How should we interpret retrospective blood glucose measurements? Sampling and Interpolation

Kent W. Stewart*. Felicity Thomas*. Chris Pretty*. J. Geoffrey Chase*. Geoffrey M. Shaw**

** Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand (e-mail: kent.stewart@pg.canterbury.ac.nz)*
*** Department of Intensive Care, Christchurch School of Medicine and Health Sciences, New Zealand*

Abstract: This study investigates blood glucose (BG) measurement interpolation techniques to represent intermediate BG dynamics, and the effect resampling of retrospective BG data has on key glycemic control (GC) performance results. Many GC protocols in the ICU have varying BG measurement intervals with gaps ranging from 0.5 to 4 hrs. Sparse data poses problems in model fitting techniques and GC performance comparisons, and thus interpolation is required to assume a continuous solution.

Retrospective data from SPRINT in the Christchurch Hospital Intensive Care Unit (ICU) (2005-2007) was used to analyze various interpolation techniques. Piece-wise linear, spline and cubic interpolation functions, which force lines through data, as well as 1st and 2nd Order B-spline basis functions, used to identify the data, are investigated. Dense data was thinned to increase sparsity and obtain measurements (Hidden measurements) for comparison after interpolation. All of the piece-wise functions performed considerably better than the fitted interpolation functions. Linear piece-wise interpolation performed the best having a mean RMSE 0.39 mmol/L, within 2 standard deviations of the BG sensor error.

The effect of minutely vs hourly sampling of the interpolated trace on key GC performance statistics was investigated using the retrospective data received from STAR GC in the Christchurch Hospital Intensive Care Unit (ICU), New Zealand (2011-2015). Minutely sampled BG resulted in significantly different key GC performance when compared to raw sparse BG measurements. Linear piece-wise interpolation provides the best estimate of intermediate BG dynamics and all analyses comparing GC protocol performance should use minutely linearly interpolated BG data.

Keywords: Bio-signals analysis and interpretation; Identification and validation; Clinical validation

1. INTRODUCTION

Glycaemic control (GC) protocols in the intensive care unit (ICU) use a range of different blood glucose (BG) measurement intervals (0.5 – 4 hours), depending on patient's BG (Chase, Shaw, *et al.*, 2008; Finfer *et al.*, 2009; Preiser *et al.*, 2009; Amrein *et al.*, 2012; Van Herpe *et al.*, 2013; Stewart *et al.*, 2016). BG data recorded for each GC protocol has varying degrees of sparsity, making a fair assessment and comparison of glycaemic performance difficult. Particularly when key criteria for comparing GC protocol performance is percentage time within or outside a targeted BG range (Finfer *et al.*, 2013). A common method to improve assessment fairness is to interpolate between BG measurements and sample the interpolated trace equally and as needed (Chase, Shaw, *et al.*, 2008; Amrein *et al.*, 2012; Van Herpe *et al.*, 2013; Stewart *et al.*, 2016). However, the most appropriate interpolation technique and sample rate is still unknown.

Similarly, many insulin-glucose models use fitting techniques requiring approximations of these same intermediate BG dynamics (Bergman, Phillips and Cobelli, 1981; Mari and Valerio, 1997; Parker and Doyle 3rd, 2001; Hann, Chase and Shaw, 2006; Wong *et al.*, 2006; Chase *et al.*, 2007; Hovorka *et al.*, 2008). Thus, interpolation of clinical BG measurements significantly effects model fit and 'accuracy'. Again, many models use linear interpolation between BG measurements (Hann, Chase and Shaw, 2006; Lin *et al.*, 2011). However, its accuracy in comparison to other interpolation techniques has not been assessed.

This paper investigates the accuracy of 5 different interpolation methods that can be used to approximate the intermediate BG dynamics over clinically typical 2, 3 and 4 hour measurement intervals. The effect of various sampling rates on the interpolated BG trace is also assessed in relation to the outcome of key GC performance statistics.

2. METHODS

2.1 Patient Data

Patient data from Christchurch Hospital ICU, New Zealand patients treated with SPRINT and STAR (Chase, Shaw, *et al.*, 2008; Evans *et al.*, 2012; Stewart *et al.*, 2016). The Upper South Regional Ethics Committee, NZ granted approval for the retrospective audit, analysis and publication of the Christchurch patient data. For the assessment of interpolation techniques a representative sample of the densely measured SPRINT cohort was used (Chase, LeCompte, *et al.*, 2008). For

assessment of the effect of sampling rate on GC performance results the sparser STAR cohort is used. SPRINT is a paper based GC protocol which offers 1-2 hour measurement intervals and allows the time of BG measurements to be recorded to an hourly resolution (Chase, Shaw, *et al.*, 2008). In contrast, STAR is a tablet-based GC protocol which offers 1-3 hours measurement intervals and allows the time of BG measurements to be recorded to a minutely resolution (Evans *et al.*, 2012; Stewart *et al.*, 2016).

