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A novel approach for the prediction of glucose concentration in type 1 diabetes ahead in time through ARIMA and differential evolution

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ABSTRACT

People affected with Diabetes Mellitus use Continuous Glucose Monitoring (CGM) devices for monitoring of their blood glucose level. The currently available CGM devices show the current glycemic level of the user and produce alarm whenever the glycemic level exceeds the normal range or is in increasing or decreasing trend. Some devices do prediction of the glucose value some time slots ahead and give an alarm of the impending Hypo/ Hyper glycemia situation. But the true scenario is that the success is only 50% due to false alarms or missing alarms. With the understanding that CGM data do have errors when the rate of change is high, in our study, we have tried the prediction of glucose levels ahead in time without intervention through Auto Regressive Integrated Moving Average (ARIMA) Model with its parameters optimized with Differential Evolution. The Method is validated with Simulated data obtained from the web based Diabetes Educator. First half of the data set is used for training and the remaining half is used for testing. Mean Absolute Difference (MAD) between the predicted and actual glucose values is used as the performance metric. The experiments conducted showed promising results with MAD in the range of 6 to 10.3. The prediction accuracy can be improved by increasing the number of iterations and the optimum selection of scaling factor.

Introduction

In a recent survey it is found that nearly 250 million people around the world are affected with Diabetes and this number will be in a growing trend every year. This has become a major health issue to be taken care of. Diabetes Mellitus is a metabolic disorder characterized by the inability of pancreas to regulate blood glucose concentration. Normally the blood glucose level should be in the range of 70 – 120 mg/dL. If glucose concentration is greater than 120 mg/dL , the situation is said to be Hyperglycemia. It will lead to long term complications like cardio vascular disease, nervous disorders and diabetic retinopathy. If the glucose concentration is less than 70 mg/dL , it is said to be hypoglycemia. It is more dangerous which leads to diabetic coma. The Diabetes Control and Complications Trial (DCCT)[1] group showed that strict glycemic control significantly reduces the short term and long term complications of diabetes.

The diabetic people follow monitoring of the glycemic level and Insulin therapy. For monitoring they use Glucometers or Continuous Glucose Monitoring (CGM) devices. The glucometer provides the glucose level of the capillary blood at that instant only. Whereas the modern Continuous Glucose Monitoring devices provide a minimally invasive mechanism to measure and record a patient's current glycemic state as frequently as every minute. It provides maximum information about the blood glucose variations throughout the day which facilitates diabetes people to make optimal treatment decisions. CGM provides information about the magnitude, direction, duration, frequency and causes of fluctuations in Blood Glucose levels. Continuous monitoring helps to study the reaction of glucose level to insulin, exercise, food and other factors. The additional information is useful for setting correct insulin doses for food intake and correction of hyperglycemia. The occurrence of hypoglycemia during nights can be identified and rectified by this CGM. Some of the CGM devices available are CGMS Gold, CGMS Gold, Glucoday, Guardian RT, Pendra, Freestyle Navigator.

The currently available CGM devices produce an alarm whenever the glycemia level goes on increasing or falls to the situation of hypoglycemia. Some CGM devices have an additional feature of predicting the glycemic level some number of time slots ahead without intervention. If a person is alerted for his forthcoming hypo/hyper glycemia he can take a quick action to avoid the complications. By these real time alarms or predicted value alarms, the diabetics can aware of their glycemic state and can absorb sugar or Insulin to overcome his hypo/hyperglycemic conditions. This is much useful especially during night times.

But the true scenario is, the performance of these devices in alert generation is not fully successful. Nearly 50% are of false alerts or of missing alerts. Since the user cannot distinguish between the true and false alerts, he would end in confusion whether to take the action or not. This poor performance is due to the noise in the sensor measurements. Or it can be said as error in the measurements of sensor.[2][3] So, work is being carried out by many researchers to make the alert generation 100% successful.

