Prediction of Hypo/Hyperglycemia through System Identification, Modeling and Regularization of Ill- Posed Data

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Abstract: A clinically important task in Diabetes management is prevention of Hypoglycemic events. Continuous Glucose Monitoring (CGM) devices have been used to find the trend and temporal variability of the glucose levels of a Diabetic person. This CGM data can be used to identify the impending Hypo/Hyperglycemia well in advance with preprocessing the CGM data and System identification and Modelling. In this paper we have tried with ARIMA model and Tikhonov regularization. The prediction process is done with 10,20 and 30 minutes ahead time slots and their RMSE have been calculated. Results show that the preprocessed data with proper system modeling give accurate prediction values with clinically acceptable time lags.

Key words : Diabetes, Hypo glycemic Alerts, Ill posed problem, System identification, Mathematical modeling, Regularization.

1. Introduction

Diabetes Mellitus is a Metabolic disorder characterized by the inability of the Pancreas to regulate blood glucose concentration. High blood glucose levels lead to chronic diseases such as Cardio vascular , Retinal, Renal and Nervous disorders. Low blood glucose levels lead to immediate effects like Seizures and Short term Coma. According to DCCT (Diabetic Complications and Trial)[1] the risks of Diabetes can be prevented by proper blood glucose monitoring and regulation. Conventional method is to use blood Glucometers which use the capillary blood obtained through finger prick. This method is associated with pain and inconvenience and gives only the instantaneous values. Whereas Continuous Glucose Monitoring represents a significant advancement in the technology because it provides real time information about the current blood glucose. Eventhough the CGM devices measure the Interstitial fluid glucocose, they provide information about magnitude, direction, duration and frequency of fluctuations in the glucose levels. The device can give an alert at instances of unacceptable high or low glucose levels. Instead of giving alerts at that instances of blood glucose excursions, it would be advantageous if the alerts are given in advance so that the regulation of blood glucose can be done in a proactive manner. Efficient generation of Hypoglycemic alert in advance is of much importance due to the dangerous nocturnal hypoglycemia.

2. Predictive monitoring

Many researchers are contributing their work in this area. Since the CGM time series is of ill posed in nature, the systems are said to be ill conditioned. The numerical treatment of ill conditioned linear system is more complicated. Therefore much effort is required in system identification and regularization. System identification is the art of building mathematical models of dynamic systems from observed input – output data. It can be as the interface between the real world of applications and mathematical world of control theory and model abstractions. A model gives a relationship between observed quantities. Model allows for prediction of properties or behaviors of the object. Data driven models represent a class of modeling techniques where the relationships between input and output process variables that characterize the underlying phenomenon being

modeled are learned during the training phase. Then that model can be used for prediction of future values.

