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Using Normalised Compression Distance to Identify Different Profiling Days in Type 1 Diabetic Patients ⋆

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Abstract: This work is devoted to providing patients and physicians with a novel tool to analyse and extract information for better management of type I diabetes. We use a clustering methodology based on the normalised compression distance to identify different profiles of days. The methodology has been validated using data generated by a simulator of virtual patients, which include an exercise model. Profiling daily data can help physicians and patients cope with information overload and assist in future planning for improved treatments and self-management of diabetes type 1.

Keywords: Diabetes, Blood glucose, Clustering, Information theory, Time series.

1. INTRODUCTION

Type 1 diabetes mellitus (T1D) is a disease resulting from an autoimmune attack on insulin-producing cells in the pancreas (β-cells). The nature of this disease influences every aspect of life. On one hand, patients receive daily doses of insulin, either by multiple daily injections (MDI) or by a continuous subcutaneous insulin infusion (CSII). On the other hand, the management of T1D involves more than just the ingestion of medication: scheduling meals carefully, counting carbohydrates, exercising, monitoring blood sugar levels, and adjusting their day-to-day activity accordingly. Furthermore, even when patients follow all orders of physicians, the unpredictable nature of the disease can undermine medication adherence leading to upward crests in blood glucose (BG) due to stress, or leading to a higher glycemic variability because of a patient's menstrual period.

Over the last decades the emergence of intensive insulin therapies (MDI and CSII) have improved the quality of life of diabetic patients by reducing microvascular complications associated with T1D [DCCT Research Group (1996)], however these therapies have been associated with an increased risk in hypoglycemia episodes [DCCT Research Group (1997)]. Insulin pumps have proven effective in glycemic control [Pickup and Keen (2002),Fatourechi et al. (2009)] and today pumps are globally regarded as a therapy to reduce the rate of hypoglycemia episodes [Russell et al. (2014)], especially in those with higher risk of severe hypoglycemia [Pickup and Sutton (2008)]. Hypoglycemia is the main fear of patients, as it is related to severe consequences, such as diabetic coma [Cryer (2002)].

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The development and commercialization of continuous glucose monitoring devices (CGM) supposed a great advance for the treatment of diabetes. Using these continuous sensors in combination with insulin pumps (CGM-CSII) demonstrated a concurrent reduction in time spent in hypoglycemia [Battelino et al. (2012)]. Thereafter, automation features in CGM-CSII were introduced. The use of an automatic suspension of insulin delivery significantly reduced the rate [Ly et al. (2013)] and severity of hypoglycaemia, thereby avoiding rebound hyperglycemia [Brazg et al. (2011)]. Later, in Danne et al. (2014) the use of a predictive low glucose management system reduced the severity of hypoglycemia beyond that already achieved by threshold-based suspension algorithms. The recent advances in CGM have led to more robust and portable devices which have demonstrated their value in improving the glycemic control working with closed-loop algorithms [Doyle et al. (2014), Phillip et al. (2013)]. However, the limited capacity to process the data extracted from glucose monitors restricts the ultimate goal in the development of diabetes management, a true closed-loop artificial pancreas (AP).

As we noted above, T1D can become dependent on a wide range of factors with high variability. Seasons, diet disturbances, exercise, age, moods, habits, climate changes or menstrual period and pregnancy in women are some of these factors. For example, in Ovalle et al. (2008) or Cramer (1942) the authors show that menstrual period could affect carbohydrate metabolism (it can even precipitate diabetic acidosis and coma), however the disturbance does not occur in all diabetic women, or even in the same patient; also, this problem may take place at different menstrual periods. Thus, the complexity of modelling overall algorithms for automated (or semi-automated) hybrid systems is accentuated when we have to deal with disturbances which can arise in the same patient. These intra-patient variables cause different effects on BG level,

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transforming the usual patterns commonly generated by patients with T1D. The ability to identify such patterns allow us to generate different daily profiles of T1D. Profiling intra-patient behaviours provides essential data which can assist in identifying causes of poor glycemic control and help in the diagnosis of treatment. Furthermore, the same methodology could be applied to an AP, resulting in control algorithms that are able to identify behavioural changes in patterns generated by BG.

