Predicting Upcoming Glucose Levels in Patients with Type 1 Diabetes Using a Generalized Autoregressive Conditional Heteroscedasticity Modelling Approach

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Abstract: Continuous blood glucose monitoring systems (CGMS) capture interstitial glucose levels at frequent intervals over time, and are used by people with diabetes and their health care professionals to assess glycaemic variability. This information helps to adjust treatment to achieve optimum glycaemic control, as well as potentially providing early warning of imminent and dangerous hypoglycaemia. Although a number of studies has reported the possibilities of predicting hypoglycaemia in insulin dependent type 1 diabetes (T1DM) patients, the prediction paradigm is still unreliable, as glucose fluctuations in people with diabetes are highly volatile and depend on many factors. Studies have proposed the use of linear auto-regressive (AR) and state space time series models to analyse the glucose profiles for predicting upcoming glucose levels. However, these modelling approaches have not adequately addressed the inherent dependencies and volatility aspects in the glucose profiles. We have investigated the utility of generalized autoregressive conditional heteroscedasticity (GARCH) models to explore glucose time-series trends and volatility, and possibility of reliable short-term forecasting of glucose levels. GARCH models were explored using CGMS profiles of young children (4 to <10 years) with T1DM. The prediction performances of GARCH approach were compared with other contemporary modelling approaches such as lower and higher order AR, and the state space models. The GARCH approach appears to be successful in both realizing the volatility in glucose profiles and offering potentially more reliable forecasting of upcoming glucose levels.

Keywords: Diabetes, blood glucose prediction, generalized ARCH models, glycaemic management.

INTRODUCTION

Hypoglycaemia is associated with a number of blood glucose lowering therapies, but is a particular problem for patients with type 1 diabetes (T1DM) receiving insulin therapy. Insulin is the most effective method of lowering blood glucose, and is an essential element of treatment for people with type 1 and longer duration type 2 diabetes. Hypoglycaemia, in which blood glucose levels become unacceptably low, can lead to acute mental and physical impairment with possible progression to coma if not treated promptly, and repeated episodes confer an increased risk of future cardiovascular events [1]. Patients who recognize the early symptoms of hypoglycaemia can take corrective action, but a significant number of patients become hypoglycaemia unaware with little or no warning of imminent danger. With increasing emphasis on the need to keep blood glucose levels as close to normal as possible to minimize the risk of diabetic complications, the likelihood of iatrogenic hypoglycaemia becomes ever greater.

Continuous Blood Glucose Monitoring Systems (CGMS) help improve glycaemic control in people with diabetes and the guidelines for diabetes management suggest the use of CGMS as a supplemental tool in those with hypoglycaemia unawareness and/or frequent hypoglycaemic episodes [2]. These devices measure interstitial glucose concentrations, typically every one to five minutes, providing real-time information about the direction, magnitude and duration of glucose fluctuations. At present, self-monitored blood glucose (SMBG) finger prick checks are used most frequently but provide sparse information at only a few time points in a day, typically 1 to 7, whereas CGMS can provide detailed 24-hour glucose profiles over several days.

The ability to continuously monitor and reliably interpret CGMS data streams in real time could, crucially, provide advance information on upcoming potentially hazardous glucose levels in time for corrective action to be taken [3-11]. Additionally, real-time CGMS analysis could offer new clinically-relevant indices of glucose control that would form the basis for automated informed choice of therapeutic strategies and dietary adjustments needed to help patients optimize their diabetes management [12, 13]. Such clinical advantages, however, will only be achieved if the extensive “time based” chaotic glucose profiles can be explored using valid mathematical methods that provide clinically-relevant information [14, 15]. Several statistical methodologies for predicting upcoming glucose values from SMBG or CGMS data have been proposed over the last decade [3, 4, 10, 14, 16-24]. The statistical and machine-learning based approaches have included generalized linear auto-regressive

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models, state space models, stochastic models and neural network approaches. Although these approaches have addressed the fluctuations in the blood glucose measures over time, most of them do not adequately address the 'volatility' aspects in the continuously measured glucose time-series data. Given the nature of volatility in the glucose data and the inherent complexities and dependencies therein, there is a need to explore more robust and generic method classes to analyses the CGM data. The rapid development in CGMS and artificial pancreas technologies provides a challenging new opportunity, which if resolved, will help to open a new horizon of treatment options for people with diabetes [25].

