Evaluation of a Guided Machine Learning Approach for Pharmacokinetic Modeling

by

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ABSTRACT

A medical control system, real-time controller, uses a predictive model of human physiology for estimation and controlling of drug concentration in the human body. Artificial Pancreas (AP) is an example of control system which regulates blood glucose in T1D patients. The predictive model in the control system such as Bergman Minimal Model (BMM) is based on physiological modeling technique which separates body into the number of anatomical compartments and each compartment's effect on body system is determined by their physiological parameters. These models are less accurate due to unaccounted physiological factors effecting target values. Estimation of large number of physiological parameters through optimization algorithm is computationally expensive and stuck in local minima. This work evaluates a machine learning(ML) framework which has a ML model guided through physiological models. A support vector regression model guided through modified BMM is implemented for estimation of blood glucose levels. Physical activity and Endogenous glucose production are key factors that contribute in the increased hypoglycemia events thus, this work modifies Bergman Minimal Model Bergman *et al.* (1981) for more accurate estimation of blood glucose levels. Results show that the SVR outperformed BMM by 0.164 average RMSE for 7 different patients in the free-living scenario. This computationally inexpensive data driven model can potentially learn parameters more accurately with time. In conclusion, advised prediction model is promising in modeling the physiology elements in living systems.

I dedicate this work to my parents and brother

for their endless love, support and encouragement.

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Chapter 1

INTRODUCTION

Control Systems, real time systems, have MPC - Model Predictive Controller - which regulates or controls substance's concentration in human body. MPC consists of a predictive model of human physiology for estimation. Physiological modeling, a mathematical technique, which separates human body into different compartments and compartment's effectiveness on blood or fluid is determined by physiological parameters. These models are widely used to estimate optimal drug scheduling and dosage.

Physiological models consist of complex non-linear differential equations for quantification of substance in each compartment and its parameters represent the biological effect on blood flows. These models are also used for statistical inference in risk assessment and drug scheduling, however these models have certain set of limitations. a) Physiological Parameters: The human population is biologically heterogeneous which means there are variations in physiology, biochemistry and molecular biology among individuals. This heterogeneity results in differences amid individual's biologically effective tissue dose associated with a given administered dose which in-turn makes physiological parameters individuals specific. These physiological parameters are not just individual dependent, in fact, they are also diurnal in nature (Lee *et al.* (1992)) and are quite few in number. Thus every-time estimation of parameters for every individual is required. This estimation is generally done by an optimization algorithm such as convex optimization. b) Factors or Variables: Human body is complex in nature where every thing is related to each other in some form, It is quite difficult to consider every factor's effect while estimating the drug. Absence of

all the affecting factors constrain the usage of these models in free living scenarios for example, Bergman minimal model doesn't account physical activity, endogenous glucose production and other factors due to which it works well only during fasting condition. c) To build a online system it should consist of a model which can be used in a plug-n-play manner. This means one should be able to add, remove or update the model without reconfiguring the whole system. Due to these limitations, there are three problems in using physiological model a) Due to its high computation, it is not easily affordable b) When there is absence of effecting features in the physiological model, predictions are less accurate for example, as shown in the evaluation, when Bergman Minimal Model (Bergman *et al.* (1981)) was factored in with physical activity, accuracy was increased significantly C) Due to the constrained usability, it can't be practically used in free living scenario.

In this work, our approach is to developed a guided machine learning model for pharmacokinetic modeling. A machine learning(ML) algorithm is applied on top of a generic physiological model for prediction of a physiological feature. This means ML takes informative features generated through physiological model along-with other important features for prediction. This guiding is necessary because it provides base values for prediction, as the physiological datasets are generally skewed. This framework eliminates the need for estimation of individualized parameters and machine learning algorithms with informative features are quite less expensive when compared against physiological models. With these advantages over physiological models, this framework can be used in a plug-n-play manner.

We have evaluated our proposed approach by developing a guided support vector regression model for prediction of blood glucose. In this model, a modified Bergman Minimal Model(BMM) (Bergman *et al.* (1981)) is used to generate informative data for support vector regression machine learning algorithm. Since, according to Chimen

et al. (2012), regular physical activity improves anomalies of the multi- metabolic syndrome: increase in insulin sensitivities, diminution in the fatty mass, improvement of the lipid profile, increase of the fibrinolysis and arterial pressure decrease and incidence reduction of the non insulin dependent diabetes and endogenous glucose production provides glucose when BG levels goes below certain levels. Thus, in this work Bergman minimal model is modified to add physical activity and endogenous glucose production effects on BG levels for more accurate estimation. As per our experiment evaluation, proposed regression model outperforms BMM by average 0.24 RMSE values. There was a significant amount of improvement, improved by 0.2 RMSE, when regression model was guided with modified BMM.

This thesis is structured as follow. Section 2 talks about the background and state-of-the-art SVR modeling and blood glucose management, Chapter 3 describes our guided machine learning approach. Chapter 4 explains modified Bergman Minimal Model . Chapter 5 lists the experiments performed and analysis drawn from the experiments. Chapter 6 concludes with future work on this novel approach.

Chapter 2

BACKGROUND

2.1 Support Vector Regression

Support Vector Machines(SVM), developed at AT&T Bell Laboratories by Vapnik and co-workers [Boser *et al.* (1992), Guyon *et al.* (1993), Cortes and Vapnik (1995), Schiilkop *et al.* (1995), Schölkopf *et al.* (1996), and Vapnik *et al.* (1997)], are learning machine based on structural risk minimization inductive principles which aims in obtaining good generalization through learning patterns. SVM has two categories, Support Vector Classification and Support Vector Regression (developed in 1997 by Vapnik, Steven Golowich, and Alex Smola).

In Support Vector Regression technique, the basic objective is to find a function $f(n)$ that has atmost ϵ deviation from target y_i in the given training data and in parallel it should be as flat as possible. This means SVR algorithm doesn't care about the error until the loss is less than ϵ. Lets consider the dataset $(x_1, y_1), ...(x_l, y_l) \subset X \times R$ where X denotes the input feature space. In the linear case, the obtained function is in the form of

$$f(x) =< W, X > +b \qquad W \in X, b \in R \tag{2.1}$$

where $< ., . >$ denotes the dot product in the obtained equation. As stated by Smola and Schölkopf (2004), this optimization can be considered as convex optimization.

$$Minimize \quad \frac{1}{2}||W||^2 \tag{2.2}$$

$$Subject \quad to \begin{cases} y_i - (w, x_i) - b & \geq \epsilon \\ (w, x_i) + b - y_i, & \geq \epsilon \end{cases} \tag{2.3}$$

where y_i are target labels, $||W||$ is the Euclidean norm of W, W is the normal form of the decision plane.