The first question on prediction was raised by Bremer and Gough[2] whether the CGM data could be used for prediction of near future glucose levels. According to them if the recent blood glucose history is not random but has an exploitable structure, it might be possible to predict the near future blood glucose values based on previous values. They used 10- min data from ambulatory Type I Diabetes Mellitus patients and identified Autoregressive models. They explored 10-min,20-min,ans 30-min prediction horizons and report that the 10- min ahead predictions are accurate. But no quantification for their predictions were given. Bellazzi et al., [3] used non uniformly and sparsely sampled T1DM (Type I Diabetes Mellitus – onset of diabetes before the age of 25) subject data collected in ambulatory conditions, linearly interpolated at 2 hour intervals, to identify low order ARX models whose inputs included meals and a filtered insulin input. They investigated with 2-h, 4-h and 6-h prediction horizons. The prediction metrics were summarized with 1 step ahead prediction for best case subject, worst case subject and mean case of 60 subject data bank. The marked difference between the results for the best case and worst case subjects illustrates a fundamental and significant inter-subject variability. But the results were somewhat positively based due to the linear interpolation. Hovorka et al., [4] performed experiments in 10 T1DM patients under clinical conditions, using their own physiological model to make predictions of 15 minutes glucose data upto 4 steps (i.e, 60 minutes) into the future. The glucose was measured intravenously, but delayed by 30 minutes to mimic subcutaneous measurement. The model parameters were recursively estimated using a sophisticated Bayesian method. The predictions of the resulting models had RMSE values of 8.6, 13.0 and 17.3 mg/dL for 2 step, 3 step and 4 step predictions respectively. Trajanosoki et al.,[5] proposed a neural predictive controller for closed loop control of glucose in subcutaneous route. The control strategy is based on off line system identification using neural networks and non linear model predictive controller design. The proposed framework combines the concept of Non linear Auto Regressive with eXogenous inputs model using a regularization approach for constructing Radial Basis Function Neural Network. The drawback of this method is that the training of neural network requires the solution of a non convex optimization and the resulting network weights or lack of model coefficient. Dua et al., [6] employ a Kalman filter to adjust the parameters of first principles model for the prediction and control of blood glucose. The performance was tested with simulated data. The Kalman filter had different implementation challenges. They require the availability of a high fidelity first principle model capable of accounting for meals and physical activity. Robert S.Parker, Doyle III [7] and their group worked on model based predictive control algorithm which was developed to maintain normoglycemia in Type 1 Diabetes patients using a closed loop Insulin infusion pump. Compartmental modeling technique was used in this work. A 19'th order non linear Pharmaco kinetic – Pharmaco dynamic representation was used in controller synthesis. Linear identification of an i/p – o/p model from noisy patient data was performed by filtering the impulse response coefficient via projection onto Laguerre basis. Palerm et al.,[9**]** have demonstrated the effect of of sampling frequency, threshold selection and prediction horizon on the sensitivity and specificity of prediction of hypoglycemia. In their view, an optimal estimator could be structured to estimate not only the value of interest (i.e. glucose concentration) but also its rate of change. They extended this to estimate the rate of change of rate of change(second derivative) to improve prediction particularly for longer prediction horizons. The same group in their earlier work [10], proposed an algorithm based on the real time glucose sensor signals and optimal estimation theory (Kalman filtering) to predict hypoglycemia. The algorithm was validated in simulation based studies. In this current work, they further refined and validated the prediction algorithm based on the analysis of clinical hypoglycemia clamp data from 13 subjects. The result of this work was that for a 30 minute prediction horizon and alarm threshold of 70 mg/dl, the sensitivity and specificity were 90 and 79% respectively. Indicating that a 21% flase alarm rate must be tolerated to predict 90% of hypoglycemic events 30 minutes ahead of time. Shorter prediction horizons yield a significant improvement in sensitivity and specificity. Palerm et al., had two challenges in when testing a real time BG prediction algorithm with clinical data. First is the necesssacity of having frequently sampled reference BG values for comparison and next is the need to separate performance of sensor from that of prediction algorithm. For their study they used the hypoglycemic clamp data from CGMS® of Medtronic Minimed. Sparacino et al. , [11] used two prediction strategies based on the description of past glucose data. One is the first order polynomial and the other is the first order Auto Regressive model. Both the methods have time varying parameters estimated by Weighted Least Squares. In both the methods, at each sampling time, a new set of model parameters is first identified by means of WLS technique. Then the model is used to forecast glucose level for a given prediction horizon. The prediction algorithm was tested with Glucoday CGM system data from 28 type1 diabetic patients for a duration of 48 hours collected at a frequency of 3 minutes. Mean Square Error and Energy of Second Order Differences (ESOD) were taken as the performance metrics. Results proved that the performance of prediction algorithm is adequate for prediction of