Prior to 2005, when CGMS technology was not generally available, several attempts were made to address the challenging issue of forecasting glucose values using SMBG profiles. Several dynamic physiological models and empirical models were proposed to describe glucose-insulin interactions in type 1 and type 2 diabetic patients: Desai *et al*. (2002) [16] used autoregressive models to predict upcoming glucose values and Magni *et al*. (2006) [17] proposed a stochastic volatility model to extract the variability in SMBG measures. Briegel *et al*. (2002) [18] described a non-linear state space model to model the blood glucose fluctuations in diabetic patients. Cox *et al*. [10] addressed the issue of predicting severe hypoglycaemia using SMBG measures in a study of both type 1 and type 2 diabetes patients.

As continuously measured glucose values retain a large degree of temporal correlation between successive glucose values, it is possible to explore the applicability of autoregressive time-series models to predict future glucose values [10, 14, 20-24, 26]. Sparacino *et al*. (2008) [14] used an autoregressive (AR) model of order one, AR(1), which continuously adapts the model coefficient to predict glucose concentrations up to 60 minutes ahead. Eren-Oruklu *et al*. [24, 27] addressed the issue of short-term prediction of upcoming glucose levels using low-order linear AR and autoregressive moving average (ARMA) models. They also evaluated this algorithm further to predict hypoglycaemia and provide early warning hypoglycaemic alarms. Gani *et al*. [19, 20] examined the possibility of predicting upcoming glucose values using data driven higher-order linear AR models. These analyses were based on 1- and 5-minute CGMS profiles from three different devices in both type 1 and type 2 diabetes patients [19]. The authors reported that near-future glucose predictions were attained only when raw glucose measurements were smoothed and the model coefficients were regularized. Smoothing the volatile time-series glucose data however loses the background physiological reasons behind the glucose fluctuations, and is likely to create an artificial prediction environment.

A data driven state space model was suggested by Wang *et al.* (2014) [28] to quantify the patient-specific effects of insulin dose and meal intake on blood glucose fluctuations. Sudharsan *et al.* (2015) [9] have recently discussed the use of machine learning techniques for hypoglycaemia prediction in patients with type 2 diabetes. Daskalaki *et al.* (2012) [26] compared glucose prediction performance with an AR model that uses only glucose information, an AR model with external insulin input, and an artificial neural network (ANN) utilising both glucose and insulin information. They reported superior performance of the ANN approach compared to the AR approach.

Prediction accuracy of various models in these studies was mainly evaluated in terms of error in glucose predictions (root mean square error (RMSE)) and Clarke Error Grid analysis (CG-EGA) [21, 29]. Facchinetti *et al.* (2011) [21] proposed a J-index to compare different prediction strategies.

We believe that the trend and inherent volatility in glucose realizations cannot adequately be captured by employing only a data driven AR process. Blood glucose dynamics in individuals with insulin-treated diabetes is a continuous process dependent on the temporal pattern of at least three external behavioural factors: dose of insulin injected, amount and nature of food intake, and extent of physical activity, as well as internal factors such as glucose counter-regulation. The volatility of a glucose series is not constant over time; periods of relatively low volatility and periods of relative high volatility tend to be grouped together on many occasions, especially in insulin treated patients. In other words, the current level of volatility tends to be positively correlated with its levels during immediately preceding periods. However, this is not necessarily true for all diabetic patients or for different insulin regimens. CGMS data have demonstrated that there are often substantial postprandial increases in plasma glucose levels in patients who use pre-meal doses of rapid-acting insulin, even in those with satisfactory HbA_{1c} (glycated haemoglobin) levels [30]. The frequent episodes of asymptomatic hypoglycaemia, especially overnight, have been common, and the CGMS systems may be less accurate at very low glucose levels [30].

We have addressed these challenging methodological issues related to the realization of trend and volatility aspects in CGMS time-series profiles to achieve short-term prediction of upcoming glucose values using generalizations of the deterministic autoregressive conditional heteroscedasticity (ARCH) approach [31-34]. ARCH models have been used extensively in modelling financial volatility [34]. They seek to explore time-dependent volatility as a function of observed prior volatility. Unlike AR models, ARCH models assume that the unexplained variation in glucose level (error) is heteroscedastic. Generalized autoregressive conditional heteroscedastic (GARCH) models consider the moments of a time series as variant, that is, the error term (real value minus forecasted value) do not have a constant variance, as with an autoregressive integrated moving average (ARIMA) process [32]. The variance of error terms is assumed to be serially correlated and can be modeled by an AR process. Thus, a GARCH process can measure the implied volatility of a time series due to glucose peaks and nadirs. Volatility models like GARCH can also account for the structural components in the volatility, such as fasting and post-prandial scenarios, along with other physiological components. In this paper we explore the utility of the GARCH class of models to revisit the problem of predicting upcoming blood glucose values from CGMS time-series data in a clinically relevant manner. We have explored the performance of GARCH model to predict glucose values for the next 30-40 minutes at both very low and very high glucose fluctuation levels. The performance of GARCH modeling approach was compared with lower and higher order AR, and the state-space model.

