Multiscale Entropy Analysis of Continuous Glucose Monitoring Data: A Comparative Study of Diabetic and Healthy Populations

Cleber França Carvalho[a], Thilini Savindya Karunarathna[b] and Zilu Liang[c]
Ubiquitous and Personal Computing Lab, Kyoto University of Advanced Science (KUAS), Kyoto, Japan

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Abstract: The advent of continuous glucose monitoring (CGM) has made it possible to measure glucose frequently in daily life. This availability of glucose time series enables advanced analysis to uncover patterns in glycaemic dynamics that were previously undetectable with traditional blood-sample-based measurements. One such analytical method is multiscale entropy (MSE), which assesses the complexity of time series data across varying time scales. In this study, we performed a comparative analysis of MSE across three cohorts: individuals with type 1 diabetes (T1D), type 2 diabetes (T2D) and prediabetes (PRED). Our goal was to identify potential differences in glucose dynamics across these groups. We applied three base entropies, including approximate entropy (ApEn), attention entropy (AttnEn) and dispersion entropy (DispEn). We found that AttnEn and DispEn were useful in distinguishing between individuals with diabetes (both T1D and T2D) and those with prediabetes, whereas ApEn did not show significant discriminative power. Furthermore, we observed no substantial differences between T1D and T2D in terms of their MSE profiles. These results suggest that MSE, with appropriate base entropy measures, holds promise as a tool for developing biomarkers to differentiate between diabetes and prediabetes. Future studies could explore additional base entropy measures and analysing larger, more diverse datasets.

1 INTRODUCTION

Diabetes mellitus is a metabolic condition characterized by high glucose levels, which can lead to several systemic complications, such as cardiovascular diseases, nephropathy, stroke, and others (Alam et al., 2014). According to the International Diabetes Federation, 537 million adults worldwide were living with diabetes in 2021, and this number is projected to rise to 783 million by 2045, which is considered a serious public health problem (IDF Diabetes Atlas, 2021). Diabetes is commonly classified into two types: Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). T1D is a chronic autoimmune condition that causes destruction of pancreatic beta-cells, which are responsible for insulin production. On the other hand, T2D is caused by insulin resistance or deficiency in the production of insulin (Kahn et al., 2006). Another emerging condition related to insulin malfunctioning is called prediabetes (PRED), which can be characterized by high glucose levels after meals but with normal fasting glucose levels. It is estimated that there are 541 million people in the world with this condition.

Since there is still no cure for diabetes, the best way to manage the disease is to change lifestyle habits and control blood glucose levels. In recent years, continuous glucose monitoring (CGM) has become popular as an effective tool for managing diabetes due to its affordability and convenience (Battelino et al., 2019). These sensors are attached to the skin, continuously measuring interstitial glucose, providing a view of glucose trends and fluctuations throughout the day and generating a large amount of data (Rice and Coursin, 2012). These data, as represented in Figure 1, can be utilized to uncover insights into glycaemic dynamics and other aspects of human physiology and behaviour (Bertrand et al., 2021; Liang, 2022).

[a] https://orcid.org/0009-0008-3740-4355
[b] https://orcid.org/0009-0002-4089-9500
[c] https://orcid.org/0000-0002-2328-5016

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CGM data is complex, containing a wealth of information encoded in the temporal and spatial patterns of glucose fluctuations. One approach to characterize this information is through multiscale entropy (MSE) analysis. MSE is based on the simple observation that complex human physiological signals often exhibit dynamics that fall between perfect regularity and complete randomness. These signals possess intricate structures that can be observed at multiple spatial and temporal scales (Costa et al., 2002). While many studies have employed MSE to analyse the complexity of glucose dynamics, most have focused only on a certain type of entropy measure and usually comparing the complexity of diabetics to that of healthy individuals. There is a lack of understanding regarding the comparative analysis of different entropy measures across different types of diabetic and prediabetic populations.

In this work, we analysed CGM time series from three distinct diabetic populations with MSE, using different base entropies: approximate entropy (ApEn), attention entropy (AttnEn) and dispersion entropy (DispEn). Our goal is to answer the following research questions: (1) What are the characteristics of these multiscale entropies of continuous glucose data? and (2) Which entropy measures are most effective at differentiating between the three populations? This study makes two key contributions. First, it provides new understanding of glycaemic complexity by employing multiple entropy measures to analyse glucose signal dynamics. Second, it offers insights into how different entropy measures can effectively differentiate between diabetic and prediabetic populations. These findings have clinical relevance, as they could lead to the development of easy-to-measure biomarkers for early diagnosis.