Literature Review on Predictive Monitoring

If a person's glycemic state is predicted in time slots ahead and is alerted for his forthcoming hypo/hyper glycemia he can

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take a quick action to avoid the complications. Therefore early warning of the impending glucose levels is important to take the regulatory actions. The first question on prediction, was raised by Bremer and Gough, [5] whether the present and future blood glucose values be predicted from the recent Blood Glucose history. Bellazi et al., [4] used non uniformly and sparsely sampled T1DM 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. Hovorka et al., [6] 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. Dua et al., [7] 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. Given the complexity of the underlying physiology of glucose regulation coupled with non linear dynamics of insulin action and glucose kinetics has been elusive and remains an active area of research. Palerm et al.,[8] 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 [9] , 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. Sparacino et al. , [10] 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. Reifman et al., [11] 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. Cobelli group (Sparacino et al.,)[10] had also suggested the use of CGM data and AR models for short term glucose level predictions of Type 1 diabetic patients. 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 among 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.,[12] 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.,[13] 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). The inputs of the NNM are the values provided by CGM sensor during the 20 minute and the output is the prediction of near future glycemia value. Pappada et al.,[14] also developed a neural network model for prediction of glucose concentration in Type 1 diabetes, with many input factors obtained through an electronic diary system.

Methodology

Differential Evolution

Differential Evolution (DE) optimizes a problem by iteratively trying to improve the candidate solutions with regard to objective function. It maintains a population of candidate solutions by combining existing ones according to its simple formulae and keeping whichever candidate has the best score or fitness on the optimization problem at hand. Since Differential Evolution does not require for the optimization problem to be differentiable, it can be applied to problems that are not even continuous, are noisy and change over time. It is a simple, parallel, direct search and easy to use method having good convergence and fast implementation properties.[15][23]

Prediction of a time dependent phenomenon is of great importance in this rapidly growing global scenario. This paper proposes a novel approach in the prediction of glucose concentration in Type 1 Diabetes Mellitus patients in various prediction horizons with Differential Evolutionary programming and ARIMA model.

Mathematical Modeling

A stochastic model that is useful in the representation of certain practically occurring series is the *Auto Regressive* model[16]. 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. Marc Breton et al., [17] have analysed and modeled the sensor errors in their study. There is an underlying time lag in the diffusion of glucose from blood to interstitial fluid. Sensor errors depend nonlinearly on the blood glucose rate of change. In addition, the sensor noise is non-gaussian and the consecutive errors are highly interdependent. The Auto Regressive

Integrated Moving Average model can suit well for the interdependence of consecutive sensor errors.

Methods

Noisy CGM Data

CGM technology continues to face challenges in terms of sensitivity, stability, calibration and time lag. CGM systems assess blood glucose fluctuations indirectly by measuring the concentration of interstitial glucose. There is a physiological time lag in the diffusion of glucose from blood to interstitial fluid.[18] But are calibrated via self monitoring to approximate the blood glucose. The calibration errors may also affect the accuracy of CGM devices. Another reason for error in measurements is deterioration in the sensor performance. In spite of these negatives, since the CGM data reflect an underlying process in time, an ordered time series model could be useful in analyzing and forecasting the glycemic fluctuations.

CGM Data Modeling

Signal modeling is the representation of signals in an efficient manner. Modeling is to identify the regularities in the given discrete time series data. Preprocessing is necessary to extract the useful information underlay in the time series, which is used for learning and to identify the model. Preprocessing removes the noise and avoids over fitting. These are data transformation techniques which convert the original data in to better terminal set. Moving Average filtering is being used in the present CGM systems.[19] This MA filter normally removes the high frequency noise present in the given signal. Integral based filters are also used. [20] Differentiation is also a data smoothing technique which reduces the large variations in the magnitude. Data regularization also improves the data quality and modeling.

ARIMA Model

The relationship between the input and output of a system is represented by a linear difference equation. The signal to be predicted will be a linear combination of previous observed values with some weightings. After stationarizing the data by preprocessing i.e, through regularization, the next step is to fitting in an ARIMA model.[21] The more systematic way to do this is 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 likelihood function is selected in order to get good starting point. 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 [22]. An ARIMA (p,d,q) model is generally given by

$$\Phi(B)\ Z(t) = \theta(B)\ \varepsilon(t) \quad \text{--- (1)}$$

Where Z(t) is the glucose level at time 't', $\Phi(B)$ and $\theta(B)$ are respectively the parameters of AR and MA processes involved and $\varepsilon(t)$ is the error term. $\Phi(B)$ and $\theta(B)$ are functions of backward shift operator. 'p' represents the number of AR terms i.e., past values , 'd' represents the number of differences i.e., integration, 'q' represents the number of MA terms i.e., the past errors. The ARIMA(2,2,2) model has been obtained from the ACF and PACF plots. The model order and the parameters have been optimized with all the training data sets. The ARIMA Expression in difference equation form can be written as

$$Z_t = \Phi_1 Z_{t-1} + \ldots + \Phi_{p+d} Z_{t-p-d} - \theta_1 A_{t-1} - \ldots - \theta_q A_{t-q} + A_t \quad \text{--- (2)}$$

