Blood Glucose Prediction Algorithms for Hypoglycemic and/or Hyperglycemic Alerts

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Abstract

Continuous glucose monitoring (CGM) sensors able to monitor blood glucose concentration continuously (i.e. with a reading every 1-5 min) for several days (up to 7 consecutive days), entered clinical research. The availability of continuous glucose monitoring (CGM) sensors allows development of new strategies for the treatment of diabetes. CGM sensors are of two types, non invasive (NI-CGM) and minimally invasive (MI-CGM). Irrespective of the type, CGM sensors can become smart by providing them with algorithms able to generate alerts, say, 20–30 min ahead of time, when glucose concentration is predicted to exceed the normal range thresholds (70-180 mg/dL). Such alerts would allow diabetes patients to take precautionary measures to prevent hypo/hyperglycemia. In this paper we review blood glucose prediction algorithms such as first-order autoregressive (AR(1)), Kalman filtering and feed forward neural network. All these algorithms have demonstrated that blood glucose can be predicted ahead in time.

Keywords— *Continuous glucose monitoring, Auto regressive, Kalman filtering, Feed forward neural network.*

1. Introduction

Diabetes is a disease that affects 285 million people in the world and this number is expected to increase to 439 million in 2030, thus making diabetes an "epidemic" disease [1]. In healthy people, glucose levels in the blood are controlled by insulin using a negative feedback. In people with diabetes, the body does not secrete insulin (type 1 diabetes) or imbalances in both insulin secretion and action (type 2 diabetes) occur. Therapy is mainly based on insulin administration and diet, which are tuned by self-monitoring of blood glucose (SMBG) levels 3-4 times a day. Nevertheless, blood glucose concentration of the patients is often outside of the normal range of 70-180 mg/dL. While hyperglycemia(high blood sugar) mostly affects long-term complications (such as neuropathy, retinopathy, cardiovascular, and heart diseases), hypoglycemia(low blood sugar) can be very dangerous in the short-term and, in the worst-case scenario, may bring the patient into hypoglycemic coma.

New scenarios in diabetes treatment were opened in the last ten years, when continuous glucose monitoring (CGM) sensors, able to monitor glucose concentration continuously (i.e. with a reading every 1-5 min) for several days (up to7 consecutive days), entered clinical research. It has been suggested that the retrospective assessment of glucose profiles measured through CGM sensors (either MI-CGM or NI-CGM) might help in the optimization of metabolic control [2] in people with diabetes.

On-line applications are potentially more appealing and with a greater impact in the patient daily life. Ideally these would include the "smart CGM sensor", i.e. a system able to generate alerts when glucose concentrations exceed the normal range thresholds [3], combined with "the artificial pancreas", i.e. a device conceived for Type 1 people with diabetes aimed at maintaining glucose concentration within safe ranges by infusing subcutaneously insulin via a pump under the control of a closed-loop algorithm [4]. However, it would be much more preferable to prevent hypo/hyperglycemic events before they occur, e.g., by generating an alert, say, 20–30 min ahead of time. This gain in time would allow e.g., to prevent hypoglycemia, since it is comparable, if not greater, than the interval required for an ingested sugar to reach the blood. Some methods have been proposed which generate alerts when the current trend of the glucose concentration profile suggests that hypoglycemia is likely to occur within a short time.

The possibility of making a short term prediction of glucose concentration exploiting its past history was originally suggested in Bremer and Gough [5], on the basis of preliminary results obtained from modeling blood glucose concentration data (not CGM), measured every 10 min in blood for up to 40 hr, and using a prediction horizon (PH) of 10 min. Since then, several approaches have been proposed using CGM sensor data and a larger, and more clinically significant, PH.

Sparacino *et al.* [6],[7] demonstrated that simple prediction algorithms based on low-order models, e.g., either a first-order polynomial or an auto-regressive of order 1 (AR(1)) model, with time-varying parameters, identified by recursive least squares (RLS) with a constant forgetting factor, can predict glycemia ahead in time with sufficient accuracy, with a PH of 30 and 45 min. Eren-Oruklu *et al.* [8] developed prediction

algorithms based on AR(3) and on auto-regressive with moving average (ARMA(3,1)) models, with time-varying parameters identified by RLS, using a forgetting factor μ which could be modulated according to the glucose trend. Reifman *et al.* [9] proposed a predictor based on an AR(10) model, with time-invariant and subject-invariant parameters identified by regularized LS. Similarly, Gani *et al.* [10] developed a prediction strategy based on an AR(30) model with time-invariant parameters identified by regularized LS on prefiltered data. Finan *et al.* [11] proposed a predictor based on an ARX(3) model with exogenous inputs given by ingested carbohydrates and insulin medications.