glucose from past data is feasible for preventing hypo/ hyperglycemic events. The importance of using a time varying approach was witnessed in this work. Reifman et al., [12**]** investigated the capabilities of data driven AR models to Capture the correlations in glucose time series data, make accurate predictions as a function of prediction horizon and be made portable from individual to individual without any need for model tuning. They had made investigation with CGM data of 9 Type 1 diabetic subjects in a continuous 5 day period. The predicted glucose values were analyzed with Clarke's Error Grid. The study shows that, for a 30 minute prediction horizon data driven AR models provide sufficiently accurate estimates of glucose levels, for timely proactive therapy and AR model can be considered as the modeling engine for predictive monitoring of patients with Diabetes Mellitus. It also suggests that AR models can be made portable with minor performance penalties which greatly reduces the burden associated with model tuning and data collection for model development. Finan et al., [13] obtained data set of 2 Type I Diabetes subjects for a period of 5 days with values taken in 5 minutes span. They also generated simulated data for reality check from a non linear physiological model of TIDM. Each data set was divided into 2 halves. First half used for calibration i.e,model identification and second half used for validation. They identified 3 types of dynamic models - AR, ARX and ARMAX. Model identification procedure is by estimating model parameters such that one step prediction error are minimized. FIT value is the metric used to quantify the accuracy of model predictions. It is the measure of how much variability in the data has been explained by the model predictions. RMSE can also be used. Predictions deteriorate as the validation prediction horizon is extended to 24 steps (120 minutes). ARX model has increased complexity than AR model. For simulated data, the best modeling results were achieved with ARMAX model. **Cobelli group (Sparacino et al.,)**[11] had also suggested the use of CGM and AR models for short term glucose level predictionsof Type 1 diabetic patients. Although they found AR models to provide adequate results for 30 minute ahead predictions. But their modeling formulation is significantly different. They found that the models with order larger than one and with fixed parameters to be unstable and yield unacceptable prediction delays. Their AR model of order m=1 is updated continuously (for each individual) as each new observation becomes available and to avoid model " over fit " the parameter update balances the weight amoung current and prior observations. This is in contrast with the Reifman's group where an AR model is developed once for individual and same model is applied to other individuals without any modifications. A.Gani et al.,[14] combined the predictive data driven models and the frequent blood glucose measurements to provide an early warning of the impending glucose excursions and proactive regulatory actions. By simulation they proved that stable and accurate models for near future glycemic predictions with clinically acceptable time lags obtained by smoothing the raw glucose data and regularizing the model coefficients. This has to be validated for real time implementation. This group has worked with AR model of higher orders. C.Perez-Gandia et al., [15] have implemented an artificial neural network algorithm for online glucose prediction from continuous glucose monitoring. The predictor is implemented with artificial neural network model (NNM). In all these approaches the large time lags reduce the clinical benefits of predictions.

In this paper we propose an Auto Regressive Integrated Moving Average model (ARIMA) for the prediction of near future glucose concentration. We compared our results with 1 step, 2 step and 3 step time ahead (i.e., 10-min, 20-min and 30-min) predictions and their corresponding relative absolute differences and the RMSE have been analysed.

3. Methodology

A stochastic model that is extremely useful in the representation of certain practically occurring series is the *Auto Regressive* model[16][17]. In this model, the current value of the process is expressed as a linear aggregate of previous values of the process. Another kind of model is the *Moving Average* model which depends on the previous deviations. To achieve greater flexibility in fitting of actual time series, it is advantageous to include both *AutoRegressive and Moving Average* terms in the model. Many time series data obtained practically are of non stationary in nature. ARIMA models are the most general class of models for forecasting a time series which can be stationarized by transformations such as differencing and logging. ARIMA models are fine tuned versions of random walk and random trend models. The fine tuning consists of adding lags of the differenced series and/or lags of the forecast errors to the prediction equation. The first step in fitting an ARIMA model is the determination of the order of differencing needed to stationarize the series. The optimal order of differencing is often the differencing at which the standard deviation is minimum.