2.2 Interpolation techniques

Five different interpolation techniques are investigated, which are separated into 2 different styles of interpolation:

1. Piece-wise interpolation: The interpolated trace goes through all of the measurement points.
2. Fitted interpolation: The interpolated trace is a combination of basis functions, fitted to the measured data points.

2.2.1 Piece-wise interpolation techniques

Three Piece-wise interpolation techniques are investigated, linear, spline and cubic interpolation.

Linear interpolation: Data between BG measurements is assumed to be a linear line. Therefore the continuous BG data is represented by a piece-wise 1st order polynomial.

Spline interpolation: Data between BG measurements is assumed to follow a spline using not-a-knot end conditions. Therefore, the continuous BG data is represented by a cubic interpolation of the spline.

Cubic interpolation: Data between BG measurements is assumed to be a cubic relationship. Therefore, the continuous BG data is represented by a piece-wise cubic polynomial.

2.2.2 Fitted Interpolation

Two fitted interpolation techniques are investigated, 1st and 2nd Order B-spline basis function fitting. Basis function widths were varied to investigate the best fit. An example comparison of the fitted interpolation techniques can be seen in Figure 1. Fitted interpolation is used to try and incorporate an approximation of the measurement error into the interpolated trace and restrict overly rapid changes in the interpolated BG trace.

1st Order B-spline Basis Functions: The BG interpolation trace is made from a linear combination of 1st Order B-spline basis functions. 1st Order B-spline basis functions (k = 1) are based off the piece-wise function defined (De Boor, 1972).

$$\emptyset_{j,k}(t) = \begin{cases} \frac{t-W_j}{W_{j+k-1}-W_j}\emptyset_{i,k-1}(t) + \frac{W_{j+k}-t}{W_{j+k}-W_{j+1}}\emptyset_{i+1,k-1}(t) & W_j \le t < W_{j+1} \\ 0 & Otherwise \end{cases} \quad (1)$$

Where:
$j = 0,1,2 \dots n\ basis$, $W_j = KnotWidth * j$,
$k = basis\ function\ order$, and:

$$\sum_{i=1}^{n} \emptyset_j(t) = 1\ \forall\ t \quad (2)$$

The B-spline basis functions are in fixed locations, occurring every instance of the chosen knot width (KW), and overlap. The inherent property of the B-spline basis functions, Equation 2, ensures no underlying waveform can be induced into the fitted data and a constant value can also be represented.

2nd Order B-spline Basis Functions: The BG interpolation trace is made from a linear combination of 2nd Order B-spline basis functions, k = 2, based off the piece-wise function in Equation 1.

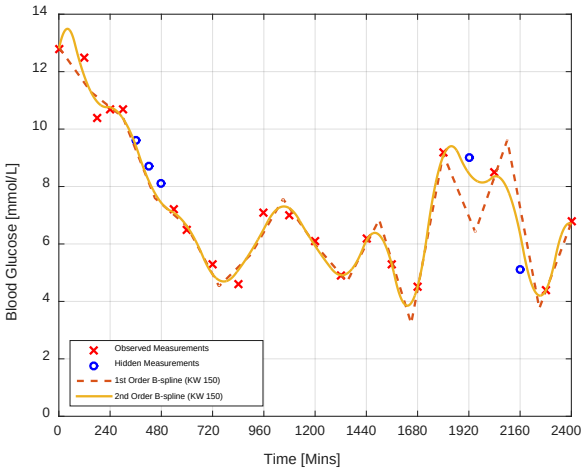

Figure 1: Comparison fitted interpolation techniques (1st and 2nd Order B-spline basis functions).

2.3 Interpolation Analysis

To assess which interpolation technique best represents the intermediate BG dynamics, the fit of the measured and intermediate BG dynamics need to be considered. BG data points are removed from dense BG data sets before interpolation, and then compared to post-interpolation estimates for independent validation. Data was thus thinned to create 2, 3 and 4 hour measurement intervals, similar to what would be expected clinically. Removed measurements are referred to as 'hidden' measurements, and remaining measurements are 'observed' measurements.