2 RELATED WORKS

Multiscale entropy (MSE) analysis is a powerful method to assess the complexity and irregularity of a signal across multiple time scales or levels of a system. By examining the temporal fluctuations of the signal, MSE offers insights into the underlying structure of the information encoded (Bar-Yam, 2004; Nawaz et at., 2024). MSE has been widely applied to analyse the complexity of physical and physiological signals, such as heart rate, electroencephalogram (EEG) and blood oxygen saturation (SpO2) (Busa et al., 2016; Chu et al. 2021; Chen et al., 2022; Liang, 2023). Regarding human signals, researchers combined MSE with Attention Entropy (AttnEn) and applied the method to SpO2 signals to generate features and in association with classification machine learning models to detect sleep apnea (Liang, 2023). Machine learning models were also used in combination with MSE and gait force signals to classify neurodegenerative diseases, such as Parkinson's disease (Nam Nguyen et al., 2020). In the context of glucose signal analysis, scientists usually apply MSE and Sample entropy (SampEn). This combination appears most frequently in the literature, such when quantifying the complexity of the temporal structure of the CGM time series in non-diabetic and diabetic people, with findings showing that the complexity of the signal is significantly higher for the non-diabetic subjects (Costa et al., 2014). In order to investigate relationship between glucose complexity, glucose variability and insulin resistance, Crenier et. al., applied SampEn and detrended fluctuations analysis into CGM data. As the main results, they found that SampEn was inversely correlated with insulin resistance, body mass index and glucose variability (Crenier et al., 2016). Another study carried out a retrospective cross-sectional analysis to evaluate and compare relationship between indices of non-linear dynamics and traditional glycaemic variability, including MSE with SampEn (Kohnert et al., 2018). Researchers also studied the comparison between SampEn and Fuzzy Entropy, in the context of artifact blood glucose time series. They found that both are sufficient robust to achieve a significant classification performance (Cuesta-Frau et al., 2018). Targeting in T2D pregnant patients under treatment, researchers analysed the complexity and fractality of glucose dynamics using MSE and applying SampEn (Chen et al., 2019). Still with the combination MSE and SampEn, this study made a comparison of the complexity of CGM signals between diabetics and control individuals. They found that the complexity of glucose dynamics fluctuation decreases in diabetes and MSE complexity index could be used as a biomarker in the monitoring of diabetes (Chen et al., 2014). In other work, scientists applied Approximate Entropy (ApEn) in glucose readings from T1D subjects, they found an increase of glucose profile complexity due to changes of insulin therapies (Lytrivi and Crenier, 2014). Previous studies did not address the use of different entropies in signal complexity analysis and considered only a single type of dataset. On the other hand, this study contributes to the analysis of different entropies in different datasets with distinct conditions related to diabetes.

3 METHODOLOGIES

3.1 Datasets

In this study, CGM data from three databases were retrospectively analyzed. The first dataset included 12 individuals with T1D, 58.3% of whom were women, with a mean age of 50 years. These individuals were undergoing treatment with Medtronic Enlite 530G or 630G insulin pumps. No glycated hemoglobin (HbA1c) data was available for this cohort. Data collection occurred over 8 weeks, which Medtronic Enlite CGM sensors recorded blood glucose levels every 5 minutes (Marling et al., 2020). The second dataset contains time series blood glucose readings from 100 individuals with T2D, 44% of whom are women, with an average age of 60.1 years. These participants wore FreeStyle Libre sensors for periods ranging from 3 to 14 days, with glucose readings automatically recorded every 15 minutes. After removing duplicate and irregular data, a total of 92 individuals were included in the final analysis and had an HbA1c average of 75.9 mmol/mol (Zhao et al., 2023). The last dataset includes data from 16 prediabetic subjects, 56.2% of whom were female, monitored using the Dexcom G6 device over a 10-day period. Glucose levels were recorded at 5-minute intervals, and the cohort's average HbA1c was 41.5 mmol/mol (Goldberger et al., 2000).

3.2 Multiscale Entropy Analysis

The MSE analysis involves a series of iterative steps for each specified scale factor (τ): a coarse-graining technique is applied to the signal, followed by the calculation of the base entropy at each scale.

Regarding the coarse-graining process, the glucose level signal is segmented into non-overlapping sequences for different temporal scales. Given a glucose signal $x(i) = \{x(1), x(2), \dots, x(N)\}, (i = 1,2, \dots, N)$, the coarse-grained signal for scale factor τ ($\tau \epsilon \mathbb{N}^+$) represented as:

$$x_g^\tau(j) = \left\{x_g^\tau(1),\ x_g^\tau(2), \dots, x_g^\tau(N/\tau)\right\} \quad (1)$$

Assuming $j = 1,2, \dots, N/\tau$, this signal can be calculated by the mean of all data points within the *j-th* window. When $\tau = 1$, $x_g^\tau(j)$ is equivalent to the initial signal. For $\tau > 1$ the length of the coarse-grained signal decreases progressively as the scale factor τ increases.