A new tool oriented to information analysis and visualization of daily diabetes profiles can be useful to physicians and patients, helping physicians to cope with the information overload, assisting in future planning for improved treatments, and assisting patients with the self-management of the disease. Furthermore, the same methodology could lead to a real-time classifier providing tools that are able to identify behavioural changes in patterns generated by BG. The remainder of the article is organized as follows. Section 2 describes the methodologies used. In Section 3, we perform a series of *In Silico* experiments with virtual patients. Finally, we conclude and discuss future directions in Section 4.

2. MATERIALS AND METHODS

Previous works have attempted to identify modal days [Bellazzi et al. (2000, 1998)], i.e., the abstraction of the time series behaviours in the GCM with the aim to identify the characteristic daily BG patterns of a patient. Instead of looking for the characteristic day of a patient, we are looking for characteristic profiles of days belonging to the same patient. With the aim to identify a series following different patterns despite the seemingly uncorrelated behaviour of the BG series, we use a data mining procedure, which is capable of building hierarchical distance trees in a blind manner for sets of daily time series of BG values collected by a CSII. We perform this task by an approximation to the not computable Kolmogorov complexity.

2.1 Clustering and Normalised Compression Distance

To analyse and extract information from time series data belonging to CGM is a complex task. Data extracted from CSII not only comprise BG values from the sensor, they also involve carbohydrates, insulin dosages, BG readings, events, etc. In this work, we analyse only BG values because they consist of a larger number of occurrences of constant periodicity. We use a cluster analysis methodology with the aim to understand the macroscopic structure and relations between the analysed BG time series. Clustering could be considered the most important unsupervised learning problem; it focuses on segmenting the complete set of information in homogeneous subgroups. Specifically, in this work we deal with time series clustering which requires a clustering algorithm or procedure to form clusters given a set of unlabelled data objects. Unlike static data, the time series of a feature is comprised of values that are changed with time. Clustering time series is concerned with determined groups of similar unlabelled time series which are monitoring data collected during different periods from one or more processes. There are other techniques applied to time series, however clustering methodology is one of the most frequently used and a trend of increasing activity exists.

Time series data are a topic of interest because of its presence in a large variety of areas, such as medicine, engineering, business, finance and biology. In the medical field, clustering methodologies were popularized by identifying effective treatments, detection of diseases or best practices. For example, in the field of medicine, time series clustering methodologies have been used for detection of the independent components of neuroimaging [Himberg et al. (2004)].