3.1 Regularization

One important property of mathematical problems is the stability of their solutions to small changes in the initial data. Problems that fail to satisfy this stability condition are said to be *ill posed*. The main objective of *regularization* is to incorporate more information about the desired solution in order to stabilize the ill posed problem and to find an useful solution. The additional information is usually in the

form of a penalty for complexity such as restrictions for smoothness or bounds on the vector space norm.The most common and well known form of regularization is that of Tikhonov.[18]

Noise in the raw data should be removed so that the estimated coefficients would reflect the underlying physiologic dependency. Smoothing of raw data removes the high frequency noise[19]. A linear smoother estimates the function value

$$\hat{Y}_j = x(t_j) \quad (1)$$

by a linear combination of the discrete observations

$$x(t_j) = \sum_{l=1}^{n} S_j(t_l)\, y_l \quad (2)$$

where $S_j(t_l)$ weights the *l*'th discrete data values in order to generate the fit to y_j. In matrix terms,

$$x(t\ ) = Sy \quad (3)$$

Where x(t) is a column vector containing the values of the function 'x' at each sampling point 't_j'.

$$S = S_d = \Phi\,(\Phi'\Phi)^{-1}\,\Phi'. \quad (4)$$

In the context of least squares estimation, the smoothing matrix has the property of being a projection matrix. This means that it creates an image of data vector 'y' on the space spanned by the columns of matrix 'Φ'such that the residual vector

$$e = y - \check{y} \quad (5)$$

is orthogonal to the fit vector ў. The key idea in Tikhonov's method is to incorporate a priori assumptions about the size and smoothness of the desired solution in the form of smoothing function. The smoothed signal is given by

$$\check{y} = S_d\ \ W \quad (6)$$

where S_d is the integral operator and W denotes the estimates of glucose signals first derivatives. The derivatives' estimate yield excellent data smoothing and do not introduce lag on the smoothed signal relative to the raw signal. To estimate the signal's derivative W, the functional f(W) is minimized. [18]

$$f(W) = \| Y - S_d \|^2 + \lambda_d^2 \| L_d W \|^2 \quad (7)$$

where 'Y' is the N*1 vector of raw CGM data and 'S_d' is the N*N integral operator, 'W' represents the rate of change of glucose with time. λ_d is the regularization parameter and L_d denotes a well conditioned matrix chosen to impose smoothness on 'W'. L_d is typically either an identity matrix, a diagonal weighting matrix or a p*n discrete approximation of a derivative operator in which case L is a banded matrix with full row rank.

$$L_2 = \begin{pmatrix} 1 & -2 & 1 & & \\ & \ddots & \ddots & \ddots & \\ & & 1 & -2 & 1 \end{pmatrix} \quad (8)$$

$L_d = L_2$ * (second derivative N × 1 matrix) (9)

The regularization parameter λ controls the weight given to minimization of the regularization term relative to the minimization of the residual norm. The most convenient graphical tool for analysis of the discrete ill posed problems is the so called L-curve which is a plot for all regularization parameters of the discrete smoothing norm. The L-curve clearly displays the compromise between minimization of these two quantities, which is the heart of any regularization method.

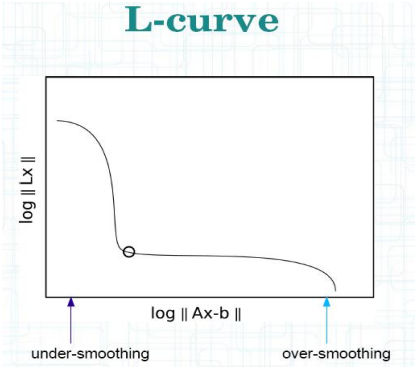

Fig 1. Graph used for selection of Regularization parameter.

The selection of the regularization parameter can either by Pragmatic parameter choice method or by Discrepancy principles or by methods based on error estimation. In our work, the optimum value of λ is obtained by minimizing the RMSE between the smoothed signal and the predicted signal.