Where the current glucose level Z_t at time 't' is obtained from the from the past values up to Z_{t-p-d} and the previous errors up to A_t . The previous errors A_t are obtained with the optimized trial vectors through differential evolution. The Prediction Equation is given by

$$Z_{t+l} = \Psi_1 Z_{t+l-1} + \ldots + \Psi_{p+d} Z_{t+l-p-d} - \theta_1 A_{t-l-1} - \ldots - \theta_q A_{t+1-q} + A_{t+l} \quad \text{--- (3)}$$

The suffix in Z i.e,'t+l' represents the number of time slots ahead prediction. $\Psi(B)$ is related to $\Phi(B)$ by

$$\Psi(B) = \Phi(B) * Ð^d * Z_t \quad \text{--- (4)}$$

where $Ð^d$ is the difference operator.

DE based Prediction Algorithm

Differential Evolution is an optimization method capable of handling non differentiable, non linear and multimodal objective functions. The population of candidate solutions is maintained by combining the existing ones by simple operations and keeping whichever candidate solution has the best score or fitness value for the optimization problem.

In other words, new trial vectors are produced by adding the weighted difference vector between two population members to a third member. Since the CGM data are non linear in nature during the sudden rise or fall of blood glucose levels, the proposed algorithm can track the physiological changes in an efficient manner.

Let $X \varepsilon R^n$ be a candidate solution (agent) in the population. Then the algorithm can be described as follows.

Step 1: Initial Data Set : $X = [x_1, x_2, \ldots\ldots x_n]$.

Step 2: For each agent x_i in the population, do

- Pick three agents x_i, x_j, x_k from the population at random, in such a way that they are distinct from each other.
- Pick a random index 'R' ε {1,2,……n} where the highest possible value 'n' is the dimensionality of the problem to be optimized.
- Compute agents' potentially new position $Z = [z_1, z_2, \ldots\ldots z_n]$ (ie., the mutant vectors) by iterating over each $i \varepsilon$ {1,2,……..n} as follows.
  - Pick 'r_i' ~ U (0,1) uniformly from the open range (0,1).
  - $z_i = x_i + F * (x_j - x_k)$

If (i = R) or (r_i < CR) let Wi = z_i else let Wi = x_i.

Where 'F' ε (0,2) is the scaling factor or the differential weight and CR ε (0,1) is the cross over probability.

- If (f(Z) < f(X)) then replace the agent in the population with the improved candidate solution, i.e., x = z in the population .
- Pick the agent from the population that has the lowest fitness and return it as the best found candidate solution.

In our problem we had the population size n = 60, CR = 0.9 and scaling factor F is optimized with the objective function of minimum Mean Absolute Difference Prediction error.

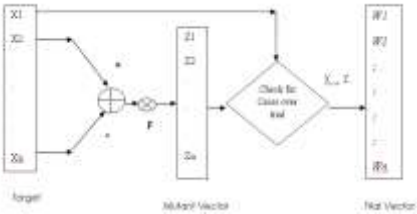

Fig 1: Differential Evolution applied to CGM data to generate Trial vectors for Optimized Parameters

