimation is the same manner as the normal infusion using five min sampling time for the estimation. This means however that there will be no advantages input wise, but it is possible that pulsatile injection gives more fluctuation in the BGL. A study on rhesus monkeys, showed oscillation with $\pm 4\%$ of average in BGL (Goodner et al., 1982). Compared with the model simulation this should be enough to get parameter convergence. Therefore it is a possibility that the pulsatile controller is better suited from adaptive control. In the model simulation the pulsatile controller did not give more fluctuations in the BGL than in the continuous case, and therefore the performance was about equal for both cases, as seen in figure 20. The adaptation was only tried with intravenous approach.

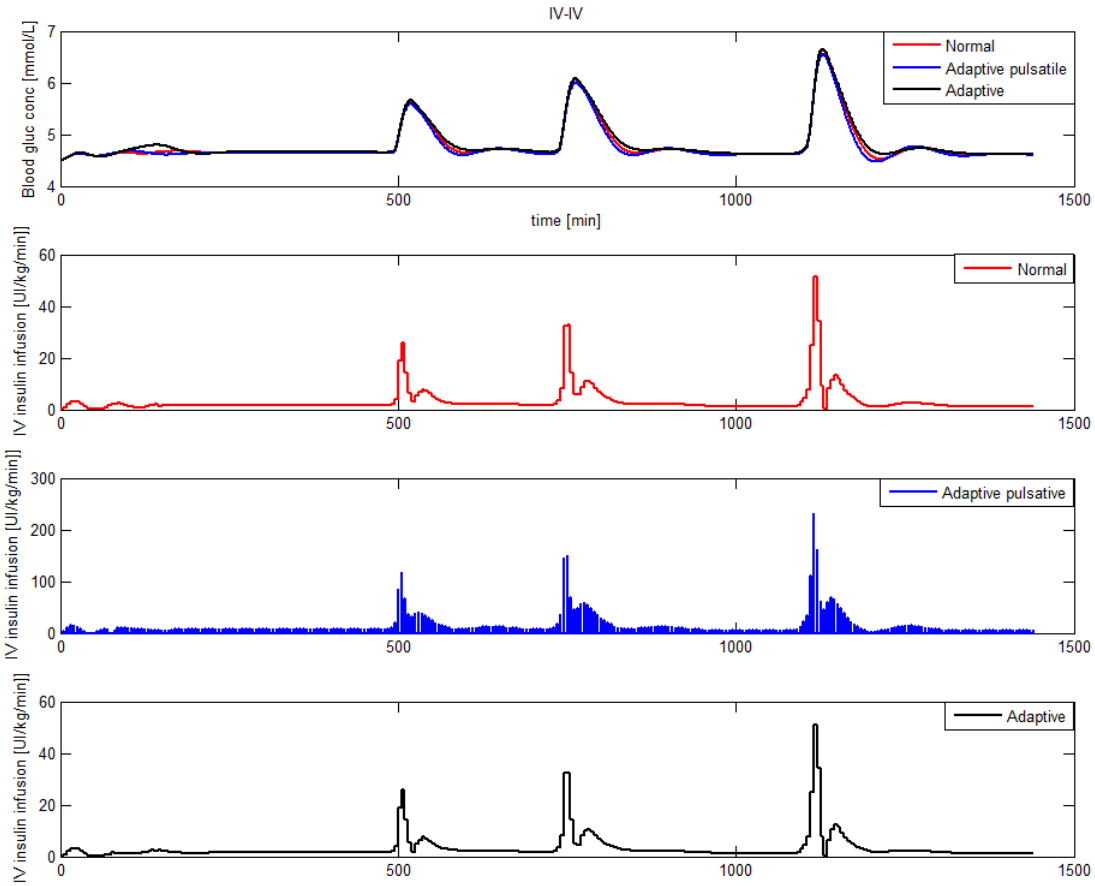


**Figure 20:** Adaptive pulsatile control compared with normal adaptive control.

Figure 21 shows the simulation with pulsatile infusion with frequencies 5 min, 10 min and 15 min. All three simulations are done by online estimation during night time only. The parameter estimation have 5 min sampling time since all simulation uses the same 5 min model.

