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Is type 1 diabetes a chaotic phenomenon?

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ABSTRACT

A database of ten type 1 diabetes patients wearing a continuous glucose monitoring device has enabled to record their blood glucose continuous variations every minute all day long during fourteen consecutive days. These recordings represent, for each patient, a time series consisting of 1 value of glycaemia per minute during 24 h and 14 days, i.e., 20,160 data points. Thus, while using numerical methods, these time series have been anonymously analyzed. Nevertheless, because of the stochastic inputs induced by daily activities of any human being, it has not been possible to discriminate chaos from noise. So, we have decided to keep only the 14 nights of these ten patients. Then, the determination of the time delay and embedding dimension according to the delay coordinate embedding method has allowed us to estimate for each patient the correlation dimension and the maximal Lyapunov exponent. This has led us to show that type 1 diabetes could indeed be a chaotic phenomenon. Once this result has been confirmed by the determinism test, we have computed the Lyapunov time and found that the limit of predictability of this phenomenon is nearly equal to half the 90 min sleep-dream cycle. We hope that our results will prove to be useful to characterize and predict blood glucose variations.

1. Introduction

Diabetes is a chronic disease which affects more than two hundred millions of people in the world [37]. There are two main types of diabetes: type 1 and type 2. In the case of type 1 diabetes, the lack of insulin due to the destruction of insulin-producing beta cells in the pancreas leads to diabetes mellitus in which insulin is required for survival to prevent the development of ketoacidosis, coma and death. Type 2 diabetes is characterized by disorders of insulin action and insulin secretion, including insulin resistance [2]. This work only concerns type 1 diabetes.

Insulin-dependent diabetes or type 1 diabetes is characterized by dramatic and recurrent variations in blood glucose levels. The effects of such variations are irregular (erratic) and unpredictable hyperglycemias, sometimes involving ketoacidosis, and sometimes serious hypoglycemias. Nowadays, the development of Continuous Glucose Monitoring (CGM) devices makes it possible to record blood glucose every minute during two weeks providing endocrinologists thousands of data in the form of time series. This has also led to prediction of continuous blood glucose variations based on computational methods such as support vector machine [17].

In the middle of the eighties, Wolf et al. [38] proposed an algorithm allowing the estimation of non-negative Lyapunov exponents from an experimental time series. Thus, determination of Lyapunov exponents enabled, on the one hand, to decide whether the time series is chaotic or not and, on the other hand, to assess the Lyapunov time corresponding to the limit of predictability of the observed phenomenon. Since this algorithm was first published in Fortran code, many other versions have been developed in various languages such as C and C++ [25]. Recently, this Fortran code has been implemented in MatLab by Wolf, as well

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as in Mathematica by Ruskeepää, see http://library.wolfram.com/infocenter/MathSource/8775/. This Mathematica software is used in the present work. The software is shortly explained in Ruskeepää [33] and is also used in http://demonstrations.wolfram.com/ChaoticDataMaximalLyapunovExponent/ (2017).

Long after the famous French mathematician, physicist and engineer, Henri Poincaré had discovered "deterministic chaos" in his seminal works concerning the motion of celestial bodies [29], many scientists searched for traces of chaotic behavior in various phenomena. The signature of chaos is the very well-known property of Sensitive Dependence upon Initial Conditions which makes the observed phenomenon unpredictable in long term. In the beginning of the sixties, Edward Norton Lorenz was the very first to identify such a feature in meteorology [27]. More than ten years later, Sir Robert May demonstrated the existence of "complex dynamics" (chaos) in ecological models [28].

During the following decades, scientists highlighted chaotic behavior in human body. Indeed, according to Ives [19] "innumerable, entwined (nonlinear) feedback loops regulate our internal processes, keeping us within the narrow bounds needed for survival. Despite this regulation, our systems are aperiodic and unpredictable in the long term." Thus, a prime example of chaos was found in the brain [3] and then, in the beating of the heart [10,35]. Although type 1 diabetes is widely and intuitively considered by endocrinologists and clinicians as a chaotic phenomenon [7,15,26], this has not yet been established by numerical methods, to our knowledge.

In this work, starting from a database of glucose from ten type 1 diabetes patients and while using well-known numerical algorithms with Mathematica, we give support to the conclusion that type 1 diabetes is a chaotic phenomenon and we provide the Lyapunov time corresponding to the limit of predictability of this phenomenon. These results will prove to be very useful to characterize and predict blood glucose variations.