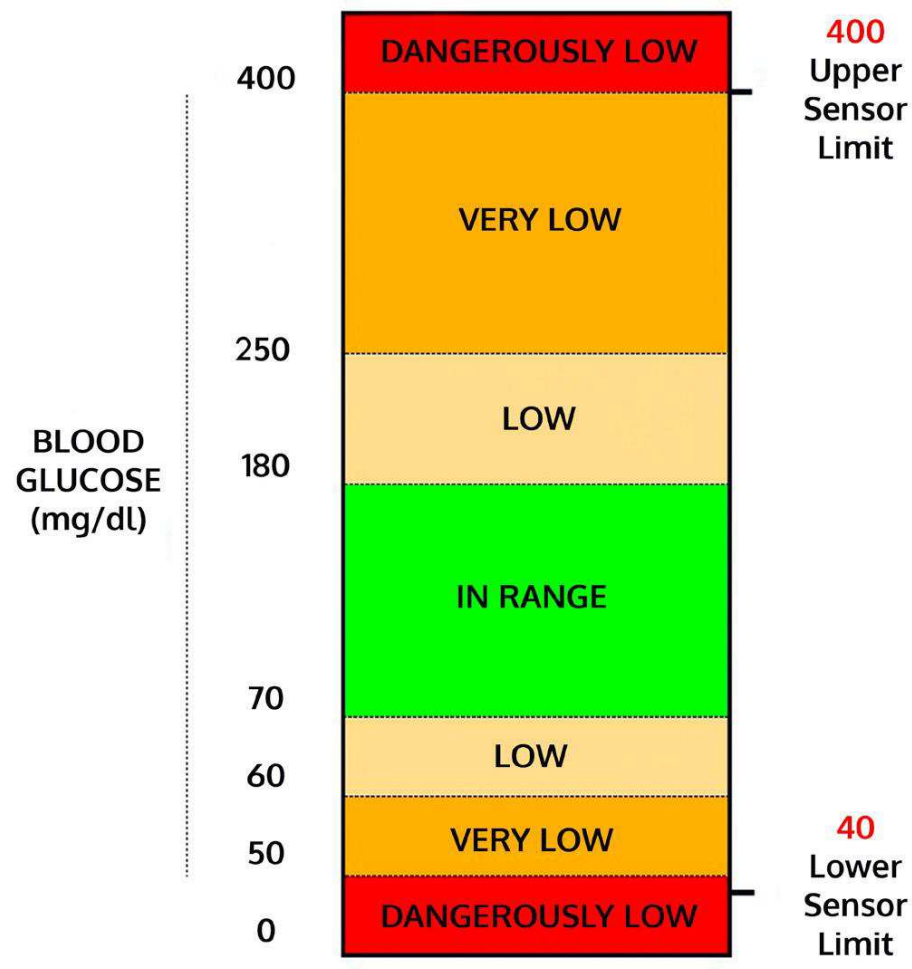

Fig. 1. Blood Glucose Ranges: Ranges of blood glucose applied in this work to discretise the time series of blood glucose extracted with continuous glucose monitoring. The recommendation ranges for the standardization of blood glucose were proposed in Bergenstal et al. (2013). The lower and upper thresholds are fixed by the limits of current commercialized systems in 40 and 400 mg/dl.

The relationship between computation, information, and randomness is studied in the field of algorithmic information theory. An important topic in this field is the Kolmogorov complexity Kolmogorov (1965) of an object, that is, broadly speaking, the measure of computational resources needed to describe an object. The idea is that the complexity of an object can be seen as an absolute and objective quantification of the amount of information in it. Since the Kolmogorov complexity is not computable, there have been raised several approximation measures which are based on the comparison of lengths of compressions between the objects and one of the most well-known is the normalised compression distance (NCD).

The NCD is a compression-based similarity distance that determines the similarity in terms of information distance between pairs of objects according to the most dominant common features. Previous works [see Contreras et al.

(2014)] have demonstrated that the NCD is a reliable tool for classification on a large number of domains. Furthermore, NCD has been applied successfully in many areas; NCD concerns the classification of genomes, pieces of music, plagiarism of computer programs, image registration, letters phylogeny, protein structure comparison, genotyping, tumour subclassifications, virus detection, etc.[Chen et al. (2004), Cilibrasi et al. (2004), Bailey et al. (2007)].

In this paper we use a novel version of the NCD to measure the differences among the time series of BG. The measure that we use was proposed in Contreras et al. (2014) as an innovative approach to the Kolmogorov complexity that exploits the management of the dictionaries used by a software compressor to reduce the redundancy. The proposed distance, called mNCD (modified normalised compression distance), is the following:

$$mNCD(x,y) = \frac{Max\{C(x|D_y), C(y|D_x)\}}{Max\{C(x|D_x), C(y|D_y)\}} \quad (1)$$

where C represents a measurable way to approximate the Kolmogorov complexity using a compressor program, C(i) is the compressed size of i and $C(i|D_j)$ means the compression size of i using the compression dictionary of j.

In the same way that songs of the same music style share patterns, or malicious software and viruses share common features, we expect multiple time series of BG could share patterns that are invisible at usual analysis. In fact, our approach is based on the assumption that the patterns formed in scenarios with perturbations, as exercise, are more similar to each other than patterns formed in other scenarios. Thus, we expect that patterns shared by two time series of BG will be translated into a high degree of similarity.

In order to discretize the values representing the daily time series of BG, and be able to calculate the NCD, we transformed the information by a symbolic representation of time series. Therefore, values of glucose will be transformed into strings of characters by the application of threshold levels representing the related glucose profiles. We follow the recommended standardization of glucose ranges in Bergenstal et al. (2013) analysing the values of time series by the six intervals showed in the Figure 1.

We perform hierarchical clustering with the intention of showing the degree of similarity of the time series. Thus, time series of BG are regrouped in a tree structure in an automatic and blind manner. The so-called hierarchical methods produce nested partitions and are represented by dendrograms. Thus, we consider a set of N time series to be clustered and a distance matrix (also called dissimilarity matrix) with N*N measurements. The employed hierarchical clustering process can be summarized as a method which builds a binary tree from individual elements by progressively merging the clusters containing the two closest elements (according to the distance matrix). The specific type of hierarchical algorithm chosen in this work to perform the clustering is the complete linkage method [Dawyndt et al. (2005)] due to compromise between simplicity, ease of analysis and its ability to obtain quality solutions. Although other non-hierarchical methods are also possible, they will not be discussed.