THE DATA

The data used for this study were taken from a subset of 172 patients participating in a randomized clinical trial to assess the efficacy and safety of real-time CGMS in the Diabetes Research in Children Network (DirecNet) who agreed to provide CGMS profiles et is a network consisting of 5 clinical centers and a coordinating center who investigate the potential use of glucose monitoring technology and its impact on the management of T1DM in children. They studied overnight counter regularity responses to spontaneous hypoglycaemia in young (3-8 y/o) vs. older (12-18 y/o) children with T1DMproviding an opportunity to evaluate CGMS profiles under hypoglycaemic conditions.

The patients visited a clinic after the 6 weeks of optimizing glycaemic control. The parents were instructed to have the child use the CGM on a daily basis and were provided training to use the device. The CGM was used for a minimum of 4 days continuously. No additional data, including the patients' food and activity diary were available. We randomly chose six patients out of 172 on the basis of the availability of both hypoglycaemia and hyperglycaemiain the same time series profile during the course of CGM assessment. Choice of only 6 patients for presentation in this study from among the patients participating in the same trial is deemed adequate, as this may be looked upon as an initial technology demonstration. This study used the FreeStyle Navigator CGM made by Abbott Diabetes Care, the Guardian REAL Time CGM made by Medtronic MiniMed and the DexCom SEVEN PLUS CGM made by DexCom Inc [35].

METHODS

For this exploratory applied methodological study, we investigated four different methods of forecasting: AR models of higher and lower orders, state space model, and the GARCH model. The AR models and the state space models have already been investigated by researchers in the context of analysing self-monitored glucose levels and the glucose measures from the CGMS. A brief description of each model is provided below.

Autoregressive (AR) Models

The autoregressive model specifies that the output variable / measurement depends linearly on its own previous values. AR(p) models for time series are Markov processes with dependence of higher order than lag 1 in the univariate setup [34]. For example, a process is AR (1) when the current value is based on the immediately preceding value, whereas AR (2) (p=2) has the current value based on previous two values. The simplest AR model is AR(0) which has no dependence between the terms. A general AR(p) model is as follows

$$y_t = \sum_{i=1}^{p} \phi_i y_{t-i} + \varepsilon_t \qquad (1)$$

where $\varepsilon_t \sim N(0, v)$ for t = 1, 2, …. These models are multiple regression models but with lagged values as predictors. These are considered as very flexible models in handling a wide range of time series patterns. The coefficients are generally estimated by ordinary least square estimation by minimizing $\|y - \Delta\phi\|^2$, where Δ is the design matrix representing the

lagged values of *y*. The order of the AR models are selected based on the RMSE. Usually, RMSE decreases quickly with the increase in the order up to some order and then more slowly. An order where RMSE curve flattens is chosen as an appropriate order. Akaike Information Criterion (AIC) is also another common measure for choosing the AR order.In our study we considered both AR model of higher order as reported by Gani *et al*. (2010) [19], and lower order AR as well as discussed by Desai *et al.* (2002) [16].

State Space Models

In the context of time series, state space models allow an observed time series being explained by some state variables which are usually a stochastic process [34]. State space is widely used in time series analyses where the model uses state variables to describe a system by a set of first order differential equations, rather than n^{th} order differential equations. The state variable can be unobserved. A simpler state space model is as follows.

$$State: x_{t+1} = A_t x_t + v_t \tag{2}$$

$$Observation: y_t = B_t x_t + \varepsilon_t \tag{3}$$

where the state variable x_t is a vector-valued stochastic process and the y_t is the observed time series. The v_t in the *State* (Equation 2) model is a Gaussian error $\sim N(0,\sum_v)$ and $\varepsilon_t \sim N(0,\sum_\varepsilon)$. It is also assumed that the error terms are uncorrelated to each other. Apart from time, the coefficients A_t and B_t could also depend on policy variables in the context of finance. Estimation of the statespace model involves Kalman filter which allows to construct the likelihood function associated with the model [34]. The Kalman filter is used to recursively obtain conditional mean and variances of both unobserved and measured (dependent) variables.