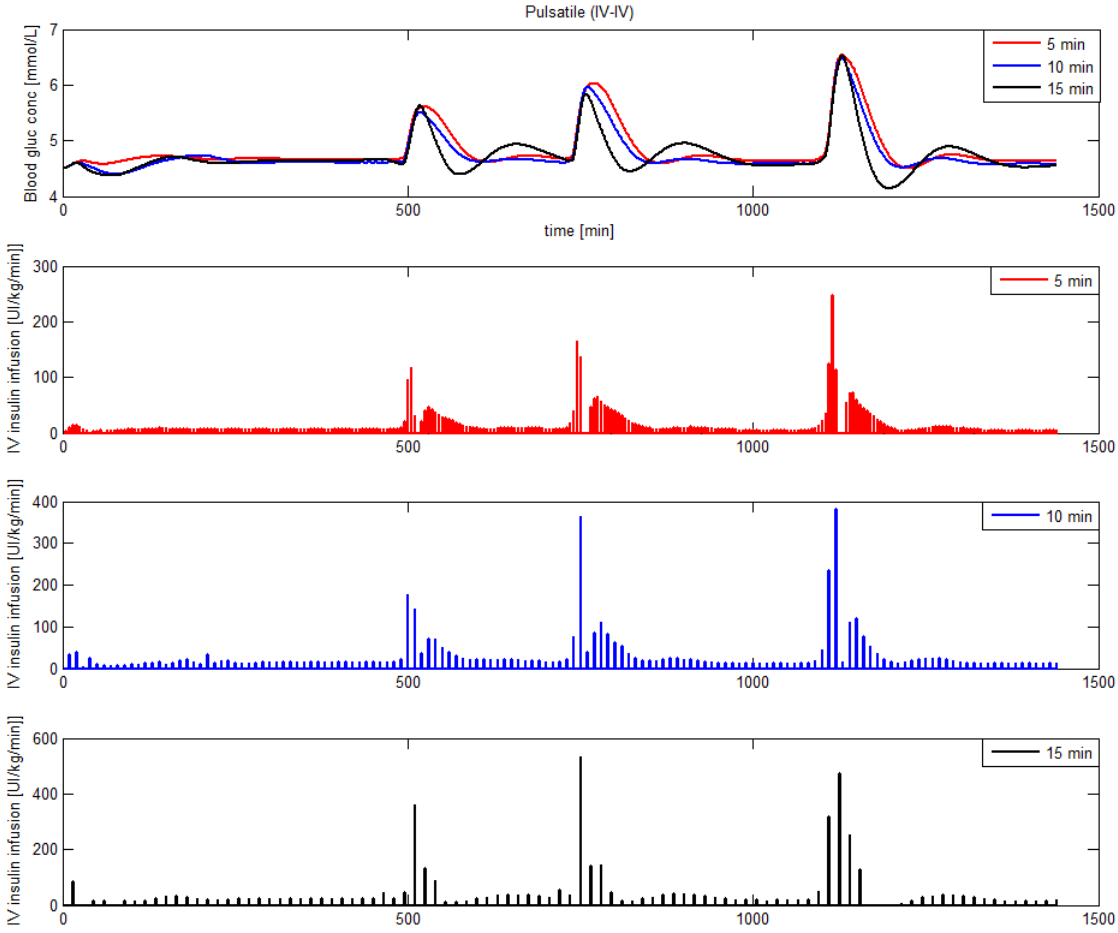


**Figure 21:** Pulsatile adaptive control for all frequencies.

# 5 Discussion

The controller was able to deliver boluses with frequencies of 5, 10 and 15 minutes with the same performance as the normal MPC controller. The controller can be used in both intraperitoneal and intravenous infusion. It is believed that a pulsatile infusion have greater hypoglycemic effect than continuous infusion, which would give better control and would reduce events of hypoglycemia. The oscillation in insulin concentration was over 20 times higher when giving insulin intravenous compare to intraperitoneal. So if this is possible with intraperitoneal approach is difficult to say. In order to do better computer simulation it is necessary to include effects of pulsatile infusion, both intravenously and intraperitoneal.

This is also necessary in order to conclude whether pulsatile infusion is more suitable for adaptive control. Based on the simulations, there seems like some oscillation is enough in order to estimate the parameter, while fasting. However since the estimation only is active during night time, no changes in parameters during the day is captured.

While the controller gives all of the insulin in boluses, only 70 % is secreted in humans, rest is given as a basal dose, which means that the insulin oscillates more than normal if the insulin is given intravenously.

# 6 Conclusion

An extension for physical activity chosen from the literature has been implemented on the APT glucose insulin model. The result of the extension was verified by comparison with result from the original article. This gives the possibility to introduce activity as a disturbance in silco simulation in order to test performance of closed loop algorithms.

A method for pulsatile insulin was presented and implemented into the model in order to mimic the natural insulin secretion better. The controller is based on a already implemented model predictive controller and delivers insulin boluses over 30 seconds with frequency of 5, 10 or 15 minutes. The results where compared with the MPC algorithm already implemented. The pulsatile controller showed good performance for all three frequencies with regard to BGL control, both in the intravenous and the intraperitoneal case. The intraperitoneal approach showed some oscillations in the blood insulin concentration but substantial less than in the intravenous case.

An adaptive scheme was implemented in order to compare the adaptive properties of the pulsatile and normal controller. In the computer simulation there where found no advantages with the pulsatile method using this method since the pulsatile infusion did not give any fast fluctuations in BGL which is presumed to be the case. Implementing this behaviour in the model could yield a different result.

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