The value of τ is different and depends on the type of dataset. For the T1D and PRED datasets, which the glucose recording time is every 5 minutes, the value of the scale factor is set to values 1 to 12, corresponding to a time range of 5-60 minutes, which means that 12 coarse-grained signals were generated. For the T2D dataset, in which glucose records are every 15 minutes, τ values were between 1 and 4, corresponding a time range 15-60 minutes and generating 4 coarse-grained new signals.

3.3 Base Entropies

Three different entropy measures were utilized: approximate entropy (ApEn), attention entropy (AttnEn), and dispersion entropy (DispEn). Unlike previous studies that typically relied on a single entropy measure, often sample entropy, our approach of using three base entropies allows us to capture a broader range of characteristics in the CGM data. ApEn has been widely used in various types of signals, such as physiological and financial data (Sabeti, 2009). DispEn was selected because it addresses some limitations of the widely used sample entropy, particularly in terms of computational cost and its ability to capture amplitude patterns in signals (Rostaghi et at., 2016). However, both entropy measures require parameter tuning, which adds complexity and uncertainly to analysis. To mitigate this, we also performed analysis on AttnEn, which has the advantage of being parameter-free and is considered robust to variations in time-series length (Yang, et al. 2020). In what follows we provide a detailed description of each of these base entropies.

- **Approximate Entropy (ApEn)**

ApEn is a technique used to quantify the amount of regularity and the unpredictability of fluctuations over time-series data (Pincus, 1991). ApEn is calculated with the following steps:

1. Define parameters: embedding dimension (m), tolerance threshold for similarity (r).
2. Create m-dimensional vectors from CGM time series $x_g^\tau(i)$.
3. For each vector $x(i)$, calculate the distance between two vectors $x_g^\tau(i)$ and $x_g^\tau(j)$ as the maximum absolute difference between their corresponding components.
4. Define a function $C_i^m(r)$ that counts the number of vectors $x_g^\tau(j)$ that are similar to $x_g^\tau(i)$, meaning the distance is less than equal to r.
5. Calculate $\Phi^m(r)$, the average of the logarithms of $C_i^m(r)$.
6. Increase the embedding dimension to $m + 1$, repeat the steps 2-5, and calculate $\Phi^{m+1}(r)$
7. The formula of Approximate Entropy is:

$$\mathrm{ApEn}(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r)$$

- **Attention Entropy (AttnEn)**

AttnEn measures the distribution or spread of attention across multiple inputs in a system. This method does not need any parameter to tune, it is robust to the time-series length and requires only linear time to compute (Yang et al., 2020). Attention entropy is calculated with the following four main steps:

1. Identify the peak points $x_g^\tau(j)$, which can be considered as local maxima or a local minimum.
2. Define the key patterns ω in Ω.
3. Calculate the intervals $I_\omega^\tau(j)$ between two adjacent peak points for each pattern ω for any given sub-series.
4. Calculate Shannon entropy over frequencies of all intervals by the equation below:

$$\mathrm{AttnEn} = -\frac{1}{4}\sum_{\omega\in\Omega}\sum_{k} p(I_\omega^\tau(k))\log\, p(I_\omega^\tau(k))$$

- **Dispersion Entropy (DispEn)**

DispEn is a recently introduced entropy metric to quantify the uncertainty of time series and is fast to compute (Rostaghi et al., 2016). To calculate DispEn, the followings steps are necessary:

1. The signal is mapped to c classes, labelled from 1 to c. The normal cumulative distribution function (NCDF) is used to map $x_g^\tau(j)$ into $y_g^\tau(j)$. Next, the linear algorithm is used to assign to an integer from 1 to c. For each member, is converted to $z_g^{\tau,c}(j) = round(c.y_g^\tau + 0.5)$.
2. Each embedding vector $z_g^{\tau,c,m}(j) = \{z_g^{\tau,c}(j), z_g^{\tau,c}(j+d) \dots, z_g^{\tau,c}(j+(m-1)d)\}$, with embedding dimension m and time delay d, is mapped to a dispersion pattern $\pi^\tau_{v_0 v_1 \dots v_{m-1}}(j)$.
3. For each c^m potential dispersion, relative frequency is obtained as follows:

$$p\left(\pi^\tau_{v_0 v_1 \dots v_{m-1}}(j)\right) = \frac{Number\{k | k \le N-(m-1)d, z_g^{\tau,c,m}(j)\ has\ type\ \pi^\tau_{v_0 v_1 \dots v_{m-1}}(j)\}}{N-(m-1)d}$$

