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Glycaemic State Analysis from Continuous Glucose Monitoring Measurements in Infants

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Abstract: Neonatal hypoglycaemia is common in at-risk infants and can cause adverse neurologic outcomes in later life. Continuous glucose monitoring (CGM) technology offers a way to continuously monitor patient condition, helping to detect hypoglycaemia as well as provide insight into the general glycaemic state of the patient. Characterising Glycaemic States can be easily done by eye, but no simple, clinically relevant algorithm exists to do this characterisation analytically or computationally. This paper presents such an algorithm to characterise Glycaemic States and detect State Changes. This algorithm was developed on a cohort of 366 infants, using a total of 12356 hours of CGM sensor data. State Changes were defined as an intersection between a 6-hour rolling average of the CGM trace and the average of the whole interstitial glucose CGM trace, with a 5 hour minimum crossover threshold defining a single State. The majority of infants were found to have experienced less than 2 State Changes in the first 48 hours of birth (279 of 366 patients, 76%). The median number of State Changes per day was 0.68 [IQR: 0.60, 1.14], while the median absolute change in IG over a State Change was 0.6 mmol/L [IQR: 0.4, 0.9 mmol/L]. Visually, the majority of algorithmically characterised State Changes matched CGM traces characterised by eye. Future use of the algorithm could associate the State Changes with clinical outcomes.

Keywords: Biosignal analysis, processing and interpretation, Medical technology, Metabolic system

1. INTRODUCTION

Continuous glucose monitoring (CGM) sensors have seen continued improvement in recent years, and provide a way to monitor patient blood glucose (BG) between intermittent measurements. Older CGM technology was inadequate for tight control, with up to 20% measurement error for some devices (Gross et al., 2000, Pishko, 2000). Newer generation CGM sensors use better BG detection techniques and give more accurate measurements up to 4 times per minute (Crane et al., 2015, Zhou et al., 2018, Damiano et al., 2014, Kosiborod et al., 2014, Luijf et al., 2013), increasing their potential use.

One potentially beneficial application of CGM sensors is in the detection and management of neonatal hypoglycaemia, which is common and is linked to adverse neurologic outcomes (Harris et al., 2012, McKinlay et al., 2015). Although the definition of neonatal hypoglycaemia is still controversial (Rozance and Hay, 2010), treatment thresholds of 2.6 mmol/L (hypoglycaemia) and 2.0 mmol/L (severe hypoglycaemia) have been used (Harris et al., 2012, McKinlay et al., 2015). In particular, in a cohort of 614 neonates considered at risk for hypoglycaemia (Harris et al., 2010, Harris et al., 2013), neonatal hypoglycaemia was not associated with adverse neurologic outcomes at 2 years of age when treatment was provided to maintain a blood glucose concentration of at least 2.6 mmol/L (McKinlay et al., 2015). However, a follow up at 4.5 years of age for 477 neonates from this cohort found that treating neonatal hypoglycaemia to maintain blood glucose concentration of at least 2.6 mmol/L, although not associated with increased risk of combined neurosensory impairment, it was associated with increased risk of poor executive function and visual motor function, in a dose-dependent manner (McKinlay et al., 2017). Thus, glucose monitoring to mitigate hypoglycaemia may have significant long-term impact on the identification of hypoglycaemic episodes that may have previously gone undetected by intermittent BG measures.

Intermittent BG samples for infants have to be taken from the foot, which may be logistically difficult to collect. Repetitive painful stimulus in the new-born period of life may also have adverse effects on brain development (Ranger et al., 2013). CGM sensors can continuously monitor an infant's BG and require fewer blood draws compared to intermittent monitoring, while providing much higher temporal resolution enabling continuous monitoring. Continuous monitoring makes it easier to assess changes in glycaemic level and state, as well as the variability reflected in dynamic CGM sensor

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traces. It may also offer significant insight into patient condition.

A "Glycaemic State" or "State" is here defined as a change in the mean BG over a short period, about which normal fluctuations occur due to patient metabolism and system inputs such as nutrition. It could be considered as the patient's glycaemic set-point or reference BG, and changes in this state, or lack of settled state due to high variability, is hypothesised to provide insight into patient condition. Evaluation of changes in glycaemic state can often be easily done by eye, but no simple, clinically relevant method or algorithm currently exists to assess level and state analytically or computationally. In addition, when dealing with large cohorts or potential bias due to subjectivity or different evaluators, an automated process is important.