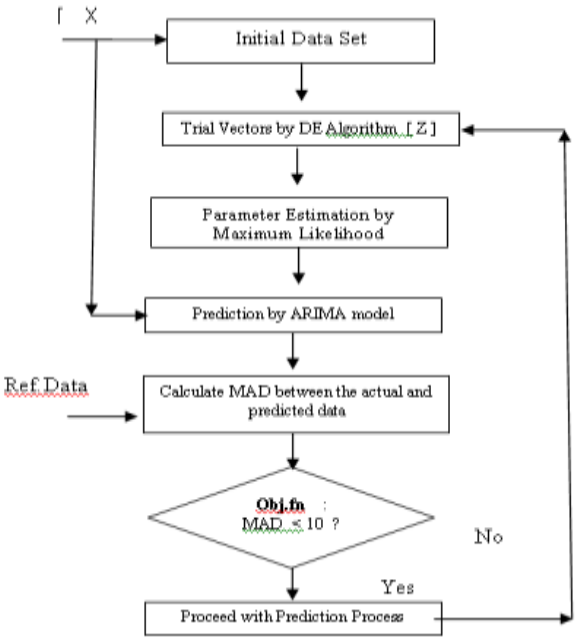

Fig 2: Prediction Process

Experiment and Results

The Type 1 Diabetes data for the experimentation are simulated using Glucosim (a web based Diabetes educator developed by Illinois Institute of Technology). It gives glucose variations for a period of 24 hours with a frequency of one minute. 30 different sets of data are obtained by altering the weight, amount of food intake in calories, exercise durations and type and amount of Insulin etc.. First half of the data set is kept for training and the second half for testing. For the optimized parameter estimation of the prediction model we had data set of size n = 60 i.e., the one hour data and tried the prediction of next 30, 45 and 60 minutes ahead values.

The simple AR model or the ARIMA model can perform well in normal stable conditions. But the performance will be poor in unstable conditions. The optimized ARIMA model will track the fluctuations in the non linear situations accurately than the simple models. The experiments were conducted in different time periods of a day and the MAD values are calculated for all the 30 data sets. Since the Kalman filter is an usual preference for state estimation and correction of any time varying process, we have compared our results with that also. The process and measurement error covariances are kept fixed. The optimization with DE track the variations of the glucose profile more accurately than the earlier estimation techniques. A sample of prediction process performance is given in figure 3 with a representative subject data. The performance is also analyzed with Mean Absolute Difference (MAD) between the actual data and predicted data in various prediction horizons of 30, 45 and 60 minutes. MAD values are listed below in table 1, with Kalman filter, Simple ARIMA method, ARIMA with optimized parameters.

Conclusion and Future work

The prediction efficiency of the ARIMA model with optimized parameters has been validated with simulated data. Performance analysis is given in terms of Mean Absolute Difference between the actual value and the predicted value. The approach shows promising results which can further be improved by increasing the number of iterations and altering the differential gain value. But there is a trade off with computational time for practical implementation. In our future work we have to test our algorithm with real patient data sets and go for real time implementation.

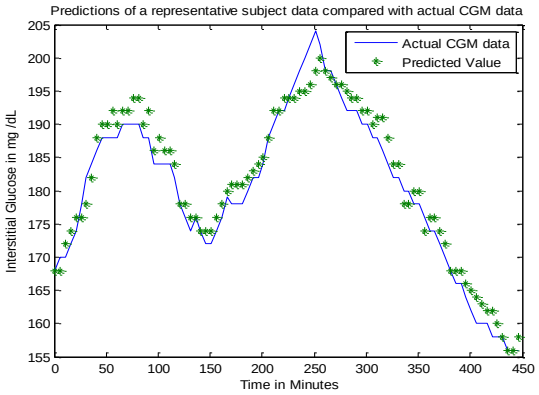

Fig: 3 Comparison of Predicted Glucose Value with Original CGM data

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Table 1: Performance Analysis

Simulated Data Set	Mean Absolute Difference between Actual and Predicted value (mg / dL) in various Prediction Horizons								
	30 minutes			45 minutes			60 minutes		
	Kalman Filter	ARIMA	ARIMA Opt. with DE	Kalman Filter	ARIMA	ARIMA Opt. with DE	Kalman Filter	ARIMA	ARIMA Opt. with DE
1	6.1	6.0	5.4	10.2	9.5	8.8	12.3	10.6	8.1
2	7.8	7.5	7.1	9.5	9.0	8.0	15.8	15.3	7.8
3	6.5	6.3	5.8	8.9	7.9	7.1	21.9	20.1	10.0
4	7.2	6.2	6.0	11.0	10.3	9.5	22.6	22.0	9.2
5	6.4	5.9	5.1	11.8	10.0	7.9	19.1	17.6	8.8
6	8.8	7.8	7.0	8.9	7.7	7.5	21.7	19.0	10.3
7	9.0	8.5	8.1	9.9	8.4	7.6	18.3	16.8	9.7
8	5.6	5.7	5.2	10.7	8.9	7.5	25.1	23.0	10.2
9	7.4	7.6	6.9	12.0	10.7	9.8	26.0	24.1	10.4