Removed BG measurements criteria:

1. Could be removed without causing a gap between the neighbouring measurements greater than the measurement period being investigated (2, 3 and 4 hours).
2. The interventions (nutrition and insulin) given to the patient over this period were constant. Changes that would only be able to be captured by a model and would not usually occur without a prior BG measurement.

An example is shown in Figure 2, and Table 1 summarises the now sparse data.

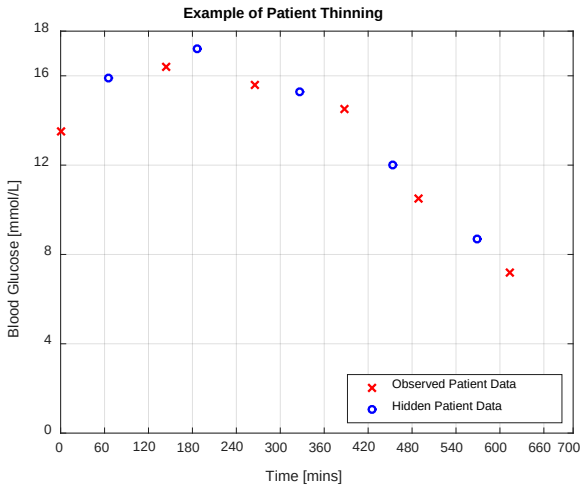

Figure 2: Example of thinning data to maximize 2 hour measurement intervals.

Table 1: Thinned patient data sets for each measurement interval to be used for evaluation of techniques.

Measurement interval	2 hr	3 hr	4 hr
# Patients	29	31	34
# Observed Meas.	3296	2922	1862
# Hidden Meas. (% Total)	853 (20.6%)	1404 (32.5%)	2512 (57.4%)

A range of basis function knot widths (KW), in Equation 1, are tested to see which option best fits both the observed and hidden data. Goodness of fit was assessed by using Root Mean Square Error (RMSE) between the observed and/or hidden measurements. Errors for observed measurements are expected to be lower as they are used in the identification process. Error for hidden measurements validates the ability of the interpolation technique to capture the intermediate BG dynamics over time intervals relevant to GC protocols. The goodness of fit for both the observed and hidden measurements are then compared to the error expected from the point of care measurement devices used in the SPRINT study, Arkray Super-Glucocard™ II glucometer (Arkray, Minnesota, USA).

2.2 Sampling Analysis

To assess which sampling rate of the pre-determined, interpolated BG trace best captures GC performance, key GC performance statistics are compared with various sampling intervals (1, 60 minute and raw measured data points).

The statistics assessed are:

- BG mean, median and standard deviation.
- Percentage of time in the targeted range (4.4-8.0 mmol/L)
- Percentage of time BG < 2.2 mmol/L, BG <4.4 mmol/L and BG >10 mmol/L.

All sampling of the interpolated BG trace starts from the first BG measurement and is therefore heavily dependent on the interpolation technique used.

3. RESULTS

3.1 Piece-wise Interpolation

Figure 3 shows the cohort hidden RMSE for the 3 different piece-wise interpolation techniques (Linear, Spline and Cubic). Linear interpolation performed the best followed closely by cubic interpolation. The longer the measurement interval interpolated, the worse the fit provided.

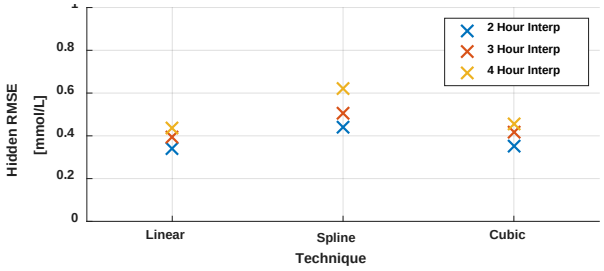

Figure 3: Piece-wise interpolation RMSE of hidden measurements.

3.1 Fitted Interpolation

Figure 4 presents the cohort RMSE, for both hidden and observed measurements, as the knot width (KW) is increased on the 1st order B-spline basis functions. RMSE of observed measurements increased with KW and the RMSE of hidden measurements decreased as the KW increased.