4. Based on Shannon's definition of entropy, the Dispersion Entropy is:

$$\mathrm{DispEn}\left(x_g^\tau, m, c, d\right) = -\sum_{\pi=1}^{c_g^m} p(\pi^\tau_{v_0 v_1 \dots v_{m-1}}(j))\log\, p(\pi^\tau_{v_0 v_1 \dots v_{m-1}}(j))$$

4 RESULTS

Figure 2 (a) shows the distribution of ApEn across the time scales. This figure reveals that the entropy values remain relatively stable, making it difficult to differentiate between the various diabetic populations and prediabetes. This suggests that ApEn is not a useful metric for separating the different populations. The distribution of AttnEn for three groups at each time scale is shown in Figure 1 (b). As seen in the figure, it is noticeable trend of entropy decreasing over time, which allows for the distinction between the T1D/T2D and prediabetic datasets from 10 minutes onward, continuing through to the time scale of 60 minutes. Finally, Figure 1 (c) illustrates the distribution of DispEn. From this figure, we observe an increase in entropy values over the time scale, with a clear separation between the diabetes groups and the prediabetic group across the entire time scale. This indicates that DispEn can effectively distinguish between the CGM data of diabetic patients and healthy people. Table 1 shows a summary of these observations.

Table 1: Trends and utilities of three base entropies in MSE analysis.

Entropy	Trend	Utility
ApEn	Stable	Not useful
AttnEn	Decrease	Useful when time scale is between 10 – 60 minutes
DispEn	Increase	Useful

5 DISCUSSIONS

There are few studies related to CGM time series and entropy analysis (Chen et al., 2019; Lytrivi and Crenier, 2014). Furthermore, most studies do not address other types of diabetes incidence, such as prediabetes and their comparisons among all groups.

This study, we selected three base entropy measures for analysis. Our analysis revealed that the three base entropy measures exhibited distinct trends as the time scale increased, and they showed differences in their effectiveness at differentiating between diabetic and the healthy population. Different patterns among different populations of diabetic and healthy individuals are expected due to the characteristic blood glucose level behaviours of everyone in these groups. Entropy algorithms manipulate the analysed signal to detect patterns and

characteristics inherent to each analysed population. We found that approximate entropy was not useful at any time scale, attention entropy was effective when the time scale ranged between 10 to 60 minutes, and dispersion entropy was useful across the entire time scale analysed. ApEn, despite being widely used in previous studies on physiological signal analysis, did not prove useful in distinguishing between the diabetes and prediabetes cohorts in our study. This suggests that popular and widely used methods are not always the most effective for every problem. In the case of glucose dynamics, ApEn may not capture the dysfunction in the physiological systems regulating blood glucose levels in individuals with diabetes. In contrast, the other two entropy measures, despite being rarely used in the literature, appear to provide more relevant insights for our analysis. This observation underscores the importance of exploring a diverse range of entropy measures, especially those that are not yet widely adopted in the literature. It is also important to note that none of the base entropy measures were able to differentiate between T1D and T2D. The possible reasons for this include similarities in glucose dynamics between T1D and T2D or limitations in the datasets used.

It is necessary to interpret these results with caution. The utility of the base entropy measures may be context dependent. Since our analysis was limited to three datasets, each homogeneous in terms of subject demographics, it is important not to overgeneralize these findings. Further research with more diverse populations and additional datasets is necessary to draw more definitive conclusions. Nonetheless, this research broadens the scope of MSE analysis applied to glucose signals, and our findings provide valuable insights that can inspire future hypotheses and research in this area.

6 CONCLUSION

In this study, we investigated the potential of MSE analysis to distinguish between individuals with T1D, T2D, and prediabetes using CGM data. Our findings highlight the importance of selecting appropriate base entropy measures. While ApEn, a widely used measure in physiological signal analysis, proved ineffective for distinguishing between the diabetes and prediabetes cohorts, AttnEn and DispEn showed promising results, especially in capturing dynamic differences across time scales. In particular, DispEn was useful across the entire time scale analysed, suggesting its potential as a more robust marker. In addition, DispEn entropy analysis showed results similar to previous studies, in which the complexity of CGM signals is greater for non-diabetic than for diabetic subjects and that this technique can detect an increased regularity in the pattern of glucose fluctuations (Costa et al, 2014; Chen et al., 2014).