This paper presents a new method of classifying Glycaemic States from CGM traces. It is developed from CGM data collected in new-born infants. The goal is to demonstrate the algorithm and do so by quantifying the number of State Changes experienced by an at-risk infant within the first 48 hours of birth.

2. METHOD

2.1 Subjects and Continuous Glucose Monitoring

The CHYLD Study recruited 614 infants born from 32 weeks gestation with one or more risk factors for neonatal hypoglycaemia, including the following: diabetic mother, preterm (<37 weeks), small (<10th centile or <2500 g), large (>90th centile or >4500 g), or acute illness (McKinlay et al., 2015). The aim of the CHYLD Study was to examine the relationship between the incidence and severity of neonatal hypoglycaemia in at-risk infants and neurodevelopmental outcome in childhood (Harris et al., 2012, McKinlay et al., 2015). A total of 481 infants had an interstitial CGMS System Gold CGM sensor (Medtronic Inc., Northridge, CA) inserted soon after birth in the lateral thigh, as previously described (Harris et al., 2010, Harris et al., 2012). Of these, 366 had more than 24 hours of CGM data in the first 48 hours after birth, leading to 12356 total hours of CGM data (median [IQR]: 35.7 [30.5 38.4] hours/patient). The CGM sensor recorded a measurement every 5 minutes but results were masked and did not influence clinical care. CGM data were downloaded and recalibrated to all blood glucose concentrations, measured on a blood gas analyser (Signal et al., 2012a). The study was approved by the New Zealand Northern Y Ethics Committee.

2.2 Calculating States

For each infant, the mean of the whole CGM trace establishes a baseline average IG level for that infant. The CGM data is then filtered using a centred 6-hour rolling average. Thus, there are 12x6-hour-average data points created using every hour of CGM data available, commencing 3 hours into the trace as the rolling average is calculated from the centre of the rolling window. Comparing the 6-hour rolling average to the arithmetic mean yields a baseline variation around the mean. Six hours is chosen because it filters out higher frequency glucose fluctuations, such as IG spikes just after feeding, and allows for any true, long term changes in average IG, characterised as a State Change in patient metabolic behaviour, to be shown. Each time the 6-hour rolling average crosses the arithmetic average line, it is considered a possible State Change if certain clinically relevant and defined conditions are met:

- More than 5 hours have passed since the last State Change, which assures "States" are 5 hours (or longer) periods of relatively constant average IG.
- The State Glycaemic Average, defined as the average IG for a given State, was more than 0.3 mmol/L higher or lower than the previous State Glycaemic Average, to reduce potential impacts of measurement error.

If either condition is not met, the CGM data for the current arithmetic average crossing is combined with the CGM data of the previous State, and that State's Glycaemic Average recalculated using the longer CGM data. This State characterisation process is shown in Figure 1.

Importantly, while the 0.3 mmol/L threshold was chosen based on experience, it can be changed for any cohort or to find only larger changes. Similarly, a shorter or larger rolling average than 6-hours can be used, or they may be "nested" to find shorter State periods. Finally, State Changes per day (24 hours) are also calculated to normalise results for comparison.

2.3 Analyses

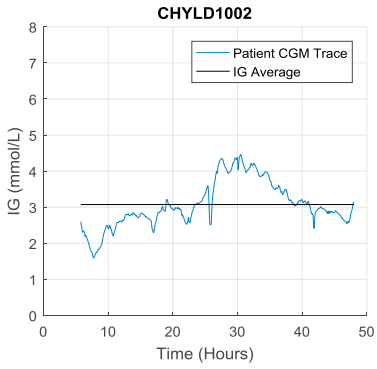
Each infant had their CGM sensor trace assessed against the algorithm to determine the number of State Changes experienced in the first 48 hours of birth. The number of babies who experienced a set number of State Changes was recorded.

The median [IQR] hours of CGM per patient are calculated, alongside the average change in IG after a State Change, the maximum State Change, the minimum State Change, number of State Changes that resulted in a higher IG (also as a percentage), and the number of State Changes that resulted in a lower IG (also as a percentage).