This paper is organized as follows. In Section 2.1, we briefly present the three main continuous glucose monitoring devices and detail the main features of the one used in this study. In Section 2.2, we recall the method of time delay reconstruction, also referred to as delay reconstruction and phase space reconstruction [29,36], and the definitions of time delay and embedding dimension. To determine their proper values we use, respectively, average mutual information [13] and the method of false nearest neighbors proposed by Kennel et al. [23]. We recall the method of correlation exponent [16] to estimate the correlation dimension and the method of local divergence rates [20] to estimate the maximal Lyapunov exponent.

In Section 3.1, we present, in some detail, all the results for the glucose data of patient 1. Then, in Section 3.2, we briefly summarize the results of all the ten patients. We also apply a direct test for determinism in a time series [22] and the programs by Perc [30] to state that type 1 diabetes is likely a chaotic phenomenon. Section 4 summarizes the results of the article, *e.g.*, an estimate of the Lyapunov time which is nearly equal to half the 90 min sleep-dream cycle.

2. Materials and methods

2.1. Continuous glucose monitoring systems

Continuous glucose monitoring devices began to be developed in the eighties. However, they became available for practical use only twenty years ago with the miniaturization and development of electronic sensors combined to growing storage capacities. These systems, which have been proven to reliably reflect glucose levels [4], replace henceforth the classical finger prick blood glucose readings by monitoring interstitial fluid (ISF) glucose levels continuously. Interstitial fluid is a thin layer of fluid that surrounds the cells of the tissues below the skin [5,8,11]. That's the reason why there is a 5 to 10 min delay in interstitial fluid glucose response to changes in blood glucose. This result of great importance will need to be compared to the Lyapunov time obtained in this study (see Section 4).

Today, the three main manufacturers which propose devices with continuous glucose monitoring reading are Abbott (Freestyle Navigator II), Medtronic (MiniMed coupled with Veo-pump), and Novalab which offers the reader Dexcom G4 coupled to the insulin pump Animas Vibe. Whatever the system, it is composed of two parts. The glucose sensor which has a small, flexible tip that, inserted just under the skin, continuously measures the glucose concentration in the interstitial fluid and stores data during several days. The blood glucose reader is used to scan the sensor and displays the current glucose reading based on the most recently updated glucose value during the latest hours of continuous glucose data. Some readers are also coupled to an external insulin pump (Paradigm VEOTM Medtronic or Animas VibeTM of Novalab).

In this work, we have chosen to use the Abbott (Freestyle Navigator II) system because the blood glucose reader records the blood glucose variations continuously every minute all day long during fourteen consecutive days. This represents, for each patient, one value of glycaemia per minute during 24 h and 14 days, i.e., 20,160 data. Thus, ten type 1 diabetes patients have accepted to provide us the recordings of their blood glucose during fourteen consecutive days so that they could be anonymously analyzed.

2.2. Methods

Following the works of Takens [36], Sauer et al. [34] and Abarbanel [1], summarized in Kodba et al. [25], we consider the reconstruction of the attractor in an m-dimensional phase space starting from the time series $\{x_1, \dots, x_i, \dots, x_T\}$ of blood glucose variations for each patient. Here x_i denotes the glycaemia in ith minute. According to Takens [36], the reconstructed attractor of the original system is given by the vector sequence

$$p(i) = \left(x_{i-(m-1)\tau}, \dots, x_{i-2\tau}, x_{i-\tau}, x_i\right) \tag{1}$$

where τ and m are the time delay and the embedding dimension, respectively. Takens' famous theorem states that for a large enough m, this procedure provides a one-to-one image of the original system. It follows that the attractor constructed according to Eq. (1) will have the same dimension and Lyapunov exponents as the original system. To reconstruct the attractor successfully, pertinent values of τ and m have to be accurately determined.

2.2.1. Time delay

Two criteria are to be taken into account for the estimation of the time delay τ:

- τ has to be large enough because the information we get from measuring the value of x at time $i+\tau$ should be significantly different from x at time i.
- τ must not be larger than the time in which the system loses memory of its initial state. This is important for chaotic systems, which are unpredictable and lose memory of the initial state.

Fraser and Swinney [13] defined the mutual information between x_i and $x_{i+\tau}$ as a suitable quantity for determining τ. The mutual information between x_i and $x_{i+\tau}$ measures the quantity of information according to the following expression

$$I(\tau) = \sum_h \sum_k P_{h,k}(\tau) \log_2 \frac{P_{h,k}(\tau)}{P_h P_k}. \tag{2}$$