3.2 ARIMA Modelling

After stationarizing the data by preprocessing i.e, through regularization, the next step is to fitting in an ARIMA model. The more systematic way to do this through Auto correlation and Partial Auto correlation plots of the regularized data. ACF plot is merely a bar chart of the coefficients of correlation between the time series and lags of itself. PACF plot is a plot of partial correlation coefficient between the series and lags of itself. The terms corresponding to exponential decline in ACF and peak in PACF would contribute to AR processes and Peak in ACF and exponential decline in PACF would contribute for MA processes. The next step is to determine the coefficients of model parameters by Maximum likelihood estimation. A conditional likelyhood function is selected in order to get good starting point to ontain an exact likelihood function.

Then the diagnosis check is carried out to validate the model. In successive trials the observation of the residuals obtained can help to refine the structure of the functions in the model[20][21]. An ARIMA model is generally given by

$$\Phi(B)\, g(t) = \theta(B)\varepsilon(t) \quad (10)$$

Where g(t) is the glucose level at time 't', Φ(B) and θ(B) are the parameters of AR and MA processes involved and ε(t) is the error term. Φ(B) and θ(B) are functions of backward shift operator i.e.,

$$B^{l}\, g_t = g_{t-l} \quad (11)$$

$$\Phi(B) = 1 - \sum_{l=1}^{\Phi} \Phi l B l \quad (12)$$

$$\theta(B) = 1 - \sum_{l=1}^{\theta} \theta l B l \quad (13)$$

The Third order ARIMA model has been selected first through empirical approach and then confirmed with optimization. The prediction efficiency of the model has been validated initially with simulated data and then with five real life subjects' data who were using the Minimed MedtronicCGM device.

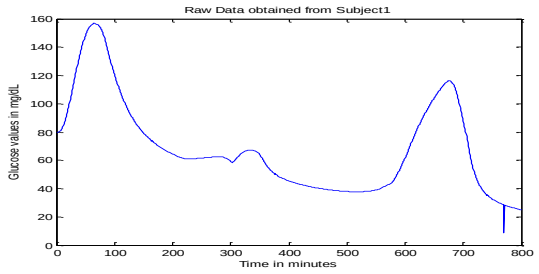

Fig. 2 Fluctuation in Glucose Profile of a Diabetic Subject

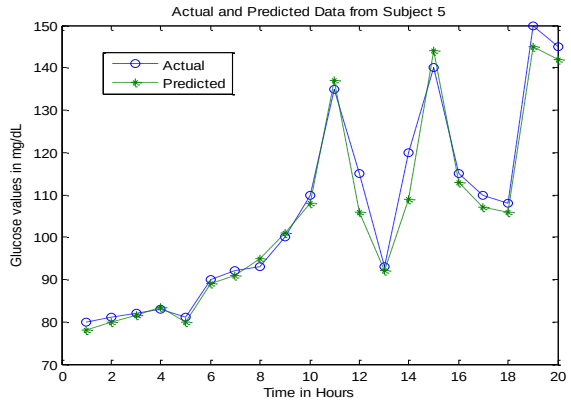

Fig .3. Actual and Predicted glucose profiles

First half of the data is used for training and the second half data is used for validation. RMSE between the predicted glucose levels and the actual value have been studied under various prediction horizons such as 10min,20-min and 30-minutes ahead. It is observed that the short term predictions provide accurate results. However the RMSE obtained for the 2 step and 3 step prediction horizons are much reduced compared to earlier approaches.

Results :

Performance Metric as Root Mean Square Error

Subject	RMSE in mg/dL for Prediction Horizons of		
	10-min	20-min	30-min
1	0.5	1.2	2.4
2	0.6	1.4	3.1
3	0.9	2.7	4.2
4	0.4	1.1	2.1
5	0.5	2.3	3.1

4. Conclusion

This paper proposes that a lower order ARIMA model could used for the prediction of near future blood glucose concentration so that the impending dangerous hypo/hyper glycemia can be inferred well in advance and preventive actions can be taken. The methodology is validated with simulated data as well as with real patient data. Avoiding false alarms and improvement in accuracy atleast by a factor of 5% is a great thing in these works. CGM devices with prediction capability will be much helpful in improving the quality of life of Diabetic society.

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