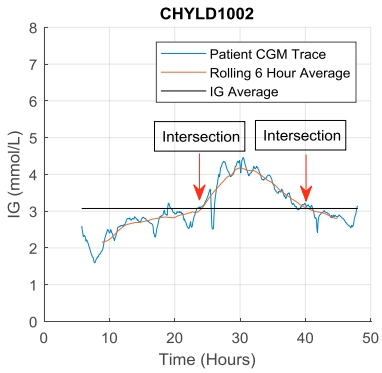
3. RESULTS

3.1 Cohort state characterisation results

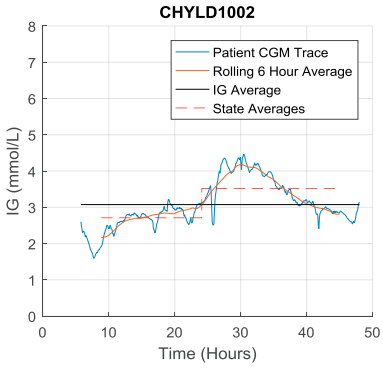
Table 1 presents the overall results of the State analysis algorithm. The number of State Changes experienced by each infant was calculated, along with the number of State Changes/day, average absolute change in IG over a State Change, minimum and maximum State Changes, and the number of State Changes with higher and lower IG.



a) Clinical data for Patient 1. Black line shows the average for all of the CGM data.



b) A centred rolling 6-hour average is calculated. Intersections between the rolling 6-hour average and IG average are noted by the red arrows.



c) After the second 6-hour average intersection, there is less than 5 hours of rolling average data available. Thus, this rolling average data is added to the rolling average data above the black IG average line, and another State Average calculated. Hence, two Glycaemic States have been identified for Patient 1 as the two states are more than 0.3 mmol/L different in IG.

Fig 1. Steps of the Glycaemic State characterisation process, showing how the rolling average and States are calculated.

3.2 Glycaemic State characterisation examples

Figure 2 shows the State characterisation process for Patient 2, where 3 separate States have been identified. The initial patient State is low IG and rising, shown by the State Average of ~3.5 mmol/L. At around 25 hours after birth, the patient enters a State of higher average IG, but also higher variability, as shown by the large fluctuations in the original CGM signal about the State Average of ~4.4 mmol/L.

At 38 hours after birth, the patient enters a steep decline in IG. However, this decline is not reflected in the rolling 6-hour average as a State change until 40 hours after birth, where the rolling average intersects the IG average line. This State is less variable than the previous State and also has an average closer to the total IG average, implying the patients becomes more stable.

Figure 3 shows the State characterisation process for Patient 3, where 2 States have been identified. Patient 3 starts with their CGM trace intersecting the IG average line frequently. However, the resulting States are less than the 0.3 mmol/L threshold required to reach a new Glycaemic State and so these are merged into one State. Finally, at approximately 33 hours, both the CGM trace and 6-hour rolling average decline enough, and for longer than the minimum 5 hour time frame, to reach a new, lower Glycaemic State.

Figure 4 shows a patient with similar States and State Changes to Patient 2 in Figure 2. The patient starts off at a lower State, experiences a State Change in which the State Average increases, and then lowers again to State Average closer to the IG average. Patient 4 differs slightly to Patient 2 in that the last State has a lot of variability in IG. This variability results in the rolling average crossing the IG average line more frequently, although subsequent changes in average State IG would not be significant (<0.3 mmol/L threshold). Thus, all of the rolling 6-hour average values between 25.3 hours and 45 hours after birth are used for the calculation of a single State Average. It is of particular note that the IG spike at 37.4 hours after birth from 3.4 mmol/L to 7.7 mmol/L occurs in 20 minutes of measurements in the absence of parenteral dextrose boluses or buccal dextrose gel, and is likely to be sensor error rather than a rise in true IG (Signal et al., 2012b).

Figure 5 shows the State characterisation for Patient 5 who displays a relatively more stable State, similar to Patient 3 in Figure 3 but with slightly more variability. Two States have been identified by the algorithm, where Patient 5 starts in a higher State and then transitions to a lower State. However, if a threshold >0.3 mmol/L was used, the algorithm would identify only one State. Thus, the choice of threshold depends on the granularity desired in defining clinically significant States. It is possible to change the algorithm threshold to determine an optimum threshold for State differentiation, which can be judged by visual inspection of the plots and

deciding if the number of States is appropriate. Measurement error might also help decide the appropriate threshold.

Table 1. State Change analysis results.