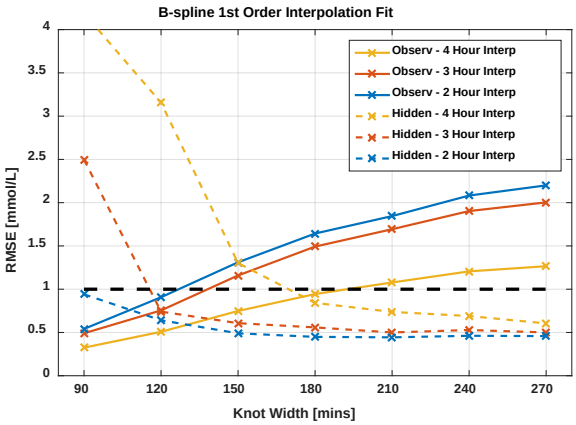

Figure 4: 1st Order B-spline basis functions fitted interpolation RMSE of observed and hidden measurements. The thick black dashed line provides a reference to Figure 3.

Table 2: Glycaemic control performance results of the STAR Cohort using different sampling intervals.

Sampling Interval	Raw Measurements	Hourly	Minutely	P-Values	
				Raw vs. Hourly	Hourly vs. Minutely
Number episodes	286	286	286	-	-
Cohort Statistics					
Mean BG	6.92	6.73	6.71	-	-
Median BG	6.80 [5.90 - 7.90]	6.61 [5.96 - 7.40]	6.60 [5.95 - 7.38]	-	-
Std Dev BG	1.29	1.23	1.23	-	-
% time < 2.2 mmol/L	0.04328	0.00456	0.00941	-	-
% time < 4.4 mmol/L	2.62	1.35	1.32	-	-
% time 4.4-8.0 mmol/L	74.32	83.30	83.78	-	-
% time > 10 mmol/L	7.13	4.10	3.88	-	-
Per-patient Statistics					
Mean BG [IQR]	6.84 [6.50 - 7.42]	6.66 [6.36 - 7.21]	6.64 [6.31 - 7.14]	<0.01	0.38
Median BG [IQR]	6.70 [6.30 - 7.20]	6.50 [6.14 - 6.90]	6.49 [6.14 - 6.87]	<0.01	0.80
Std Dev BG [IQR]	1.43 [1.08 - 1.98]	1.17 [0.85 - 1.65]	1.07 [0.79 - 1.51]	<0.01	0.08
% time < 2.2 mmol/L	0.00 [0.00 - 0.00]	0.00 [0.00 - 0.00]	0.00 [0.00 - 0.00]	0.18	0.18
% time < 4.4 mmol/L	0.00 [0.00 - 5.34]	0.00 [0.00 - 1.79]	0.00 [0.00 - 1.49]	<0.01	0.09
% time 4.4-8.0 mmol/L	81.50 [66.67 - 90.00]	88.42 [77.42 - 94.44]	88.80 [77.89 - 95.52]	<0.01	0.37
% time > 10 mmol/L	2.78 [0.00 - 8.70]	1.22 [0.00 - 5.56]	0.78 [0.00 - 4.48]	<0.05	0.56

Figure 5 presents the same results for the 2nd order B-spline basis functions.

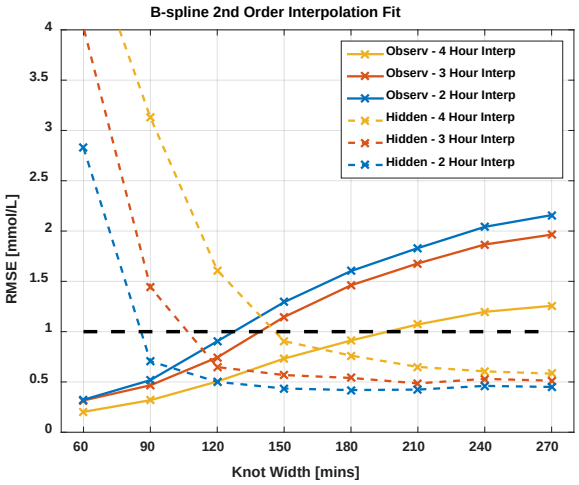

Figure 5: 2nd Order B-spline basis functions fitted interpolation RMSE of observed and hidden measurements. The thick black dashed line provides a reference to Figure 3.

3.2 Sampling interval

The prior analysis shows linear interpolation provided the best approximation of BG data. Using linear interpolation, the effect of sampling rate on STAR cohort results was investigated. Table 2 shows results are significantly skewed if resampling is not used, and slight variations in some results can be observed if interpolated BG is sampled more frequently.

4. DISCUSSION

4.1 Piece-wise interpolation performance

Figure 3 shows all the piece-wise interpolation techniques performed extremely well in capturing intermediate BG dynamics. Linear interpolation performed the best with an average RMSE of 0.39 mmol/L, over all measurement intervals assessed. As the measurement interval assessed increased, so did the hidden RMSE. This result is likely due to the greater time for the intermediate BG dynamics to deviate from the interpolated trace, as expected.