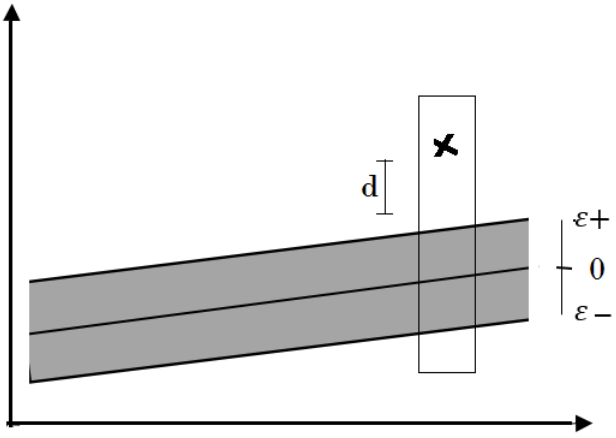


Figure 2.1: The Margin Loss Setting for linear SVR . Source: Smola and Schölkopf (2004)

2.2 Bergman Minimal Model

A closed loop insulin delivery system also known as Artificial Pancreas (AP) automates blood-sugar management, exponentially reducing hypoglycemia events. Closed loop insulin delivery system consists of a glucose monitoring device which calculates BG levels every 5 minutes, an insulin pump which infuses insulin inside the body and a controlled algorithm which would estimate the amount of insulin required to be delivered. This section discusses a control algorithm which requires a mathematical model, Bergman Minimal Model, that predicts BG levels by estimating the pancreatic responsiveness and insulin sensitivity towards blood glucose. Further, this

section also discusses a modification in the mathematical model to include the effect of carbohydrate intake on BG levels while estimating it. At the end, this section talks about different literatures which outline the effect of physical activity and the importance of endogenous glucose production on BG levels.

2.3 Blood Glucose Regulation for T1DM

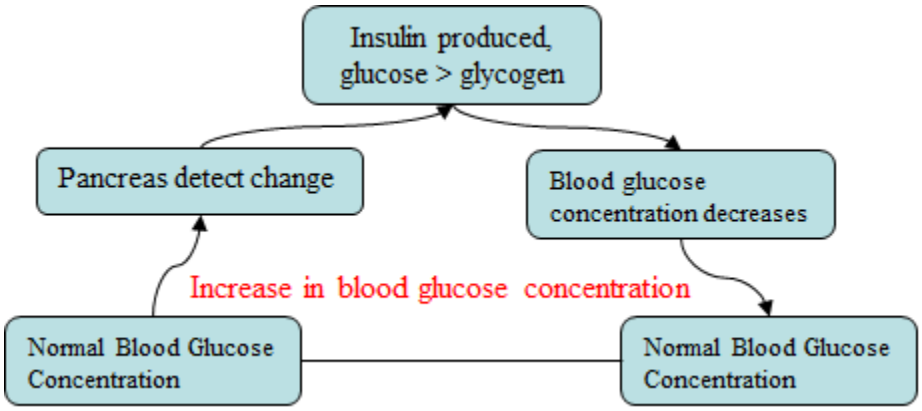


Figure 2.2: Blood Glucose Regulation when BG levels is high.

BG levels regulation highly depends on the amount of insulin secreted by pancreatic β cells and effectiveness of insulin on disposing carbohydrate intake. In order to understand more about T1DM diabetes, figure 2.2 shows how BG levels is maintained in normal non-diabetic person. As described in the figure, when BG levels go high, pancreas β cells produce insulin which decreases BG levels to normal range whereas, in case of T1DM diabetes, pancreatic β cells are not capable of producing insulin to decrease BG levels. Richard Bergman and his fellow colleagues developed a model to estimate right amount of insulin required by a body for maintaining BG levels in normal range.

Bergman *et al.* (1981) developed a two compartment minimal model to quantify both pancreatic responsiveness and insulin sensitivity to the entire organism. Pan-

creatic responsiveness is the ability to dispose carbohydrates and insulin sensitivity is the sensitivity of insulin on disposing off blood glucose. The author has interpreted the dynamics of the plasma glucose and insulin through two mathematical equations. One equation, the insulin kinetics model, yields parameters which depict the pancreatic responsiveness to glucose and second equation, glucose kinetics, yields the insulin sensitivity to glucose.

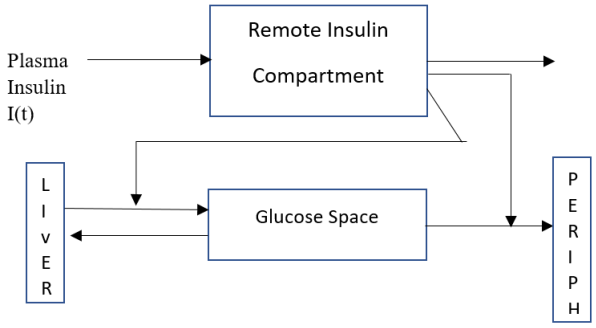


Figure 2.3: Minimal model of Glucose Kinetics. Source : Bergman *et al.* (1981)

The Bergman *et al.* (1981) has followed a partition and minimal modeling approach. The glucose concentration regulation system is partitioned into two parts: (a) the glucose dependent segment which determines the plasma insulin. (b) the insulin dependent segment which determines the plasma glucose (glucose producing and utilizing tissues). The two segments are used to estimate the parameter of insulin sensitivity S_I and parameters of pancreatic responsiveness to glucose respectively.

Figure 2.3 represents glucose kinetics which would calculate parameter of insulin sensitivity. The coefficients of the minimal model are estimated by allowing model to predict the observed fall in plasma-glucose when the measured plasma$-$insulin is supplied. S_I can be calculated as the ratio of two of the parameters of glucose disappearance model. The ratio is proportional to the concentration of "active"

insulin in a compartment remote from plasma, and the ability of that insulin to enhance glucose disappearance.

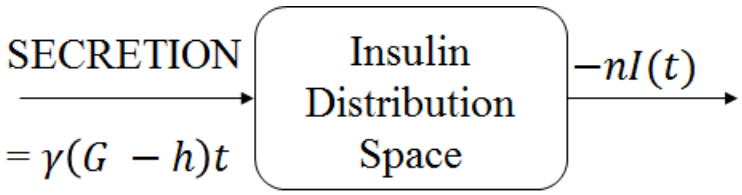


Figure 2.4: Minimal model of Insulin Kinetics. Source : Bergman *et al.* (1981)

Figure 2.4 represents insulin kinetics which would quantify parameters of pancreatic responsiveness to glucose, ϕ_1 and ϕ_2. In this model, the author assumed that the early peak in insulin secretion depicts the injection of insulin into plasma by the pancreas in direct proportion to the rise in glucose. ϕ_1 responsivity is the amount of insulin that can be accounted by this assumed insulin injection per unit change in BG levels whereas ϕ_2 responsivity is proportionality factor between glucose and the rate of arrival.