Patients	366
Total hours	12356
Hours/Patient (median) [IQR]	35.7 [30.5 38.4]
Number patients with no state changes	77 (21.0%)
1 State Change	202 (55.2%)
2 State Changes	57 (15.6%)
3 State Changes	29 (7.9%)
4 State Changes	1 (0.3%)
State Changes/day (median [IQR], (90% range))	0.68 [0.60 1.14], (0-1.89)
Median [IQR] absolute ΔIG State Change (mmol/L)	0.6 [0.4 0.9]
Max State Change (mmol/L)	2.8
Minimum State Change (mmol/L)	0.3
Number of State Changes from lower to higher average IG	243
Number of State Changes from higher to lower average IG	164

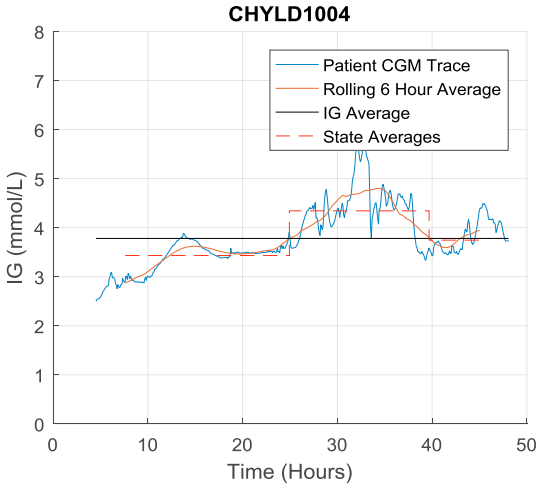


Fig 2. CGM data and Glycaemic State characterisation for Patient 2.

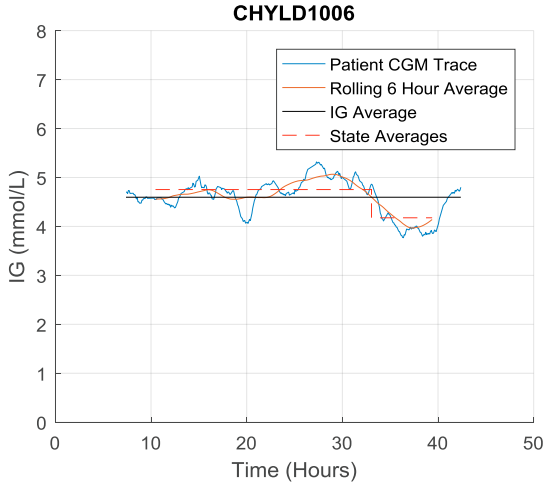


Fig 3. CGM data and Glycaemic State characterisation for Patient 3.

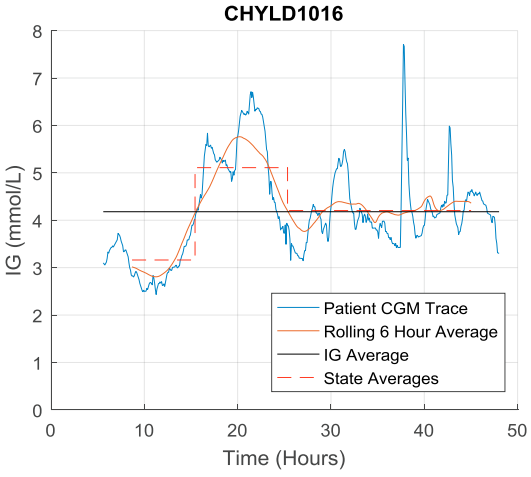


Fig 4. CGM data and Glycaemic State characterisation for Patient 4.

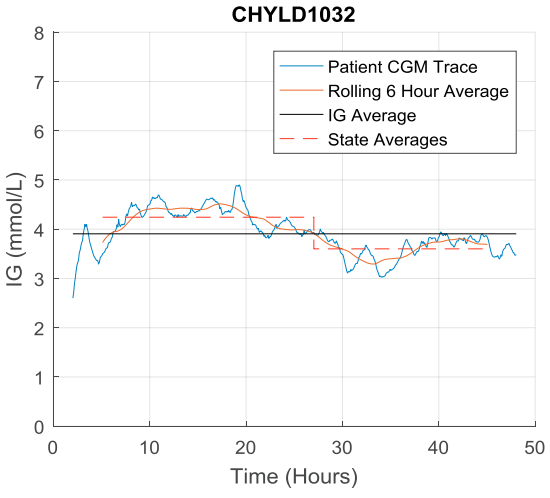


Fig 5. CGM data and Glycaemic State characterisation for Patient 5.