4.2 Fitted interpolation performance

From Figures 4-5 there is a trade-off of the fit of the interpolated trace, between the hidden and observed measurements. In general, as KW is increased, the RMSE on the observed data points is increased and the RMSE on the hidden data points is decreased. The 150 minute knot width 1st order B-spline basis functions provided the best compromise of fit to the observed (mean RMSE 1.07 mmol/L) and hidden (mean RMSE 0.80 mmol/L) measurements. The 150 minute 2nd order B-spline basis functions also provided the best compromise of fit to the observed (mean RMSE 1.06 mmol/L) and hidden (mean RMSE 0.64 mmol/L) measurements. Overall, the 2nd order B-spline basis function interpolation provided the best fit to both observed and hidden measurements.

4.3 Optimal Interpolation

From the results it can be seen that the piece-wise interpolation techniques provided a better approximation of the hidden measurements, and inherently have no fitting error to the observed measurements, in comparison to the fitted interpolation techniques. Thus, the trade-off of fit between the observed and hidden measurements resulted in a much larger RMSE overall compared to the piece-wise interpolation techniques. The SPRINT cohort BG measurements were measured using a Super Glucocard II (Arkray, Minnesota, USA), which has a standard deviation of measurement error ranging from 0.15–0.56 mmol/L, depending on the BG value (Arkray, 2007). Only the linear and cubic piece-wise interpolation techniques provided a RMSE within this measurement error.

4.4 Sampling Analysis

The raw BG results were at minutely and hourly intervals, using linear interpolation. Table 2 clearly shows there are significant differences in key results using raw measurement and interpolated BG result for both cohort and per-patient metrics. The most significant impact is on percentage of time statistics; 81.5% vs ~88% of time BG within 4.4-8.0 mmol/L, per-patient $P < 0.01$; 2.78% vs ~1.0% of time BG > 10 mmol/L, per-patient $P < 0.05$. A significant difference can also be seen in the BG mean and median results (mean BG of 6.84 vs ~6.65 mmol/L, $P < 0.01$, and median BG of 6.7 vs ~6.49 mmol/L, $P < 0.01$). The discrepancy is largely due to the varying measurement frequency in and out of band for the given GC protocol, inherently causing higher numbers of raw measurements to occur outside of the targeted band than within.

Only a small benefit is observed from sampling the interpolated trace more frequently (minutely). The largest difference between minutely vs hourly interpolated results in Table 2, occurred in the percentage of time BG > 10 mmol/L measurements (0.78% vs 1.22%, $P = 0.56$). This result could be due to the hourly sampling of the interpolated trace truncating the measured peaks seen in the minutely sampling, which is important especially when considering the number of patients within the hyper- and hypo- glycaemic region (BG > 10 mmol/L and < 4.44 mmol/L). A negligible difference in BG mean, median was seen in Table 2. However, a slight difference could be seen in the standard deviation of BG between sampling rates (1.17 vs 1.07, $P = 0.08$).

4.5 Limitations

The SPRINT protocol has measurement intervals of 1-2 hrs (Chase, Shaw, *et al.*, 2008). As per protocol, the SPRINT data is denser in regions where a patient is variable or out of the target band. Thus, the measurements removed (hidden measurements) to make the data sparse are more likely to be removed from more variable and higher (BG > 6.1 mmol/L) BG regions. Hence, the hidden measurement error is a stronger validation test, but will likely have higher BG measurement error associated with it than if more stable periods were included. The results are thus conservative.

The number of observed and hidden BG measurement varies as the measurement interval assessed is increased, due to the data needing to be denser to assess smaller measurement intervals. However, there is still a significant amount (20.6%) of data for assessment of the 2 hour measurement interval to provide a fair assessment of the BG interpolation techniques.

5. CONCLUSIONS

Overall the linear piece-wise performed the best out of all interpolation techniques (mean RMSE 0.39 mmol/L), providing the best estimate of the intermediate BG dynamics. The fitted interpolation techniques failed to capture the hidden BG measurements without providing a poor fit to the observed measurements. Thus linear interpolation provides the best estimate of intermediate BG dynamics.

There is a significant difference in key GC performance statistics when comparing raw to resampled interpolated measurements, especially when the GC protocols being investigated have varying measurement frequency depending on BG. Therefore, for fair comparison of a GC protocol's performance, minutely resampled linear interpolation of BG results should be used.

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