Later the above insulin-glucose dynamics model was modified for more accurate estimation of input values, an additional meal sub-model is used to describe meal dynamics by Hovorka *et al.* (2004); Gillis *et al.* (2007) .According to the Gillis *et al.* (2007), as shown in figure 2.5, the meal sub- model is a two compartment based model in which glucose appearance in first-compartment is the glucose calculated from carbohydrate intake whereas, second compartment contains plasma appearance glucose which would directly impact BG levels.

2.4 Endogenous Glucose Production and Physical Activity

Blood glucose regulation is not just all about insulin and meal intakes. There are other physiological factors - endogenous glucose production (EGP) and physi-

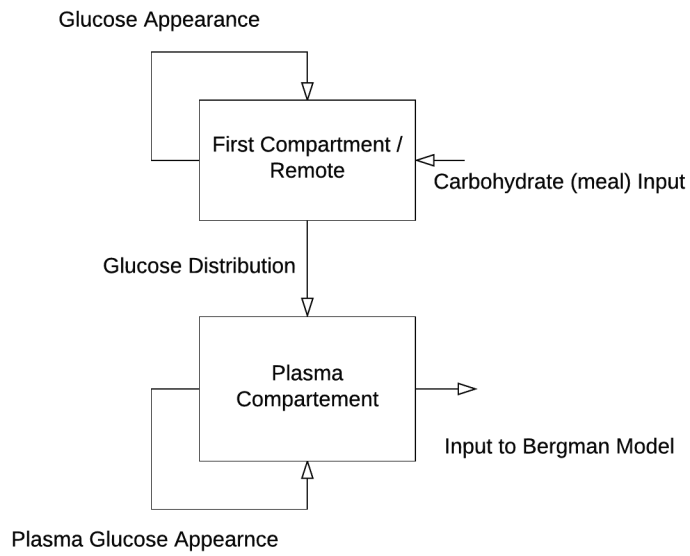


Figure 2.5: Two Compartment based Meal Sub Model

cal activity - as well which play an important role in maintaining blood glucose in normal range. As described in figure 2.6, when BG levels decease from the normal range, pancreatic α cells detect this change and release glucose from glucagon through glycogenolysis and gluconeogenesis process. It is well know that physical activity, bodily movements, consumes energy and according to the Breton (2008) , BG levels decreases with consumption of energy.

According to Young (2005), Glucagon primarily acts on liver to initiate glycogenolysis and gluconeogensis, resulting in a rapid increase in endogenous glucose production. With prolonged stimulation, glucagon action at the liver results in a glucose sparing activation of fatty acid oxidation and production of ketones. As said in the Young (2005) paper, there are two kinds of stimulated glucagon secretion, hypoglycemia and nutrient. In any case, it is quite necessary to include the effect of endogenous glucose production in blood glucose regulation for better accuracy.

As mentioned by Yardley *et al.* (2012), insulin sensitivity changes when a person

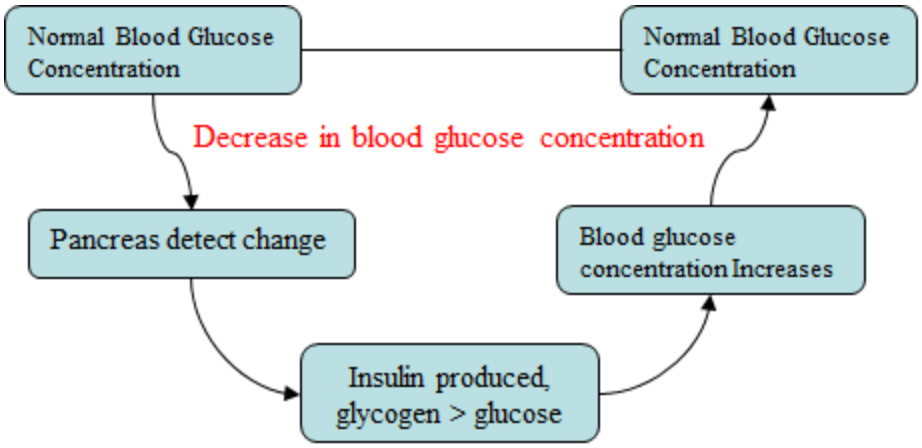


Figure 2.6: Endogenous Glucose Production Process

with T1DM diabetes exercises and these changes affect responsiveness of insulin on glucose. Similarly, Colberg *et al.* (2015) states that many individuals experience a decline in post-activity glucose levels during night-time. Currently insulin pumps are available which take into account insulin basal bolus, glucose distribution, and meal intake. However, these insulin pumps have sheltered the effects of physical activity on blood glucose though, as stated in my litertaure, it is quite factor in blood glucose management. Thus, we have modified Bergman Minimal Model to include effects of physical activity and endogenous glucose production.

2.5 Optimization Algorithm: Least Square Function

Optimization algorithms are used for approximation of unknowns in given equations. Least square functions are widely used for optimization algorithms where best curve fitting is done by minimizing residuals(a residual being: the difference between an observed value and the fitted value obtained from given model). Least square fall into two categories: linear and non linear least squares, depending on the linearity of given equations and unknowns.

Consider a set of m data points, $(x_1, y_1), (x_2, y_2), ..., (x_m, y_m)$, and a mathematical

model $y = f(x, P)$, x depends on the n parameters, $P = p_1, p_2, ..., p_n$ with $m > n$. The objective is to find P such that the curve fits best the given data by minimizing the sum of squares

$$S = \sum_{1}^{m} r_i^2 \tag{2.4}$$

is minimized, where errors r_i,

$$r_i = y_i - f(x_i, P) \qquad for \quad i = 1, 2, 3.....m \tag{2.5}$$

Minimum value of S can be obtained when the gradient is zero. Therefore, n gradient equations:

$$\frac{\partial S}{\partial p_j} = 2 \sum_{i} r_i \frac{\partial r_i}{\partial p_j} = 0 \qquad (j = 1, 2, ..., n) \tag{2.6}$$

The derivatives $\frac{\partial r_i}{\partial p_j}$ consists of independent variables and the parameters, hence these equations don't have a closed solution. Therefore, initial values of parameters are given and these are updated iteratively.

Chapter 3

RECENT WORK AND APPROACHES

With the availability of real-time monitoring sensors, there has been a boost in the research of closed loop insulin delivery systems, also know as artificial pancreas. Artificial pancreas is a system of body sensors which closely caricatures the blood glucose regulation of a healthy pancreas. This system mainly consists of three devices, continuous glucose monitoring sensor(CGM) for measuring BG levels in the subcutaneous tissue, a controlled algorithm to calculate the amount of insulin that has to be delivered and a continuous SC insulin infusion (CSII) pump to deliver calculated insulin. The controlled algorithm uses MPC - model predictive controllers approach - which estimate the amount of insulin through a non linear complex differential equation. According to the Cobelli *et al.* (2011), control algorithm needs further development in the areas of model prediction, individualization, automated meal and exercise control and real-time adaptation to patient physiology and behavior.