Overall, our work suggests that MSE analysis holds promise for developing biomarkers to distinguish between diabetes and prediabetes. Although no significant differences were observed between T1D and T2D cohorts, future studies with larger and more diverse datasets may help clarify the utility of MSE analysis in differentiating these two groups. In the next step, we plan to explore additional entropy measures to deepen our understanding of glucose dynamics across different populations.

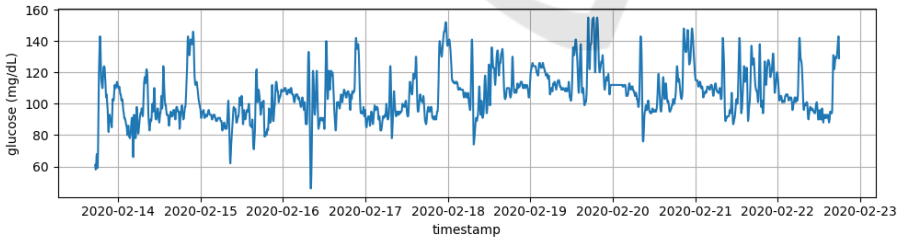

Figure 1: Time-series Continuous Glucose Monitoring.

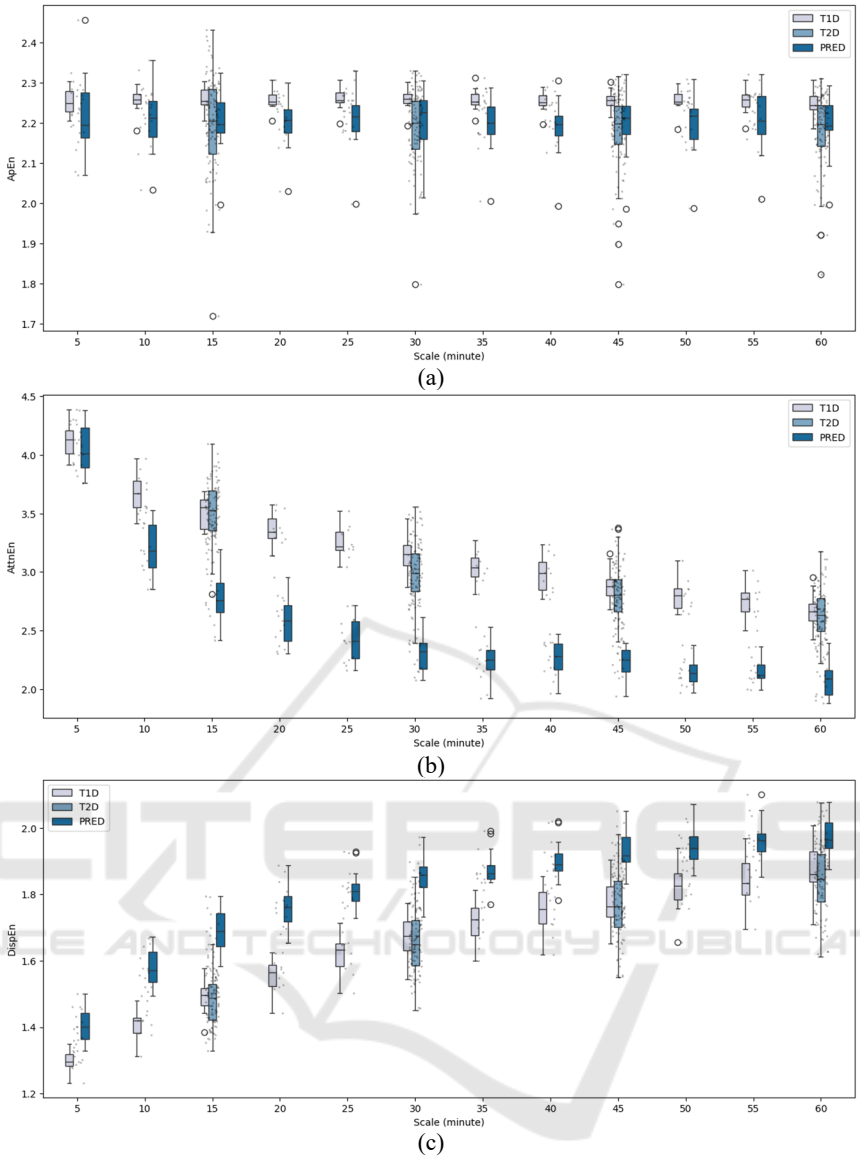

Figure 2: Multiscale entropy analysis on CGM data for T1D, T2D, and prediabetes using different base entropy: (a) Approximate entropy, (b) Attention entropy, (c) Dispersion entropy.

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