ARCH / GARCH Models

In econometrics, the ARCH models are used to characterize and model observed time series measures. It is assumed that the current measure not only depends on the past measure(s), but also depends on the variability in the past measure(s). The original ARCH model devised by Engle [36] modelled the variance of the regression residuals as a linear function of the lagged values of the squared regression residuals. A typical ARCH(p) model can be defined as

$$y_t = x_t\beta + \varepsilon_t, \varepsilon_t \sim D(0,\sigma_t^2) \tag{4}$$

$$\sigma_t^2 = a_o + \sum_{i=1}^{p} a_i \varepsilon_{t-i}^2 (Conditional\ Variance) \tag{5}$$

where β is the structural parameter, ε_t^2 is the innovations and a_i are the ARCH parameters with p lags. σ_t^2 is the volatility at time t. D may be normal or variants of t-distribution. This model was generalized by Bollerslev [32] to include the lagged values of the conditional variance – the GARCH model. A typical GARCH (p, q) model specification will extend the residual variance as

$$\sigma_t^2 = a_o + \sum_{i=1}^{p} a_i\ \varepsilon_{t-i}^2 + \sum_{j=1}^{q} g_j\ \sigma_{t-j}^2 \tag{6}$$

where g_j are the GARCH parameters. This describes the volatility process as dependent on its own lagged values and on the residuals of the mean equation. The GARCH coefficients capture the autoregressive structure of the conditional volatility process and GARCH (1, 1) would imply that both p and q are equal to unity. The GARCH model may be looked upon as an autoregressive moving average (ARMA) process in the squared innovations or residuals also [32]. It provides parsimonious models that are easy to estimate and has been proven to be surprisingly successful in predicting conditional variances. A GARCH (p, q) model can be shown to be equivalent to a particular ARCH (∞) model. A GARCH (1, 1) model, containing only three parameters in the conditional variance equation, allows an infinite number of past squared errors to influence the current conditional variance.

A typical GARCH (1, 1) model with additional AR component of order 2 [GARCH (1, 1) – AR (2)] can be formulated as

$$y_t = x_t\beta + \tau_1 y_{t-1} + \tau_2 y_{t-2} + \varepsilon_t, \varepsilon_t \sim D(0,\sigma_t^2) \tag{7}$$

$$\sigma_t^2 = a_o + a_1\ \varepsilon_{t-1}^2 + g_1\ \sigma_{t-1}^2 \tag{8}$$

where τ_i's are AR parameters associated with the autoregressive order.

The Model Estimation, Validation and Diagnostics Aspects

The presence of ARCH effect in time-series data can be tested using a simple Lagrange Multiplier (LM) test. Since ARCH model implies an AR process for the squared residual ε_t^2, the LM test for ARCH effects can be constructed based on auxiliary regression $\varepsilon_t^2 = a_0 + \sum_{i=1}^{p} a_i\ \varepsilon_{t-i}^2 + u_t$ where $u_t = \varepsilon_t^2 - \sigma_t^2$ is a martingale difference sequence. Under the null hypothesis that there are no ARCH effects, $a_1 = a_2 = \cdots . = a_p = 0$, the test statistic $LM = T.\ R^2$ has an asymptotic chi-square distribution with *p* degrees of freedom, where *T* is the sample size and R^2 is

computed from the regression mentioned above. Although the LM test is constructed from an ARCH model, Lee *et al*. (1995) [37] have shown that it also has the power against more general GARCH alternatives and so can be used as a general specification test for GARCH effects.

The exploration of the distribution of error component (innovation) plays a crucial role in the assessment of GARCH model fits. The likely leptokurtic innovation distribution plays an important role in determining the relative performance of the two competing GARCH model estimation methods, namely the maximum quasi-likelihood estimator (QMLE) based on a Gaussian likelihood (QMLE) and the log-transform-based least absolutely deviations estimator (LADE) [31, 38].

In general, GARCH model fitting assumes student-t underlying distribution to capture the fat tails (leptokurtosis) of innovation that is frequently observed in high frequency data series in financial studies. As the nature of this distribution for blood glucose data is completely unknown, we have compared both normal and t-distribution in terms of model fitting and out-of-sample forecasting ability. Wilhelmsson (2006) [39] showed that allowing for a leptokurtic error distribution leads to significant improvements in variance forecasts compared to using the normal distribution. They compared nine different error distributions (variants of t-distribution) and found that allowing for skewness and time variation in the higher moments of the residual distribution does not further improve forecasts. It is worth mentioning here that in the context of non-normality, the usual standard error estimate will be inappropriate. For models with normality assumption, we have used quasi-maximum likelihood estimates of variance-covariance matrix that is robust to symmetric non-normality in the disturbances.