Dr Breton, in 2008, proposed a modified minimal model for glucose kinetics(MMGK) (Breton (2008)) which accounted physical activity in closed loop insulin delivery system. This model considers both increased glucose uptake due to increased energy consumption and longer lasting changes in insulin action. Below are the modified equations for estimation of glucose.

$$\frac{dG}{dt} = -p_1(G - G_b) - (1 + \alpha Z)X.G - \beta YG + \frac{D}{V_g} \tag{3.1}$$

$$\frac{dX}{dt} = -p_2 + p_3(I - I_b) \tag{3.2}$$

$$\frac{dY}{dt} = \frac{-1}{\tau_{HR} * Y} + \frac{1}{\tau_{HR}}(HR - HR_b) \tag{3.3}$$

$$\frac{dZ}{dt} = -(f(Y) + \frac{1}{\tau})Z + f(Y) \tag{3.4}$$

where, $f(Y) = \frac{(\frac{Y}{a.HR_b})^n}{1+(\frac{Y}{a.HR_b})^n}$. In this model exercise intensity and duration were accounted for through the use of heart rate. Physiological parameters were fit using a combination on non-linear least-square fitting and Bayesian constraints. There are two major things which this model did not considered, modeling of endogenous glucose production and the change in insulin sensitivity due to the activities preformed in last 24-hours.

Chapter 4

GUIDED MACHINE LEARNING MODELING APPROACH

4.1 System Layout

The proposed System, figure 4.1, consists of two models, Physiological model and ML model. Physiological model, guide to ML model, generates informative features through raw physiological data. ML generates a patient specific predictive model through the input features which also includes informative feature obtained from physiological model along-with other features.

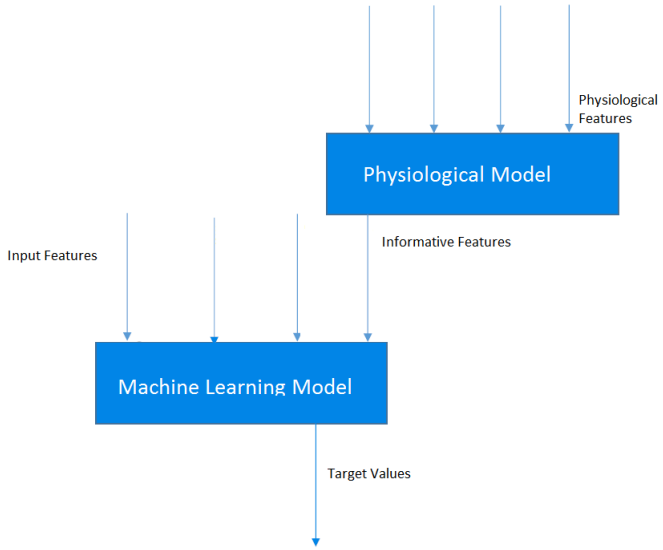


Figure 4.1: Guided System Layout

Suppose, we have a physiological dataset with $[x_1, x_2, ..., x_n]$ features and the target value $[Y]$, has to be estimated. As mentioned in Bischoff (1987), physiological model is constructed from a set of differential equations and its respective physiological parameters. Hence we can represent the model's equation in the following way:

$$y_0 \times \frac{dy}{dt} = p_1 \times \frac{dx_1}{dt} + p_2 \times \frac{dx_2}{dt} ... + p_n \times \frac{dx_n}{dt} \tag{4.1}$$

The $Y^{'}$, informative feature obtained by solving the non linear differential equations, is passed on to the ML algorithm along-with other input features, $[x_1^{'}, ..., x_n^{'}, Y^{'}]$. ML algorithm learns a model through these features and generates a predictive function, $h(x)$. Considering $h(x)$ as a linear function, we can represent it as below:

$$h(x) = \theta_1 + \theta_2 \times x_1^{'} + ... + \theta_{n+1} \times x_n^{'} + \theta_{n+2} \times Y^{'} \tag{4.2}$$

$$Subjectto \qquad h(x) - Y < \epsilon \tag{4.3}$$

These $[\theta_1 + .. + \theta_{n+2}]$ weights are maximized such that $h(x) - Y$ is always less than ϵ - error threshold - for the given training dataset. If an input feature x_i is more correlated as compare to other feature then, its impact on the predicted values will be more. Hence, more accurate estimated values from physiological model as a informative feature will give more accurate result from ML model.

4.2 Guided Support Vector Regression Machine

This section talks about a guided machine learning model, Support Vector Regression Model, developed based on the system framework described in the previous section. This model, guided by a glucose regulation physiological model, predicts the blood glucose levels of T1DM patients in living scenario.

This model has four input features - estimated blood glucose levels, insulin input, intensity of physical activity and food intake. Estimated blood glucose levels are the values generated through the physiological model used in this system. Insulin input is the amount of insulin taken by the patients. It includes both intravenous insulin (bolus) and subcutaneous insulin input (basal). Intensity of physical activity

is the amount of activity done that particular time interval. It is calculated through accelerometer values. Food intake accounts for the amount of carbohydrate comsumed by a patient. All the input data is standardized to zero mean and unity standard deviation. This preprocessing is done for two reasons, all the input features are measured at different scale and this allow regression model to converge at a faster rate.

This model predicts blood glucose levels in an iterative manner which means it takes 576 data points for training and predicts 6 data points. After prediction, model again learns with next 576 data points. Each data point represents 5 minutes state. The iterative process of updating weights is done because the impact of input features on blood glucose varies with time (Bergman *et al.* (1981); Lee *et al.* (1992); Van Cauter *et al.* (1992)). This model is also patient specific model as the effect of every features on glucose differs inter- individually.

The next chapter discusses about the physiological model used as a guide to our proposed SVR model for estimation of blood glucose.

Chapter 5

GLUCOSE REGULATION MODELING APPROACH

Glucose and insulin dynamics have been modeled since early 20th century, thus, many models have been proposed for the estimation of blood glucose. These mathematical models are used to estimate the glucose disappearance and insulin sensitivity, a part of glucose-insulin dynamics research. These models can be classified mathematically as: ordinary differential equations Steil *et al.* (2005); Bolie (1961); Bergman *et al.* (1981); Parker *et al.* (1999), delay differential equations Engelborghs *et al.* (2001); Bennett and Gourley (2004), partial differential equations Wach *et al.* (1995); Keener (2001), stochastic differential equations Bleckert *et al.* (1998); De Vries and Sherman (2000), and integro-differential equations De Gaetano and Arino (2000); Li *et al.* (2006).