2.2 In Silico Materials: Virtual Patients

Just as for the design of any complex system of engineering, computer simulations are a prerequisite for leading real data tests. Although in silico validation does not guarantee in vivo performance, it provides valuable information about efficiency, limitations and expected behaviour of the classification algorithm. In order to create scenarios simulating the variability and the possibilities of the daily life of individuals we used the implementation of different models extracted from Girona APSim and LabVIEW software [León-Vargas et al. (2013)] where challenging simulated scenarios are created. A cohort of ten virtual patients from Dalla Man et al. (2007) were subjected to individualized circadian variations in insulin sensitivity and sinusoidal day-to-day variations of 20% amplitude with 19 and 29 h periods in insulin sensitivity and insulin absorption, respectively. Rate of BG appearance profiles corresponding to different mixed meals from Herrero et al. (2012) are also implemented. The exercise model described in Dalla Man et al. (2009) was included to complete the simulator. The three scenarios implemented are:

- Basic Scenario: Composed of a set of ten simulation days with values each minute. Table 1 summarizes the main variables measured in these simulations.
- Exercise Scenario: The same parameters as the Basic Scenario with exercise every 2 days, following the guidelines in Iscoe and Riddell (2011). We use a 45 min exercise at 17:00 with the heart rate progression present in Figure 2. No corrective actions were performed, resulting in a number of hypoglycemic events. Table 2 presents a summary of the simulation results.
- Exercise Scenario with corrective measures: The same features as the Exercise Scenario but adding corrective actions, snacks before and after exercise and a reduction of basal insulin. The results are summarized in Table 3.

Tables 1, 2 and 3 summarize the results of the series of simulations presenting the next variables: minutes with BG values above 180 and 140, respectively, minutes with BG values bellow 70 and 50, respectively, total number of hypoglycemic episodes, average time per hypoglycemic episode (min) and average blood glucose.

	t>180	t>140	t<70	t<50	N hipo	min	Mean glucose
P1	19,57	20,32	0	0	0	0	148
P2	19,43	20,18	1,6	0	2	150	151
P3	3,73	4,48	0,11	0	1	20	126
P4	9,4	10,15	0	0	0	0	136
P5	4,01	4,76	0	0	0	0	128
P6	9,62	10,37	0,56	0	1	104	128
P7	23,31	24,05	2,48	0	2	232	145
P8	16,14	16,89	1,1	0	2	102	143
P9	10,2	10,95	0,89	0	1	166	143
P10	35,83	36,59	0,97	0	3	60	166

Table 1. Results of the ten virtual patient simulations in the Exercise Basic Scenario.

3. IN SILICO EXPERIMENTS: A PROOF OF CONCEPT

In the in silico experiments we build a series of hierarchical trees using the methodology and modelled data-sets

	t>180	t>140	t<70	t<50	N hipo	min	Mean glucose
P1	11,67	12,42	7,65	2,52	8	179	127
P2	12	12,75	15,75	5,94	9	327	125
P3	1,3	2,05	15,99	5,75	8	374	107
P4	5,35	6,1	15,77	5,45	13	227	113
P5	1,47	2,22	24,15	13,58	14	322	98
P6	6,66	7,41	13,56	3,82	13	195	112
P7	6,02	6,76	28,75	17,82	13	414	102
P8	6,06	6,81	28,59	18,96	12	446	100
P9	6,88	7,63	6,39	2,38	6	199	124
P10	30,2	30,95	9,17	2,82	10	171	148

Table 2. Results of the ten virtual patient simulations in the Exercise Scenario.

	t>180	t>140	t<70	t<50	N hipo	(min)	Mean glucose
P1	18,36	19,11	0,52	0	1	97	150
P2	24,42	25,16	1,63	0	3	102	150
P3	5,55	6,3	0,15	0	1	28	127
P4	17,53	18,27	1,1	0	4	51	51
P5	11,24	11,99	5,54	0,29	12	86	123
P6	12,63	13,38	1,78	0	3	111	134
P7	16,97	17,71	9,26	1,05	15	115	133
P8	17,02	17,77	13,52	1,98	17	148	134
P9	21,76	22,51	0,37	0	1	70	150
P10	45,28	46,03	1,16	0,59	3	72	176

Table 3. Results of the ten virtual patient simulations in the Exercise Scenario with corrective measures.