Palerm *et al.* [12],[13], after having posed the problem in a state-space setting, used the Kalman filtering methodology to predict glucose level after a given PH, using a double integrated random walk as a prior for glucose dynamics.

Pappada *et al.* [14],[15] have proposed an NN approach to predict glycemia with a PH of 75min. The network is a feed forward one, with nine hidden neurons with a tangent sigmoid activation function, and one output, with a linear transfer function. The inputs include SMBG readings, CGM data and its trend, information on insulin dosages, nutritional intake, hypo- and hyperglycemic symptoms, lifestyle, activities, and emotional factors. The output of the NN is the vector of all the future glucose values till the chosen PH (e.g., 15 future BG values, for PH = 75 min and sensor sampling time of 5 min).

In the next section we briefly review blood glucose prediction algorithms such as first-order autoregressive (AR(1)), Kalman filtering, feed forward neural network proposed by Sparacino *et al.*, Palerm *et al.*, Pappada *et al*, respectively. All these algorithms have demonstrated that blood glucose can be predicted ahead in time.

2. Prediction Algorithms

2.1 Auto regressive

The glucose time series is described locally by an auto-regressive model of first-order (AR(1)), corresponding to the following time-domain difference equation:

$$y_i = a\, y_{i-1} + w_i \qquad (1)$$

In equation (1), i = 1, 2, …n denotes the order of glucose samples collected till the n^{th} sampling time t_n and $\{w_i\}$ is a random white noise process with zero mean and variance equal to σ^2.

The prediction strategy is as follows. Let θ denote the vector of the parameters of the model employed to describe the glucose time-series, i.e., $\theta = (a, \sigma^2)$. At each sampling time t_n, a new value of θ is first determined by fitting the model against past glucose data $y_n, y_{n-1}, y_{n-2}, \ldots$ by weighted linear least squares. Once θ is determined, the model is used to calculate the prediction of glucose level T steps ahead, i.e., $\hat{\theta}_{n+T}$. For a sampling interval of 3 min, a value of T equal to 10 or 15 corresponds to a PH equal to 30 or 45, respectively. The value $\hat{\theta}_{n+T}$ is calculated iteratively for i = n+1, n+2, ….. , n+T with $w_i \equiv 0$.

In determining the model parameters θ at a given time, all the past data $y_n, y_{n-1}, y_{n-2}, \ldots, y_1$ participate, with different relative weights. A typical choice is to employ exponential weighting, *i.e.*, μ^k is the weight of the sample taken k instants before the actual sampling time i.e., μ^k is the weight of the sample taken at time t_{n-k} (k = 0,1,…,n-1). With μ, taken in the range (0,1), acts as a forgetting factor [16]. If a forgetting factor is not used (which is equivalent to letting μ= 1), glucose samples collected tens of hours, if not days, before the actual sampling time would influence prediction, with a possible deterioration of the algorithm capability to promptly track changes in the signal, in particular those due to perturbations, e.g., meals. From an algorithmic point of view, recursive least squares (RLS) implementations are possible in order to estimate the unknown model parameters θ in a computationally efficient manner.

2.2 Kalman filtering

Predictions are made using an estimate of the rate of change of the blood glucose, using a Kalman filter (an optimal estimation method). The Kalman filter trades off the probability that a measured glucose change is due to sensor noise versus an actual change in glucose, to obtain the maximum likelihood estimate of glucose (and its first and second derivatives). In this case, the model is given by

$$\underbrace{\begin{bmatrix} g_{k+1} \\ v_{k+1} \\ a_{k+1} \end{bmatrix}}_{x_{k+1}} = \underbrace{\begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix}}_{\Phi} \underbrace{\begin{bmatrix} g_k \\ v_k \\ a_k \end{bmatrix}}_{x_k} + \underbrace{\begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}}_{\Gamma^w} w_k \qquad (2a)$$

$$y_k = \underbrace{\begin{bmatrix} 1 & 0 & 0 \end{bmatrix}}_{c} \begin{bmatrix} g_k \\ v_k \\ a_k \end{bmatrix} + u_k \qquad (2b)$$

where the indices *k* and *k* + 1 denote the current time step and one time step into the future, respectively. The states

are the blood glucose concentration (g_k), its rate of change (v_k, i.e., the velocity), and the rate of change of the rate of change (a_k, i.e., the acceleration). The latter is assumed to vary in a random fashion, driven by the input noise w_k (with covariance matrix Q), which describes changes to the process. The blood glucose measurements are assumed to contain noise, described by u_k (with covariance matrix R). The Kalman filter uses a two-step process. It first calculates the estimate of the states (denoted by $\hat{x}$) using the model based on the information up to the previous time step. Then