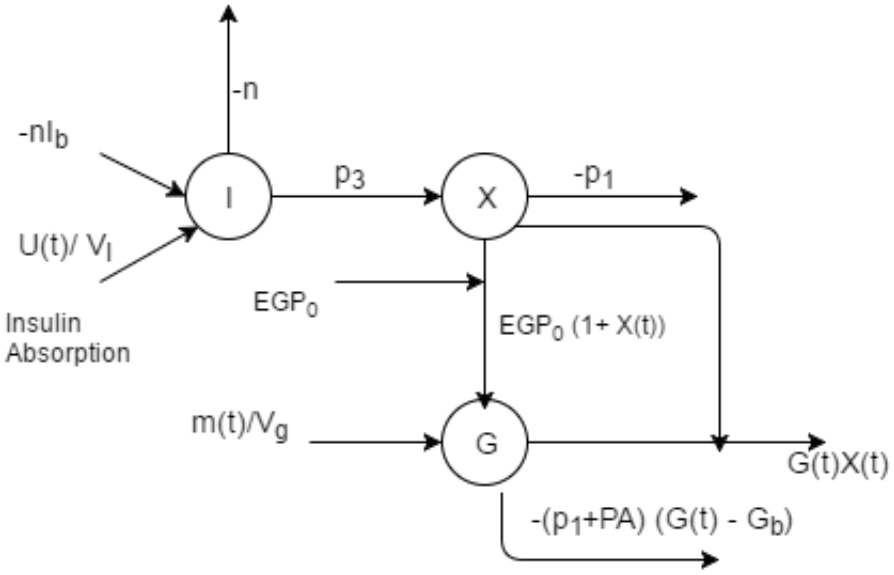


Figure 5.1: Two Compartment Based Bergman Minimal Model

In this work, modified Bergman Minimal Model (Bergman *et al.* (1981)) is used for estimation of BG levels. The BMM model was proposed in early eights by Bergman *et al.* (1981) for the interpretation of glucose and insulin dynamics. This thesis also modifies BMM for more accurate estimation of BG levels by inducing the effect of physical activity intensity and endogenous glucose production on the blood glucose. This model consists of two physiological compartment model: a glucose compartment, and a plasma insulin compartment which effects the glucose remotely. For profound understanding of the minimal model, I attempt to explain the two compartment based model in simpler manner, dividing it into two parts: a glucose subsystem and an insulin subsystem.

5.1 Glucose Subsystem

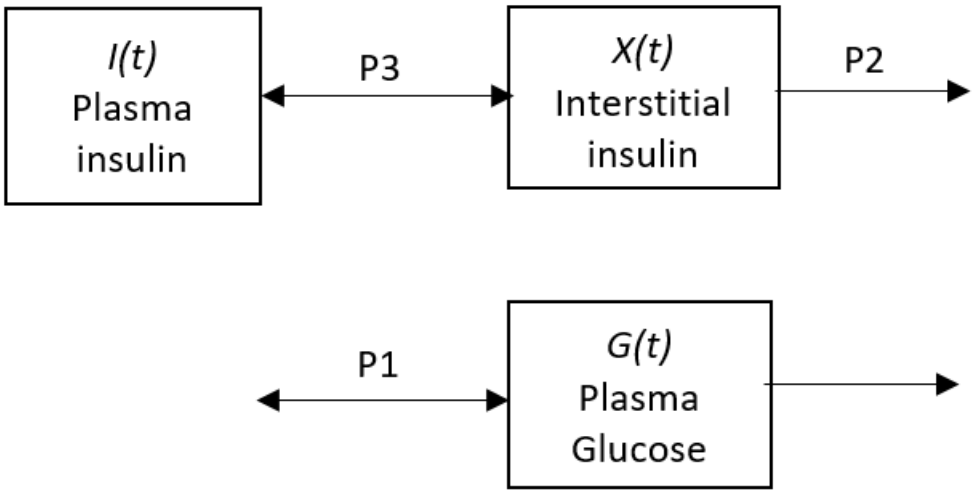


Figure 5.2: Minimal model for glucose kinetics. Source: Van Riel (2004)

The glucose subsystem consists of a set of three differential equations- glucose plasma concentration, interstitial insulin and insulin plasma. Figure 5.2 summarizes the minimal model for glucose kinetics.

As depicted from 4.1 equation, glucose leaves or enters the plasma compartment at a rate proportional to the difference between the plasma glucose level, $G(t)$ and the basal plasma level, G_b; if the plasma glucose level falls below the basal level, glucose enters the plasma compartment, and if the glucose level rises above the basal level, glucose leaves the plasma compartment. Glucose also disappears from the plasma compartment via a second pathway at a rate proportional to the ""activity" of insulin in the interstitial tissue $X(t)$. (Van Riel (2004))

Similarly, in equation 4.3, Insulin leaves or enters the interstitial tissue compartment at a rate proportional to the difference between the plasma insulin level, $I(t)$, and the basal plasma level, I_b; if the plasma insulin level falls below the basal level, insulin leaves the interstitial tissue compartment, and if the plasma insulin level rises above the basal level, insulin enters the interstitial tissue compartment. Insulin also disappears from the interstitial tissue compartment via a second pathway at a rate proportional to the amount of insulin in the interstitial tissue compartment. (Van Riel (2004))

In this work, equation 4.1 is modified by adding two more elements to the base BMM, physical activity factor PA (coorelation of physical activity and BG levels is explained later in this chapter) and endogenous glucose production (EGP) - $EGP_0(1+X(t))$. As explained by Hovorka *et al.* (2004), the minimal model insulin sensitivity is tightly and linearly related to sensitivity of EGP, thus to quantify effects of interstitial insulin on endogenous production of glucose, EGP is accumulate with $X(t)$.

The glucose kinetics equations are described as below :

$$\frac{dG}{dt} = -(p_1 + PA)(G(t) - G_b) - X(t)G(t) + \frac{m(t) + EGP_0(1 - X(t))}{V_g} \quad (5.1)$$

$$\frac{dX}{dt} = -p_2 X(t) + p_3 I(t) \tag{5.2}$$

$$\frac{dI}{dt} = \begin{cases} \gamma(G(t) - h) * t - n(I(t) + I_b) + \frac{U(t)}{V_I}, & \text{if } G(t) \geq h \\ -n(I(t) + I_b) + \frac{U(t)}{V_I}, & \text{otherwise} \end{cases} \tag{5.3}$$

where,

$G(t)(mg/dl)$ is the relative differential plasma glucose,

$G_b(mg/dl)$ is the basal glucose,

$X(unitless)$ represents the remote effects of insulin on glucose distribution and endogenous glucose production.