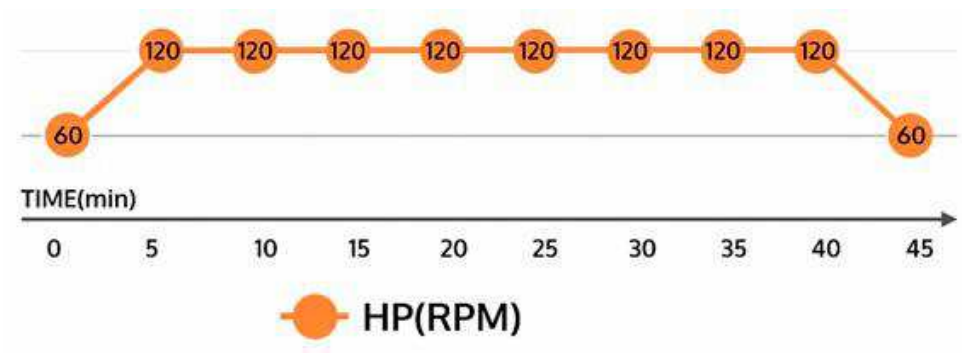

Fig. 2. Heart Rate: Revolutions per minute of heart patients through the exercise interval (45 min). The intensity of the exercise is gradually increasing during the first 5 min and gradually decreasing during the last 5 min.

explained in the last section. We analyse and visualize the clustering by undirected graphs using a spring model based on the force-directed approach (Fruchterman and Reingold (1991)). The graphs show the results of binary hierarchical tree building by the mNCD. Each node showed in the graphs is linked with a specific BG time series. The smaller the distance between nodes, the greater the similarity between them. Figure 3 presents the results of clustering tests in the ten virtual patients in the three modelled scenarios. Red nodes represent the *Basic* scenario time series, light grey nodes the *Exercise* scenario and dark grey nodes the *Exercise with corrective measures* scenario.

The results of our clustering experiment in silico scenarios display significant clusters of two types of series: well-controlled BG levels and poorly controlled BG levels. For instance, the graphs of Patients 8, 7 and 5 show clusters related with the *Basic Scenario* (red nodes) which in turn are the most the most poorly controlled with 17, 15 and 12 episodes of hypoglycaemia, respectively (Table 3). We can find misclassified time series of BG in both types, probably due to the similarity of the curves in some days; that is because the phase values of the simulator were fixed for all the used scenarios. Thus, this fact adds some misclassification errors, while simultaneously shows us that the methodology is able to extract the information we seek beyond the apparent similarity of values.

4. DISCUSSION AND FUTURE DIRECTIONS

The hybrid systems CSII-CGM with automation features are currently considered one of the best ways to achieve substantial short-term improvements in the quality of life of patients with T1D. Not only the promise of reducing the rate of hypoglycaemia, but also the time spent on hypoglycaemia is a reality being gradually adopted in the daily lives of T1D patients. The approach towards fully automatic hybrid AP systems capable of accurately modelling the behaviour of BG is hindered by the high glycemic variability of T1D. In this work we have analysed the glycemic variability through the application of clustering methodologies to time series of BG. The experiments have shown that it is possible to cluster different behaviour profiles identifying patterns on different days for the same patient.

The results of this work encourage us in two ways. On the one hand, we want to analyse the feasibility of tools based on this methodology and ability to cope automatically with real data. The automated interpretation of the knowledge extracted by clustering techniques is essential to move from the field of data analysis research towards a user-oriented environment. On the other hand, we want to validate the extraction of behavioural profiles in a larger scope. Therefore, our current and future work is based on the application of clustering methodologies on easily-labelled data and data extracted from patients with differentiated BG behaviours, for instance, time series of BG during menstrual periods or pregnancy.

Finally, as we mentioned in the introduction, closed-loop algorithms have proven their utility assisting T1D patients and they are established as one of the most important strands to reach a true AP. Therefore, the hybrid use of this methodology with closed-loop algorithms could offer better control models for T1D patients. The identification of personalized TD1 profiles would allow the selection of more suitable controllers for the management of the disease which in turn may bring us towards a better semi-automated AP.