$$\hat{x}_{(k|k-1)} = \Phi\, \hat{x}_{(k-1|k-1)} \qquad (3)$$

where the subscript ($k \mid k-1$) indicates the estimate at time step k, using measurements up to time step k - 1. Once the measurement at time step k is available, it is used to correct the estimate of the states, using

$$\hat{x}_{(k|k)} = \hat{x}_{(k|k-1)} + L\left(y_k - C\,\hat{x}_{(k|k-1)}\right) \qquad (4)$$

where L is the steady-state Kalman gain and $\left(y_k - C\,\hat{x}_{(k|k-1)}\right)$ is the difference between the measured output and the expected output using the estimate from equation (3). The Kalman gain L is calculated using the covariances Q and R. Given that these covariances are not known in advance, they become tuning parameters. Changing the relative weight between Q and R serves to trade off the confidence in the model versus the confidence in the measurement. Putting a significant weight on the trust in the measurement means that the estimates will track the sensor signal very closely, even if noisy. Conversely, weighing the model significantly more than the measurement, results in a heavily filtered estimate. The tuning is thus selected manually based on the best trade-off sought between these two extremes, which in this case is done as to maximize the sensitivity and specificity of the hypoglycemia predictions. For example, when Q/R = 1.25e-3 then L = [0.4821 0.1699 0.0254]T. The model [equation (2)] can then be used to estimate blood glucose into the future.

2.3 Feed forward neural network

An NN is a modeling tool that consists of simple processing elements, called neurons in analogy to biological structures, linked to each other through weighted connections [17]. NNs are able to "learn" the relationship between a set of input and output data. This makes it possible to create input–output models without making strong assumptions on the system. NNs provide a suitable structure for prediction when the relationships among the involved signals are known only partially. In the context of glucose prediction, an additional interesting feature of NNs is that they can combine information from different sources such as CGM, meals, and insulin.

The neural network model we are discussing in this section is a time-lagged feed-forward neural network. This neural network contains multilayer perceptrons that have memory components to store previous values of data within the network. The existence of such memory components provides the system the ability to learn relationships and patterns existent in the data over time. These neural networks consist of multiple layers of processing elements that are connected together in a feed-forward manner. Various connections (synapses) were constructed to facilitate connections between the processing elements of the neural network (axons). The neural networks generated were trained using a method known as the back propagation of errors. Elements in the neural network known as back propagation axons (BackAxons) facilitate the training process. BackAxons derive a relative error at their input, which is to be back propagated to any processing elements preceding them in the neural network design. The back propagation of errors is completed as an error is presented at the output of each BackAxon in the neural network, and the BackAxon is charged with calculating the gradient information associated with calculating weights for the minimization of total error in the neural network. Optimal weights for the minimization of error in the predictive model are obtained via a gradient descent algorithm performed within the BackAxon elements.

This gradient descent algorithm calculates the optimal weight for the minimization of the total error in the neural network model. The optimization value of the step size in such an algorithm is integral in the amount of time it takes to train the neural network. A small step size could lead to a large training time, and conversely, a large step size could lead to overestimation of the desired local minimum. Neural networks were trained via batch training, i.e., network weights were updated after each epoch (single cycle or pass through the dataset). The neural networks were configured to stop training after 1000 epochs or if the mean squared error was less than 0.1. Figure 1 includes the neural network design and architecture of one of the processing and output layers of the neural network models designed using the NeuroSolutions software by Papada et.al [15].

The various components in the neural network design are labeled 1–5. Component 1 is a hyperbolic tangent axon (tanh axon). The tanh axon has the processing elements for the hidden layer of the neural network. Each