$I(t)(\mu I/dl)$ is the blood insulin concentration

$I_b(\mu I/dl)$ is the basal insulin concentration

$P_1(min^{-1})$ is the glucose "mass action" rate constant

$P_2(min^{-1})$ is the rate constant expressing the spontaneous decrease of tissue glucose uptake ability

$P_3(min^{-1})$ is the insulin-dependent increase in tissue glucose uptake ability, per unit of insulin concentration excess over baseline insulin

$n(min^{-1})$ is the first order decay rate constant for Insulin in plasma

$\gamma(min^{-1})$ is the rate of pancreatic release of insulin after the bolus, per minute and per mg/dl of glucose concentration above the target glycemia

$h(mg/dl)$ is the pancreatic "target glycemia"

$V_I(dl/kg)$ is the glucose volume distribution

$V_G(dl/kg)$ is the insulin volume distribution

$m(t)(mg)$ is the effect of carbohydrate intake on plasma glucose

$EGP_0(mg/dl)$ represents endogenous glucose production extrapolated to the zero in-

sulin concentration

$U(t)(\mu I/dl)$ is the modification for T1DM in which insulin appears only from an exogenous source

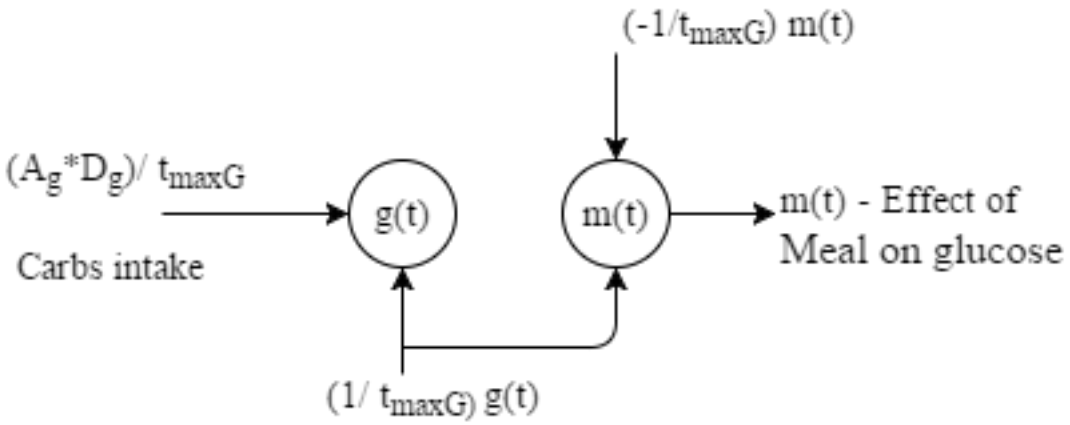


Figure 5.3: Meal Intake Sub-Model

Gillis *et al.* (2007) added one more component, meal intake sub-model, to stimulate the dynamics of insulin, more accurately. The meal sub-model which describes meal dynamics with input of carbohydrate (mg) is based on the gut absorption model proposed by Hovorka *et al.* (2004).

According to the Gillis *et al.* (2007), meal sub-model is expressed as a two compartment gut absorption model:

$$\frac{dm}{dt} = \frac{-1}{t_{maxG}} m(t) + \frac{1}{t_{maxG}} g(t) \tag{5.4}$$

$$\frac{dg}{dt} = \frac{-1}{t_{maxG}} g(t) + \frac{A_g}{t_{maxG}} D_g(t) \tag{5.5}$$

where,

$g(t)(mg)$ is the glucose appearance in the first compartment,

$m(t)(mg)$ is the plasma appearance of glucose, input to the Bergman minimal model.

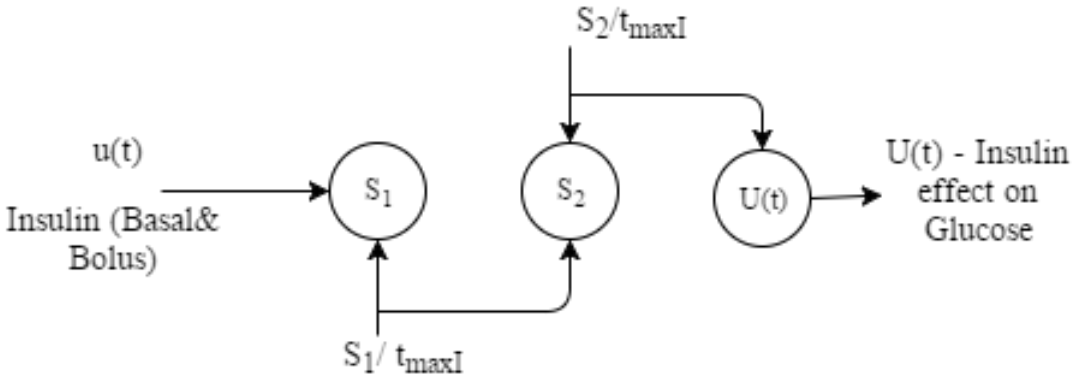


Figure 5.4: Insulin Sub-Model

According to the Hovorka *et al.* (2004) model, the insulin absorption model is also a two compartment based model which describes the subcutaneous insulin transportation to plasma insulin and its effect on glucose production. The model is described as below:

$$\frac{dS_2}{dt} = \frac{-S_1(t)}{t_{maxI}} - \frac{S_2(t)}{t_{maxI}} \tag{5.6}$$

$$\frac{dS_1}{dt} = -u(t) - \frac{S_1(t)}{t_{maxI}} \tag{5.7}$$

where,

S_1,S_2 is the amount of insulin in first and second compartment,

t_{maxI} is the time -to-maximum insulin absorption,

$u(t)$ is the administration of insulin, which is basal and bolus infusion.

The plasma appearance rate is given as:

$$U(t) = \frac{S_2}{t_{maxI}} \tag{5.8}$$

5.3 Model Parameter

In this model, out of thirteen parameters, six parameters were estimated using a nonlinear least square curve fitting algorithm and rest were kept constant. The reason of doing so was to reduce the estimated parameters while keeping the capacity to cover wide range of glucose variation observed in T1DM subjects. According to the Hovorka *et al.* (2004), Table 5.1 represents the constant parameters along-with the values used for T1DM subjects.

Table 5.1: Constant Parameters of Model

Symbol	Description	Value
EGP_0	Endogenous Glucose Production	0.0161 $\mu kg^{-1}min^{-1}$
V_g	Glucose Distribution Volume	0.16 LKg^{-1}
V_I	Insulin Distribution Volume	0.12 LKg^{-1}
t_{maxG}	Time-to-maximum of CHO absorption	40 min^{-1}
t_{maxI}	Time-to-maximum of injected insulin	55 min^{-1}
A_g	Carbohydrate Bio-availablity	0.8 $unitless$

Table 5.2 represents the estimated parameters by minimizing a weighted non-linear least square function recursively. A non-linear square function is a regression analysis approach estimates the unknowns in given equations. In this approach the overall solution minimizes the sum of the squares of the difference between the observed values and fitting value from the model. Least square problems fall into two categories: linear and non-linear squares depending whether fitting equation are linear and non-linear. Estimated parameters were constrained with upper and lower bound to keep physiological features of the models.