The most challenging problem in time-series based forecasting (especially with the economics and finance data) is the evaluation of the ability of the model to appropriately forecast the volatility in the time-series. Many “loss function” based measures have been proposed to evaluate the forecasting of conditional variance [40]. Two most widely used loss functions in the literature are root mean squared error (RMSE) and absolute mean squared error (AMSE) loss functions. To evaluate the ability of the GARCH models to capture the volatility in the blood glucose profiles we have used the RMSE and AMSE:

$$RMSE: \sqrt{\frac{1}{m}\sum_{t=1}^{m}(y_t - \widehat{y}_t)^2} \quad , \tag{9}$$

$$AMSE = \frac{1}{m}\sum_{t=1}^{m}\left|y_t - \widehat{y}_t\right|, \tag{10}$$

where y_t is the observed glucose measurements at time t and $\widehat{y}_t$ is the predicted glucose measurements. We have also computed the relative error (RE) of the prediction ability of other models compared to G(1,1) in both hypo and hyperglycaemic situations. The RE is defined as

$$RE = (RMSE_{G(1,1)} - RMSE_{other})/RMSE_{G(1,1)} *100 \tag{11}$$

The RE indicates the amount of prediction error (in percentage) in higher and lower order AR and the state space model in comparison to G (1, 1).

RESULTS

All time-series measures of glucose levels (in mmol/L) from the individual CGMS profiles from the 6 patients are provided in the first columns of Figures **1A** and **B**. We conducted formal statistical tests (as described in the method section) to evaluate the presence of ARCH effect in the individual time series. For all six CGMS profiles, the LM test was highly significant, even up to lag 10, clearly suggesting the presence of ARCH effects. The high volatility and the significant autoregressive process (as tested) of these CGMS profiles can also be seen from the time-series plots in Figures **1A** and **B**.

The second columns of Figures **1A** and **B** represent the zoomed graphs of original glucose measures and the predicted glucose measures by four different methods under hypoglycaemic scenario. Similarly, the third columns in Figures **1A** and **B** represent the zoomed plots of original and predicted glucose measures under hyperglycaemic scenario. The dotted perpendicular lines represent the time point at which the dynamic prediction for 30 – 40 minutes by different methods started. We considered blood glucose level less than 3.2 mmol/L as hypoglycaemia region and higher than 12 mmol/L as hyperglycaemia region.

As evident from Figure **1** and Table **1**, that GARCH model performed better in terms of prediction performance compared to the other models in comparison. While predicting for hypoglycaemia, the RMSE and AMSE estimates were the smallest with G (1, 1) fits for all 6 profiles, compared to those obtained from the other models. Only for one patient’s profile