Figure 6 shows the State characterisation for an infant who was characterised by the algorithm as being fairly stable, with only one State, but on visual inspection there is moderate variability of the CGM trace with possibly 2 States. At the start of the CGM trace, IG starts low and appears to be hypoglycaemic for around 2.5 hours, appearing to be at a single State of low glucose concentrations. IG starts to rise back to normal levels at around 17 hours after birth. Due to the mathematical constraints on the 6-hour rolling average, the average line only starts at 15.5 hours, rising quickly past the entire IG average at 19.5 hours due to the quick increase in IG between 17 and 19 hours after birth. Due to the 5 hour minimum threshold chosen for our State definition, the IG transition at 19.5 hours has not been defined as a State. Similarly, the 6-hour average crosses the IG average again at 43.5 hours, but does not exist for long enough to define another State. Thus, only 1 state has been characterised for this patient. However, different threshold choices or a change in beginning the moving average could be used to capture such early potential States, if clinically relevant and desired.

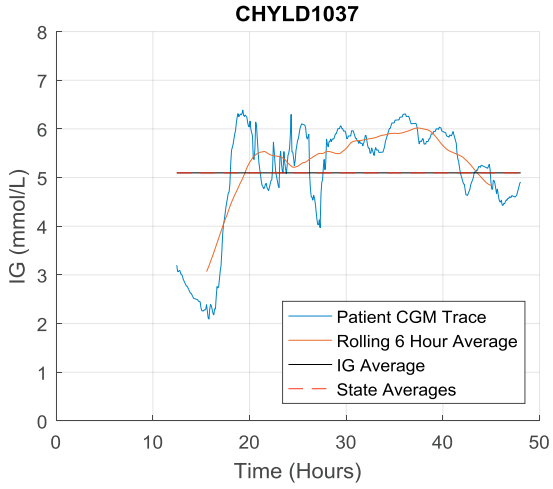


Fig 6. CGM data and glycaemic state characterisation for Patient 6.

Only 1 patient recorded 4 State Changes, the maximum number experienced for this cohort. This variability could have been due to systematic sensor error or excessive sensor recalibration leading to an abnormal amount of quantified State Changes. Figure 7 shows this patient, where it is clearer that the IG average is abnormally high for this cohort. In particular, in the last portion of the CGM trace the infant is hyperglycaemic.

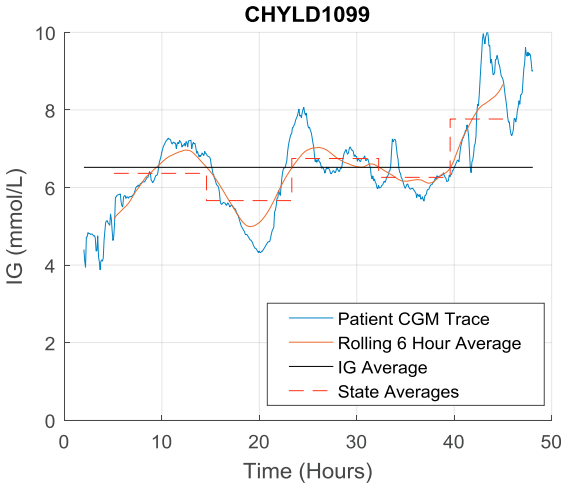


Fig 7. CGM data and Glycaemic State characterisation for Patient 7.

4. DISCUSSION

The majority of infants experienced less than 2 State Changes in the first 48 hours of birth (279 of 366 patients, 76%), suggesting these patients at risk of hypoglycaemia remained in a relatively stable condition despite high rates of hypoglycaemia (Harris et al., 2010, Harris et al., 2012).

There were more State Changes to a higher than lower IG. This may relate to fact that the CHYLD cohort recruited infants at risk of hypoglycaemia. Equally, BG tends to rise in days after birth as the infant's metabolism stabilises and their ability to take up nutrition and absorb it develops.

Only around a quarter of the infants (96 out of 366) were parenterally fed; the majority were entirely enterally fed. Thus, these State Changes are most likely not due to changes in PN feed rate. The States, defined by the 0.3 mmol/L threshold chosen here, are by design larger than the expected rise due to a single enteral feed. The 5-hour minimum State length is greater a feed interval. Thus, it is unlikely that feeds would cause false State Changes.

5. CONCLUSIONS

Identification of Glycaemic State Change in infants with CGM can be easily done visually, but is hard to do algorithmically. We have developed and present an algorithm for classifying CGM State Changes in infants. Results show promise and match expectations when reviewing the results visually. It remains to be determined whether such State Changes are related to other glycaemic indicators and clinical outcomes.

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