Table 5.2: Estimated Parameters of Model

Symbol	Description	Upper bound	Lower bound
P_1	Glucose Transfer Rate(min^{-1})	$7 * 10^{-3}$	$4.6 * 10^{-2}$
P_2	Deactivitation Rate(min^{-1})	$3.4 * 10^{-3}$	$6.7 * 10^{-2}$
P_3	Activitation Rate(min^{-1})	$5.5 * 10^{-7}$	$1.9 * 10^{-5}$
n	Fraction Elmination Rate(min^{-1})	0.1	0.5
G_b	Basal Glucose Value(mg/dl)	40	200
I_b	Basal Insulin Value($\mu I/dt$)	0	365

5.4 Correlation between Physical Activity and Blood Glucose

According to Derouich and Boutayeb (2002); Control *et al.* (1995); UKPDS (1998); Boutayeb and Kerfati (1994), long-term complications such as heart disease, cancer, lipid levels can be avoided or at least delayed by a good regular control of glycemia. A good regular control of glycemia needs proper dose of insulin for controlling BG levels. According to the authors of the recent papers Bellazzi *et al.* (2001); Derouich and Boutayeb (2002), the regulation of blood glucose concentration is mainly achieved by acting on three control variables: insulin, meals and physical exercise. However, all the proposed control systems have focused on the definition of insulin therapy strategies and considering meals and physical exercise as (known) disturbances. Further, though a lot of medical literatures have been published on the effect of physical activities on BG levels and how physical activity is a contributing factor in hypoglycemia events, most of them do not go on to build an accurate mathematical model which takes physical activity's effects into account.

According to the Colberg *et al.* (2015), the impact of physical activity(PA) on BG

levels is quite complicated since there are many dependent parameters such as type, duration and intensity of physical activity which influences the effect on BG levels. To measure the intensity of physical activity, numerically, we have used figures from a wearable device called accelerometer sensors. These accelerometer sensors capture the body movement for every five minute in all the three orientations.

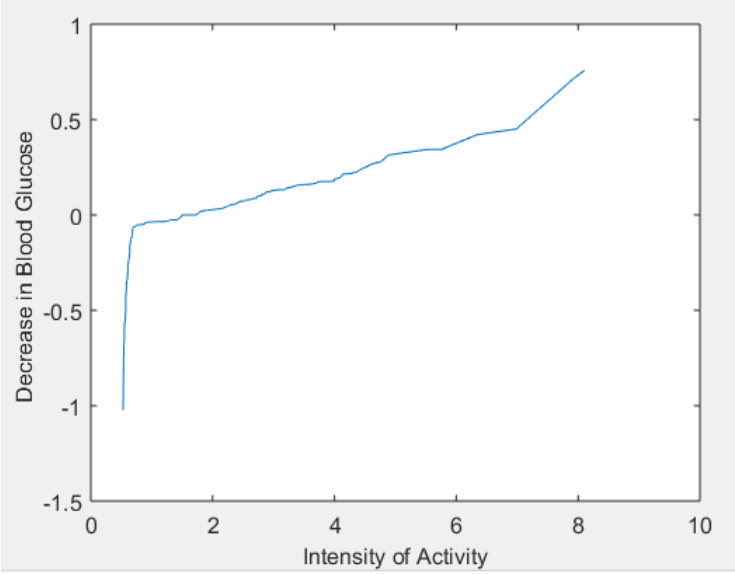


Figure 5.5: Intensity of Physical Activity versus Decrease in BG levels.

Figure 5.5 represents the variation of BG levels against the intensity of physical activity for every 30 minutes over a week long period. The intensity of physical activity is numerically defined as area under curve of accelerometer readings and decrease in BG is the difference between maximum and minimum BG levels in that particular 30 minutes. The figure 5.5 clearly demonstrates a linear dependency of PA on BG levels but this linearity is piecewise. This piecewise linearity means the influence of PA on BG levels differs non−linearly on complete range but looking in slots, the impact is linear. As mentioned by Colberg *et al.* (2015), the impact of physical activity on blood glucose changes with respect to the intensity of physical activity. Through our analysis we can clearly conclude that intensity of physical

activity can be categorized in three - low, medium, and high. The effect of low intensified activity on BG levels will be less as compared to the high one. This effect is accounted in estimation of blood glucose levels by adding physical activity factor(PA). PA component is described as below:

$$PA = \frac{k_1 \times D_G}{(G_{mean} \times IPA)} \tag{5.9}$$

where k_1 is the slope factor which is dependent on intensity of physical activity. D_G is difference between max and mini BG levels and G_{mean} is the mean of BG levels. IPA is the intensity of physical activity for the particular time period which is 5 minutes.

Chapter 6

EXPERIMENTS AND RESULTS

6.1 Subjects and Protocols

For this research, data was gathered by Mayo clinic. Mayo Clinic captured continuous variation of variables- food intake, physical activity and limitations of current insulin preparations and use, influencing blood glucose. Blood glucose levels were monitored every 5 minutes by DexCom G4 Platinum Profession CGM and physical activity was measured every 5 minutes by highly accurate accelerometers, wore around the waist, that capture data on body movements. Mayo Clinic followed a meal plan provided by the CRU metabolic kitchen during the one week CGM and physical activity monitoring protocol. This weighed meals include 55% carbohydrate, 15% protein and 30% fat. Mayo Clinic provided us a dataset of 6T1DM subjects who underwent the above protocols for 1 -week in free living scenario.

6.2 Power Analysis for Estimation of Sample Size

Coming up with an optimum sample size is a crucial factor in experimental design as too many participants in an experiment can be very expensive whereas less number of participants can result in an underpowered study resulting into inaccurate results (Suresh and Chandrashekara (2012)). Power analysis is one such procedure which allows us to determine the sample size required to detect the effect of given sample size on the experiments such that we get statistically significant results. Power Analysis depends on four interrelated variables viz. Power, Significance level, Alternate Hypothesis and Sample Size. If any three of them are known, it is possible to esti-

mate the fourth one. We use this concept to derive the sample size. The alternative hypothesis that we have used here is that the two means will differ (Two sided) . Significance level corresponds to the probability of false positives. Sample size is the number of subjects that we aim to estimate in Power Analysis. We set up a null hypothesis stating there is no difference between the means and disproves it. It can result in 2 errors. First error, Type II error can occur if we find a true difference then the null hypothesis is rejected and we get a false negative result. Type I error can occur as false positive is detected when it is found that there is a difference but in fact is just due to the chance sample variation. The results of power analysis done in this study are shown in the figure 6.1 in the form of power vs. number of observations. 450 observations were recorded for 7 subjects. The power for sample size 350 was observed to be 0.08 and for 400, it was 1.00. In conclusion, an effective sample size should be at least greater than 350.