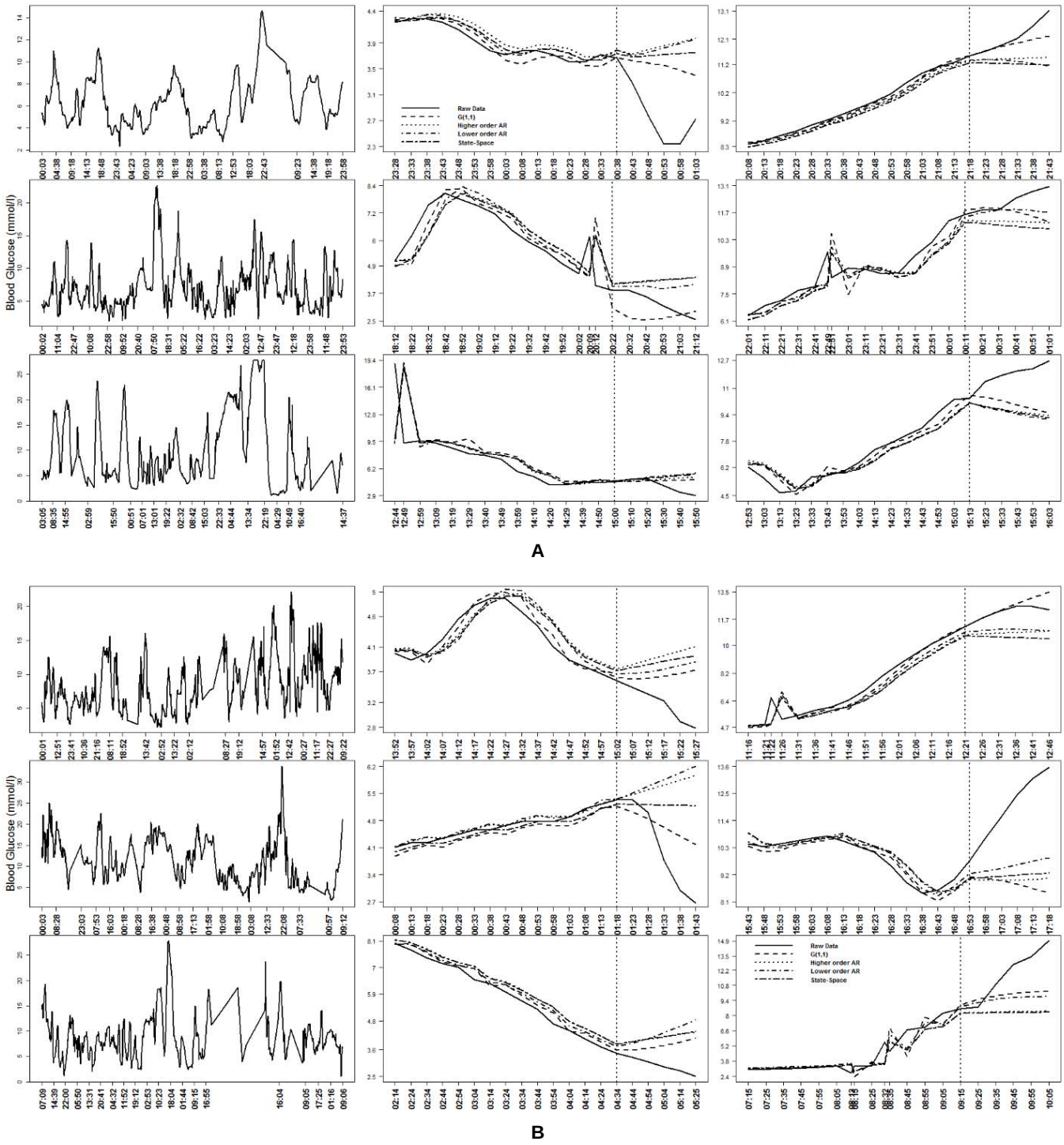

Figure 1: (**A**) Column 1 - CGMS profiles from three of the six selected patients; Column 2 - zoomed graph of predicted glucose levels from different models in hypoglycaemia region, with dotted vertical line presenting the start of dynamic prediction; Column 3 - zoomed graph of predicted glucose levels from different models in hyperglycaemia region, with dotted vertical line presenting the start of dynamic prediction.

(**B**) Column 1 - CGMS profiles from the second set of three of the six selected patients; Column 2 - zoomed graph of predicted glucose levels from different models in hypoglycaemia region, with dotted vertical line presenting the start of dynamic prediction; Column 3 - zoomed graph of predicted glucose levels from different models in hyperglycaemia region, with dotted vertical line presenting the start of dynamic prediction.

(Patient ID 104, Table **1**), the RMSE estimate was higher for prediction in hyperglycaemia region with the G(1,1) model fit, compared to one of the comparator models, with the negative estimates of RE at 7%, 12%

Table 1: Forecasting Comparisons between Four Models, G(1,1), Higher Order AR, Lower Order AR and State Space Model for Six Randomly Selected CGMS Profiles Shown in Figure 1 (A and B)

Models	G(1,1)		Higher Order AR		Lower Order AR		State space	
	Hypo	Hyper	Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
Patient ID 16								
RMSE	0.84	0.42	1.13	0.90	1.11	1.05	1.00	1.09
RE (in %)			34%	114%	32%	151%	19%	160%
AMSE	0.78	0.26	1.01	0.74	0.99	0.84	0.86	0.92
Min, Max	(-1.22, 0.46)	(-0.02, 0.91)	(-1.58, -0.25)	(0.18, 1.66)	(-1.56, -0.27)	(0.15, 1.97)	(-1.41, 0.00)	(0.24, 1.94)
Patient ID 25								
RMSE	0.76	0.95	1.11	1.17	0.87	0.73	1.13	1.40
RE (in %)			45%	23%	14%	23%	47%	46%
AMSE	0.67	0.70	0.94	1.03	0.71	0.54	0.96	1.23
Min, Max	(-0.38, 1.19)	(-0.19, 1.82)	(-1.84, -0.27)	(0.33, 1.88)	(-1.55, -0.16)	(0.01, 1.37)	(-1.84, -0.28)	(0.41, 2.20)
Patient ID 42								
RMSE	1.01	1.97	1.22	2.28	1.48	2.43	1.41	2.34
RE (in %)			21%	16%	47%	23%	40%	19%
AMSE	0.74	1.71	0.87	2.06	1.03	2.18	0.97	2.11
Min, Max	(-1.90, 0.29)	(-0.16, 3.16)	(-2.29, 0.22)	(0.29, 3.32)	(-2.72, 0.01)	(0.26, 3.58)	(-2.59, 0.04)	(0.29, 3.45)
Patient ID 73								
RMSE	0.55	0.52	0.83	1.36	0.64	1.21	0.74	1.67
RE (in %)			51%	163%	17%	133%	35%	222%
AMSE	0.43	0.31	0.72	1.30	0.53	1.13	0.64	1.58
Min, Max	(-0.96, -0.05)	(-1.14, 0.02)	(-1.33, -0.19)	(0.52, 1.72)	(-1.08, -0.10)	(0.37, 1.55)	(-1.19, -0.16)	(0.59, 2.08)
Patient ID 104								
RMSE	0.92	3.39	1.96	3.14	2.10	2.56	1.48	2.98
RE (in %)			112%	-7%	128%	-24%	61%	-12%
AMSE	0.73	3.01	1.47	2.86	1.58	2.30	1.09	2.70
Min, Max	(-1.51, 0.31)	(-0.66, 5.08)	(-3.29, -0.01)	(0.79, 4.51)	(-3.53, -0.01)	(0.53, 3.67)	(-2.51, 0.12)	(0.73, 4.29)
Patient ID 145								
RMSE	0.93	2.63	1.19	3.94	1.43	2.94	1.21	4.03
RE (in %)			29%	50%	54%	12%	31%	53%
AMSE	0.78	2.13	1.09	3.22	1.24	2.32	1.10	3.30
Min, Max	(-1.57, -0.15)	(-0.73, 4.67)	(-1.82, -0.38)	(0.40, 6.50)	(-2.35, -0.31)	(0.40, 6.50)	(-1.84, -0.39)	(0.43, 6.63)