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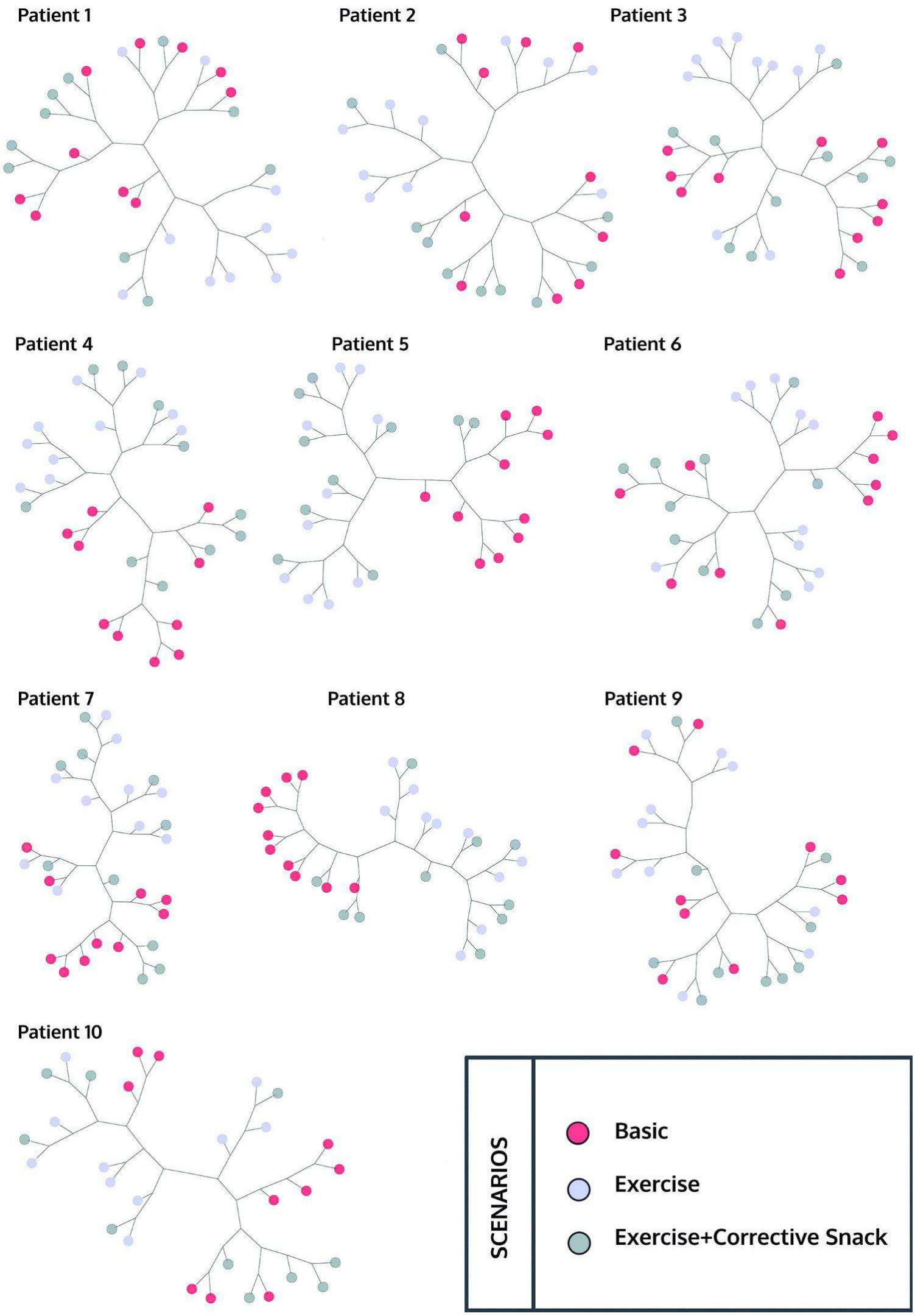

Fig. 3. *In Silico* Experiments: Hierarchical trees related to ten virtual patients simulated with Girona APSIM in the proposed scenarios. The nodes represent daily time series of blood glucose values, a total of 30 modelled days covering the three scenarios. A clustering methodology has been applied with the aim to identify profiles of poorly and well-controlled profiles

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