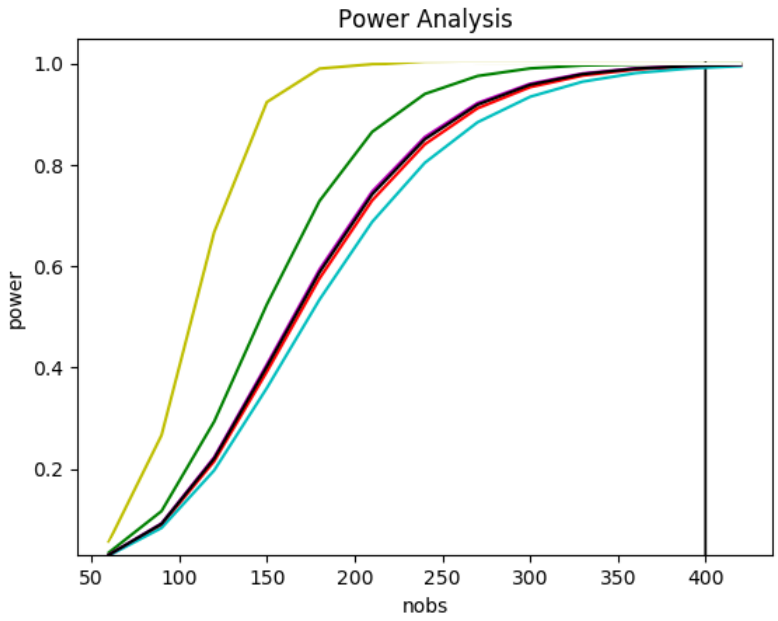


Figure 6.1: Power Analysis graph to estimate effective size

6.3 Preprocessing And Experiment Execution

This work generates a subject specific model for estimation of BG levels. we followed a strategy generally used in a game called chess. In this strategy, on the basis of past game, next few ahead moves are decided but only first move is implementation, and then again our decided steps are re-assessed with opponent's move. Similarly we provide two days data and next 30 minutes values, after this prediction again we learns the with two days and estimate 30 minutes data. The reason of doing so is to include the daily changes done in the person's activity. Another thing, physiological parameter estimation using least square optimization is done only one time unlike Bergman Minimal Model. In BMM, the parameters are estimated time-to-time for inclusion of changes in the effectiveness of physiology variable.

With this strategy, the preprocessing time required is the time required to estimate physiology parameters for every subject. Runtime execution is the time required for the prediction of BG levels for next 2 days in a iteratively manner. This means after every six prediction we update the weights of SVR by providing next 2 days data. Table below shows the preprocessing time(time required fr estimation of physiological parameters through optimization), execution time for 6 prediction (Time required for prediction of 6 values without any weight updated of SVR model) and execution time for 300 predictions (Time required for prediction with relearn of SVR after every 6 predictions)

6.4 Evaluation and Outcome

The data collected from seven Type I Diabetes patients over a period of three days was subjected to the model mentioned above. Experiments were carried out to evaluate the estimation of BG levels by BMM and SVR while factoring in the effects

Table 6.1: Execution time required by Guided SVR model

Subjects	Preprocessing time (sec)	Execution Time for 6 prediction(sec)	Execution time for 300 predictions(sec)
1	527	0.003	55
2	397	0.010	43
3	437	0.017	45
4	689	0.002	78
5	378	0.0087	35
6	435	0.019	59
7	397	0.007	49

of physical activity and EGP. The evaluation metric of these experiments was the Root Mean Squared Error (RMSE). This metric is used to measure the deviation of the predicted values of blood glucose levels from the actual blood glucose values or the ground truth values. The lower RMSE values denotes that the predicted values are being estimated with more accuracy. Since the inputs were standardized to zero mean and unity standard deviation, preferred RMSE values lie as close to zero as possible for high accuracy predictions.

Table 6.2 shows RMSE values of glucose levels, estimated by three different BMM models - BMM without PA and EGP (Model I), BMM with PA (Model II) and BMM with PA and EGP (Model III) - for seven subjects. We observe that Model III which includes both physical activities and EGP effects outperforms other two models. One more thing which is observed, is the difference of RMSE values between model II and model III is quite less and this is because EGP effects comes into play when BG levels goes below certain level thus it is averaged out.

Table 6.3 shows RMSE values of glucose levels, predicted by four different SVR models - SVR without bergman estimation as a guide path (Guided Model I), SVR without PA and EGP(Guided Model II), SVR with PA effects (Guided Model III) and SVR with PA and EGP(Guide Model IV). Comparing RMSE values from table

Table 6.2: RMSE Values for Bergman Minimal Model

Subjects	Model I	Model II	Model III
1	0.555	0.408	0.410
2	0.523	0.404	0.394
3	0.551	0.501	0.537
4	0.566	0.466	0.473
5	0.653	0.503	0.455
6	0.577	0.474	0.420
7	0.639	0.554	0.492

6.2 and table 6.3 clearly concludes that SVR models outperform BMM models in free living scenario.

Through this values we observe that the RMSE values are very high in the case of SVR model without guide by the estimated values of glucose. This indicates that the support vector regression models were unable to learn the underlying pattern and hence unable to predict the correct values of blood glucose for the given into values. Without any notion of the pharmacokinetics involved in the data, the support vector regression models are unable to learn the trends the input data.

Another interesting thing which we can draw out from the results is that the performance guided models becomes better by 10 % when physical activity and endogenous glucose production effects are introduced. But there are few subjects for which SVR model with only physical activity outperformed. The reason behind this is that the correlation of EGP effect with actual glucose is quite low, as EGP comes into play only when glucose levels goes down to a certain level.

Table 6.3: SVR Models

Subjects	Model I	Model II	Model III	Model IV
1	0.428	0.241	0.164	0.169
2	0.221	0.054	0.043	0.044
3	0.335	0.157	0.128	0.154
4	0.417	0.275	0.256	0.249
5	0.369	0.174	0.162	0.167
6	0.376	0.219	0.204	0.194
7	0.451	0.231	0.16	0.091

Chapter 7

CONCLUSION AND FUTURE WORK

This work proposed a guided machine learning framework for pharmacokinetic modeling. This framework's practicality is evaluated by implementing a support vector regression model for blood glucose regulation. This model is build on to a physiological model, which provides estimated blood glucose values. Our result analysis concludes three things. First, a guided machine learning predicts physiological features more accurately as compared to physiological based pharmacokinetic model. This model is also less computational expensive. Second, through the results, we can conclude that if all effecting factors are included in estimation by physiological, we will obtain values more close to the actual values. Thirdly, these machine learning models can be in a plug-n-play manner unlike physiological model and these guided models can be used in the controlled system. Areas of future works can be classified as follows:

- The proposed model's practically is evaluated with one physiological model. In the future work, the proposed model's should be extend for every kind of physiological model(Bagade *et al.* (2016), Bagade *et al.* (2013)).

- These regression models are being evaluated for seven subjects but when it comes to health model it is quite important to evaluate test throughly in clinical environment(Banerjee *et al.* (2012)).

- An end to end pervasive system which would monitor real time activities and generate a subject specific regression estimation model. This system will provide

more flexibility incorporating this system in free living environment (Gupta *et al.* (2013), Banerjee and Gupta (2015), Banerjee *et al.* (2013)).

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