and 24% with higher AR, state space and lower AR models respectively. The relative errors for higher order AR, lower order AR and state space models in comparison with G (1, 1) were in general remarkably higher, ranging from 14% to 54% in the hypoglycaemia region, and between 12% to 222% in the hyperglycaemia region.

The GARCH model fits were highly significant for all the patient profiles (Wald test). The AR parameters within the GARCH formulation were highly significant on both lags 1 and 2 for all the models. We note here that in all cases models were fitted without intercept for the structural components.

The observed glucose levels from the CGM profile and the model-based predicted glucose values from the G(1, 1) models are presented in Figure **2**. This figure also contains the residual (observed – predicted glucose values) over time. As evident from the predicted glucose and prediction residuals in Figure **2**, in the absence of any additional behavioral and dosing

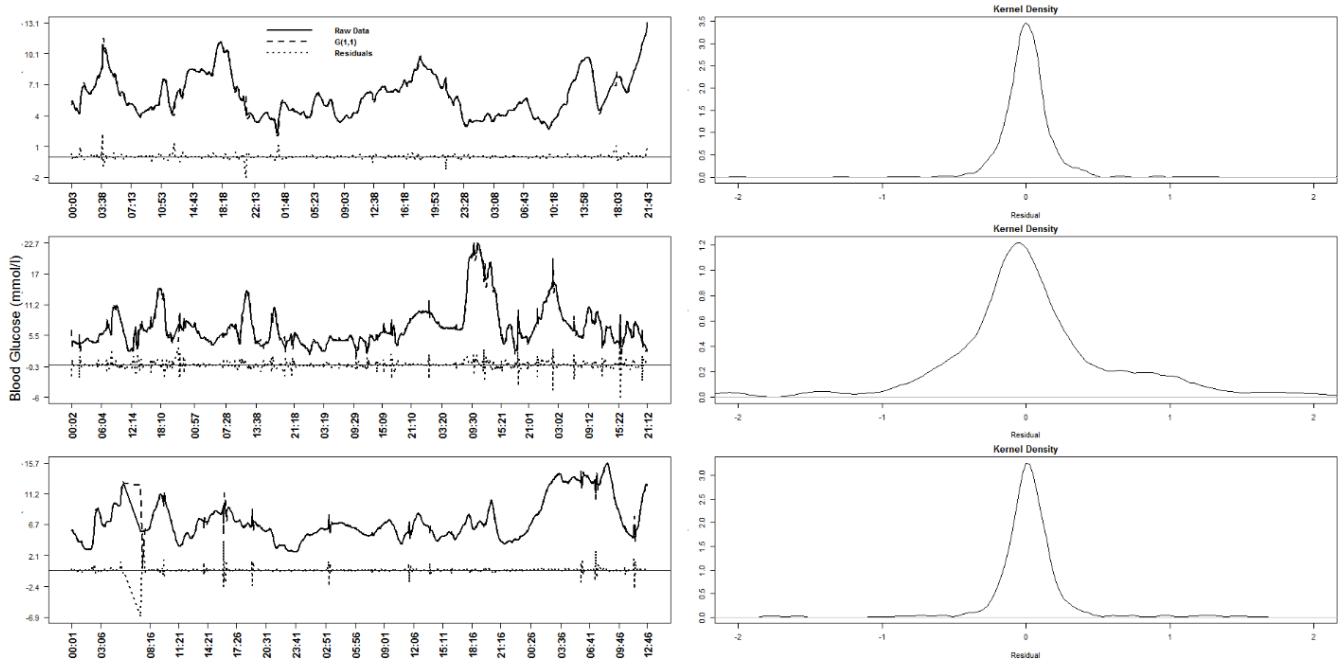

Figure 2: The observed and predicted glucose measures along with the model-based residuals based on training data from three selected patients, using G (1, 1) fit. The selected profiles are from Patient ID 16, 25 and 73 respectively.