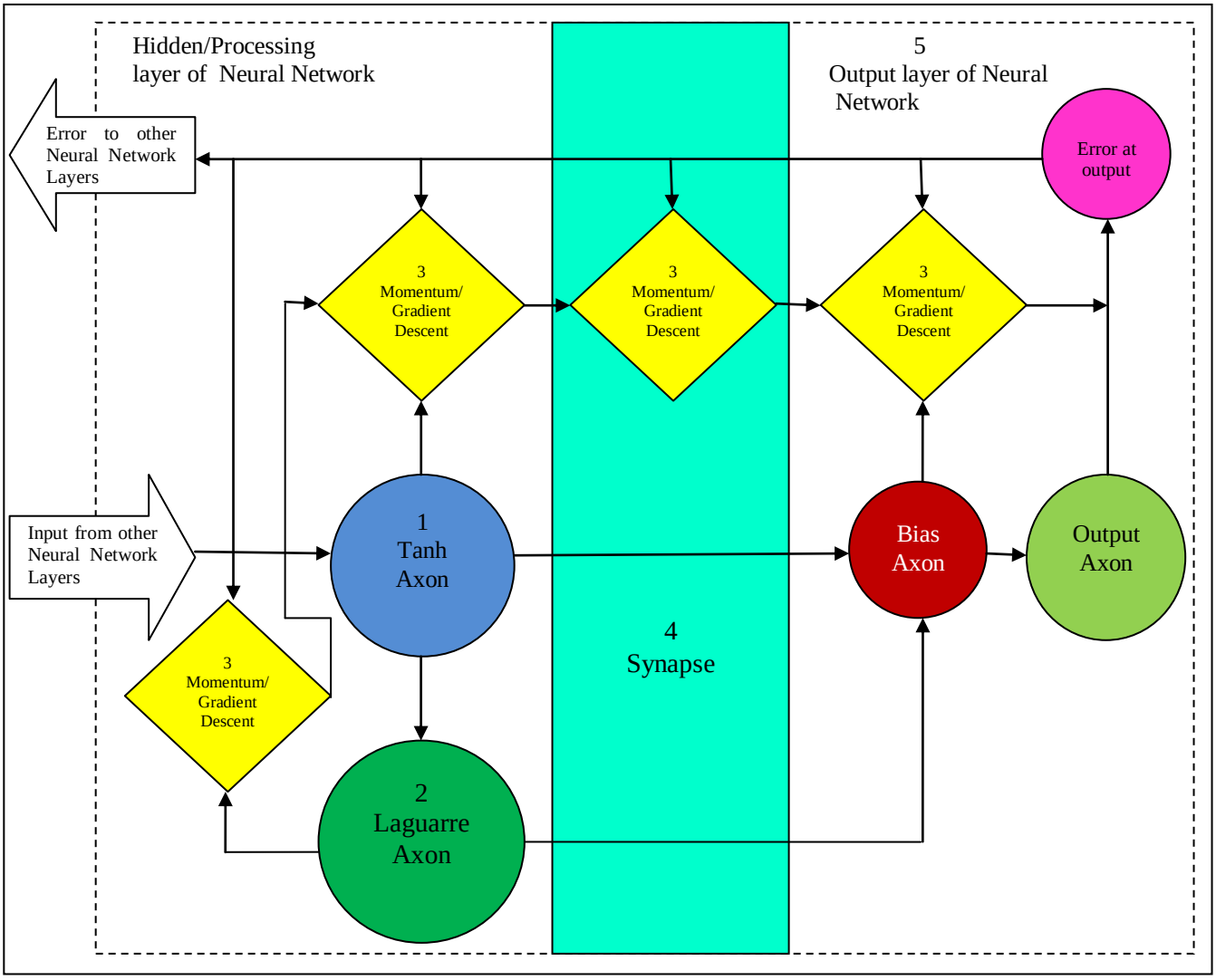

Fig. 1 Design and architecture of the processing (hidden) and output layer of the neural network model proposed by Pappada et al.[15].

processing element sums the weighted connections from the inputs into the axon. Component 2 is a Laguarre axon that functions to store delayed versions of the processing elements output and pass it onto the next layer of the neural network. The Laguarre axon therefore serves to provide the neural network with memory, thus enabling the processing of information in time. Component 3 is the momentum/gradient descent component of the network. This component serves to adjust the weights with information about the error within the network. Optimal step sizes and momentum values in these elements for the minimization of error are determined via the implementation of a genetic algorithm. Component 4 is an example of the synapses of the neural network, which serve to connect the various axons and processing elements of the neural network. Component 5 is the output layer of the neural network, which consists of a bias axon (leftmost element in Component 5) and an output axon (rightmost element in Component 5). The bias axon has the processing elements for the output layer, each of which sums the weighted connections from the second hidden layer. The output axon yields the predicted values in the original format (i.e., the desired response) as originally presented to the neural network.

3. Conclusion

Noninvasive and minimally invasive sensors have been developed that allow continuous glucose monitoring (CGM) for several days. There is a general agreement that, in the near future, CGM will improve diabetes management by facilitating the appropriate patient

reaction to hazardous and potentially life-threatening events, such as hypo- and hyperglycemia. For instance, in order to allow the patient to prevent such events, alerts could be generated on the basis of prediction of glucose concentration ahead of time using past CGM data and appropriate time-series models. CGM sensors allow the development of new strategies for the treatment of diabetes. A clinically important task in diabetes management is the prevention of hypo/hyperglycemic events. Blood glucose prediction algorithms such as first-order auto regressive (AR(1)) , Kalman filtering, feed forward neural network demonstrated that blood glucose can be predicted ahead in time.

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