information on individual patients, the simple G (1, 1) model with AR component can only partially capture the volatility in the glucose profile. The residual (error) level from the model fit (dotted lines at level '0' of horizontal axis) is relatively high at volatile regions when the glucose levels fall or increase rapidly (Figure **2**). However, the 30-40 minute prediction performance was promising. The forecasting performance of the GARCH model was compared with AR and state space models using RMSE (Equation 9) and AMSE (Equation 10). Table **1** displays the RMSE, AMSE and the RE for all relevant modelling approaches for both hypoglycaemic and hyperglycaemic episodes in individual CGM profiles.

DISCUSSIONS

The main aim of this study was to explore the utility of the GARCH modeling approach in understanding the trend and volatility of highly chaotic glucose profiles, and its ability to reasonably forecast upcoming glucose levels. The GARCH models have been able to capture the volatility in the glucose time-series to a great extent. The forecasting ability looks promising despite the highly chaotic scenario (Figure **1**) and the use of the minimum possible structural information relating to day-to-day fluctuations in glucose values. These fluctuations in glucose levels are of course not purely random. Various physiological aspects, including the real time activities of the patients and the insulin intake time, play a major role in the variations of glucose levels.

The observed AMSE ranging between 0.55 mmol/L to 0.78 mmol/L in the hypoglycaemic region is really promising. The estimated minimum and maximum prediction error (Min, Max in Table **1**) in the hypoglycaemia region is mainly due to irregular behavior of the realized glucose levels produced by the system below 2.5 mmol/L. This particular problem has also been reported earlier [30].

In terms of the forecasting, the key issue is the variance of the error terms and what makes them large. Here the dependent variable is the average glucose realization over a period of five minutes and the variance of the realized glucose represents the risk level for the patients. These are time series applications, but it is nonetheless likely that heteroscedasticity is an issue. Given the nature of glucose fluctuations in patients with T1DM, it is clinically obvious that some time periods are riskier than others; that is, the expected value of the magnitude of error terms at some times is greater than at others. This aspect is clearly evident from the residual plots, along with the observed and predicted glucose levels shown in Figure **2**. The residuals are clearly higher during the sudden peaks in the glucose fluctuations. Moreover, these risky times are not purely random, especially in patients treated with insulin. Instead, there is a degree of autocorrelation in the

riskiness of glucose realizations. The 'volatility clustering' issue is realized here and the proposed G(1, 1) have been able to capture the complexities to a great extent. However, other clinically important structural information need to be fed into the class of models to understand the system better and to capture the fluctuations more accurately. Better understanding of the volatility aspects through such models should enhance clinical decision making concerning the likelihood of an upcoming hypoglycaemic or hyperglycaemic episode.

Some CGM devices incorporate early warning alarms for hypoglycaemia, generally by extrapolating the rate of change of glucose concentration. The performance of early alarms is highly dependent on the value of the threshold and prediction horizon selected [35, 41-43]. A high frequency of false alarms is reported particularly for predicting hypoglycaemia glucose levels below 4.0 mmol/L, which limits their credibility and use by patients [42, 43]. The fundamental issue with the currently available alarm systems is the background methodologies for prediction. As reported, most of these systems use the simple 'rate of change' of glucose levels along with other basic control-level information which do not take into account the volatility aspects in the glucose measures. Therefore, there is a need to improve the current methodologies to predict hypoglycaemia more accurately from CGM data. The development of ARCH class of models can play a great role in this direction. While the progress on research work for the development of "artificial pancreas" is promising, development of more robust methodological support for risk prediction will be of great value.

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ETHICS

The DirecNet study protocol and the CGMS sub study were approved by appropriate authorities. This study uses the publicly available data from DirecNet.

AUTHOR CONTRIBUTION

SP conceived the idea of the study and was responsible for the design of the study. SP and MS conducted the analyses. SP is the guarantor.

CONFLICTS OF INTEREST

Both authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) SP and MS have support from QIMR Berghofer Medical Research Institute for the submitted work; (2) SP has acted as a consultant and speaker for Novartis and Amylin Pharmaceuticals Inc. He has received grants in support of investigator and investigator initiated clinical studies from Merck, Novo Nordisk and Pfizer; (3) Their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) SP and MS have no nonfinancial interests that may be relevant to the submitted work.

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